Introduction and Methodology: *Standards of Care in Diabetes—2023*

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Diabetes is a complex, chronic condition requiring continuous medical care with multifactorial risk-reduction strategies beyond glucose management. Ongoing diabetes self-management education and support are critical to empowering people, preventing acute complications, and reducing the risk of long-term complications. Significant evidence exists that supports a range of interventions to improve diabetes outcomes.

The American Diabetes Association (ADA) "Standards of Care in Diabetes," referred to here as the Standards of Care, is intended to provide clinicians, researchers, policy makers, and other interested individuals with the components of diabetes care, general treatment goals, and tools to evaluate the quality of care.

The ADA Professional Practice Committee (PPC) updates the Standards of Care annually and strives to include discussion of emerging clinical considerations in the text, and as evidence evolves, clinical guidance is added to the recommendations in the Standards of Care. The Standards of Care is a "living" document where important updates are published online should the PPC determine that new evidence or regulatory changes (e.g., drug or technology approvals, label changes) merit immediate inclusion. More information on the "Living Standards" can be found on the ADA professional website DiabetesPro at professional.diabetes.org/content-page/living-standards. The Standards of Care supersedes all previously published ADA position statements—and the recommendations therein—on clinical topics within the purview of the Standards of Care; while still containing valuable analysis, ADA position statements should not be considered the current position of the ADA. The Standards of Care receives annual review and approval by the ADA Board of Directors and is reviewed by ADA staff and clinical leadership. The Standards of Care also undergoes external peer review annually.

SCOPE OF THE GUIDELINES

The recommendations in the Standards of Care include screening, diagnostic, and therapeutic actions that are known or believed to favorably affect health outcomes of people with diabetes. They also cover the prevention, screening, diagnosis, and management of diabetes-associated complications and comorbidities. The recommendations encompass care throughout the lifespan, for youth (children aged birth to 11 years and adolescents aged 12–17 years), adults (aged 18–64 years), and older adults (aged ≥65 years). The recommendations cover the management of type 1 diabetes, type 2 diabetes, gestational diabetes mellitus, and other types of diabetes.

The Standards of Care does not provide comprehensive treatment plans for complications associated with diabetes, such as diabetic retinopathy or diabetic foot ulcers, but offers guidance on how and when to screen for diabetes complications, management of complications in the primary care and diabetes care settings, and referral to specialists as appropriate. Similarly, regarding the psychosocial factors often associated with diabetes and that can affect diabetes care, the Standards of Care provides guidance on how and when to screen, management in the primary care and

The "Standards of Care in Diabetes," formerly called "Standards of Medical Care in Diabetes," was originally approved in 1988. Most recent review/revision: December 2022.

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diabetes care settings, and referral but does not provide comprehensive management plans for conditions that require specialized care, such as mental illness.

TARGET AUDIENCE

The target audience for the Standards of Care includes primary care physicians, endocrinologists, nurse practitioners, physician associates/assistants, pharmacists, dietitians, and diabetes care and education specialists. The Standards of Care also provides guidance to specialists caring for people with diabetes and its multitude of complications, such as cardiologists, nephrologists, emergency physicians, internists, pediatricians, psychologists, neurologists, ophthalmologists, and podiatrists. Additionally, these recommendations help payers, policy makers, researchers, research funding organizations, and advocacy groups to align their policies and resources and deliver optimal care for people living with diabetes.

The ADA strives to improve and update the Standards of Care to ensure that clinicians, health plans, and policy makers can continue to rely on it as the most authoritative source for current guidelines for diabetes care. The Standards of Care recommendations are not intended to preclude clinical judgment. They must be applied in the context of excellent clinical care, with adjustments for individual preferences, comorbidities, and other patient factors. For more detailed information about the management of diabetes, please refer to *Medical Management of Type 1 Diabetes* (1) and *Medical Management of Type 2 Diabetes* (2).

METHODOLOGY AND PROCEDURE

The Standards of Care includes discussion of evidence and clinical practice recommendations intended to optimize care for people with diabetes by assisting providers and individuals in making shared decisions about diabetes care. The recommendations are informed by a systematic review of evidence and an assessment of the benefits and risks of alternative care options.

Professional Practice Committee

The PPC of the ADA is responsible for the Standards of Care. The PPC is a multidisciplinary expert committee comprising physicians, nurse practitioners, pharmacists, diabetes care and education specialists, registered dietitian nutritionists, behavioral health scientists, and others who have expertise in a range of areas including but not limited to adult/pediatric endocrinology, epidemiology, public health, behavioral health, cardiovascular risk management, microvascular complications, nephrology, neurology, ophthalmology, podiatry, clinical pharmacology, preconception and pregnancy care, weight management and diabetes prevention, and use of technology in diabetes management. Appointment to the PPC is based on excellence in clinical practice and research, with attention to appropriate representation of members based on considerations including but not limited to demographic, geographic, work setting, or identity characteristics (e.g., gender, ethnicity, ability level). For the 2023 Standards of Care, as in previous years, two representatives from the American College of Cardiology (ACC) acted as ad hoc PPC members and reviewed and approved Section 10, "Cardiovascular Disease and Risk Management." A PPC chairperson is appointed by the ADA (currently N.A.E.) for a 1-year term and oversees the committee.

Each section of the Standards of Care is reviewed annually and updated with the latest evidence-based recommendations by a PPC member designated as the section lead as well as subcommittee members. The subcommittees perform systematic literature reviews and identify and summarize the scientific evidence. An information specialist with knowledge and experience in literature searching (a librarian) is consulted as necessary. A guideline methodologist (R.R.B. for the 2023 Standards of Care) with expertise and training in evidence-based medicine and guideline development methodology oversees all methodological aspects of the development of the Standards of Care and serves as a statistical analyst.

Disclosure and Duality of Interest Management

All members of the expert panel (the PPC members, ad hoc members, and subject matter experts) and ADA staff are required to comply with the ADA policy on duality of interest, which requires disclosure of any financial, intellectual, or other interests that might be construed as constituting an actual, potential, or apparent conflict, regardless of relevancy to the guideline topic. For transparency, ADA requires full disclosure of all relationships. Full disclosure statements from all committee members are solicited and reviewed during the appointment process. Disclosures are then updated throughout the guideline development process (specifically before the start of every meeting), and disclosure statements are submitted by every Standards of Care author upon submission of the revised Standards of Care section. Members are required to disclose for a time frame that includes 1 year prior to initiation of the committee appointment process until publication of that year's Standards of Care. Potential dualities of interest are evaluated by a designated review group and, if necessary, the Legal Affairs Division of the ADA. The duality of interest assessment is based on the relative weight of the financial relationship (i.e., the monetary amount) and the relevance of the relationship (i.e., the degree to which an independent observer might reasonably interpret an association as related to the topic or recommendation of consideration). In addition, the ADA adheres to Section 7 of the Council for Medical Specialty Societies "Code for Interactions with Companies" (3). The duality of interest review group also ensures the majority of the PPC and the PPC chair are without potential conflict relevant to the subject area. Furthermore, the PPC chair is required to remain unconflicted for 1 year after the publication of the Standards of Care. Members of the committee who disclose a potential duality of interest pertinent to any specific recommendation are prohibited from participating in discussions related to those recommendations. No expert panel members were employees of any pharmaceutical or medical device company during the development of the 2023 Standards of Care. Members of the PPC, their employers, and their disclosed potential dualities of interest are listed in the section "Disclosures: *Standards of Medical Care in Diabetes—2023*." The ADA funds the development of the Standards of Care from general revenue and does not use industry support for this purpose.

Evidence Review

The Standards of Care subcommittee for each section creates an initial list of

relevant clinical questions that is reviewed and discussed by the expert panel. In consultation with a systematic review expert, each subcommittee devises and executes systematic literature searches. For the 2023 Standards of Care, PubMed, Medline, and EMBASE were searched for the time periods of 1 June 2021 to 26 July 2022. Searches are limited to studies published in English. Subcommittee members also manually search journals, reference lists of conference proceedings, and regulatory agency websites. All potentially relevant citations are then subjected to a full-text review. In consultation with the methodologist, the subcommittees prepare the evidence summaries and grading for each section of the Standards of Care. All PPC members discuss and review the evidence summaries and make revisions as appropriate. The final evidence summaries are then deliberated on by the PPC, and the recommendations that will appear in the Standards of Care are drafted.

Table 1—ADA evidence-grading system for *Standards of Care in Diabetes*

Level of evidence	Description
A	Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including: • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including: • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	Supportive evidence from well-conducted cohort studies • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies Supportive evidence from a well-conducted case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies • Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) • Evidence from case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

Grading of Evidence and Recommendation Development

A grading system (**Table 1**) developed by the ADA and modeled after existing methods is used to clarify and codify the evidence that forms the basis for the recommendations in the Standards of Care. All of the recommendations in the Standards of Care are critical to comprehensive care regardless of rating. ADA recommendations are assigned ratings of **A**, **B**, or **C**, depending on the quality of the evidence in support of the recommendation. Expert opinion **E** is a separate category for recommendations in which there is no evidence from clinical trials, clinical trials may be impractical, or there is conflicting evidence. Recommendations assigned an **E** level of evidence are informed by key opinion leaders in the field of diabetes (members of the PPC) and cover important elements of clinical care. All Standards of Care recommendations receive a rating for the strength of the evidence and not for the strength of the recommendation. Recommendations with **A**-level evidence are based on large, well-designed randomized controlled trials or well-done meta-analyses of randomized controlled trials. Generally, these recommendations have the best chance of improving outcomes when applied to the population for which they are appropriate. Recommendations with lower levels of evidence may be equally important but are not as well supported.

Of course, published evidence is only one component of clinical decision-making. Clinicians care for people, not populations; guidelines must always be interpreted with the individual person in mind. Individual circumstances, such as comorbid and coexisting diseases, age, education, disability, and, above all, the values and preferences of the person with diabetes, must be considered and may lead to different treatment targets and strategies. Furthermore, conventional evidence hierarchies, such as the one adapted by the ADA, may miss nuances important in diabetes care. For example, although there is excellent evidence from clinical trials supporting the importance of achieving multiple risk factor control, the optimal way to achieve this result is less clear. It is difficult to assess each component of such a complex intervention.

In preparation of the 2023 Standards of Care, the expert panel met for a 2-day in-person/virtual meeting in Arlington, Virginia, in July 2022, to present the evidence summaries and to develop the recommendations. All PPC members participate annually in updating the Standards of Care and approve the recommendations therein.

Revision Process

Public comment is particularly important in the development of clinical practice recommendations; it promotes transparency and provides key stake holders the opportunity to identify and address gaps in care. The ADA holds a year-long public comment period requesting feedback on the Standards of Care. The PPC reviews compiled feedback from the public in preparation for the annual update but considers more pressing updates throughout the year, which may be published as "living" Standards updates. Feedback from the larger clinical community and general public was invaluable for the revision of the Standards of Care—2022. Readers who wish to comment on the 2023 Standards of Care are invited to do so at professional.diabetes.org/SOC.

Feedback for the Standards of Care is also obtained from external peer reviewers. The Standards of Care is reviewed by ADA clinical leadership and scientific and medical staff and is approved by the ADA Board of Directors, which includes health care professionals, scientists, and lay people. The ACC performs an independent external peer review and the ACC Board of Directors provides endorsement of Section 10, "Cardiovascular and Metabolic Risk." The

ADA adheres to the Council for Medical Specialty Societies "Revised CMSS Principles for Clinical Practice Guideline Development" (4).

ADA STANDARDS, STATEMENTS, REPORTS, AND REVIEWS

The ADA has been actively involved in developing and disseminating diabetes care clinical practice recommendations and related documents for more than 30 years. The ADA Standards of Care is an essential resource for health care professionals caring for people with diabetes. ADA Statements, Consensus Reports, and Scientific Reviews support the recommendations included in the Standards of Care.

Standards of Care

The annual Standards of Care supplement to Diabetes Care contains the official ADA position, is authored by the ADA, and provides all of the ADA's current clinical practice recommendations.

ADA Statement

An ADA statement is an official ADA point of view or belief that does not contain clinical practice recommendations and may be issued on advocacy, policy, economic, or medical issues related to diabetes. ADA statements undergo a formal review process, including a review by the appropriate ADA national committee, ADA clinical leadership, science and health care staff, and the ADA Board of Directors.

Consensus Report

A consensus report on a particular topic contains a comprehensive examination, is authored by an expert panel (i.e., consensus panel), and represents the panel's collective analysis, evaluation, and opinion. The need for a consensus report arises when clinicians, scientists, regulators, and/or policy makers desire guidance and/or clarity on a medical or scientific issue related to diabetes for which the evidence is contradictory, emerging, or incomplete. Consensus reports may also highlight evidence gaps and propose future research areas to address these gaps. A consensus report is not an ADA position but represents expert opinion only and is produced under the auspices of the ADA by invited experts. A consensus report may be developed after an ADA Clinical Conference or Research Symposium.

Scientific Review

A scientific review is a balanced review and analysis of the literature on a scientific or medical topic related to diabetes. A scientific review is not an ADA position and does not contain clinical practice recommendations but is produced under the auspices of the ADA by invited experts. The scientific review may provide a scientific rationale for clinical practice recommendations in the Standards of Care. The category may also include task force and expert committee reports.

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Summary of Revisions: *Standards of Care in Diabetes—2023*

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GENERAL CHANGES

The field of diabetes care is rapidly changing as new research, technology, and treatments that can improve the health and well-being of people with diabetes continue to emerge. With annual updates since 1989, the American Diabetes Association (ADA) has long been a leader in producing guidelines that capture the most current state of the field.

The 2023 Standards of Care includes revisions to incorporate person-first and inclusive language. Efforts were made to consistently apply terminology that empowers people with diabetes and recognizes the individual at the center of diabetes care.

Although levels of evidence for several recommendations have been updated, these changes are not outlined below where the clinical recommendation has remained the same. That is, changes in evidence level from, for example, **E** to **C** are not noted below. The 2023 Standards of Care contains, in addition to many minor changes that clarify recommendations or reflect new evidence, more substantive revisions detailed below.

SECTION CHANGES

Section 1. Improving Care and Promoting Health in Populations

(https://doi.org/10.2337/dc23-S001)

Recommendation 1.7 was added to address the use of community health workers to support the management of diabetes and cardiovascular risk factors, especially in underserved communities and health care systems.

Additional language and definitions regarding digital health, telehealth, and telemedicine were added, along with the benefits of these modalities of care delivery, including social determinants of health in the telehealth subsection.

The subsection "Access to Care and Quality Improvement" was revised to add language regarding value-based payments to listed quality improvement efforts.

The "Migrant and Seasonal Agricultural Workers" subsection was updated to include more recent data for this population.

More defining terms were added for non-English speakers and diabetes education in the "Language Barriers" subsection.

Section 2. Classification and Diagnosis of Diabetes

(https://doi.org/10.2337/dc23-S002)

Recommendation 2.1b was added to the "A1C" subsection to address the utility of point-of-care A1C testing for diabetes screening and diagnosis.

Section 3. Prevention or Delay of Type 2 Diabetes and Associated Comorbidities

(https://doi.org/10.2337/dc23-S003)

Recommendation 3.9 was added to address statin use and the risk of type 2 diabetes, including the recommendation to monitor glucose status regularly and enforce diabetes prevention approaches in individuals at high risk of developing type 2 diabetes who were prescribed statin therapy.

Recommendation 3.10 was added to address the use of pioglitazone for reducing the risk of stroke or myocardial infarction in people with history of stroke and evidence of insulin resistance and prediabetes.

Recommendation 3.12 was added to communicate that pharmacotherapy (e.g., weight management, minimizing the progression of hyperglycemia, cardiovascular risk reduction) may be considered to support person-centered care goals for people at high risk of developing diabetes.

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Recommendation 3.13 was added to state that more intensive preventive approaches should be considered for individuals who are at particularly high risk of progression to diabetes.

Section 4. Comprehensive Medical Evaluation and Assessment of Comorbidities

(https://doi.org/10.2337/dc23-S004)

In Recommendation 4.3, language was modified to include evaluation for overall health status and setting of initial goals.

Considerable changes were made in the immunizations subsection to reflect new indications and guidance, particularly for COVID-19 and pneumococcal pneumonia vaccinations, including age-specific recommendations and the bivalent COVID-19 booster.

Table 4.1 was modified to include changes throughout Section 4.

The subsection "Nonalcoholic Fatty Liver Disease" (NAFLD) incorporates more detail regarding its diagnosis and risk stratification in primary care and diabetes clinics, such as using the fibrosis-4 index to assess the risk of liver fibrosis, and includes a fibrosis-4 index risk calculator. It expands on the rationale for fibrosis risk stratification in people with diabetes and when to refer to a gastroenterologist or hepatologist for further workup.

Discussion was added about the management of people with type 2 diabetes who have NAFLD, highlighting lifestyle changes that promote weight loss, the use of obesity pharmacotherapy with emphasis on treatment with glucagon-like peptide 1 (GLP-1) receptor agonists, bariatric surgery, and the role of diabetes medications (e.g., pioglitazone and GLP-1 receptor agonists) to treat people with type 2 diabetes and nonalcoholic fatty liver disease (NASH).

Revisions to Section 4, including the addition of **Fig. 4.2**, are based on the American Gastroenterological Association 2021 "Preparing for the NASH Epidemic: A Call to Action" (reference 64 in this section) and its associated "Clinical Care Pathway for the Risk Stratification and Management of Patients with Nonalcoholic Fatty Liver Disease" (reference 66 in this section), agreed upon by a multidisciplinary task force of experts, including representatives of the ADA. Detailed recommendations from an ADA consensus statement will be published separately in 2023.

Section 5. Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes

(https://doi.org/10.2337/dc23-S005)

The title has been changed from "Facilitating Behavior Change and Well-being to Improve Health Outcomes" to be inclusive of strength-based language.

Recommendation 5.8 was added to the "Diabetes Self-Management Education and Support" subsection to address social determinants of health in guiding design and delivery of diabetes self-management education and support (DSMES). Additional information was also added supporting use of telehealth delivery of care and other digital health solutions to deliver DSMES.

Screening for food insecurity by any members of the health care team was added to the nutrition section.

A section on intermittent fasting and time-restricted eating was included in the "Eating Patterns and Meal Planning" subsection.

Emphasis was placed on supporting larger weight losses (up to 15%) based on efficacy and access of newer medications.

Language was added to Recommendation 5.23 about the harms of β-carotene supplementation based on the U.S. Preventative Services Task Force report.

The new subsection "Supporting Positive Health Behaviors" was added, including the addition of Recommendation 5.37, which encourages use of behavioral strategies by members of the diabetes care team, with the goal to support diabetes self-management and engagement in health behaviors to promote optimal diabetes health outcomes.

The "Psychosocial Issues" subsection was renamed "Psychosocial Care" to highlight the recommendations' emphasis on providing appropriate psychosocial support to people with diabetes as part of or in conjunction with standard diabetes care.

The "Psychosocial Care" subsection includes a new Recommendation 5.55 to screen for sleep health in people with diabetes and make referrals to sleep medicine and/or qualified behavioral health professional as indicated.

Other recommendations in this subsection were revised to specify the roles of diabetes care professionals as well as qualified mental/behavioral health professionals to provide psychosocial care, to specify topics for psychosocial screening, treatment, and referrals when indicated, and to include caregivers and family members of people with diabetes. Details were added about resources for developing psychosocial screening protocols and about intervention. Across the specific psychosocial domains (e.g., diabetes distress, anxiety), details were added about data supporting intervention and care approaches to support psychosocial and behavioral outcomes in people with diabetes and their family members.

Section 6. Glycemic Targets

(https://doi.org/10.2337/dc23-S006)

New language was added to Recommendation 6.5b to outline that for those with frailty or at high risk of hypoglycemia, a target of >50% time in range with <1% time below range is now recommended.

Recommendation 6.9 was added to address the effectiveness of goal setting for glycemic control.

Section 7. Diabetes Technology

(https://doi.org/10.2337/dc23-S007)

The importance of "preference" for diabetes devices was added in all recommendations.

Recommendation 7.12 for the use of continuous glucose monitoring (CGM) in adults with diabetes treated with basal insulin was reworded to reflect updated evidence in the literature.

Recommendation 7.15 was modified to state that people with diabetes should have uninterrupted access to their supplies to minimize gaps in CGM use.

Recommendation 7.19 was added to address CGM interfering substances, with evidence level **C**.

A new paragraph addressing substances and factors affecting CGM accuracy was added to the "Continuous Glucose Monitoring Devices" subsection. **Table 7.4** was added to address interfering substances for CGM.

Information was added on all three integrated CGM devices available, and it was specified that although there is more than one CGM system approved by the U.S. Food and Drug Administration (FDA) for use with automated insulin delivery systems, only one system with integrated CGM designation is FDA approved for

use with automated insulin delivery systems.

Literature and information was added on benefits on glycemic outcomes of early initiation of real-time CGM in children and adults and the need to continue CGM use to maximize benefits.

The paragraph on connected pens was updated to include smart pen caps.

References were updated for automated insulin delivery systems to include all the approved systems in the U.S. in 2022.

The text was updated to include do-it-yourself closed loop systems.

The "Inpatient Care" subsection was updated to include updated evidence and a paragraph on the use of CGM in the inpatient setting during the COVID-19 pandemic.

Section 8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes

(https://doi.org/10.2337/dc23-S008)

Language was amended to reinforce that obesity is a chronic disease.

Recommendation 8.5 was added to reinforce that both small and larger weight losses should be considered as treatment goals on a case-by-case basis. Notably, larger (10% or more) weight loss may have disease-modifying effects, including diabetes remission, and may improve long-term cardiovascular outcomes.

Dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (tirzepatide) was added as a glucose-lowering option with the potential for weight loss.

Section 9. Pharmacologic Approaches to Glycemic Treatment

(https://doi.org/10.2337/dc23-S009)

Section 9 was updated to align with the latest consensus report on management of hyperglycemia in type 2 diabetes by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Recommendation 9.4a was added to state that healthy lifestyle behaviors, DSMES, avoidance of clinical inertia, and social determinants of health (SDOH) should be considered in the glucose-lowering management of type 2 diabetes.

Recommendation 9.4b was added to indicate that in adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment plan should include agents that reduce cardiorenal risk.

Recommendation 9.4c was added to address the consideration of pharmacologic approaches that provide the efficacy to achieve treatment goals.

Recommendation 9.4d was added to address weight management as an impactful component of glucose-lowering management in type 2 diabetes.

Information was added to address considerations for a GLP-1 receptor agonist prior to prandial insulin to further address prandial control and to minimize the risks of hypoglycemia and weight gain associated with insulin therapy.

Information was added to address alternative insulin routes.

Table 9.2 and **Fig. 9.3** were updated based on the latest consensus report on management of hyperglycemia in type 2 diabetes by the ADA and the EASD.

Section 10. Cardiovascular Disease and Risk Management

(https://doi.org/10.2337/dc23-S010)

Recommendation 10.1 was revised with updated definitions of hypertension. These recommendations align with the current definition of hypertension according to the American College of Cardiology and American Heart Association.

Recommendation 10.4 on blood pressure treatment goals in individuals with diabetes was revised to target a blood pressure of $<$130/80 mmHg. The discussion of the evidence to support this recommendation was extensively revised. In addition, the recently reported results of the STEP (Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients) trial were added. Recommendation 10.7 was updated to consider pharmacological treatment in people with diabetes and a confirmed blood pressure $\geq$130/80. **Table 10.1** and **Fig. 10.2** were updated accordingly.

In the subsection "Pregnancy and Antihypertensive Medications," the results of the CHAP (Chronic Hypertension and Pregnancy) trial were included to further support the current treatment goal recommendations in pregnant individuals with diabetes.

Recommendation 10.20 was revised to recommend the use of high-intensity statin therapy in individuals with diabetes aged 40–75 years at higher risk, including those with one or more atherosclerotic cardiovascular disease risk factors, to reduce the LDL cholesterol by $\geq$50% of baseline and to target an LDL cholesterol goal of $<$70 mg/dL.

Recommendation 10.21 was added to consider adding treatment with ezetimibe or a PCSK9 inhibitor to maximum tolerated statin therapy in these individuals.

Recommendations 10.22 and 10.23 were added to recommend continuing statin therapy in adults with diabetes aged $>$75 years currently receiving statin therapy and to recommend that it may be reasonable to initiate moderate-intensity statin therapy in adults with diabetes aged $>$75 years, respectively.

Recommendation 10.26 was updated to recommend treatment with high-intensity statin therapy in individuals with diabetes and established atherosclerotic cardiovascular disease to target an LDL cholesterol reduction of $\geq$50% from baseline and an LDL cholesterol goal of $<$55 mg/dL. If this goal is not achieved on maximum tolerated statin therapy, the addition of ezetimibe or a PCSK9 inhibitor is now recommended.

Language regarding evidence in the section "Statin Treatment" was revised to consider the evidence supporting lower LDL cholesterol goals in people with diabetes with and without established cardiovascular disease.

In the subsection "Combination Therapy for LDL Cholesterol Lowering" a paragraph was added to include inclisiran, an siRNA directed against PCSK9, as a new FDA-approved cholesterol-lowering therapy.

Recommendation 10.42b was added to recommend treatment with a sodium–glucose cotransporter 2 inhibitor in individuals with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction to improve symptoms, physical limitations, and quality of life. The discussion of evidence to support this new recommendation was included in the last paragraph of the section "Glucose-Lowering Therapies and Heart Failure."

Recommendation 10.43 was added to recommend the addition of finerenone in the treatment of individuals with type 2 diabetes and chronic kidney disease with albuminuria treated with maximum tolerated doses of ACE inhibitor or angiotensin receptor blocker.

This section is endorsed for the fifth consecutive year by the American College of Cardiology.

Section 11. Chronic Kidney Disease and Risk Management

(https://doi.org/10.2337/dc23-S011)

The recommendation order was rearranged to reflect the appropriate order for clinical interventions aimed at preventing and slowing progression of chronic kidney disease.

In Recommendation 11.5a, the levels at which a sodium–glucose cotransporter 2 inhibitor could be initiated were changed. The new levels for initiation are an estimated glomerular filtration rate $\geq$20 mL/min/1.73 m^2 and urinary albumin $\geq$200 mg/g creatinine.

Recommendation 11.5b also recommends that sodium–glucose cotransporter 2 inhibitor might also be effective in people with urinary albumin of normal to $\geq$200 mg/g creatinine, but this is **B** level at this time, as the study reporting this has not been published.

Mineralocorticoid receptor antagonists are now recommended along with other medications for cardiovascular and kidney protection rather than as alternatives when other treatments have not been effective.

Recommendation 11.8 addressing referral to a nephrologist was expanded to include referrals for continuously increasing urine albumin-to-creatinine ratio and/or for continuously decreasing estimated glomerular filtration rate.

Section 12. Retinopathy, Neuropathy, and Foot Care

(https://doi.org/10.2337/dc23-S012)

Language regarding pregnancy as a risk factor for retinopathy in people with preexisting type 1 or type 2 diabetes was revised and updated.

Screening details about autonomic neuropathy were added to Recommendation 12.17.

Language was added to the neuropathy screening subsection to clarify that treatments of other modifiable risk factors (including lipids and blood pressure) can aid in prevention of diabetic peripheral neuropathy progression in type 2 diabetes and may reduce disease progression in type 1 diabetes.

Information was added to the "Diabetic Autonomic Neuropathy" subsection to include criteria for screening for symptoms of autonomic neuropathy.

Additional references were added to support Recommendation 12.18.

Recommendation 12.20 was revised to reflect that gabapentinoids, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and sodium channel blockers are recommended as initial pharmacologic treatments for neuropathic pain in diabetes and that health care professionals should refer to a neurologist or pain specialist when pain control is not achieved within the scope of practice of the treating physician.

New information was added in the "Neuropathy" subsection, under "Treatment," to address lipid control and blood pressure control.

The "Neuropathic Pain" subsection includes an expanded discussion of treating neuropathic pain in people with diabetes.

Recommendation 12.25 was added to address screening for peripheral arterial disease.

Recommendation 12.26 was revised to include peripheral arterial disease.

Recommendation 12.27 was edited to signify that not all people who smoke are referred to foot care specialists but that a referral is now recommended for people who smoke and also have other risk factors or symptoms.

Recommendation 12.29 was edited to reflect a change from "severe neuropathy" to "loss of protective sensation," which is consistent with other recommendations.

Recommendation 12.30 was edited to reflect that topical oxygen therapy is not equivalent to hyperbaric oxygen therapy.

Section 13. Older Adults

(https://doi.org/10.2337/dc23-S013)

The language in Recommendation 13.5 was strengthened for older adults with type 1 diabetes to recommend continuous glucose monitoring to reduce hypoglycemia with an evidence grade of **A** based on a 6-month extension of the Wireless Innovation in Seniors with Diabetes Mellitus (WISDM) trial and observational data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study.

Recommendation 13.6 was added to communicate that for older adults with type 2 diabetes on multiple daily doses of insulin, continuous glucose monitoring should be considered to improve glycemic outcomes and decrease glucose variability, with an evidence grade of **B** based on results of the DIAMOND (Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes) trial.

A new Recommendation 13.7 was added: for older adults with type 1 diabetes, consider the use of automated insulin delivery systems (evidence grade **B**) and other advanced insulin delivery devices such as connected pens (evidence grade **E**) should be considered to reduce risk of hypoglycemia, based on individual ability. The addition of this recommendation was based on the results of two small randomized controlled trials (RCTs) in older adults, which demonstrated that hybrid closed-loop advanced insulin delivery improved glucose metrics relative to sensor-augmented pump therapy.

Blood pressure treatment goals in **Table 13.1** were lowered to align with evidence from multiple recent trials.

Recommendation 13.15 was split into two recommendations (now 13.17 and 13.18) to acknowledge the conceptual differences between deintensification of goals (13.17) and simplification of complex regimens (13.18).

In recommendation 13.17, deintensification of treatment goals is now recommended to reduce the risk of hypoglycemia if it can be achieved within the individualized A1C target.

In a new recommendation 13.18, simplification of complex treatment plans (especially insulin) is now recommended to reduce the risk of hypoglycemia and polypharmacy and decrease the burden of the disease if it can be achieved within the individualized A1C target.

Recommendation 13.22 was added to consider use of CGM to assess risk for hypoglycemia in older adults treated with sulfonylureas or insulin, despite the lack of evidence.

Section 14. Children and Adolescents

(https://doi.org/10.2337/dc23-S014)

In Recommendations 14.14, 14.106, and 14.107, the language was changed from "assess" to "screen" for consistency with Section 5.

In Recommendations 14.14 and 14.17, text was added for referral to a qualified mental health professional for further assessment and treatment.

More details were added to Recommendation 14.50 on foot examinations for neuropathy.

In Recommendations 14.97 and 14.98, "girls" was changed to "female individuals"

for more consistency in the Standards of Care.

In Recommendation 14.110, "patients" was changed to "adolescents and young adults" for clarity.

In Recommendation 14.111,"pediatric diabetes provider" was changed to "pediatric diabetes care teams" to reflect the team-based nature of diabetes care.

In Recommendation 14.113, "patient" was changed to "young adult" for clarity.

Section 15. Management of Diabetes in Pregnancy

(https://doi.org/10.2337/dc23-S015)

Recommendation 15.13 was added to endorse nutrition counseling to improve the quality of carbohydrates and promote a balance of macronutrients including nutrient-dense fruits, vegetables, legumes, whole grains, and healthy fats with n-3 fatty acids that include nuts and seeds and fish in the eating pattern.

Evidence for preconception counseling was strengthened.

A new study demonstrates that the cost of CGM in pregnancies complicated by type 1 diabetes is offset by improved maternal and neonatal outcomes and provides further support for the use CGM.

Recommendation 15.20 is now a composite recommendation based on two different multicentered RCTs with different methodologies and different outcomes. Both RCTs support stricter blood pressure targets in pregnancy to improve outcomes. This modification is based on new data from the Chronic Hypertension and Pregnancy (CHAP) trial, which included individuals with preexisting diabetes.

The new Recommendation 15.27 supports breastfeeding to reduce the risk of maternal type 2 diabetes. The benefit of breastfeeding should be considered when choosing whether to breastfeed or formula feed.

New language was added to the text regarding the role of weight/BMI after gestational diabetes mellitus (GDM). Systematic reviews and meta-analyses demonstrate each of the following: weight loss reduces the risk of developing GDM in the subsequent pregnancy, the risk of type 2 diabetes increases by 18% per unit of BMI above the prepregnancy BMI at follow-up, and post-delivery lifestyle interventions are effective in reducing risk of type 2 diabetes. These studies highlight the importance of effective weight management after GDM.

Section 16. Diabetes Care in the Hospital

(https://doi.org/10.2337/dc23-S016)

In Recommendation 16.2, additional information was added to support the use of computerized prescriber order entry (CPOE) to facilitate glycemic management as well as insulin dosing algorithms using machine learning in the future to inform these algorithms.

In Recommendation 16.5, the need for individualization of targets was expanded to include a target range of 100–180 mg/dL (5.6–10.0 mmol/L) for noncritically ill patients with "new" hyperglycemia as well as patients with known diabetes prior to admission.

Recommendation 16.7 was revised to reflect that an insulin regimen with basal, prandial, and correction components is the preferred treatment for most noncritically ill hospitalized patients with adequate nutritional intake.

Use of personal CGM and automated insulin delivery devices that can automatically deliver correction insulin doses and change basal insulin delivery rates in real time should be supported during hospitalization when independent self-management is feasible and proper management supervision is available.

Section 17. Diabetes Advocacy

(https://doi.org/10.2337/dc23-S017)

The Diabetes Care and Detention Facilities advocacy statement has been removed from this section pending future updates.

1. Improving Care and Promoting Health in Populations: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

DIABETES AND POPULATION HEALTH

Recommendations

1.1 Ensure treatment decisions are timely, rely on evidence-based guidelines, include social community support, and are made collaboratively with patients based on individual preferences, prognoses, comorbidities, and informed financial considerations. **B**

1.2 Align approaches to diabetes management with the Chronic Care Model. This model emphasizes person-centered team care, integrated long-term treatment approaches to diabetes and comorbidities, and ongoing collaborative communication and goal setting between all team members. **A**

1.3 Care systems should facilitate in-person and virtual team–based care, including those knowledgeable and experienced in diabetes management as part of the team, and utilization of patient registries, decision support tools, and community involvement to meet patient needs. **B**

1.4 Assess diabetes health care maintenance (**Table 4.1**) using reliable and relevant data metrics to improve processes of care and health outcomes, with attention to care costs. **B**

Population health is defined as "the health outcomes of a group of individuals, including the distribution of health outcomes within the group"; these outcomes can be measured in terms of health outcomes (mortality, morbidity, health, and functional status), disease burden (incidence and prevalence), and behavioral and metabolic factors (physical activity, nutrition, A1C, etc.) (1). Clinical practice recommendations for health care professionals are tools that can ultimately improve health across populations; however, for optimal outcomes, diabetes care must also be individualized for

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each patient. Thus, efforts to improve population health will require a combination of policy-level, system-level, and patient-level approaches. With such an integrated approach in mind, the American Diabetes Association (ADA) highlights the importance of patient-centered care, defined as care that considers individual patient comorbidities and prognoses; is respectful of and responsive to patient preferences, needs, and values; and ensures that patient values guide all clinical decisions (2). Furthermore, social determinants of health (SDOH)—often out of direct control of the individual and potentially representing lifelong risk—contribute to health care and psychosocial outcomes and must be addressed to improve all health outcomes (3). Clinical practice recommendations, whether based on evidence or expert opinion, are intended to guide an overall approach to care. The science and art of health care come together when the clinician makes treatment decisions for a patient who may not meet the eligibility criteria used in the studies on which guidelines are based. Recognizing that one size does not fit all, the standards presented here provide guidance for when and how to adapt recommendations for an individual. This section provides guidance for health care professionals as well as health systems and policymakers.

Care Delivery Systems

The proportion of people with diabetes who achieve recommended A1C, blood pressure, and LDL cholesterol levels has fluctuated over the years (4). Glycemic management and management of cholesterol through dietary intake remain challenging. In 2013–2016, 64% of adults with diagnosed diabetes met individualized A1C target levels, 70% achieved recommended blood pressure target, 57% met the LDL cholesterol target level, and 85% were nonsmokers (4). However, only 23% met targets for glycemic, blood pressure, and LDL cholesterol measures while also avoiding smoking (4). The mean A1C nationally among people with diabetes increased slightly from 7.3% in 2005–2008 to 7.5% in 2013–2016 based on the National Health and Nutrition Examination Survey (NHANES), with younger adults, women, and non-Hispanic Black individuals less likely to meet treatment targets (4). Certain segments of the population, such as young adults and individuals with complex comorbidities, financial or other social hardships, and/or limited English proficiency, face particular challenges to goal-based care (5–7). Even after adjusting for these patient factors, the persistent variability in the quality of diabetes care across health care professionals and practice settings indicates that substantial system-level improvements are still needed.

Diabetes poses a significant financial burden to individuals and society. It is estimated that the annual cost of diagnosed diabetes in the U.S. in 2017 was $327 billion, including $237 billion in direct health care costs and $90 billion in reduced productivity. After adjusting for inflation, the economic costs of diabetes increased by 26% from 2012 to 2017 (8). This is attributed to the increased prevalence of diabetes and the increased cost per person with diabetes. Therefore, on going population health strategies are needed to reduce costs and provide optimized care.

Chronic Care Model

Numerous interventions to promote the recommended standards have been implemented. However, a major barrier to optimal care is a delivery system that is often fragmented, lacks clinical information capabilities, duplicates services, and is poorly designed for the coordinated delivery of chronic care. The Chronic Care Model (CCM) takes these factors into consideration and is an effective framework for improving the quality of diabetes care (9).

Six Core Elements. The CCM includes six core elements to optimize the care of people with chronic disease:

1. Delivery system design (moving from a *reactive* to a *proactive* care delivery system where planned visits are coordinated through a team-based approach)
2. Self-management support
3. Decision support (basing care on evidence-based, effective care guidelines)
4. Clinical information systems (using registries that can provide patient-specific and population-based support to the care team)
5. Community resources and policies (identifying or developing resources to support healthy lifestyles)
6. Health systems (to create a quality-oriented culture)

A 5-year effectiveness study of the CCM in 53,436 people with type 2 diabetes in the primary care setting suggested that the use of this model of care delivery reduced the cumulative incidence of diabetes-related complications and all-cause mortality (10). Patients who were enrolled in the CCM experienced a reduction in cardiovascular disease risk by 56.6%, microvascular complications by 11.9%, and mortality by 66.1% (10). In addition, another study suggested that health care utilization was lower in the CCM group, which resulted in health care savings of $7,294 per individual over the study period (11).

Redefining the roles of the health care delivery team and empowering patient self-management are fundamental to the successful implementation of the CCM (12). Collaborative, multidisciplinary teams are best suited to provide care for people with chronic conditions such as diabetes and to facilitate patients' self-management (13–15). There are references to guide the implementation of the CCM into diabetes care delivery, including opportunities and challenges (16).

Strategies for System-Level Improvement

Optimal diabetes management requires an organized, systematic approach and the involvement of a coordinated team of dedicated health care professionals working in an environment where patient-centered, high-quality care is a priority (7,16,17). While many diabetes care processes have improved nationally in the past decade, the overall quality of care for people with diabetes remains suboptimal (4). Efforts to increase the quality of diabetes care include providing care that is concordant with evidence-based guidelines (18); expanding the role of teams to implement more intensive disease management strategies (7,19,20); tracking medication-taking behavior at a systems level (21); redesigning the organization of the care process (22); implementing electronic health record tools (23,24); empowering and educating patients (25,26); removing financial barriers and reducing patient out-of-pocket costs for diabetes education, eye exams, diabetes technology, and necessary medications (7); assessing and addressing psychosocial issues (27,28);

and identifying, developing, and engaging community resources and public policies that support healthy lifestyles (29). The National Diabetes Education Program maintains an online resource (cdc.gov/diabetes/professional-info/training.html) to help health care professionals design and implement more effective health care delivery systems for those with diabetes. Given the pluralistic needs of people with diabetes and that the constant challenges they experience vary over the course of disease management (complex insulin treatment plans, new technology, etc.), a diverse team with complementary expertise is consistently recommended (30).

Care Teams

The care team, which centers around the patient, should avoid therapeutic inertia and prioritize timely and appropriate intensification of behavior change (nutrition and physical activity) and/or pharmacologic therapy for patients who have not achieved the recommended metabolic targets (31–33). Strategies shown to improve care team behavior and thereby catalyze reductions in A1C, blood pressure, and/or LDL cholesterol include engaging in explicit and collaborative goal setting with patients (34,35); integrating evidence-based guidelines and clinical information tools into the process of care (18,36,37); identifying and addressing language, numeracy, or cultural barriers to care (37–39); soliciting performance feedback, setting reminders, and providing structured care (e.g., guidelines, formal case management, and patient education resources) (7); and incorporating care management teams including nurses, dietitians, pharmacists, and other health care professionals (19,38). In addition, initiatives such as the Patient-Centered Medical Home can improve health outcomes by fostering comprehensive primary care and offering new opportunities for team-based chronic disease management (39).

Telehealth

Telehealth is a growing field that may increase access to care for people with diabetes. The American Telemedicine Association defines telemedicine as the use of medical information exchanged from one site to another via electronic communications to improve a patient's clinical health status. Telehealth includes a growing variety of applications and services using two-way video, smartphones, wireless tools, and other forms of telecommunications technology (40). Often used interchangeably with telemedicine, telehealth describes a broader range of digital health services in health care delivery (41). This includes synchronous, asynchronous, and remote patient monitoring.

Telehealth should be used complementary to in-person visits to optimize glycemic management in people with unmanaged diabetes (42). Increasingly, evidence suggests that various telehealth modalities may facilitate reducing A1C in people with type 2 diabetes compared with usual care or in addition to usual care (43), and findings suggest that telemedicine is a safe method of delivering type 1 diabetes care to rural patients (44). For rural populations or those with limited physical access to health care, telemedicine has a growing body of evidence for its effectiveness, particularly with regard to glycemic management as measured by A1C (45–47). In addition, evidence supports the effectiveness of telehealth in diabetes, hypertension, and dyslipidemia interventions (48) as well as the telehealth delivery of motivational interviewing (49). Interactive strategies that facilitate communication between health care professionals and patients, including the use of web-based portals or text messaging and those that incorporate medication adjustment, appear more effective. Telehealth and other virtual environments can also be used to offer diabetes self-management education and clinical support and remove geographic and transportation barriers for patients living in underresourced areas or with disabilities (50). Telehealth resources can also have a role in addressing the social determinants of health in young adults with diabetes (51). However, limited data are available on the effectiveness across different populations (52).

Behaviors and Well-being

Successful diabetes care also requires a systematic approach to supporting patients' behavior change efforts. High-quality diabetes self-management education and support (DSMES) has been shown to improve patient self-management, satisfaction, and glucose outcomes. National DSMES standards call for an integrated approach that includes clinical content and skills, behavioral strategies (goal setting, problem-solving), and engagement with psychosocial concerns. Increasingly, such support is being adapted for online platforms that have the potential to promote patient access to this important resource. These curriculums need to be tailored to the needs of the intended populations, including addressing the "digital divide," i.e., access to the technology required for implementation (53–56).

For more information on DSMES, see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes."

Cost Considerations for Medication-Taking Behaviors

The cost of diabetes medications and devices is an ongoing barrier to achieving glycemic goals. Up to 25% of patients who are prescribed insulin report cost-related insulin underuse (57). Insulin underuse due to cost has also been termed "cost-related medication nonadherence" (here referrred to as cost-related barriers to medication use). The cost of insulin has continued to increase in recent years for reasons that are not entirely clear. There are recommendations from the ADA Insulin Access and Affordability Working Group for approaches to this issue from a systems level (58). Recommendations including concepts such as cost-sharing for insured people with diabetes should be based on the lowest price available, the list price for insulins that closely reflects the net price, and health plans that ensure people with diabetes can access insulin without undue administrative burden or excessive cost (58).

The cost of medications (not only insulin) influences prescribing patterns and medication use because of patient burden and lack of secondary payer support (public and private insurance) for effective approved glucose-lowering, cardiovascular disease risk-reducing, and weight management therapeutics. Financial barriers remain a major source of health disparities, and costs should be a focus of treatment goals (59). (See TAILORING TREATMENT FOR SOCIAL CONTEXT and TREATMENT CONSIDERATIONS.) Reduction in cost-related barriers to medication use is associated with better biologic and psychologic outcomes, including quality of life.

Access to Care and Quality Improvement

The Affordable Care Act and Medicaid expansion have increased access to care for many individuals with diabetes, emphasizing the protection of people with preexisting conditions, health promotion, and disease prevention (60). In fact, health insurance coverage increased from 84.7% in 2009 to 90.1% in 2016 for adults with diabetes aged 18–64 years. Coverage for those aged ≥65 years remained nearly universal (61). Patients who have either private or public insurance coverage are more likely to meet quality indicators for diabetes care (62). As mandated by the Affordable Care Act, the Agency for Healthcare Research and Quality developed a National Quality Strategy based on triple aims that include improving the health of a population, overall quality and patient experience of care, and per capita cost (63,64). As health care systems and practices adapt to the changing landscape of health care, it will be important to integrate traditional disease-specific metrics with measures of patient experience, as well as cost, in assessing the quality of diabetes care (65,66). Information and guidance specific to quality improvement and practice transformation for diabetes care are available from the National Institute of Diabetes and Digestive and Kidney Diseases guidance on diabetes care and quality (67). Using patient registries and electronic health records, health systems can evaluate the quality of diabetes care being delivered and perform intervention cycles as part of quality improvement strategies (68). Improvement of health literacy and numeracy is also a necessary component to improve care (69,70). Critical to these efforts is health professional adherence to clinical practice recommendations (**Table 4.1**) and the use of accurate, reliable data metrics that include sociodemographic variables to examine health equity within and across populations (71).

In addition to quality improvement efforts, other strategies that simultaneously improve the quality of care and potentially reduce costs are gaining momentum and include reimbursement structures that, in contrast to visit-based billing, reward the provision of appropriate and high-quality care to achieve metabolic goals (72), value-based payments, and incentives that accommodate personalized care goals (7,73). (Also see COST CONSIDERATIONS FOR MEDICATION-TAKING BEHAVIORS, above, regarding cost-related barriers to medication use.)

TAILORING TREATMENT FOR SOCIAL CONTEXT

Recommendations

- **1.5** Assess food insecurity, housing insecurity/homelessness, financial barriers, and social capital/social community support to inform treatment decisions, with referral to appropriate local community resources. **A**
- **1.6** Provide patients with additional self-management support from lay health coaches, navigators, or community health workers when available. **A**
- **1.7** Consider the involvement of community health workers to support the management of diabetes and cardiovascular risk factors, especially in underserved communities and health care systems. **B**

Health inequities related to diabetes and its complications are well documented, are heavily influenced by SDOH, and have been associated with greater risk for diabetes, higher population prevalence, and poorer diabetes outcomes (74–78). SDOH are defined as the economic, environmental, political, and social conditions in which people live and are responsible for a major part of health inequality worldwide (79). Greater exposure to adverse SDOH over the life course results in worse health (80). The ADA recognizes the association between social and environmental factors and the prevention and treatment of diabetes and has issued a call for research that seeks to understand better how these social determinants influence behaviors and how the relationships between these variables might be modified for the prevention and management of diabetes (81,82). While a comprehensive strategy to reduce diabetes-related health inequities in populations has not been formally studied, general recommendations from other chronic disease management and prevention models can be drawn upon to inform systems-level strategies in diabetes (83). For example, the National Academy of Medicine has published a framework for educating health care professionals on the importance of SDOH (84). Furthermore, there are resources available for the inclusion of standardized sociodemographic variables in electronic health records to facilitate the measurement of health inequities and the impact of interventions designed to reduce those inequities (65,84,85).

SDOH are not consistently recognized and often go undiscussed in the clinical encounter (77). Among people with chronic illnesses, two-thirds of those who reported not taking medications as prescribed due to cost-related barriers to medication use never shared this with their physician (86). In a study using data from the National Health Interview Survey (NHIS), Patel et al. (77) found that one-half of adults with diabetes reported financial stress and one-fifth reported food insecurity. A recent Canadian study noted an association of one or more adverse SDOH and health care utilization and poor diabetes outcomes in high-risk children with type 1 diabetes (86).

Another population in which such issues must be considered is older adults, where social difficulties may impair quality of life and increase the risk of functional dependency (87) (see Section 13, "Older Adults," for a detailed discussion of social considerations in older adults). Creating systems-level mechanisms to screen for SDOH may help overcome structural barriers and communication gaps between patients and health care professionals (77,88). In addition, brief, validated screening tools for some SDOH exist and could facilitate discussion around factors that significantly impact treatment during the clinical encounter. Below is a discussion of assessment and treatment considerations in the context of food insecurity, homelessness, limited English proficiency, limited health literacy, and low literacy.

Food Insecurity

Food insecurity is the unreliable availability of nutritious food and the inability to consistently obtain food without resorting to socially unacceptable practices. Over 18% of the U.S. population reported food insecurity between 2005 and 2014 (89). The rate is higher in some racial/ethnic minority groups, including African American and Latino populations, low-income households, and homes

headed by single mothers. The food insecurity rate in individuals with diabetes may be up to 20% (90). Additionally, the risk for type 2 diabetes is increased twofold in those with food insecurity (81) and has been associated with lower engagement in self-care behaviors and medication use, depression, diabetes distress, and worse glycemic management when compared with individuals who are food secure (91–93). Older adults with food insecurity are more likely to have emergency department visits and hospitalizations compared with older adults who do not report food insecurity (94). Risk for food insecurity can be assessed with a validated two-item screening tool (95) that includes the following statements: *1*) "Within the past 12 months, we worried whether our food would run out before we got money to buy more" and *2*) "Within the past 12 months the food we bought just didn't last, and we didn't have money to get more." An affirmative response to either statement had a sensitivity of 97% and specificity of 83%. Interventions such as food prescription programs are considered promising to address food insecurity by integrating community resources into primary care settings and directly dealing with food deserts in underserved communities (96,97).

Treatment Considerations

In those with diabetes and food insecurity, the priority is mitigating the increased risk for uncontrolled hyperglycemia and severe hypoglycemia. The reasons for the increased risk of hyperglycemia include the steady consumption of inexpensive carbohydrate-rich processed foods, binge eating, financial constraints to filling diabetes medication prescriptions, and anxiety/depression leading to poor diabetes self-care behaviors. Hypoglycemia can occur due to inadequate or erratic carbohydrate consumption following the administration of sulfonylureas or insulin. See **Table 9.2** for drug-specific and patient factors, including cost and risk of hypoglycemia, which may be important considerations for adults with food insecurity and type 2 diabetes. Health care professionals should consider these factors when making treatment decisions for people with food insecurity and seek local resources to help people with diabetes and their family members obtain nutritious food more regularly (98).

Homelessness and Housing Insecurity

Homelessness/housing insecurity often accompanies many additional barriers to diabetes self-management, including food insecurity, literacy and numeracy deficiencies, lack of insurance, cognitive dysfunction, and mental health issues (99). The prevalence of diabetes in the homeless population is estimated to be around 8% (100). Additionally, people with diabetes who are homeless need secure places to keep their diabetes supplies and refrigerator access to properly store their insulin and take it on a regular schedule. The risk for homelessness can be ascertained using a brief risk assessment tool developed and validated for use among veterans (101). Housing insecurity has also been shown to be directly associated with a person's ability to maintain their diabetes self-management (102). Given the potential challenges, health care professionals who care for either homeless or housing-insecure individuals should be familiar with resources or have access to social workers who can facilitate stable housing for their patients as a way to improve diabetes care (103).

Migrant and Seasonal Agricultural Workers

Migrant and seasonal agricultural workers may have a higher risk of type 2 diabetes than the overall population. While migrant farmworker–specific data are lacking, most agricultural workers in the U.S. are Latino, a population with a high rate of type 2 diabetes. In addition, living in severe poverty brings with it food insecurity, high chronic stress, and an increased risk of diabetes; there is also an association between the use of certain pesticides and the incidence of diabetes (104).

Data from the Department of Labor indicate that there are 2.5–3 million agricultural workers in the U.S. These agricultural workers travel throughout the country, serving as the backbone for a multibillion-dollar agricultural industry. According to 2021 health center data, 175 health centers across the U.S. reported that they provided health care services to 893,260 adult agricultural patients, and 91,124 had encounters for diabetes (10.2%) (105).

Migrant farmworkers encounter numerous and overlapping barriers to receiving care. Migration, which may occur as frequently as every few weeks for farmworkers, disrupts care. In addition, cultural and linguistic barriers, lack of transportation and money, lack of available work hours, unfamiliarity with new communities, lack of access to resources, and other barriers prevent migrant farmworkers from accessing health care. Without regular care, those with diabetes may suffer severe and often expensive complications that affect quality of life.

Health care professionals should be attuned to all patients' working and living conditions. For example, if a migrant farmworker with diabetes presents for care, appropriate referrals should be initiated to social workers and community resources, as available, to assist with removing barriers to care.

Language Barriers

Health care professionals who care for non–English speakers should develop or offer educational programs and materials in languages specific to these patients with the specific goals of preventing diabetes and building diabetes awareness in people who cannot easily read or write in English. The National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care (National CLAS Standards) provide guidance on how health care professionals can reduce language barriers by improving their cultural competency, addressing health literacy, and ensuring communication with language assistance (106). In addition, the National CLAS Standards website (thinkculturalhealth.hhs.gov) offers several resources and materials that can be used to improve the quality of care delivery to non–English-speaking patients (106).

Health Literacy and Numeracy

Health literacy is defined as the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate decisions (69). Health literacy is strongly associated with patients engaging in complex disease management and self-care (107). Approximately 80 million adults in the U.S. are estimated to have limited or low health literacy (70). Clinicians and

diabetes care and education specialists should ensure they provide easy-to-understand information and reduce unnecessary complexity when developing care plans with patients. Interventions addressing low health literacy in populations with diabetes seem effective in improving diabetes outcomes, including ones focusing primarily on patient education, self-care training, or disease management. Combining easily adapted materials with formal diabetes education demonstrates effectiveness on clinical and behavioral outcomes in populations with low literacy (108). However, evidence supporting these strategies is largely limited to observational studies. More research is needed to investigate the most effective strategies for enhancing both acquisition and retention of diabetes knowledge and examine different media and strategies for delivering interventions to patients (109).

Health numeracy is also essential in diabetes prevention and management. Health numeracy requires primary numeric skills, applied health numeracy, and interpretive health numeracy. An emotional component also affects a person's ability to understand concepts of risk, probability, and communication of scientific evidence (110). People with prediabetes or diabetes often need to perform numeric tasks such as interpreting food labels and blood glucose levels to make treatment decisions such as medication dosing. Thus, both health literacy and numeracy are necessary for enabling effective communication between patient and health professional, arriving at a treatment plan, and making diabetes self-management task decisions. If patients appear not to understand concepts associated with treatment decisions, both can be assessed using standardized screening measures (111). Adjunctive education and support may be indicated if limited health literacy and numeracy are barriers to optimal care decisions (27).

Social Capital/Community Support

Social capital, which comprises community and personal network instrumental support, promotes better health, whereas lack of social support is associated with poorer health outcomes in individuals with diabetes (82). Of particular concern are the SDOH, including racism and discrimination, which are likely to be lifelong (112). These factors are rarely addressed in routine treatment or disease management but may be underlying reasons for lower engagement in self-care behaviors and medication use. Identification or development of community resources to support healthy lifestyles is a core element of the CCM (9), with a particular need to incorporate relevant social support networks. There is currently a paucity of evidence regarding enhancing these resources for those most likely to benefit from such intervention strategies.

Health care community linkages are receiving increasing attention from the American Medical Association, the Agency for Healthcare Research and Quality, and others to promote the translation of clinical recommendations for nutrition and physical activity in real-world settings (113). Community health workers (CHWs) (114), peer supporters (115–117), and lay leaders (118) may assist in the delivery of DSMES services (84,119), particularly in underserved communities. The American Public Health Association defines a CHW as a "frontline public health worker who is a trusted member of and/or has an unusually close understanding of the community served" (120). CHWs can be part of a cost-effective, evidence-based strategy to improve the management of diabetes and cardiovascular risk factors in underserved communities and health care systems (121). The CHW scope of practice in areas such as outreach and communication, advocacy, social support, basic health education, referrals to community clinics, etc., has successfully provided social and primary preventive services to underserved populations in rural and hard-to-reach communities. Even though CHWs' core competencies are not clinical in nature, in some circumstances, clinicians may delegate limited clinical tasks to CHWs. If such is the case, these tasks must always be performed under the direction and supervision of the delegating health professional and following state health care laws and statutes (122,123).

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2. Classification and Diagnosis of Diabetes: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

CLASSIFICATION

Diabetes can be classified into the following general categories:

1. Type 1 diabetes (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes of adulthood)
2. Type 2 diabetes (due to a non-autoimmune progressive loss of adequate β-cell insulin secretion frequently on the background of insulin resistance and metabolic syndrome)
3. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)
4. Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)

This section reviews most common forms of diabetes but is not comprehensive. For additional information, see the American Diabetes Association (ADA) position statement "Diagnosis and Classification of Diabetes Mellitus" (1).

Type 1 diabetes and type 2 diabetes are heterogeneous diseases in which clinical presentation and disease progression may vary considerably. Classification is important for determining therapy, but some individuals cannot be clearly classified as having type 1 or type 2 diabetes at the time of diagnosis. The traditional paradigms of type 2 diabetes occurring only in adults and type 1 diabetes only in children are no longer accurate, as both diseases occur in both age groups. Children with type 1 diabetes often present with the hallmark symptoms of polyuria/polydipsia, and

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approximately half present with diabetic ketoacidosis (DKA) (2–4). The onset of type 1 diabetes may be more variable in adults; they may not present with the classic symptoms seen in children and may experience temporary remission from the need for insulin (5–7). The features most useful in discrimination of type 1 diabetes include younger age at diagnosis (<35 years) with lower BMI (<25 kg/m^2), unintentional weight loss, ketoacidosis, and glucose >360 mg/dL (20 mmol/L) at presentation (8). Occasionally, people with type 2 diabetes may present with DKA (9,10), particularly members of ethnic and racial minorities (11). It is important for the health care professional to realize that classification of diabetes type is not always straightforward at presentation and that misdiagnosis is common (e.g., adults with type 1 diabetes misdiagnosed as having type 2 diabetes, individuals with maturity-onset diabetes of the young [MODY] misdiagnosed as having type 1 diabetes). Although difficulties in distinguishing diabetes type may occur in all age groups at onset, the diagnosis becomes more obvious over time in people with β-cell deficiency as the degree of β-cell deficiency becomes clear.

In both type 1 and type 2 diabetes, various genetic and environmental factors can result in the progressive loss of β-cell mass and/or function that manifests clinically as hyperglycemia. Once hyperglycemia occurs, people with all forms of diabetes are at risk for developing the same chronic complications, although rates of progression may differ. The identification of individualized therapies for diabetes in the future will be informed by better characterization of the many paths to β-cell demise or dysfunction (12). Across the globe, many groups are working on combining clinical, pathophysiological, and genetic characteristics to more precisely define the subsets of diabetes that are currently clustered into the type 1 diabetes versus type 2 diabetes nomenclature with the goal of optimizing personalized treatment approaches. Many of these studies show great promise and may soon be incorporated into the diabetes classification system (13).

Characterization of the underlying pathophysiology is more precisely developed in type 1 diabetes than in type 2 diabetes. It is now clear from prospective studies that the persistent presence of two or more islet autoantibodies is a near-certain predictor of clinical diabetes (14). The rate of progression is dependent on the age at first detection of autoantibody, number of autoantibodies, autoantibody specificity, and autoantibody titer. Glucose and A1C levels rise well before the clinical onset of diabetes, making diagnosis feasible well before the onset of DKA. Three distinct stages of type 1 diabetes can be identified (**Table 2.1**) and serve as a framework for research and regulatory decision-making (12,15). There is debate as to whether slowly progressive autoimmune diabetes with an adult onset should be termed latent autoimmune diabetes in adults (LADA) or type 1 diabetes. The clinical priority with detection of LADA is awareness that slow autoimmune β-cell destruction can occur in adults leading to a long duration of marginal insulin secretory capacity. For the purpose of this classification, all forms of diabetes mediated by autoimmune β-cell destruction are included under the rubric of type 1 diabetes. Use of the term LADA is common and acceptable in clinical practice and has the practical impact of heightening awareness of a population of adults likely to have progressive autoimmune β-cell destruction (16), thus accelerating insulin initiation prior to deterioration of glucose management or development of DKA (6,17).

The paths to β-cell demise and dysfunction are less well defined in type 2 diabetes, but deficient β-cell insulin secretion, frequently in the setting of insulin resistance, appears to be the common denominator. Type 2 diabetes is associated with insulin secretory defects related to genetics, inflammation, and metabolic stress. Future classification schemes for diabetes will likely focus on the pathophysiology of the underlying β-cell dysfunction (12,13,18–20).

DIAGNOSTIC TESTS FOR DIABETES

Diabetes may be diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) value or the 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT) or A1C criteria (21) (**Table 2.2**).

Generally, FPG, 2-h PG during 75-g OGTT, and A1C are equally appropriate for diagnostic screening. It should be noted that detection rates of different screening tests vary in both populations and individuals. Moreover, the efficacy of interventions for primary prevention of type 2 diabetes has mainly been demonstrated among individuals who have impaired glucose tolerance (IGT) with or without elevated fasting glucose, not for individuals with isolated impaired fasting glucose (IFG) or for those with prediabetes defined by A1C criteria (22,23).

The same tests may be used to screen for and diagnose diabetes and to detect individuals with prediabetes (**Table 2.2** and **Table 2.5**) (24). Diabetes may be identified anywhere along the spectrum of clinical

Table 2.1—Staging of type 1 diabetes (12,16)

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• Autoimmunity • Overt hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple islet autoantibodies • No IGT or IFG	• Islet autoantibodies (usually multiple) • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Autoantibodies may become absent • Diabetes by standard criteria

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose.

Table 2.2—Criteria for the diagnosis of diabetes

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; NGSP, National Glycohemoglobin Standardization Program; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

scenarios—in seemingly low-risk individuals who happen to have glucose testing, in individuals screened based on diabetes risk assessment, and in symptomatic patients. For additional details on the evidence used to establish the criteria for the diagnosis of diabetes, prediabetes, and abnormal glucose tolerance (IFG, IGT), see the ADA position statement "Diagnosis and Classification of Diabetes Mellitus" (1) and other reports (21,25,26).

Fasting and 2-Hour Plasma Glucose

The FPG and 2-h PG may be used to diagnose diabetes (**Table 2.2**). The concordance between the FPG and 2-h PG tests is imperfect, as is the concordance between A1C and either glucose-based test. Compared with FPG and A1C cut points, the 2-h PG value diagnoses more people with prediabetes and diabetes (27). In people in whom there is discordance between A1C values and glucose values, FPG and 2-h PG are more accurate (28).

A1C

Recommendations

2.1a To avoid misdiagnosis or missed diagnosis, the A1C test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized to the Diabetes Control and Complications Trial (DCCT) assay. **B**

2.1b Point-of-care A1C testing for diabetes screening and diagnosis should be restricted to U.S. Food and Drug Administration–approved devices at laboratories proficient in performing testing of moderate complexity or higher by trained personnel. **B**

2.2 Marked discordance between measured A1C and plasma glucose levels should raise the possibility of A1C assay interference and consideration of using an assay without interference or plasma blood glucose criteria to diagnose diabetes. **B**

2.3 In conditions associated with an altered relationship between A1C and glycemia, such as hemoglobinopathies including sickle cell disease, pregnancy (second and third trimesters and the postpartum period), glucose-6-phosphate dehydrogenase deficiency, HIV, hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only plasma blood glucose criteria should be used to diagnose diabetes. **B**

2.4 Adequate carbohydrate intake (at least 150 g/day) should be assured for 3 days prior to oral glucose tolerance testing as a screen for diabetes. **A**

The A1C test should be performed using a method that is certified by the NGSP (ngsp.org) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. Point-of-care A1C assays may be NGSP certified and cleared by the U.S. Food and Drug Administration (FDA) for use in monitoring glycemic control in people with diabetes in both Clinical Laboratory Improvement Amendments (CLIA)-regulated and CLIA-waived settings. FDA-approved point-of-care A1C testing can be used in laboratories or sites that are CLIA certified, are inspected, and meet the CLIA quality standards. These standards include specified personnel requirements (including documented annual competency assessments) and participation three times per year in an approved proficiency testing program (29–32). As discussed in Section 6, "Glycemic Targets," point-of-care A1C assays may be more generally applied for assessment of glycemic stability in the clinic.

A1C has several advantages compared with FPG and OGTT, including greater convenience (fasting not required), greater preanalytical stability, and fewer day-to-day perturbations during stress, changes in nutrition, or illness. However, these advantages may be offset by the lower sensitivity of A1C at the designated cut point, greater cost, limited availability of A1C testing in certain regions of the developing world, and the imperfect correlation between A1C and average glucose in certain individuals. The A1C test, with a diagnostic threshold of ≥6.5% (48 mmol/mol), diagnoses only 30% of the diabetes cases identified collectively using A1C, FPG, or 2-h PG, according to National Health and Nutrition Examination Survey (NHANES) data (33). Despite these limitations with A1C, in 2009, the International Expert Committee added A1C to the diagnostic criteria with the goal of increased screening (21).

When using A1C to diagnose diabetes, it is important to recognize that A1C is an indirect measure of average blood glucose levels and to take other factors into consideration that may impact hemoglobin glycation independently of glycemia, such as hemodialysis, pregnancy, HIV treatment (34,35), age, race/ethnicity, genetic background, and anemia/hemoglobinopathies. (See OTHER CONDITIONS ALTERING THE RELATIONSHIP OF A1C AND GLYCEMIA below for more information.)

Age

The epidemiologic studies that formed the basis for recommending A1C to

diagnose diabetes included only adult populations (33). However, recent ADA clinical guidance concluded that A1C, FPG, or 2-h PG could be used to test for prediabetes or type 2 diabetes in children and adolescents (see SCREENING AND TESTING FOR PREDIABETES AND TYPE 2 DIABETES IN CHILDREN AND ADOLESCENTS below for additional information) (36).

Race/Ethnicity/Hemoglobinopathies

Hemoglobin variants can interfere with the measurement of A1C, although most assays in use in the U.S. are unaffected by the most common variants. Marked discrepancies between measured A1C and plasma glucose levels should prompt consideration that the A1C assay may not be reliable for that individual. For individuals with a hemoglobin variant but normal red blood cell turnover, such as those with the sickle cell trait, an A1C assay without interference from hemoglobin variants should be used. An updated list of A1C assays with interferences is available at ngsp.org/interf.asp.

African American individuals heterozygous for the common hemoglobin variant HbS may have, for any given level of mean glycemia, lower A1C by about 0.3% compared with those without the trait (37). Another genetic variant, X-linked glucose-6-phosphate dehydrogenase G202A, carried by 11% of African American individuals, was associated with a decrease in A1C of about 0.8% in homozygous men and 0.7% in homozygous women compared with those without the variant (38). For example, in Tanzania, where there is a high likelihood of hemoglobinopathies in people with HIV, A1C may be lower than expected based on glucose, limiting its usefulness for screening (39).

Even in the absence of hemoglobin variants, A1C levels may vary with race/ethnicity independently of glycemia (40–42). For example, African American individuals may have higher A1C levels than non-Hispanic White individuals with similar fasting and post–glucose load glucose levels (43). Though conflicting data exist, African American individuals may also have higher levels of fructosamine and glycated albumin and lower levels of 1,5-anhydroglucitol, suggesting that their glycemic burden (particularly postprandially) may be higher (44,45). Similarly, A1C levels may be higher for a given mean glucose concentration when measured with continuous glucose monitoring (46). A recent report in Afro-Caribbean people demonstrated a lower A1C than predicted by glucose levels (47). Despite these and other reported differences, the association of A1C with risk for complications appears to be similar in African American and non-Hispanic White populations (42,48). In the Taiwanese population, age and sex have been reported to be associated with increased A1C in men (49); the clinical implications of this finding are unclear at this time.

Other Conditions Altering the Relationship of A1C and Glycemia

In conditions associated with increased red blood cell turnover, such as sickle cell disease, pregnancy (second and third trimesters), glucose-6-phosphate dehydrogenase deficiency (50,51), hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only plasma blood glucose criteria should be used to diagnose diabetes (52). A1C is less reliable than blood glucose measurement in other conditions such as the postpartum state (53–55), HIV treated with certain protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) (34), and iron-deficient anemia (56).

Confirming the Diagnosis

Unless there is a clear clinical diagnosis (e.g., patient in a hyperglycemic crisis or with classic symptoms of hyperglycemia and a random plasma glucose ≥200 mg/dL [11.1 mmol/L]), diagnosis requires two abnormal screening test results, either from the same sample (57) or in two separate test samples. If using two separate test samples, it is recommended that the second test, which may either be a repeat of the initial test or a different test, be performed without delay. For example, if the A1C is 7.0% (53 mmol/mol) and a repeat result is 6.8% (51 mmol/mol), the diagnosis of diabetes is confirmed. If two different tests (such as A1C and FPG) are both above the diagnostic threshold when analyzed from the same sample or in two different test samples, this also confirms the diagnosis. On the other hand, if a patient has discordant results from two different tests, then the test result that is above the diagnostic cut point should be repeated, with careful consideration of the possibility of A1C assay interference. The diagnosis is made on the basis of the confirmatory screening test. For example, if a patient meets the diabetes criterion of the A1C (two results ≥6.5% [48 mmol/mol]) but not FPG (<126 mg/dL [7.0 mmol/L]), that person should nevertheless be considered to have diabetes.

Each of the screening tests has preanalytic and analytic variability, so it is possible that a test yielding an abnormal result (i.e., above the diagnostic threshold), when repeated, will produce a value below the diagnostic cut point. This scenario is likely for FPG and 2-h PG if the glucose samples remain at room temperature and are not centrifuged promptly. Because of the potential for preanalytic variability, it is critical that samples for plasma glucose be spun and separated immediately after they are drawn. If patients have test results near the margins of the diagnostic threshold, the health care professional should discuss signs and symptoms with the patient and repeat the test in 3–6 months.

People should consume a mixed diet with at least 150 g of carbohydrates on the 3 days prior to oral glucose tolerance testing (58–60). Fasting and carbohydrate restriction can falsely elevate glucose level with an oral glucose challenge.

Diagnosis

In a patient with classic symptoms, measurement of plasma glucose is sufficient to diagnose diabetes (symptoms of hyperglycemia or hyperglycemic crisis plus a random plasma glucose ≥200 mg/dL [11.1 mmol/L]). In these cases, knowing the plasma glucose level is critical because, in addition to confirming that symptoms are due to diabetes, it will inform management decisions. Some health care professionals may also want to know the A1C to determine the chronicity of the hyperglycemia. The criteria to diagnose diabetes are listed in **Table 2.2**.

TYPE 1 DIABETES

Recommendations

2.5 Screening for presymptomatic type 1 diabetes using screening tests that detect autoantibodies to insulin, glutamic acid decarboxylase (GAD), islet antigen 2, or zinc transporter 8 is currently recommended in the setting of a research study or

can be considered an option for first-degree family members of a proband with type 1 diabetes. **B**

2.6 Development of and persistence of multiple islet autoantibodies is a risk factor for clinical diabetes and may serve as an indication for intervention in the setting of a clinical trial or screening for stage 2 type 1 diabetes. **B**

Immune-Mediated Diabetes

This form, previously called "insulin-dependent diabetes" or "juvenile-onset diabetes," accounts for 5–10% of diabetes and is due to cell-mediated autoimmune destruction of the pancreatic β-cells. Autoimmune markers include islet cell autoantibodies and autoantibodies to GAD (glutamic acid decarboxylase, GAD65), insulin, the tyrosine phosphatases islet antigen 2 (IA-2) and IA-2β, and zinc transporter 8. Numerous clinical studies are being conducted to test various methods of preventing type 1 diabetes in those with evidence of islet autoimmunity (trialnet.org/our-research/prevention-studies) (14,17,61–64). Stage 1 of type 1 diabetes is defined by the presence of two or more of these autoimmune markers. The disease has strong HLA associations, with linkage to the *DQB1* and *DRB1* haplotypes, and genetic screening has been used in some research studies to identify high-risk populations. Specific alleles in these genes can be either predisposing or protective (**Table 2.1**).

The rate of β-cell destruction is quite variable, being rapid in some individuals (particularly but not exclusively in infants and children) and slow in others (mainly but not exclusively adults) (65,66). Children and adolescents often present with DKA as the first manifestation of the disease, and the rates in the U.S. have increased dramatically over the past 20 years (2–4). Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or DKA with infection or other stress. Adults may retain sufficient β-cell function to prevent DKA for many years; such individuals may have remission or decreased insulin needs for months or years and eventually become dependent on insulin for survival and are at risk for DKA (5–7,67,68). At this later stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide. Immune-mediated diabetes is the most common form of diabetes in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life.

Autoimmune destruction of β-cells has multiple genetic factors and is also related to environmental factors that are still poorly defined. Although individuals do not typically have obesity when they present with type 1 diabetes, obesity is increasingly common in the general population; as such, obesity should not preclude testing for type 1 diabetes. People with type 1 diabetes are also prone to other autoimmune disorders such as Hashimoto thyroiditis, Graves disease, celiac disease, Addison disease, vitiligo, autoimmune hepatitis, myasthenia gravis, and pernicious anemia (see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities"). Type 1 diabetes can be associated with monogenic polyglandular autoimmune syndromes, including immune dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome, which is an early-onset systemic autoimmune, genetic disorder caused by mutation of the forkhead box protein 3 (*FOXP3*) gene, and another caused by the autoimmune regulator (*AIRE*) gene mutation (69,70). As indicated by the names, these disorders are associated with other autoimmune and rheumatological diseases.

Introduction of immunotherapy, specifically checkpoint inhibitors, for cancer treatment has led to unexpected adverse events, including immune system activation precipitating autoimmune disease. Fulminant onset of type 1 diabetes can develop, with DKA and low or undetectable levels of C-peptide as a marker of endogenous β-cell function (71,72). Fewer than half of these patients have autoantibodies that are seen in type 1 diabetes, supporting alternate pathobiology. This immune-related adverse event occurs in just under 1% of checkpoint inhibitor-treated patients but most commonly occurs with agents that block the programmed cell death protein 1/programmed cell death ligand 1 pathway alone or in combination with other checkpoint inhibitors (73). To date, the majority of immune checkpoint inhibitor–related cases of type 1 diabetes occur in people with high-risk HLA-DR4 (present in 76% of patients), whereas other high-risk HLA alleles are not more common than those in the general population (73). To date, risk cannot be predicted by family history or autoantibodies, so all health care professionals administering these medications should be mindful of this adverse effect and educate patients appropriately.

Idiopathic Type 1 Diabetes

Some forms of type 1 diabetes have no known etiologies. These individuals have permanent insulinopenia and are prone to DKA but have no evidence of β-cell autoimmunity. However, only a minority of people with type 1 diabetes fall into this category. Individuals with autoantibody-negative type 1 diabetes of African or Asian ancestry may suffer from episodic DKA and exhibit varying degrees of insulin deficiency between episodes (possibly ketosis-prone diabetes) (74). This form of diabetes is strongly inherited and is not HLA associated. An absolute requirement for insulin replacement therapy in affected individuals may be intermittent. Future research is needed to determine the cause of β-cell destruction in this rare clinical scenario.

Screening for Type 1 Diabetes Risk

The incidence and prevalence of type 1 diabetes are increasing (75). People with type 1 diabetes often present with acute symptoms of diabetes and markedly elevated blood glucose levels, and 40–60% are diagnosed with life-threatening DKA (2–4). Multiple studies indicate that measuring islet autoantibodies in relatives of those with type 1 diabetes (15) or in children from the general population (76,77) can effectively identify those who will develop type 1 diabetes. A study reported the risk of progression to type 1 diabetes from the time of seroconversion to autoantibody positivity in three pediatric cohorts from Finland, Germany, and the U.S. Of the 585 children who developed more than two autoantibodies, nearly 70% developed type 1 diabetes within 10 years and 84% within 15 years (14). These findings are highly significant because while the German group was recruited from offspring of parents with type 1 diabetes, the Finnish and American groups were

recruited from the general population. Remarkably, the findings in all three groups were the same, suggesting that the same sequence of events led to clinical disease in both "sporadic" and familial cases of type 1 diabetes. Indeed, the risk of type 1 diabetes increases as the number of relevant autoantibodies detected increases (63,78,79). In The Environmental Determinants of Diabetes in the Young (TEDDY) study, type 1 diabetes developed in 21% of 363 subjects with at least one autoantibody at 3 years of age (80). Such testing, coupled with education about diabetes symptoms and close follow-up, has been shown to enable earlier diagnosis and prevent DKA (81,82).

While widespread clinical screening of asymptomatic low-risk individuals is not currently recommended due to lack of approved therapeutic interventions, several innovative research screening programs are available in Europe (e.g., Fr1da, gppad.org) and the U.S. (trialnet.org, askhealth.org). Participation should be encouraged to accelerate development of evidence-based clinical guidelines for the general population and relatives of those with type 1 diabetes. Individuals who test positive should be counseled about the risk of developing diabetes, diabetes symptoms, and DKA prevention. Numerous clinical studies are being conducted to test various methods of preventing and treating stage 2 type 1 diabetes in those with evidence of autoimmunity with promising results (see clinicaltrials.gov and trialnet.org). Delay of overt diabetes development in stage 2 type 1 diabetes with the anti-CD3 antibody teplizumab in relatives at risk for type 1 diabetes was reported in 2019, with an extension of the randomized controlled trial in 2021 (83,84). Based on these data, this agent has been submitted to the FDA for the indication of delay or prevention of clinical type 1 diabetes in at-risk individuals. Neither this agent nor others in this category are currently available for clinical use.

PREDIABETES AND TYPE 2 DIABETES

Recommendations

2.7 Screening for prediabetes and type 2 diabetes with an informal assessment of risk factors or validated risk calculator should be done in asymptomatic adults. **B**

2.8 Testing for prediabetes and/or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian American individuals) who have one or more risk factors (**Table 2.3**). **B**

2.9 For all people, screening should begin at age 35 years. **B**

2.10 If tests are normal, repeat screening recommended at a minimum of 3-year intervals is reasonable, sooner with symptoms or change in risk (i.e., weight gain). **C**

2.11 To screen for prediabetes and type 2 diabetes, fasting plasma glucose, 2-h plasma glucose during 75-g oral glucose tolerance test, and A1C are each appropriate (**Table 2.2** and **Table 2.5**). **B**

2.12 When using oral glucose tolerance testing as a screen for diabetes, adequate carbohydrate intake (at least 150 g/day) should be assured for 3 days prior to testing. **A**

2.13 In people with prediabetes and type 2 diabetes, identify and treat cardiovascular disease risk factors. **A**

2.14 Risk-based screening for prediabetes and/or type 2 diabetes should be considered after the onset of puberty or after 10 years of age, whichever occurs earlier, in children and adolescents with overweight (BMI ≥85th percentile) or obesity (BMI ≥95th percentile) and who have one or more risk factors for diabetes. (See **Table 2.4** for evidence grading of risk factors.) **B**

2.15 People with HIV should be screened for diabetes and prediabetes with a fasting glucose test before starting antiretroviral therapy, at the time of switching antiretroviral therapy, and 3–6 months after starting or switching antiretroviral therapy. If initial screening results are normal, fasting glucose should be checked annually. **E**

Prediabetes

"Prediabetes" is the term used for individuals whose glucose levels do not meet the criteria for diabetes yet have abnormal carbohydrate metabolism (48,85). People with prediabetes are defined by the presence of IFG and/or IGT and/or A1C 5.7–6.4% (39–47 mmol/mol)

Table 2.3—Criteria for screening for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in adults with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian American individuals) who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of CVD
   - Hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Individuals with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. People with prediabetes (A1C ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.
3. People who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other people, testing should begin at age 35 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.
6. People with HIV

CVD, cardiovascular disease; GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Table 2.4—Risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting

Screening should be considered in youth* who have overweight (≥85th percentile) or obesity (≥95th percentile) **A** and who have one or more additional risk factors based on the strength of their association with diabetes:

- Maternal history of diabetes or GDM during the child's gestation **A**
- Family history of type 2 diabetes in first- or second-degree relative **A**
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander) **A**
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight) **B**

GDM, gestational diabetes mellitus. *After the onset of puberty or after 10 years of age, whichever occurs earlier. If tests are normal, repeat testing at a minimum of 3-year intervals (or more frequently if BMI is increasing or risk factor profile deteriorating) is recommended. Reports of type 2 diabetes before age 10 years exist, and this can be considered with numerous risk factors.

(**Table 2.5**). Prediabetes should not be viewed as a clinical entity in its own right but rather as a risk factor for progression to diabetes and cardiovascular disease (CVD). Criteria for screening for diabetes or prediabetes in asymptomatic adults are outlined in **Table 2.3**. Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension. The presence of prediabetes should prompt comprehensive screening for cardiovascular risk factors.

Diagnosis

IFG is defined as FPG levels from 100 to 125 mg/dL (from 5.6 to 6.9 mmol/L) (82,83) and IGT as 2-h PG levels during 75-g OGTT from 140 to 199 mg/dL (from 7.8 to 11.0 mmol/L) (25). It should be noted that the World Health Organization and numerous other diabetes organizations define the IFG lower limit at 110 mg/dL (6.1 mmol/L).

As with the glucose measures, several prospective studies that used A1C to predict the progression to diabetes as defined by A1C criteria demonstrated a strong, continuous association between A1C and subsequent diabetes. In a systematic review of 44,203 individuals from 16 cohort studies with a follow-up interval averaging 5.6 years (range 2.8–12 years), those with A1C between 5.5% and 6.0% (between 37 and 42 mmol/mol) had a substantially increased risk of diabetes (5-year incidence from 9% to 25%). Those with an A1C range of 6.0–6.5% (42–48 mmol/mol) had a 5-year risk of developing diabetes between 25% and 50% and a relative risk 20 times higher compared with A1C of 5.0% (31 mmol/mol) (86). In a community-based study of African American and non-Hispanic White adults without diabetes, baseline A1C was a stronger predictor of subsequent diabetes and cardiovascular events than fasting glucose (87). Other analyses suggest that A1C of 5.7% (39 mmol/mol) or higher is associated with a diabetes risk similar to that of the high-risk participants in the Diabetes Prevention Program (DPP) (88), and A1C at baseline was a strong predictor of the development of glucose-defined diabetes during the DPP and its follow-up (89).

Table 2.5—Criteria defining prediabetes*

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4% (39–47 mmol/mol)

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose. *For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

Hence, it is reasonable to consider an A1C range of 5.7–6.4% (39–47 mmol/mol) as identifying individuals with prediabetes. Similar to those with IFG and/or IGT, individuals with A1C of 5.7–6.4% (39–47 mmol/mol) should be informed of their increased risk for diabetes and CVD and counseled about effective strategies to lower their risks (see Section 3, "Prevention or Delay of Type 2 Diabetes and Associated Comorbidities"). Similar to glucose measurements, the continuum of risk is curvilinear, so as A1C rises, the diabetes risk rises disproportionately (86). Aggressive interventions and vigilant follow-up should be pursued for those considered at very high risk (e.g., those with A1C >6.0% [42 mmol/mol]).

Table 2.5 summarizes the categories of prediabetes, and **Table 2.3** outlines the criteria for screening for prediabetes. The ADA Diabetes Risk Test is an additional option for assessment to determine the appropriateness of screening for diabetes or prediabetes in asymptomatic adults (**Fig. 2.1**) (diabetes.org/socrisktest). For additional background regarding risk factors and screening for prediabetes, see SCREENING AND TESTING FOR PREDIABETES AND TYPE 2 DIABETES IN ASYMPTOMATIC ADULTS and also SCREENING AND TESTING FOR PREDIABETES AND TYPE 2 DIABETES IN CHILDREN AND ADOLESCENTS below. For details regarding individuals with prediabetes most likely to benefit from a formal behavioral or lifestyle intervention, see Section 3, "Prevention or Delay of Type 2 Diabetes and Associated Comorbidities."

Type 2 Diabetes

Type 2 diabetes, previously referred to as "non-insulin-dependent diabetes" or "adult-onset diabetes," accounts for 90–95% of all diabetes. This form encompasses individuals who have relative (rather than absolute) insulin deficiency and have peripheral insulin resistance. At least initially, and often throughout their lifetime, these individuals may not need insulin treatment to survive.

There are various causes of type 2 diabetes. Although the specific etiologies are not known, autoimmune destruction of β-cells does not occur, and patients do not have any of the other known causes of diabetes. Most, but not all, people with type 2 diabetes have

American Diabetes Association®
Connected for Life

Are you at risk for type 2 diabetes?

Diabetes Risk Test:

WRITE YOUR SCORE IN THE BOX.

1. How old are you? .....
Less than 40 years (0 points)
40–49 years (1 point)
50–59 years (2 points)
60 years or older (3 points)

2. Are you a man or a woman? .....
Man (1 point) Woman (0 points)

3. If you are a woman, have you ever been diagnosed with gestational diabetes?.....
Yes (1 point) No (0 points)

4. Do you have a mother, father, sister or brother with diabetes? .....
Yes (1 point) No (0 points)

5. Have you ever been diagnosed with high blood pressure? .....
Yes (1 point) No (0 points)

6. Are you physically active? .....
Yes (0 points) No (1 point)

7. What is your weight category? .....
See chart at right.

ADD UP YOUR SCORE.

Height	Weight (lbs.)		
4' 10"	119–142	143–190	191+
4' 11"	124–147	148–197	198+
5' 0"	128–152	153–203	204+
5' 1"	132–157	158–210	211+
5' 2"	136–163	164–217	218+
5' 3"	141–168	169–224	225+
5' 4"	145–173	174–231	232+
5' 5"	150–179	180–239	240+
5' 6"	155–185	186–246	247+
5' 7"	159–190	191–254	255+
5' 8"	164–196	197–261	262+
5' 9"	169–202	203–269	270+
5' 10"	174–208	209–277	278+
5' 11"	179–214	215–285	286+
6' 0"	184–220	221–293	294+
6' 1"	189–226	227–301	302+
6' 2"	194–232	233–310	311+
6' 3"	200–239	240–318	319+
6' 4"	205–245	246–327	328+
	1 point	2 points	3 points

If you weigh less than the amount in the left column: 0 points

Adapted from Bang et al., Ann Intern Med 151:775–783, 2009 • Original algorithm was validated without gestational diabetes as part of the model.

If you scored 5 or higher:

You are at increased risk for having type 2 diabetes. However, only your doctor can tell for sure if you do have type 2 diabetes or prediabetes, a condition in which blood glucose levels are higher than normal but not yet high enough to be diagnosed as diabetes. Talk to your doctor to see if additional testing is needed.

Type 2 diabetes is more common in African Americans, Hispanics/Latinos, Native Americans, Asian Americans, and Native Hawaiians and Pacific Islanders.

Higher body weight increases diabetes risk for everyone. Asian Americans are at increased diabetes risk at lower body weight than the rest of the general public (about 15 pounds lower).

Lower Your Risk

The good news is you can manage your risk for type 2 diabetes. Small steps make a big difference in helping you live a longer, healthier life.

If you are at high risk, your first step is to visit your doctor to see if additional testing is needed.

Visit diabetes.org or call 1-800-DIABETES (800-342-2383) for information, tips on getting started, and ideas for simple, small steps you can take to help lower your risk.

Learn more at diabetes.org/risktest | 1-800-DIABETES (800-342-2383)

Diabetes Risk Test | American Diabetes Association®

Figure 2.1—ADA risk test (diabetes.org/socrisktest).

overweight or obesity. Excess weight itself causes some degree of insulin resistance. Individuals who do not have obesity or overweight by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region.

DKA seldom occurs spontaneously in type 2 diabetes; when seen, it usually arises in association with the stress of another illness such as infection or myocardial infarction or with the use of certain drugs (e.g., corticosteroids, atypical antipsychotics, and sodium–glucose cotransporter 2 inhibitors) (90,91). Type 2 diabetes frequently goes

undiagnosed for many years because hyperglycemia develops gradually and, at earlier stages, is often not severe enough for the patient to notice the classic diabetes symptoms caused by hyperglycemia, such as dehydration or unintentional weight loss. Nevertheless, even undiagnosed people with diabetes are at increased risk of developing macrovascular and microvascular complications.

People with type 2 diabetes may have insulin levels that appear normal or elevated, yet the failure to normalize blood glucose reflects a relative defect in glucose-stimulated insulin secretion. Thus, insulin secretion is defective in these individuals and insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction, physical activity, and/or pharmacologic treatment of hyperglycemia but is seldom restored to normal. Recent interventions with intensive diet and exercise or surgical weight loss have led to diabetes remission (92–98) (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes").

The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity (99,100). It occurs more frequently in individuals with prior gestational diabetes mellitus (GDM) or polycystic ovary syndrome. It is also more common in people with hypertension or dyslipidemia and in certain racial/ethnic subgroups (African American, Native American, Hispanic/Latino, and Asian American). It is often associated with a strong genetic predisposition or family history in first-degree relatives (more so than type 1 diabetes). However, the genetics of type 2 diabetes are poorly understood and under intense investigation in this era of precision medicine (18). In adults without traditional risk factors for type 2 diabetes and/or of younger age, consider islet autoantibody testing (e.g., GAD65 autoantibodies) to exclude the diagnosis of type 1 diabetes (8).

Screening and Testing for Prediabetes and Type 2 Diabetes in Asymptomatic Adults

Screening for prediabetes and type 2 diabetes risk through an informal assessment of risk factors (**Table 2.3**) or with an assessment tool, such as the ADA risk test (**Fig. 2.1**) (online at diabetes.org/socrisktest), is recommended to guide health care professionals on whether performing a diagnostic test (**Table 2.2**) is appropriate. Prediabetes and type 2 diabetes meet criteria for conditions in which early detection via screening is appropriate. Both conditions are common and impose significant clinical and public health burdens. There is often a long presymptomatic phase before the diagnosis of type 2 diabetes. Simple tests to detect preclinical disease are readily available (101). The duration of glycemic burden is a strong predictor of adverse outcomes. There are effective interventions that prevent progression from prediabetes to diabetes. It is important to individualize risk/benefit of formal intervention for people with prediabetes and consider patient-centered goals. Risk models have explored the benefit, in general finding higher benefit of intervention in those at highest risk (102) (see Section 3, "Prevention or Delay of Type 2 Diabetes and Associated Comorbidities") and reduce the risk of diabetes complications (103) (see Section 10, "Cardiovascular Disease and Risk Management," Section 11, "Chronic Kidney Disease and Risk Management," and Section 12, "Retinopathy, Neuropathy, and Foot Care"). In the most recent National Institutes of Health (NIH) Diabetes Prevention Program Outcomes Study (DPPOS) report, prevention of progression from prediabetes to diabetes (104) resulted in lower rates of developing retinopathy and nephropathy (105). Similar impact on diabetes complications was reported with screening, diagnosis, and comprehensive risk factor management in the U.K. Clinical Practice Research Datalink database (103). In that report, progression from prediabetes to diabetes augmented risk of complications.

Approximately one-quarter of people with diabetes in the U.S. and nearly half of Asian and Hispanic American people with diabetes are undiagnosed (106,107). Although screening of asymptomatic individuals to identify those with prediabetes or diabetes might seem reasonable, rigorous clinical trials to prove the effectiveness of such screening have not been conducted and are unlikely to occur. Clinical conditions, such as hypertension, hypertensive pregnancy, and obesity, enhance risk (108). Based on a population estimate, diabetes in people of childbearing age is underdiagnosed (109). Employing a probabilistic model, Peterson et al. (110) demonstrated cost and health benefits of preconception screening.

A large European randomized controlled trial compared the impact of screening for diabetes and intensive multifactorial intervention with that of screening and routine care (111). General practice patients between the ages of 40 and 69 years were screened for diabetes and randomly assigned by practice to intensive treatment of multiple risk factors or routine diabetes care. After 5.3 years of follow-up, CVD risk factors were modestly but significantly improved with intensive treatment compared with routine care, but the incidence of first CVD events or mortality was not significantly different between the groups (26). The excellent care provided to patients in the routine care group and the lack of an unscreened control arm limited the authors' ability to determine whether screening and early treatment improved outcomes compared with no screening and later treatment after clinical diagnoses. Computer simulation modeling studies suggest that major benefits are likely to accrue from the early diagnosis and treatment of hyperglycemia and cardiovascular risk factors in type 2 diabetes (112); moreover, screening, beginning at age 30 or 45 years and independent of risk factors, may be cost-effective (<$11,000 per quality-adjusted life year gained—2010 modeling data) (113). Cost-effectiveness of screening has been reinforced in cohort studies (114,115).

Additional considerations regarding testing for type 2 diabetes and prediabetes in asymptomatic individuals include the following.

Age

Age is a major risk factor for diabetes. Testing should begin at no later than age 35 years for all people (116). Screening should be considered in adults of any age with overweight or obesity and one or more risk factors for diabetes.

BMI and Ethnicity

In general, BMI ≥25 kg/m^2 is a risk factor for diabetes. However, data suggest that the BMI cut point should be lower for the Asian American population (117,118). The BMI cut points fall consistently between 23 and 24 kg/m^2

(sensitivity of 80%) for nearly all Asian American subgroups (with levels slightly lower for Japanese American individuals). This makes a rounded cut point of 23 kg/m^2 practical. An argument can be made to push the BMI cut point to lower than 23 kg/m^2 in favor of increased sensitivity; however, this would lead to an unacceptably low specificity (13.1%). Data from the World Health Organization also suggest that a BMI of ≥23 kg/m^2 should be used to define increased risk in Asian American individuals (119). The finding that one-third to one-half of diabetes in Asian American people is undiagnosed suggests that testing is not occurring at lower BMI thresholds (99,120).

Evidence also suggests that other populations may benefit from lower BMI cut points. For example, in a large multiethnic cohort study, for an equivalent incidence rate of diabetes, a BMI of 30 kg/m^2 in non-Hispanic White individuals was equivalent to a BMI of 26 kg/m^2 in African American individuals (121).

Medications

Certain medications, such as glucocorticoids, thiazide diuretics, some HIV medications (34), and atypical antipsychotics (92), are known to increase the risk of diabetes and should be considered when deciding whether to screen.

HIV

Individuals with HIV are at higher risk for developing prediabetes and diabetes on antiretroviral (ARV) therapies; a screening protocol is therefore recommended (122). The A1C test may underestimate glycemia in people with HIV; it is not recommended for diagnosis and may present challenges for monitoring (35). In those with prediabetes, weight loss through healthy nutrition and physical activity may reduce the progression toward diabetes. Among people with HIV and diabetes, preventive health care using an approach used in people without HIV is critical to reduce the risks of microvascular and macrovascular complications. Diabetes risk is increased with certain PIs and NRTIs. New-onset diabetes is estimated to occur in more than 5% of individuals infected with HIV on PIs, whereas more than 15% may have prediabetes (123).

PIs are associated with insulin resistance and may also lead to apoptosis of pancreatic β-cells. NRTIs also affect fat distribution (both lipohypertrophy and lipoatrophy), which is associated with insulin resistance. For people with HIV and ARV-associated hyperglycemia, it may be appropriate to consider discontinuing the problematic ARV agents if safe and effective alternatives are available (124). Before making ARV substitutions, carefully consider the possible effect on HIV virological control and the potential adverse effects of new ARV agents. In some cases, antihyperglycemic agents may still be necessary.

Testing Interval

The appropriate interval between screening tests is not known (125). The rationale for the 3-year interval is that with this interval, the number of false-positive tests that require confirmatory testing will be reduced, and individuals with false-negative tests will be retested before substantial time elapses and complications develop (125). In especially high-risk individuals, particularly with weight gain, shorter intervals between screening may be useful.

Community Screening

Ideally, screening should be carried out within a health care setting because of the need for follow-up and treatment. Community screening outside a health care setting is generally not recommended because people with positive tests may not seek, or have access to, appropriate follow-up testing and care. However, in specific situations where an adequate referral system is established beforehand for positive tests, community screening may be considered. Community screening may also be poorly targeted; i.e., it may fail to reach the groups most at risk and inappropriately test those at very low risk or even those who have already been diagnosed (126).

Screening in Dental Practices

Because periodontal disease is associated with diabetes, the utility of screening in a dental setting and referral to primary care as a means to improve the diagnosis of prediabetes and diabetes has been explored (127–129), with one study estimating that 30% of patients ≥30 years of age seen in general dental practices had dysglycemia (129,130). A similar study in 1,150 dental patients >40 years old in India reported 20.69% and 14.60% meeting criteria for prediabetes and diabetes, respectively, using random blood glucose. Further research is needed to demonstrate the feasibility, effectiveness, and cost-effectiveness of screening in this setting.

Screening and Testing for Prediabetes and Type 2 Diabetes in Children and Adolescents

In the last decade, the incidence and prevalence of type 2 diabetes in children and adolescents has increased dramatically, especially in racial and ethnic minority populations (75). See **Table 2.4** for recommendations on risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting (36). See **Table 2.2** and **Table 2.5** for the criteria for the diagnosis of diabetes and prediabetes, respectively, that apply to children, adolescents, and adults. See Section 14, "Children and Adolescents," for additional information on type 2 diabetes in children and adolescents.

Some studies question the validity of A1C in the pediatric population, especially among certain ethnicities, and suggest OGTT or FPG as more suitable diagnostic tests (131). However, many of these studies do not recognize that diabetes diagnostic criteria are based on long-term health outcomes, and validations are not currently available in the pediatric population (132). The ADA acknowledges the limited data supporting A1C for diagnosing type 2 diabetes in children and adolescents. Although A1C is not recommended for diagnosis of diabetes in children with cystic fibrosis or symptoms suggestive of acute onset of type 1 diabetes, and only A1C assays without interference are appropriate for children with hemoglobinopathies, the ADA continues to recommend A1C and the criteria in **Table 2.2** for diagnosis of type 2 diabetes in this cohort to decrease barriers to screening (133,134).

CYSTIC FIBROSIS–RELATED DIABETES

Recommendations

2.16 Annual screening for cystic fibrosis–related diabetes with an oral glucose tolerance test should begin by age 10 years in all people with cystic fibrosis

not previously diagnosed with cystic fibrosis–related diabetes. B

2.17 A1C is not recommended as a screening test for cystic fibrosis–related diabetes. B

2.18 People with cystic fibrosis–related diabetes should be treated with insulin to attain individualized glycemic goals. A

2.19 Beginning 5 years after the diagnosis of cystic fibrosis–related diabetes, annual monitoring for complications of diabetes is recommended. E

Cystic fibrosis–related diabetes (CFRD) is the most common comorbidity in people with cystic fibrosis, occurring in about 20% of adolescents and 40–50% of adults (135). Diabetes in this population, compared with individuals with type 1 or type 2 diabetes, is associated with worse nutritional status, more severe inflammatory lung disease, and greater mortality. Insulin insufficiency is the primary defect in CFRD. Genetically determined β-cell function and insulin resistance associated with infection and inflammation may also contribute to the development of CFRD. Milder abnormalities of glucose tolerance are even more common and occur at earlier ages than CFRD. Whether individuals with IGT should be treated with insulin replacement has not currently been determined. Although screening for diabetes before the age of 10 years can identify risk for progression to CFRD in those with abnormal glucose tolerance, no benefit has been established with respect to weight, height, BMI, or lung function. OGTT is the recommended screening test; however, recent publications suggest that an A1C cut point threshold of 5.5% (5.8% in a second study) would detect more than 90% of cases and reduce patient screening burden (136,137). Ongoing studies are underway to validate this approach, and A1C is not recommended for screening (138). Regardless of age, weight loss or failure of expected weight gain is a risk for CFRD and should prompt screening (136,137). The Cystic Fibrosis Foundation Patient Registry (139) evaluated 3,553 people with cystic fibrosis and diagnosed 445 (13%) with CFRD. Early diagnosis and treatment of CFRD was associated with preservation of lung function. The European Cystic Fibrosis Society Patient Registry reported an increase in CFRD with age (increased 10% per decade), genotype, decreased lung function, and female sex (140,141). Continuous glucose monitoring or HOMA of β-cell function (142) may be more sensitive than OGTT to detect risk for progression to CFRD; however, evidence linking these results to long-term outcomes is lacking, and these tests are not recommended for screening outside of the research setting (143).

CFRD mortality has significantly decreased over time, and the gap in mortality between people with cystic fibrosis with and without diabetes has considerably narrowed (144). There are limited clinical trial data on therapy for CFRD. The largest study compared three regimens: premeal insulin aspart, repaglinide, or oral placebo in people with cystic fibrosis and diabetes or abnormal glucose tolerance. Participants all had weight loss in the year preceding treatment; however, in the insulin-treated group, this pattern was reversed, and participants gained 0.39 (± 0.21) BMI units (P = 0.02). The repaglinide-treated group had initial weight gain, but it was not sustained by 6 months. The placebo group continued to lose weight (144). Insulin remains the most widely used therapy for CFRD (145). The primary rationale for the use of insulin in people with CFRD is to induce an anabolic state while promoting macronutrient retention and weight gain.

Additional resources for the clinical management of CFRD can be found in the position statement "Clinical Care Guidelines for Cystic Fibrosis–Related Diabetes: A Position Statement of the American Diabetes Association and a Clinical Practice Guideline of the Cystic Fibrosis Foundation, Endorsed by the Pediatric Endocrine Society" (146) and in the International Society for Pediatric and Adolescent Diabetes 2018 clinical practice consensus guidelines (135).

POSTTRANSPLANTATION DIABETES MELLITUS

Recommendations

2.20 After organ transplantation, screening for hyperglycemia should be done. A formal diagnosis of posttransplantation diabetes mellitus is best made once the individual is stable on an immunosuppressive regimen and in the absence of an acute infection. B

2.21 The oral glucose tolerance test is the preferred test to make a diagnosis of posttransplantation diabetes mellitus. B

2.22 Immunosuppressive regimens shown to provide the best outcomes for patient and graft survival should be used, irrespective of posttransplantation diabetes mellitus risk. E

Several terms are used in the literature to describe the presence of diabetes following organ transplantation (147). "New-onset diabetes after transplantation" (NODAT) is one such designation that describes individuals who develop new-onset diabetes following transplant. NODAT excludes people with pretransplant diabetes that was undiagnosed as well as posttransplant hyperglycemia that resolves by the time of discharge (148). Another term, "posttransplantation diabetes mellitus" (PTDM) (148,149), describes the presence of diabetes in the posttransplant setting irrespective of the timing of diabetes onset.

Hyperglycemia is very common during the early posttransplant period, with ~90% of kidney allograft recipients exhibiting hyperglycemia in the first few weeks following transplant (148–151). In most cases, such stress- or steroid-induced hyperglycemia resolves by the time of discharge (151,152). Although the use of immunosuppressive therapies is a major contributor to the development of PTDM, the risks of transplant rejection outweigh the risks of PTDM, and the role of the diabetes care health care professional is to treat hyperglycemia appropriately regardless of the type of immunosuppression (148). Risk factors for PTDM include both general diabetes risks (such as age, family history of diabetes, etc.) as well as transplant-specific factors, such as use of immunosuppressant agents (153–155). Whereas posttransplantation hyperglycemia is an important risk factor for subsequent PTDM, a formal diagnosis of PTDM is optimally made once the patient is stable on maintenance mmunosuppression and

in the absence of acute infection (151–153,156). In a recent study of 152 heart transplant recipients, 38% had PTDM at 1 year. Risk factors for PTDM included elevated BMI, discharge from the hospital on insulin, and glucose values in the 24 h prior to hospital discharge (157). In an Iranian cohort, 19% had PTDM after heart and lung transplant (158). The OGTT is considered the gold-standard test for the diagnosis of PTDM (1 year posttransplant) (148, 149,159,160). Pretransplant elevation in hs-CRP was associated with PTDM in the setting of renal transplant (161,162). However, screening people with fasting glucose and/or A1C can identify high-risk individuals requiring further assessment and may reduce the number of overall OGTTs required.

Few randomized controlled studies have reported on the short- and long-term use of antihyperglycemic agents in the setting of PTDM (153,163,164). Most studies have reported that transplant patients with hyperglycemia and PTDM after transplantation have higher rates of rejection, infection, and rehospitalization (151,153,165). Insulin therapy is the agent of choice for the management of hyperglycemia, PTDM, and preexisting diabetes and diabetes in the hospital setting. After discharge, people with preexisting diabetes could go back on their pretransplant regimen if they were in good control before transplantation. Those with previously poor glycemic stability or with persistent hyperglycemia should continue insulin with frequent home glucose monitoring to determine when insulin dose reductions may be needed and when it may be appropriate to switch to noninsulin agents.

No studies to date have established which noninsulin agents are safest or most efficacious in PTDM. The choice of agent is usually made based on the side effect profile of the medication and possible interactions with the patient's immunosuppression regimen (153). Drug dose adjustments may be required because of decreases in the glomerular filtration rate, a relatively common complication in transplant patients. A small short-term pilot study reported that metformin was safe to use in renal transplant recipients (166), but its safety has not been determined in other types of organ transplant. Thiazolidinediones have been used successfully in people with liver and kidney transplants, but side effects include fluid retention, heart failure, and osteopenia (167,168). Dipeptidyl peptidase 4 inhibitors do not interact with immunosuppressant drugs and have demonstrated safety in small clinical trials (169,170). Well-designed intervention trials examining the efficacy and safety of these and other antihyperglycemic agents in people with PTDM are needed.

MONOGENIC DIABETES SYNDROMES

Recommendations

2.23 Regardless of current age, all people diagnosed with diabetes in the first 6 months of life should have immediate genetic testing for neonatal diabetes. **A**

2.24 Children and young adults who do not have typical characteristics of type 1 or type 2 diabetes and who often have a family history of diabetes in successive generations (suggestive of an autosomal dominant pattern of inheritance) should have genetic testing for maturity-onset diabetes of the young. **A**

2.25 In both instances, consultation with a center specializing in diabetes genetics is recommended to understand the significance of genetic mutations and how best to approach further evaluation, treatment, and genetic counseling. **E**

Monogenic defects that cause β-cell dysfunction, such as neonatal diabetes and MODY, represent a small fraction of people with diabetes (<5%). **Table 2.6** describes the most common causes of monogenic diabetes. For a comprehensive list of causes, see *Genetic Diagnosis of Endocrine Disorders* (171).

Neonatal Diabetes

Diabetes occurring under 6 months of age is termed "neonatal" or "congenital" diabetes, and about 80–85% of cases can be found to have an underlying monogenic cause (8,172–175). Neonatal diabetes occurs much less often after 6 months of age, whereas autoimmune type 1 diabetes rarely occurs before 6 months of age. Neonatal diabetes can either be transient or permanent. Transient diabetes is most often due to overexpression of genes on chromosome 6q24, is recurrent in about half of cases, and may be treatable with medications other than insulin. Permanent neonatal diabetes is most commonly due to autosomal dominant mutations in the genes encoding the Kir6.2 subunit (*KCNJ11*) and SUR1 subunit (*ABCC8*) of the β-cell K_{ATP} channel. A recent report details a de novo mutation in *EIF2B1* affecting eIF2 signaling associated with permanent neonatal diabetes and hepatic dysfunction, similar to Wolcott-Rallison syndrome but with few severe comorbidities (176). The recent ADA-European Association for the Study of Diabetes type 1 diabetes consensus report recommends that regardless of current age, individuals diagnosed under 6 months of age should have genetic testing (8). Correct diagnosis has critical implications because 30–50% of people with K_{ATP}-related neonatal diabetes will exhibit improved blood glucose levels when treated with high-dose oral sulfonylureas instead of insulin. Insulin gene (*INS*) mutations are the second most common cause of permanent neonatal diabetes, and while intensive insulin management is currently the preferred treatment strategy, there are important genetic counseling considerations, as most of the mutations that cause diabetes are dominantly inherited.

Maturity-Onset Diabetes of the Young

MODY is frequently characterized by onset of hyperglycemia at an early age (classically before age 25 years, although diagnosis may occur at older ages). MODY is characterized by impaired insulin secretion with minimal or no defects in insulin action (in the absence of coexistent obesity). It is inherited in an autosomal dominant pattern with abnormalities in at least 13 genes on different chromosomes identified to date (177). The most commonly reported forms are GCK-MODY (MODY2), HNF1A-MODY (MODY3), and HNF4A-MODY (MODY1).

For individuals with MODY, the treatment implications are considerable and warrant genetic testing (178,179). Clinically, people with GCK-MODY exhibit mild, stable fasting hyperglycemia and do not require antihyperglycemic therapy except commonly during pregnancy.

Table 2.6—Most common causes of monogenic diabetes (171)

	Gene	Inheritance	Clinical features
MODY	*HNF1A*	AD	HNF1A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2-h PG level on OGTT (>90 mg/dL [5 mmol/L]); sensitive to sulfonylureas
	HNF4A	AD	HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight and transient neonatal hypoglycemia; sensitive to sulfonylureas
	HNF1B	AD	HNF1B-MODY: developmental renal disease (typically cystic); genitourinary abnormalities; atrophy of the pancreas; hyperuricemia; gout
	GCK	AD	GCK-MODY: higher glucose threshold (set point) for glucose-stimulated insulin secretion, causing stable, nonprogressive elevated fasting blood glucose; typically, does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (<54 mg/dL [3 mmol/L])
Neonatal diabetes	*KCNJ11*	AD	Permanent or transient: IUGR; possible developmental delay and seizures; responsive to sulfonylureas
	INS	AD	Permanent: IUGR; insulin requiring
	ABCC8	AD	Permanent or transient: IUGR; rarely developmental delay; responsive to sulfonylureas
	6q24 (*PLAGL1, HYMA1*)	AD for paternal duplications	Transient: IUGR; macroglossia; umbilical hernia; mechanisms include UPD6, paternal duplication, or maternal methylation defect; may be treatable with medications other than insulin
	GATA6	AD	Permanent: pancreatic hypoplasia; cardiac malformations; pancreatic exocrine insufficiency; insulin requiring
	EIF2AK3	AR	Permanent: Wolcott-Rallison syndrome: epiphyseal dysplasia; pancreatic exocrine insufficiency; insulin requiring
	EIF2B1	AD	Permanent diabetes: can be associated with fluctuating liver function (172)
	FOXP3	X-linked	Permanent: immunodysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome: autoimmune diabetes, autoimmune thyroid disease, exfoliative dermatitis; insulin requiring

AD, autosomal dominant; AR, autosomal recessive; IUGR, intrauterine growth restriction; OGTT, oral glucose tolerance test; UPD6, uniparental disomy of chromosome 6; 2-h PG, 2-h plasma glucose.

Individuals with HNF1A- or HNF4A-MODY usually respond well to low doses of sulfonylureas, which are considered first-line therapy; in some instances, insulin will be required over time. Mutations or deletions in *HNF1B* are associated with renal cysts and uterine malformations (renal cysts and diabetes [RCAD] syndrome). Other extremely rare forms of MODY have been reported to involve other transcription factor genes, including *PDX1* (*IPF1*) and *NEUROD1.*

Diagnosis of Monogenic Diabetes

A diagnosis of one of the three most common forms of MODY, including HFN1A-MODY, GCK-MODY, and HNF4A-MODY, allows for more cost-effective therapy (no therapy for GCK-MODY; sulfonylureas as first-line therapy for HNF1A-MODY and HNF4A-MODY). Additionally, diagnosis can lead to identification of other affected family members. Genetic screening is increasingly available and cost-effective (176,178).

A diagnosis of MODY should be considered in individuals who have atypical diabetes and multiple family members with diabetes not characteristic of type 1 or type 2 diabetes, although admittedly, "atypical diabetes" is becoming increasingly difficult to precisely define in the absence of a definitive set of tests for either type of diabetes (173–175, 178–184). In most cases, the presence of autoantibodies for type 1 diabetes precludes further testing for monogenic diabetes, but the presence of autoantibodies in people with monogenic diabetes has been reported (185). Individuals in whom monogenic diabetes is suspected should be referred to a specialist for further evaluation if available, and consultation can be obtained from several centers. Readily available commercial genetic testing following the criteria listed below now enables a cost-effective (186), often cost-saving, genetic diagnosis that is increasingly supported by health insurance. A biomarker screening pathway, such as the combination of urinary C-peptide/creatinine ratio and antibody screening, may aid in determining who should get genetic testing for MODY (187). It is critical to correctly diagnose one of the monogenic forms of diabetes because these individuals may be incorrectly diagnosed with type 1 or type 2 diabetes, leading to suboptimal, even potentially harmful, treatment plans and delays in diagnosing other family members (188). The correct diagnosis is especially critical for those with GCK-MODY mutations, where multiple studies have shown that no complications ensue in the absence of glucose-lowering therapy (189). The risks of microvascular and macrovascular complications with HNFIA- and HNF4A-MODY are similar to those observed in people with type 1 and type 2 diabetes (190,191). Genetic counseling is recommended to ensure that affected individuals understand the patterns of inheritance and the importance of a correct diagnosis and addressing comprehensive cardiovascular risk.

The diagnosis of monogenic diabetes should be considered in children and adults diagnosed with diabetes in early adulthood with the following findings:

- Diabetes diagnosed within the first 6 months of life (with occasional cases presenting later, mostly *INS* and *ABCC8* mutations) (172,192)

- Diabetes without typical features of type 1 or type 2 diabetes (negative diabetes-associated autoantibodies, no obesity, lacking other metabolic features, especially with strong family history of diabetes)
- Stable, mild fasting hyperglycemia (100–150 mg/dL [5.5–8.5 mmol/L]), stable A1C between 5.6% and 7.6% (between 38 and 60 mmol/mol), especially if no obesity

PANCREATIC DIABETES OR DIABETES IN THE CONTEXT OF DISEASE OF THE EXOCRINE PANCREAS

Pancreatic diabetes includes both structural and functional loss of glucose-normalizing insulin secretion in the context of exocrine pancreatic dysfunction and is commonly misdiagnosed as type 2 diabetes. Hyperglycemia due to general pancreatic dysfunction has been called "type 3c diabetes," and, more recently, diabetes in the context of disease of the exocrine pancreas has been termed pancreoprivic diabetes (1). The diverse set of etiologies includes pancreatitis (acute and chronic), trauma or pancreatectomy, neoplasia, cystic fibrosis (addressed elsewhere in this chapter), hemochromatosis, fibrocalculous pancreatopathy, rare genetic disorders (193), and idiopathic forms (1); as such, pancreatic diabetes is the preferred umbrella terminology.

Pancreatitis, even a single bout, can lead to postpancreatitis diabetes mellitus (PPDM). Both acute and chronic pancreatitis can lead to PPDM, and the risk is highest with recurrent bouts. A distinguishing feature is concurrent pancreatic exocrine insufficiency (according to the monoclonal fecal elastase 1 test or direct function tests), pathological pancreatic imaging (endoscopic ultrasound, MRI, computed tomography), and absence of type 1 diabetes-associated autoimmunity (194–199). There is loss of both insulin and glucagon secretion and often higher-than-expected insulin requirements. Risk for microvascular complications appears to be similar to that of other forms of diabetes. In the context of pancreatectomy, islet autotransplantation can be done to retain insulin secretion (200,201). In some cases, autotransplant can lead to insulin independence. In others, it may decrease insulin requirements (202).

GESTATIONAL DIABETES MELLITUS

Recommendations

2.26a In individuals who are planning pregnancy, screen those with risk factors **B** and consider testing all individuals of childbearing potential for undiagnosed diabetes. **E**

2.26b Before 15 weeks of gestation, test individuals with risk factors **B** and consider testing all individuals **E** for undiagnosed diabetes at the first prenatal visit using standard diagnostic criteria if not screened preconception.

2.26c Individuals of childbearing potential identified as having diabetes should be treated as such. **A**

2.26d Before 15 weeks of gestation, screen for abnormal glucose metabolism to identify individuals who are at higher risk of adverse pregnancy and neonatal outcomes, are more likely to need insulin, and are at high risk of a later gestational diabetes mellitus diagnosis. **B** Treatment may provide some benefit. **E**

2.26e Screen for early abnormal glucose metabolism using fasting glucose of 110–125 mg/dL (6.1 mmol/L) or A1C 5.9–6.4% (41–47 mmol/mol). **B**

2.27 Screen for gestational diabetes mellitus at 24–28 weeks of gestation in pregnant individuals not previously found to have diabetes or high-risk abnormal glucose metabolism detected earlier in the current pregnancy. **A**

2.28 Screen individuals with gestational diabetes mellitus for prediabetes or diabetes at 4–12 weeks postpartum, using the 75-g oral glucose tolerance test and clinically appropriate nonpregnancy diagnostic criteria. **B**

2.29 Individuals with a history of gestational diabetes mellitus should have lifelong screening for the development of diabetes or prediabetes at least every 3 years. **B**

2.30 Individuals with a history of gestational diabetes mellitus found to have prediabetes should receive intensive lifestyle interventions and/or metformin to prevent diabetes. **A**

Definition

For many years, GDM was defined as any degree of glucose intolerance that was first recognized during pregnancy (86), regardless of the degree of hyperglycemia. This definition facilitated a uniform strategy for detection and classification of GDM, but this definition has serious limitations (203). First, the best available evidence reveals that many cases of GDM represent preexisting hyperglycemia that is detected by routine screening in pregnancy, as routine screening is not widely performed in nonpregnant individuals of reproductive age. It is the severity of hyperglycemia that is clinically important with regard to both short- and long-term maternal and fetal risks.

The ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in people of reproductive age, with an increase in the number of pregnant individuals with undiagnosed type 2 diabetes in early pregnancy (204–206). Ideally, undiagnosed diabetes should be identified preconception in individuals with risk factors or in high-risk populations (207–212), as the preconception care of people with preexisting diabetes results in lower A1C and reduced risk of birth defects, preterm delivery, perinatal mortality, small-for-gestational-age birth weight, and neonatal intensive care unit admission (213). If individuals are not screened prior to pregnancy, universal early screening at $<$15 weeks of gestation for undiagnosed diabetes may be considered over selective screening (**Table 2.3**), particularly in populations with high prevalence of risk factors and undiagnosed diabetes in people of childbearing age. Strong racial and ethnic disparities exist in the prevalence of undiagnosed diabetes. Therefore, early screening provides an initial step to identify these health disparities so that they can begin to be addressed (209–212). Standard diagnostic criteria for identifying undiagnosed diabetes in early pregnancy are the same as those used in the nonpregnant population (**Table 2.2**). Individuals found to have

diabetes by the standard diagnostic criteria used outside of pregnancy should be classified as having diabetes complicating pregnancy (most often type 2 diabetes, rarely type 1 diabetes or monogenic diabetes) and managed accordingly.

Early abnormal glucose metabolism, defined as fasting glucose threshold of 110 mg/dL (6.1 mmol/L) or an A1C of 5.9% (39 mmol/mol), may identify individuals who are at higher risk of adverse pregnancy and neonatal outcomes (preeclampsia, macrosomia, shoulder dystocia, perinatal death), are more likely to need insulin treatment, and are at high risk of a later GDM diagnosis (214–220). An A1C threshold of 5.7% has not been shown to be associated with adverse perinatal outcomes (221,222).

If early screening is negative, individuals should be rescreened for GDM between 24 and 28 weeks of gestation (see Section 15, "Management of Diabetes in Pregnancy"). The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) GDM diagnostic criteria for the 75-g OGTT, as well as the GDM screening and diagnostic criteria used in the two-step approach, were not derived from data in the first half of pregnancy and should not be used for early screening (223). To date, most randomized controlled trials of treatment of early abnormal glucose metabolism have been underpowered for outcomes. Therefore, the benefits of treatment for early abnormal glucose metabolism remain uncertain. Nutrition counseling and periodic "block" testing of glucose levels weekly to identify individuals with high glucose levels are suggested. Testing frequency may proceed to daily, and treatment may be intensified, if the fasting glucose is predominantly >110 mg/dL prior to 18 weeks of gestation.

Both the fasting glucose and A1C are low-cost tests. An advantage of the A1C is its convenience, as it can be added to the prenatal laboratories and does not require an early-morning fasting appointment. Disadvantages include inaccuracies in the presence of increased red blood cell turnover and hemoglobinopathies (usually reads lower) and higher values with anemia and reduced red blood cell turnover (224). A1C is not reliable to screen for GDM or for preexisting diabetes at 15 weeks of gestation or later. See Recommendation 2.3 above.

GDM is often indicative of underlying β-cell dysfunction (225), which confers marked increased risk for later development of diabetes, generally but not always type 2 diabetes, in the mother after delivery (226,227). As effective prevention interventions are available (228,229), individuals diagnosed with GDM should receive lifelong screening for prediabetes to allow interventions to reduce diabetes risk and for type 2 diabetes to allow treatment at the earliest possible time (230).

Diagnosis

GDM carries risks for the mother, fetus, and neonate. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (231), a large-scale multinational cohort study completed by more than 23,000 pregnant individuals, demonstrated that risk of adverse maternal, fetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24–28 weeks of gestation, even within ranges previously considered normal for pregnancy. For most complications, there was no threshold for risk. These results have led to careful reconsideration of the diagnostic criteria for GDM.

GDM diagnosis (**Table 2.7**) can be accomplished with either of two strategies:

1. The "one-step" 75-g OGTT derived from the IADPSG criteria, or
2. The older "two-step" approach with a 50-g (nonfasting) screen followed by a 100-g OGTT for those who screen positive based on the work of Carpenter-Coustan's interpretation of the older O'Sullivan and Mahan (232) criteria.

Different diagnostic criteria will identify different degrees of maternal hyperglycemia and maternal/fetal risk, leading some experts to debate, and disagree on, optimal strategies for the diagnosis of GDM.

One-Step Strategy

The IADPSG defined diagnostic cut points for GDM as the average fasting, 1-h, and 2-h PG values during a 75-g OGTT in individuals at 24–28 weeks of gestation who participated in the HAPO study at which odds for adverse outcomes reached 1.75 times the estimated odds of these outcomes at the mean fasting, 1-h, and 2-h PG levels of the study population. This one-step strategy was anticipated to significantly increase the incidence of GDM (from 5–6% to 15–20%), primarily because only one abnormal value,

Table 2.7—Screening for and diagnosis of GDM

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in individuals not previously diagnosed with diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in individuals not previously diagnosed with diabetes.

If the plasma glucose level measured 1 h after the load is ≥130, 135, or 140 mg/dL (7.2, 7.5, or 7.8 mmol/L, respectively), proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made when at least two* of the following four plasma glucose levels (measured fasting and at 1, 2, and 3 h during OGTT) are met or exceeded (Carpenter-Coustan criteria [251]):

- Fasting: 95 mg/dL (5.3 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 155 mg/dL (8.6 mmol/L)
- 3 h: 140 mg/dL (7.8 mmol/L)

GDM, gestational diabetes mellitus; GLT, glucose load test; OGTT, oral glucose tolerance test. *American College of Obstetricians and Gynecologists notes that one elevated value can be used for diagnosis (247).

not two, became sufficient to make the diagnosis (233). Many regional studies have investigated the impact of adopting the IADPSG criteria on prevalence and have seen a roughly one- to threefold increase (234). The anticipated increase in the incidence of GDM could have a substantial impact on costs and medical infrastructure needs and has the potential to "medicalize" pregnancies previously categorized as normal. A recent follow-up study of individuals participating in a blinded study of pregnancy OGTTs found that 11 years after their pregnancies, individuals who would have been diagnosed with GDM by the one-step approach, as compared with those without, were at 3.4-fold higher risk of developing prediabetes and type 2 diabetes and had children with a higher risk of obesity and increased body fat, suggesting that the larger group of individuals identified by the one-step approach would benefit from the increased screening for diabetes and prediabetes that would accompany a history of GDM (235,236). The ADA recommends the IADPSG diagnostic criteria with the intent of optimizing gestational outcomes because these criteria are the only ones based on pregnancy outcomes rather than end points such as prediction of subsequent maternal diabetes.

The expected benefits of using IADPSG criteria to the offspring are inferred from intervention trials that focused on individuals with lower levels of hyperglycemia than identified using older GDM diagnostic criteria. Those trials found modest benefits including reduced rates of large-for-gestational-age births and preeclampsia (237,238). It is important to note that 80–90% of participants being treated for mild GDM in these two randomized controlled trials could be managed with lifestyle therapy alone. The OGTT glucose cutoffs in these two trials overlapped the thresholds recommended by the IADPSG, and in one trial (238), the 2-h PG threshold (140 mg/dL [7.8 mmol/L]) was lower than the cutoff recommended by the IADPSG (153 mg/dL [8.5 mmol/L]).

No randomized controlled trials of treating versus not treating GDM diagnosed by the IADPSG criteria but not the Carpenter-Coustan criteria have been published to date. However, a recent randomized trial of testing for GDM at 24–28 weeks of gestation by the one-step method using IADPSG criteria versus the two-step method using a 1-h 50-g glucose loading test (GLT) and, if positive, a 3-h OGTT by Carpenter-Coustan criteria identified twice as many individuals with GDM using the one-step method compared with the two-step method. Despite treating more individuals for GDM using the one-step method, there was no difference in pregnancy and perinatal complications (239). However, concerns have been raised about sample size estimates and unanticipated suboptimal engagement with the protocol with regard to screening and treatment. For example, in the two-step group, 165 participants who did not get counted as having GDM were treated for isolated elevated fasting glucose >95 mg/dL (240). The high prevalence of prediabetes in people of childbearing age may support the more inclusive IADPSG criteria. NHANES data demonstrate a 21.5% prevalence of prediabetes in people of reproductive age 20–44 years, which is comparable to or higher than the prevalence of GDM diagnosed by the one-step method (241).

The one-step method identifies the long-term risks of maternal prediabetes and diabetes and offspring abnormal glucose metabolism and adiposity. Post hoc GDM in individuals diagnosed by the one-step method in the HAPO cohort was associated with higher prevalence of IGT; higher 30-min, 1-h, and 2-h glucoses during the OGTT; and reduced insulin sensitivity and oral disposition index in their offspring at 10–14 years of age compared with offspring of mothers without GDM. Associations of mother's fasting, 1-h, and 2-h values on the 75-g OGTT were continuous with a comprehensive panel of offspring metabolic outcomes (236,242). In addition, HAPO Follow-up Study (HAPO FUS) data demonstrate that neonatal adiposity and fetal hyperinsulinemia (cord C-peptide), both higher across the continuum of maternal hyperglycemia, are mediators of childhood body fat (243).

Data are lacking on how the treatment of mother's hyperglycemia in pregnancy affects her offspring's risk for obesity, diabetes, and other metabolic disorders. Additional well-designed clinical studies are needed to determine the optimal intensity of monitoring and treatment of individuals with GDM diagnosed by the one-step strategy (244,245).

Two-Step Strategy

In 2013, the NIH convened a consensus development conference to consider diagnostic criteria for diagnosing GDM (246). The 15-member panel had representatives from obstetrics and gynecology, maternal-fetal medicine, pediatrics, diabetes research, biostatistics, and other related fields. The panel recommended a two-step approach to screening that used a 1-h 50-g GLT followed by a 3-h 100-g OGTT for those who screened positive. The American College of Obstetricians and Gynecologists (ACOG) recommends any of the commonly used thresholds of 130, 135, or 140 mg/dL for the 1-h 50-g GLT (247). Updated from 2014, a 2021 U.S. Preventive Services Task Force systematic review continues to conclude that one-step versus two-step screening is associated with increased likelihood of GDM (11.5% vs. 4.9%) but without improved health outcomes. It reports that the oral glucose challenge test using 140 or 135 mg/dL thresholds had sensitivities of 82% and 93% and specificities of 82% and 79%, respectively, against Carpenter-Coustan criteria. Fasting plasma glucose cutoffs of 85 mg/dL or 90 mg/dL had sensitivities of 88% and 81% and specificities of 73% and 82%, respectively, against Carpenter-Coustan criteria (248). The use of A1C at 24–28 weeks of gestation as a screening test for GDM does not function as well as the GLT (249).

Key factors cited by the NIH panel in their decision-making process were the lack of clinical trial data demonstrating the benefits of the one-step strategy and the potential negative consequences of identifying a large group of individuals with GDM, including medicalization of pregnancy with increased health care utilization and costs. Moreover, screening with a 50-g GLT does not require fasting and therefore is easier to accomplish for many individuals. Treatment of higher-threshold maternal hyperglycemia, as identified by the two-step approach, reduces rates of neonatal macrosomia, large-for-gestational-age births (250), and shoulder dystocia without increasing small-for-gestational-age births. ACOG currently supports the two-step approach but notes that one elevated value, as opposed to two, may be used for the diagnosis of GDM (247). If this approach is implemented, the incidence of GDM by the two-step strategy will likely increase markedly. ACOG recommends

either of two sets of diagnostic thresholds for the 3-h 100-g OGTT–Carpenter-Coustan or National Diabetes Data Group (251,252). Each is based on different mathematical conversions of the original recommended thresholds by O'Sullivan and Mahan (232), which used whole blood and nonenzymatic methods for glucose determination. A secondary analysis of data from a randomized clinical trial of identification and treatment of mild GDM (253) demonstrated that treatment was similarly beneficial in people meeting only the lower thresholds per Carpenter-Coustan (251) and in those meeting only the higher thresholds per National Diabetes Data Group (252). If the two-step approach is used, it would appear advantageous to use the Carpenter-Coustan lower diagnostic thresholds, as shown in step 2 in **Table 2.7**.

Future Considerations

The conflicting recommendations from expert groups underscore the fact that there are data to support each strategy. A systematic review of economic evaluations of GDM screening found that the one-step method identified more cases of GDM and was more likely to be cost-effective than the two-step method (254). The decision of which strategy to implement must therefore be made based on the relative values placed on factors that have yet to be measured (e.g., willingness to change practice based on correlation studies rather than intervention trial results, available infrastructure, and importance of cost considerations).

The IADPSG criteria ("one-step strategy") have been adopted internationally as the preferred approach. Data comparing population-wide outcomes with one-step versus two-step approaches have been inconsistent to date (239,255–257). In addition, pregnancies complicated by GDM per the IADPSG criteria, but not recognized as such, have outcomes comparable to pregnancies with diagnosed GDM by the more stringent two-step criteria (258,259). There remains strong consensus that establishing a uniform approach to diagnosing GDM will benefit patients, caregivers, and policymakers. Longer-term outcome studies are currently underway.

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3. Prevention or Delay of Type 2 Diabetes and Associated Comorbidities: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For guidelines related to screening for increased risk for type 2 diabetes (prediabetes), please refer to Section 2, "Classification and Diagnosis of Diabetes." For guidelines related to screening, diagnosis, and management of type 2 diabetes in youth, please refer to Section 14, "Children and Adolescents."

Recommendation

3.1 Monitor for the development of type 2 diabetes in those with prediabetes at least annually; modify based on individual risk/benefit assessment. **E**

Screening for prediabetes and type 2 diabetes risk through an informal assessment of risk factors (**Table 2.3**) or with an assessment tool, such as the American Diabetes Association risk test (**Fig. 2.1**), is recommended to guide health care professionals on whether performing a diagnostic test for prediabetes (**Table 2.5**) and previously undiagnosed type 2 diabetes (**Table 2.2**) is appropriate (see Section 2, "Classification and Diagnosis of Diabetes"). Testing high-risk adults for prediabetes is warranted because the laboratory assessment is safe and reasonable in cost, substantial time exists before the development of type 2 diabetes and its complications during which one can intervene, and there is an effective means of preventing or delaying type 2 diabetes in those determined to have prediabetes with an A1C 5.7–6.4% (39–47 mmol/mol), impaired glucose tolerance, or impaired fasting glucose. The utility of A1C screening for prediabetes and diabetes may be limited in the presence of hemoglobinopathies and conditions that affect red blood cell turnover. See Section 2, "Classification and Diagnosis of Diabetes," and Section 6, "Glycemic Targets," for additional details on the appropriate use and limitations of A1C testing.

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LIFESTYLE BEHAVIOR CHANGE FOR DIABETES PREVENTION

Recommendations

3.2 Refer adults with overweight/obesity at high risk of type 2 diabetes, as typified by the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and ≥150 min/week of moderate-intensity physical activity. **A**

3.3 A variety of eating patterns can be considered to prevent diabetes in individuals with prediabetes. **B**

3.4 Given the cost-effectiveness of lifestyle behavior modification programs for diabetes prevention, such diabetes prevention programs should be offered to adults at high risk of type 2 diabetes. **A** Diabetes prevention programs should be covered by third-party payers, and inconsistencies in access should be addressed.

3.5 Based on individual preference, certified technology-assisted diabetes prevention programs may be effective in preventing type 2 diabetes and should be considered. **B**

The Diabetes Prevention Program

Several major randomized controlled trials, including the Diabetes Prevention Program (DPP) trial (1), the Finnish Diabetes Prevention Study (DPS) (2), and the Da Qing Diabetes Prevention Study (Da Qing study) (3), demonstrate that lifestyle/behavioral intervention with an individualized reduced-calorie meal plan is highly effective in preventing or delaying type 2 diabetes and improving other cardiometabolic markers (such as blood pressure, lipids, and inflammation) (4). The strongest evidence for diabetes prevention in the U.S. comes from the DPP trial (1). The DPP demonstrated that intensive lifestyle intervention could reduce the risk of incident type 2 diabetes by 58% over 3 years. Follow-up of three large studies of lifestyle intervention for diabetes prevention showed sustained reduction in the risk of progression to type 2 diabetes: 39% reduction at 30 years in the Da Qing study (5), 43% reduction at 7 years in the Finnish DPS (2), and 34% reduction at 10 years (6) and 27% reduction at 15 years (7) in the U.S. Diabetes Prevention Program Outcomes Study (DPPOS).

The two major goals of the DPP intensive lifestyle intervention were to achieve and maintain a minimum of 7% weight loss and 150 min moderate-intensity physical activity per week, such as brisk walking. The DPP lifestyle intervention was a goal-based intervention. All participants were given the same weight loss and physical activity goals, but individualization was permitted in the specific methods used to achieve the goals (8). Although weight loss was the most important factor in reducing the risk of incident diabetes, it was also found that achieving the target behavioral goal of at least 150 min of physical activity per week, even without achieving the weight loss goal, reduced the incidence of type 2 diabetes by 44% (9).

The 7% weight loss goal was selected because it was feasible to achieve and maintain and likely to lessen the risk of developing diabetes. Participants were encouraged to achieve the ≥7% weight loss during the first 6 months of the intervention. Further analysis suggests maximal prevention of diabetes with at least 7–10% weight loss (9). The recommended pace of weight loss was 1–2 lb/week. Calorie goals were calculated by estimating the daily calories needed to maintain the participant's initial weight and subtracting 500–1,000 calories/day (depending on initial body weight). The initial focus of the dietary intervention was on reducing total fat rather than calories. After several weeks, the concept of calorie balance and the need to restrict calories and fat was introduced (8).

The goal for physical activity was selected to approximate at least 700 kcal/week expenditure from physical activity. For ease of translation, this goal was described as at least 150 min of moderate-intensity physical activity per week, similar in intensity to brisk walking. Participants were encouraged to distribute their activity throughout the week with a minimum frequency of three times per week and at least 10 min per session. A maximum of 75 min of strength training could be applied toward the total 150 min/week physical activity goal (8).

To implement the weight loss and physical activity goals, the DPP used an individual model of treatment rather than a group-based approach. This choice was based on a desire to intervene before participants had the possibility of developing diabetes or losing interest in the program. The individual approach also allowed for the tailoring of interventions to reflect the diversity of the population (8).

The DPP intervention was administered as a structured core curriculum followed by a flexible maintenance program of individual counseling, group sessions, motivational campaigns, and restart opportunities. The 16-session core curriculum was completed within the first 24 weeks of the program. It included sessions on lowering calories, increasing physical activity, self-monitoring, maintaining healthy lifestyle behaviors, and guidance on managing psychological, social, and motivational challenges. Further details are available regarding the core curriculum sessions (8).

Nutrition

Nutrition counseling for weight loss in the DPP lifestyle intervention arm included a reduction of total dietary fat and calories (1,8,9). However, evidence suggests that there is not an ideal percentage of calories from carbohydrate, protein, and fat for all people to prevent diabetes; therefore, macronutrient distribution should be based on an individualized assessment of current eating patterns, preferences, and metabolic goals (10). Based on other intervention trials, a variety of eating patterns characterized by the totality of food and beverages habitually consumed (10,11) may also be appropriate for individuals with prediabetes (10), including Mediterranean-style and low-carbohydrate eating plans (12–15). Observational studies have also shown that vegetarian, plant-based (may include some animal products), and Dietary Approaches to Stop Hypertension (DASH) eating patterns are associated with a lower risk of developing type 2 diabetes (16–19). Evidence suggests that the overall quality of food consumed (as measured by the Healthy Eating Index, Alternative Healthy Eating Index, and DASH score), with an emphasis on whole grains, legumes, nuts, fruits, and vegetables and minimal refined and processed foods, is also associated with a lower risk of type 2 diabetes (18,20–22). As is

the case for those with diabetes, individualized medical nutrition therapy (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for more detailed information) is effective in lowering A1C in individuals diagnosed with prediabetes (23).

Physical Activity

Just as 150 min/week of moderate-intensity physical activity, such as brisk walking, showed beneficial effects in those with prediabetes (1), moderate-intensity physical activity has been shown to improve insulin sensitivity and reduce abdominal fat in children and young adults (24,25). Based on these findings, health care professionals are encouraged to promote a DPP-style program, including a focus on physical activity, to all individuals who have been identified to be at an increased risk of type 2 diabetes. In addition to aerobic activity, a physical activity plan designed to prevent diabetes may include resistance training (8,26,27). Breaking up prolonged sedentary time may also be encouraged, as it is associated with moderately lower postprandial glucose levels (28,29). The preventive effects of physical activity appear to extend to the prevention of gestational diabetes mellitus (GDM) (30).

Delivery and Dissemination of Lifestyle Behavior Change for Diabetes Prevention

Because the intensive lifestyle intervention in the DPP was effective in preventing type 2 diabetes among those at high risk for the disease and lifestyle behavior change programs for diabetes prevention were shown to be cost-effective, broader efforts to disseminate scalable lifestyle behavior change programs for diabetes prevention with coverage by third-party payers ensued (31–35). Group delivery of DPP content in community or primary care settings has demonstrated the potential to reduce overall program costs while still producing weight loss and diabetes risk reduction (36–40).

The Centers for Disease Control and Prevention (CDC) developed the National Diabetes Prevention Program (National DPP), a resource designed to bring such evidence-based lifestyle change programs for preventing type 2 diabetes to communities (cdc.gov/diabetes/prevention/index.htm). This online resource includes locations of CDC-recognized diabetes prevention lifestyle change programs (cdc.gov/diabetes/prevention/find-a-program.html). To be eligible for this program, individuals must have a BMI in the overweight range and be at risk for diabetes based on laboratory testing, a previous diagnosis of GDM, or a positive risk test (cdc.gov/prediabetes/takethetest/). During the first 4 years of implementation of the CDC's National DPP, 35.5% achieved the 5% weight loss goal (41). The CDC has also developed the Diabetes Prevention Impact Tool Kit (nccd.cdc.gov/toolkit/diabetesimpact) to help organizations assess the economics of providing or covering the National DPP lifestyle change program (42). In an effort to expand preventive services using a cost-effective model, the Centers for Medicare & Medicaid Services expanded Medicare reimbursement coverage for the National DPP lifestyle intervention to organizations recognized by the CDC that become Medicare suppliers for this service (innovation.cms.gov/innovation-models/medicare-diabetes-prevention-program). The locations of Medicare DPPs are available online at innovation.cms.gov/innovation-models/medicare-diabetes-prevention-program/mdpp-map. To qualify for Medicare coverage, individuals must have BMI >25 kg/m^2 (or BMI >23 kg/m^2 if self-identified as Asian) and laboratory testing consistent with prediabetes in the last year. Medicaid coverage of the DPP lifestyle intervention is also expanding on a state-by-state basis.

While CDC-recognized behavioral counseling programs, including Medicare DPP services, have met minimum quality standards and are reimbursed by many payers, lower retention rates have been reported for younger adults and racial/ethnic minority populations (43). Therefore, other programs and modalities of behavioral counseling for diabetes prevention may also be appropriate and efficacious based on individual preferences and availability. The use of community health workers to support DPP efforts has been shown to be effective and cost-effective (44,45) (see Section 1, "Improving Care and Promoting Health in Populations," for more information). The use of community health workers may facilitate the adoption of behavior changes for diabetes prevention while bridging barriers related to social determinants of health. However, coverage by third-party payers remains problematic. Counseling by a registered dietitian nutritionist (RDN) has been shown to help individuals with prediabetes improve eating habits, increase physical activity, and achieve 7–10% weight loss (10,46–48). Individualized medical nutrition therapy (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for more detailed information) is also effective in improving glycemia in individuals diagnosed with prediabetes (23,46). Furthermore, trials involving medical nutrition therapy for adults with prediabetes found significant reductions in weight, waist circumference, and glycemia. Individuals with prediabetes can benefit from referral to an RDN for individualized medical nutrition therapy upon diagnosis and at regular intervals throughout their treatment plan (47,49). Other health care professionals, such as pharmacists and diabetes care and education specialists, may be considered for diabetes prevention efforts (50,51).

Technology-assisted programs may effectively deliver the DPP program (52–57). Such technology-assisted programs may deliver content through smartphones, web-based applications, and telehealth and may be an acceptable and efficacious option to bridge barriers, particularly for low-income individuals and people residing in rural locations; however, not all programs are effective in helping people reach targets for diabetes prevention (52,58–60). The CDC Diabetes Prevention Recognition Program (DPRP) (cdc.gov/diabetes/prevention/requirements-recognition.htm) certifies technology-assisted modalities as effective vehicles for DPP-based programs; such programs must use an approved curriculum, include interaction with a coach, and attain the DPP outcomes of participation, physical activity reporting, and weight loss. Therefore, health care professionals should consider referring adults with prediabetes to certified technology-assisted DPP programs based on their preferences.

PHARMACOLOGIC INTERVENTIONS

Recommendations

3.6 Metformin therapy for the prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes, as typified by the Diabetes Prevention

Program, especially those aged 25–59 years with BMI ≥35 kg/m^2, higher fasting plasma glucose (e.g., ≥110 mg/dL), and higher A1C (e.g., ≥6.0%), and in individuals with prior gestational diabetes mellitus. **A**

3.7 Long-term use of metformin may be associated with biochemical vitamin B12 deficiency; consider periodic measurement of vitamin B12 levels in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. **B**

Because weight loss through behavior changes in diet and physical activity alone can be difficult to maintain long term (6), people at high risk of diabetes may benefit from support and additional pharmacotherapeutic options, if needed. Various pharmacologic agents used to treat diabetes have been evaluated for diabetes prevention. Metformin, α-glucosidase inhibitors, glucagon-like peptide 1 receptor agonists (liraglutide, semaglutide), thiazolidinediones, testosterone (61), and insulin have been shown to lower the incidence of diabetes in specific populations (62–67), whereas diabetes prevention was not seen with nateglinide (68).

In the DPP, weight loss was an important factor in reducing the risk of progression, with every kilogram of weight loss conferring a 16% reduction in risk of progression over 3.2 years (9). In postpartum individuals with GDM, the risk of type 2 diabetes increased by 18% for every 1 unit BMI above the preconception baseline (69). Several medications evaluated for weight loss (e.g., orlistat, phentermine topiramate, liraglutide, semaglutide, and tirzepatide) have been shown to decrease the incidence of diabetes to various degrees in those with prediabetes (67, 70–72).

Studies of other pharmacologic agents have shown some efficacy in diabetes prevention with valsartan but no efficacy in preventing diabetes with ramipril or anti-inflammatory drugs (73–76). Although the Vitamin D and Type 2 Diabetes (D2d) prospective randomized controlled trial showed no significant benefit of vitamin D versus placebo on the progression to type 2 diabetes in individuals at high risk (77), post hoc analyses and meta-analyses suggest a potential benefit in specific populations (77–80). Further research is needed to define characteristics and clinical indicators where vitamin D supplementation may be of benefit (61).

No pharmacologic agent has been approved by the U.S. Food and Drug Administration for a specific indication of type 2 diabetes prevention. The risk versus benefit of each medication in support of person-centered goals must be weighed in addition to cost, side effects, and efficacy considerations. Metformin has the longest history of safety data as a pharmacologic therapy for diabetes prevention (81).

Metformin was overall less effective than lifestyle modification in the DPP, though group differences declined over time in the DPPOS (7), and metformin may be cost-saving over a 10-year period (33). In the DPP, metformin was as effective as lifestyle modification in participants with BMI ≥35 kg/m^2 and in younger participants aged 25–44 years (1). In individuals with a history of GDM in the DPP, metformin and intensive lifestyle modification led to an equivalent 50% reduction in diabetes risk (82). Both interventions remained highly effective during a 10-year follow-up period (83). By the time of the 15-year follow-up (DPPOS), exploratory analyses demonstrated that participants with a higher baseline fasting glucose (≥110 mg/dL vs. 95–109 mg/dL), those with a higher A1C (6.0–6.4% vs. <6.0%), and individuals with a history of GDM (vs. individuals without a history of GDM) experienced higher risk reductions with metformin, identifying subgroups of participants that benefitted the most from metformin (84). In the Indian Diabetes Prevention Program (IDPP-1), metformin and lifestyle intervention reduced diabetes risk similarly at 30 months; of note, the lifestyle intervention in IDPP-1 was less intensive than that in the DPP (85). Based on findings from the DPP, metformin should be recommended as an option for high-risk individuals (e.g., those with a history of GDM or those with BMI ≥35 kg/m^2). Consider periodic monitoring of vitamin B12 levels in those taking metformin chronically to check for possible deficiency (86,87) (see Section 9, "Pharmacologic Approaches to Glycemic Treatment," for more details). While there is not a universally accepted recommended periodicity of monitoring, it is notable that the lowering effect of metformin on vitamin B12 increases with time (88), with a significantly higher risk for vitamin B12 deficiency (<150 pmol/L) noted at 4.3 years in the HOME (Hyperinsulinaemia: the Outcome of its Metabolic Effects) study (88) and significantly greater risk of low B12 levels (≤203 pg/mL) at 5 years in the DPP (87). It has been suggested that a person who has been on metformin for more than 4 years or is at risk for vitamin B12 deficiency should be monitored for vitamin B12 deficiency annually (89).

PREVENTION OF VASCULAR DISEASE AND MORTALITY

Recommendations

3.8 Prediabetes is associated with heightened cardiovascular risk; therefore, screening for and treatment of modifiable risk factors for cardiovascular disease are suggested. **B**

3.9 Statin therapy may increase the risk of type 2 diabetes in people at high risk of developing type 2 diabetes. In such individuals, glucose status should be monitored regularly and diabetes prevention approaches reinforced. It is not recommended that statins be discontinued. **B**

3.10 In people with a history of stroke and evidence of insulin resistance and prediabetes, pioglitazone may be considered to lower the risk of stroke or myocardial infarction. However, this benefit needs to be balanced with the increased risk of weight gain, edema, and fracture. **A** Lower doses may mitigate the risk of adverse effects. **C**

People with prediabetes often have other cardiovascular risk factors, including hypertension and dyslipidemia (90), and are at increased risk for cardiovascular disease (91,92). If indicated, evaluation for tobacco use and referral for tobacco cessation should be part of routine care for those at risk for diabetes. Of note, the years immediately following smoking cessation may represent a time of increased risk for diabetes (93–95), a time when individuals should

be monitored for diabetes development and receive concurrent evidence-based lifestyle behavior change for diabetes prevention described in this section. See Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for more detailed information. The lifestyle interventions for weight loss in study populations at risk for type 2 diabetes have shown a reduction in cardiovascular risk factors and the need for medications used to treat these cardiovascular risk factors (96,97). In longer-term follow-up, lifestyle interventions for diabetes prevention also prevented the development of microvascular complications among women enrolled in the DPPOS and in the study population enrolled in the China Da Qing Diabetes Prevention Outcome Study (7,98). The lifestyle intervention in the latter study was also efficacious in preventing cardiovascular disease and mortality at 23 and 30 years of follow-up (3,5). Treatment goals and therapies for hypertension and dyslipidemia in the primary prevention of cardiovascular disease for people with prediabetes should be based on their level of cardiovascular risk. Increased vigilance is warranted to identify and treat these and other cardiovascular diseases risk factors (99). Statins have been associated with a modestly increased risk of diabetes (100–104). In the DPP, statin use was associated with greater diabetes risk irrespective of the treatment group (pooled hazard ratio [95% CI] for incident diabetes 1.36 [1.17–1.58]) (102). In studies of primary prevention of cardiovascular disease, cardiovascular and mortality benefits of statin therapy exceed the risk of diabetes (105,106), suggesting a favorable benefit-to-harm balance with statin therapy. Hence, discontinuation of statins is not recommended in this population due to concerns of diabetes risk.

Cardiovascular outcome trials in people without diabetes also inform risk reduction potential in people without diabetes at increased cardiometabolic risk (see Section 10, "Cardiovascular Disease and Risk Management," for more details). The IRIS (Insulin Resistance Intervention after Stroke) trial was a dedicated study of people with a recent (<6 months) stroke or transient ischemic attack, without diabetes but with insulin resistance, as defined by a HOMA of insulin resistance index of ≥3.0, evaluating pioglitazone (target dose of 45 mg daily) compared with placebo. At 4.8 years, the risk of stroke or myocardial infarction, as well as the risk of diabetes, was lower within the pioglitazone group than with placebo, though risks of weight gain, edema, and fracture were higher in the pioglitazone treatment group (107–109). Lower doses may mitigate the adverse effects, though further study is needed to confirm the benefit at lower doses (110).

PERSON-CENTERED CARE GOALS

Recommendations

3.11 In adults with overweight/obesity at high risk of type 2 diabetes, care goals should include weight loss or prevention of weight gain, minimizing the progression of hyperglycemia, and attention to cardiovascular risk and associated comorbidities. **B**

3.12 Pharmacotherapy (e.g., for weight management, minimizing the progression of hyperglycemia, cardiovascular risk reduction) may be considered to support person-centered care goals. **B**

3.13 More intensive preventive approaches should be considered in individuals who are at particularly high risk of progression to diabetes, including individuals with BMI ≥35 kg/m^2, those at higher glucose levels (e.g., fasting plasma glucose 110–125 mg/dL, 2-h postchallenge glucose 173–199 mg/dL, A1C ≥6.0%), and individuals with a history of gestational diabetes mellitus. **A**

Individualized risk/benefit should be considered in screening, intervention, and monitoring to prevent or delay type 2 diabetes and associated comorbidities. Multiple factors, including age, BMI, and other comorbidities, may influence the risk of progression to diabetes and lifetime risk of complications (111,112). In the DPP, which enrolled high-risk individuals with impaired glucose tolerance, elevated fasting glucose, and elevated BMI, the crude incidence of diabetes within the placebo arm was 11.0 cases per 100 person-years, with a cumulative 3-year incidence of diabetes of 28.9% (1). Characteristics of individuals in the DPP/DPPOS who were at particularly high risk of progression to diabetes (crude incidence of diabetes 14–22 cases/100 person-years) included BMI ≥35 kg/m^2, those at higher glucose levels (e.g., fasting plasma glucose 110–125 mg/dL, 2-h postchallenge glucose 173–199 mg/dL, and A1C ≥6.0%), and individuals with a history of gestational diabetes (1,82,83). In contrast, in the community-based Atherosclerosis Risk in Communities (ARIC) study, observational follow-up of older adults (mean age 75 years) with laboratory evidence of prediabetes (based on A1C 5.7–6.4% and/or fasting glucose 100–125 mg/dL), but not meeting specific BMI criteria, found much lower progression to diabetes over 6 years: 9% of those with A1C-defined prediabetes, 8% with impaired fasting glucose (112).

Thus, it is important to individualize the risk/benefit of intervention and consider person-centered goals. Risk models have explored risk-based benefit, generally finding higher benefit of the intervention in those at highest risk (9). Diabetes prevention and observational studies highlight key principles that may guide person-centered goals. In the DPP, which enrolled a high-risk population meeting criteria for overweight/obesity, weight loss was an important mediator of diabetes prevention or delay, with greater metabolic benefit generally seen with greater weight loss (9,113). In the DPP/DPPOS, progression to diabetes, duration of diabetes, and mean level of glycemia were important determinants of the development of microvascular complications (7). Furthermore, the ability to achieve normal glucose regulation, even once, during the DPP was associated with a lower risk of diabetes and lower risk of microvascular complications (114). Observational follow-up of the Da Qing study also showed that regression from impaired glucose tolerance to normal glucose tolerance or remaining with impaired glucose tolerance rather than progressing to type 2 diabetes at the end of the 6-year intervention trial resulted in significantly lower risk of cardiovascular disease and microvascular disease over 30 years (115). Prediabetes is associated with increased cardiovascular disease and mortality (92), emphasizing the importance of attending to cardiovascular risk in this population.

Pharmacotherapy for weight management (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes," for more details), minimizing the progression of hyperglycemia (see Section 9, "Pharmacologic Approaches to Glycemic Treatment," for more details), and cardiovascular risk reduction (see Section 10, "Cardiovascular Disease and Risk Management," for more details) are important tools that can be considered to support individualized person-centered goals, with more intensive preventive approaches considered in individuals at high risk of progression.

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4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

PERSON-CENTERED COLLABORATIVE CARE

Recommendations

4.1 A person-centered communication style that uses person-centered, culturally sensitive, and strength-based language and active listening; elicits individual preferences and beliefs; and assesses literacy, numeracy, and potential barriers to care should be used to optimize health outcomes and health-related quality of life. **B**

4.2 People with diabetes can benefit from a coordinated multidisciplinary team that may include and is not limited to diabetes care and education specialists, primary care and subspecialty clinicians, nurses, registered dietitian nutritionists, exercise specialists, pharmacists, dentists, podiatrists, and mental health professionals. **E**

A successful medical evaluation depends on beneficial interactions between the person with diabetes and the care team. The Chronic Care Model (1–3) (see Section 1, "Improving Care and Promoting Health in Populations") is a person-centered approach to care that requires a close working relationship between the person with diabetes and clinicians involved in treatment planning. People with diabetes should receive health care from a coordinated interdisciplinary team that may include but is not limited to diabetes care and education specialists, primary care and subspecialty clinicians, nurses, registered dietitian nutritionists, exercise specialists, pharmacists, dentists, podiatrists, and mental health professionals. Individuals with diabetes must assume an active role in their care. Based on the preferences of the

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person with diabetes, the family or support group and health care team together formulate the management plan, which includes lifestyle management (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes").

The goals of treatment for diabetes are to prevent or delay complications and optimize quality of life (**Fig. 4.1**). Treatment goals and plans should be created with people with diabetes based on their individual preferences, values, and goals. This individualized management plan should take into account the person's age, cognitive abilities, school/work schedule and conditions, health beliefs, support systems, eating patterns, physical activity, social situation, financial concerns, cultural factors, literacy and numeracy (mathematical literacy), diabetes history (duration, complications, current use of medications), comorbidities, disabilities, health priorities, other medical conditions, preferences for care, and life expectancy. Various strategies and techniques should be used to support the person's self-management efforts, including providing education on problem-solving skills for all aspects of diabetes management.

Health care professional communication with people with diabetes and families should acknowledge that multiple factors impact glycemic management but also emphasize that collaboratively developed treatment plans and a healthy lifestyle can significantly improve disease outcomes and well-being (4–8). Thus, the goal of communication between health care professionals and people with diabetes is to establish a collaborative relationship and to assess and address self-management barriers without blaming people with diabetes for "noncompliance" or "nonadherence" when the outcomes of self-management are not optimal (9). The familiar terms "noncompliance" and "nonadherence" denote a passive, obedient role for a person with diabetes in "following doctor's orders" that is at odds with the active role people with diabetes take in directing the day-to-day decision-making, planning, monitoring, evaluation, and problem-solving involved in diabetes self-management. Using a nonjudgmental approach that normalizes periodic lapses in management may help minimize the person's resistance to reporting problems with self-management. Empathizing and using active listening techniques, such as open-ended questions, reflective statements, and summarizing what the person said, can help facilitate communication. Perceptions of people with diabetes about their own ability, or self-efficacy, to self-manage diabetes constitute one important psychosocial factor related to improved diabetes self-management and treatment outcomes in diabetes (10–12) and should be a target of ongoing assessment, education, and treatment planning.

Language has a strong impact on perceptions and behavior. The use of empowering language in diabetes care and education can help to inform and motivate people, yet language that shames

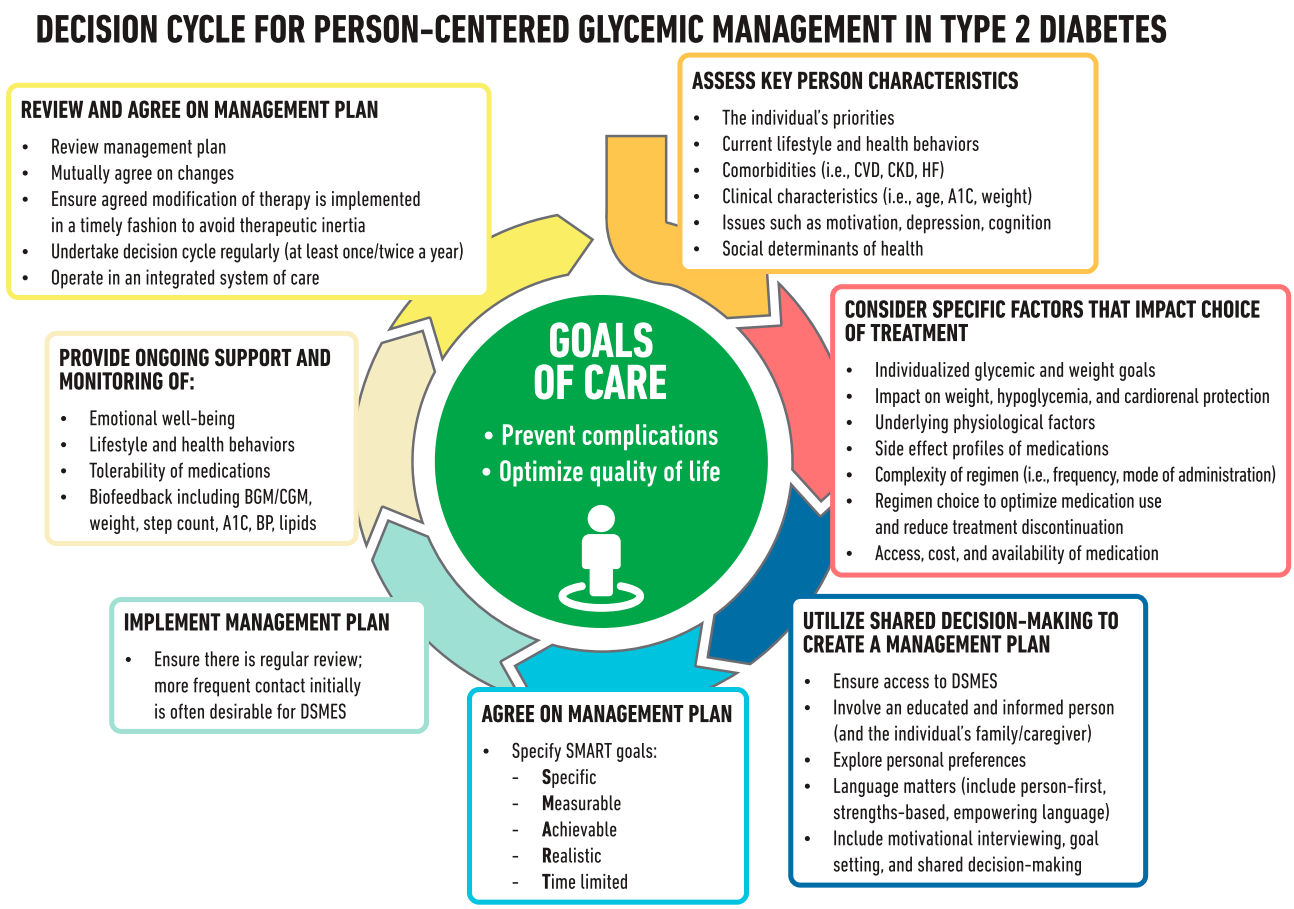

Figure 4.1—Decision cycle for person-centered glycemic management in type 2 diabetes. Adapted from Davies et al. (211). BGM, blood glucose monitoring; BP, blood pressure; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CVD, atherosclerotic cardiovascular disease; DSMES, diabetes self-management education and support; HF, heart failure.

and judges may undermine this effort. The American Diabetes Association (ADA) and the Association of Diabetes Care & Education Specialists (formerly called the American Association of Diabetes Educators) joint consensus report, "The Use of Language in Diabetes Care and Education," provides the authors' expert opinion regarding the use of language by health care professionals when speaking or writing about diabetes for people with diabetes or for professional audiences (13). Although further research is needed to address the impact of language on diabetes outcomes, the report includes five key consensus recommendations for language use:

- Use language that is neutral, nonjudgmental, and based on facts, actions, or physiology/biology.
- Use language free from stigma.
- Use language that is strength based, respectful, and inclusive and that imparts hope.
- Use language that fosters collaboration between people with diabetes and health care professionals.
- Use language that is person centered (e.g., "person with diabetes" is preferred over "diabetic").

COMPREHENSIVE MEDICAL EVALUATION

Recommendations

4.3 A complete medical evaluation should be performed at the initial visit to:
- Confirm the diagnosis and classify diabetes. **A**
- Evaluate for diabetes complications, potential comorbid conditions, and overall health status. **A**
- Review previous treatment and risk factor management in people with established diabetes. **A**
- Begin engagement with the person with diabetes in the formulation of a care management plan including initial goals of care. **A**
- Develop a plan for continuing care. **A**

4.4 A follow-up visit should include most components of the initial comprehensive medical evaluation (**Table 4.1**). **A**

4.5 Ongoing management should be guided by the assessment of overall health status, diabetes complications, cardiovascular risk, hypoglycemia risk, and shared decision-making to set therapeutic goals. **B**

The comprehensive medical evaluation includes the initial and follow-up evaluations, assessment of complications, psychosocial assessment, management of comorbid conditions, overall health status, and engagement of the person with diabetes throughout the process. While a comprehensive list is provided in **Table 4.1**, in clinical practice the health care professional may need to prioritize the components of the medical evaluation given the available resources and time. The goal is to provide the health care team information so it can optimally support people with diabetes. In addition to the medical history, physical examination, and laboratory tests, health care professionals should assess diabetes self-management behaviors, nutrition, social determinants of health, and psychosocial health (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes") and give guidance on routine immunizations. The assessment of sleep pattern and duration should be considered; a meta-analysis found that poor sleep quality, short sleep, and long sleep were associated with higher A1C in people with type 2 diabetes (14). Interval follow-up visits should occur at least every 3–6 months individualized to the person and then at least annually.

Lifestyle management and psychosocial care are the cornerstones of diabetes management. People with diabetes should be referred for diabetes self-management education and support, medical nutrition therapy, and assessment of psychosocial/emotional health concerns if indicated. People with diabetes should receive recommended preventive care services (e.g., immunizations, cancer screening); smoking cessation counseling; and ophthalmological, dental, and podiatric referrals, as needed.

The assessment of risk of acute and chronic diabetes complications and treatment planning are key components of initial and follow-up visits (**Table 4.2**). The risk of atherosclerotic cardiovascular disease and heart failure (see Section 10, "Cardiovascular Disease and Risk Management"), chronic kidney disease staging (see Section 11, "Chronic Kidney Disease and Risk Management"), presence of retinopathy (see Section 12, "Retinopathy, Neuropathy, and Foot Care"), and risk of treatment-associated hypoglycemia (**Table 4.3**) should be used to individualize targets for glycemia (see Section 6, "Glycemic Targets"), blood pressure, and lipids and to select specific glucose-lowering medication (see Section 9, "Pharmacologic Approaches to Glycemic Treatment"), antihypertension medication, and statin treatment intensity.

Additional referrals should be arranged as necessary (**Table 4.4**). Clinicians should ensure that people with diabetes are appropriately screened for complications and comorbidities. Discussing and implementing an approach to glycemic management with the person is a part, not the sole goal, of the clinical encounter.

IMMUNIZATIONS

Recommendation

4.6 Provide routinely recommended vaccinations for children and adults with diabetes as indicated by age (see **Table 4.5** for highly recommended vaccinations for adults with diabetes). **A**

The importance of routine vaccinations for people living with diabetes has been elevated by the coronavirus disease 2019 (COVID-19) pandemic. Preventing avoidable infections not only directly prevents morbidity but also reduces hospitalizations, which may additionally reduce risk of acquiring infections such as COVID-19. Children and adults with diabetes should receive vaccinations according to age-appropriate recommendations (15,16). The Centers for Disease Control and Prevention (CDC) provides vaccination schedules specifically for children, adolescents, and adults with diabetes (cdc.gov/vaccines/). The CDC Advisory Committee on Immunization Practices (ACIP) makes recommendations based on its own review and rating of the evidence, provided in **Table 4.5** for selected vaccinations. The ACIP evidence

Table 4.1 - Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PAST MEDICAL AND FAMILY HISTORY	**Diabetes history**			
	▪ Characteristics at onset (e.g., age, symptoms)	✓		
	▪ Review of previous treatment plans and response	✓		
	▪ Assess frequency/cause/severity of past hospitalizations	✓		
	Family history			
	▪ Family history of diabetes in a first-degree relative	✓		
	▪ Family history of autoimmune disorder	✓		
	Personal history of complications and common comorbidities			
	▪ Common comorbidities (e.g., obesity, OSA, NAFLD)	✓		
	▪ High blood pressure or abnormal lipids	✓		✓
	▪ Macrovascular and microvascular complications	✓		✓
	▪ Hypoglycemia: awareness/frequency/causes/timing of episodes	✓	✓	✓
	▪ Presence of hemoglobinopathies or anemias	✓		✓
	▪ Last dental visit	✓		✓
	▪ Last dilated eye exam			✓
	▪ Visits to specialists			✓
	Interval history			
	▪ Changes in medical/family history since last visit		✓	✓
BEHAVIORAL FACTORS	▪ Eating patterns and weight history	✓	✓	✓
	▪ Assess familiarity with carbohydrate counting (e.g., type 1 diabetes, type 2 diabetes treated with MDI)	✓		✓
	▪ Physical activity and sleep behaviors	✓	✓	✓
	▪ Tobacco, alcohol, and substance use	✓		✓
MEDICATIONS AND VACCINATIONS	▪ Current medication plan	✓	✓	✓
	▪ Medication-taking behavior	✓	✓	✓
	▪ Medication intolerance or side effects	✓	✓	✓
	▪ Complementary and alternative medicine use	✓	✓	✓
	▪ Vaccination history and needs	✓		✓
TECHNOLOGY USE	▪ Assess use of health apps, online education, patient portals, etc.	✓		✓
	▪ Glucose monitoring (meter/CGM): results and data use	✓	✓	✓
	▪ Review insulin pump settings and use, connected pen and glucose data	✓	✓	✓
SOCIAL LIFE ASSESSMENT	**Social network**			
	▪ Identify existing social supports	✓		✓
	▪ Identify surrogate decision maker, advanced care plan	✓		✓
	▪ Identify social determinants of health (e.g., food security, housing stability & homelessness, transportation access, financial security, community safety)	✓		✓

Continued on p. S53

Table 4.1 (cont.) - Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PHYSICAL EXAMINATION	▪ Height, weight, and BMI; growth/pubertal development in children and adolescents	✓	✓	✓
	▪ Blood pressure determination	✓	✓	✓
	▪ Orthostatic blood pressure measures (when indicated)	✓		
	▪ Fundoscopic examination (refer to eye specialist)	✓		✓
	▪ Thyroid palpation	✓		✓
	▪ Skin examination (e.g., acanthosis nigricans, insulin injection or insertion sites, lipodystrophy)	✓	✓	✓
	▪ Comprehensive foot examination			
	• Visual inspection (e.g., skin integrity, callous formation, foot deformity or ulcer, toenails)**	✓		✓
	• Screen for PAD (pedal pulses—refer for ABI if diminished)	✓		✓
	• Determination of temperature, vibration or pinprick sensation, and 10-g monofilament exam	✓		✓
	▪ Screen for depression, anxiety, and disordered eating	✓		✓
	▪ Consider assessment for cognitive performance*	✓		✓
	▪ Consider assessment for functional performance*	✓		✓
LABORATORY EVALUATION	▪ A1C, if the results are not available within the past 3 months	✓	✓	✓
	▪ If not performed/available within the past year	✓		✓
	• Lipid profile, including total, LDL, and HDL cholesterol and triglycerides#	✓		✓^
	• Liver function tests#	✓		✓
	• Spot urinary albumin-to-creatinine ratio	✓		✓
	• Serum creatinine and estimated glomerular filtration rate+	✓		✓
	• Thyroid-stimulating hormone in people with type 1 diabetes#	✓		✓
	• Vitamin B12 if on metformin	✓		✓
	• Serum potassium levels in people with diabetes on ACE inhibitors, ARBs, or diuretics+	✓		✓

ABI, ankle-brachial pressure index; ARBs, angiotensin receptor blockers; CGM, continuous glucose monitors; MDI, multiple daily injections; NAFLD, nonalcoholic fatty liver disease; OSA, obstructive sleep apnea; PAD, peripheral arterial disease.

*At 65 years of age or older.

+May be needed more frequently in people with diabetes with known chronic kidney disease or with changes in medications that affect kidney function and serum potassium (see **Table 11.1**).

#May also need to be checked after initiation or dose changes of medications that affect these laboratory values (i.e., diabetes medications, blood pressure medications, cholesterol medications, or thyroid medications).

^In people without dyslipidemia and not on cholesterol-lowering therapy, testing may be less frequent.

**Should be performed at every visit in people with diabetes with sensory loss, previous foot ulcers, or amputations.

review has evolved over time with the adoption of Grading of Recommendations Assessment, Development and Evaluation (GRADE) in 2010 and then the Evidence to Decision or Evidence to Recommendation frameworks in 2018 (17). Here we discuss the particular importance of specific vaccines.

Influenza

Influenza is a common, preventable infectious disease associated with high mortality and morbidity in vulnerable populations, including youth, older adults, and people with chronic diseases. Influenza vaccination in people with diabetes has been found to significantly reduce influenza and diabetes-related hospital admissions (18). In people with diabetes and cardiovascular disease, influenza vaccine has been associated with lower risk of all-cause mortality, cardiovascular mortality, and cardiovascular events (19). Given the benefits of the annual influenza vaccination, it is recommended for all individuals ≥6 months of age who do not have a contraindication. Influenza vaccination is critically important as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza viruses will both be active in the U.S. during the 2022–2023 season (20). The live attenuated influenza vaccine, which is delivered by nasal spray, is an option for people who are age 2 years through age 49 years and who are

Table 4.2—Assessment and treatment plan*

Assessing risk of diabetes complications
• ASCVD and heart failure history
• ASCVD risk factors and 10-year ASCVD risk assessment
• Staging of chronic kidney disease (see **Table 11.1**)
• Hypoglycemia risk (see **Table 4.3**)
• Assessment for retinopathy
• Assessment for neuropathy
Goal setting
• Set A1C/blood glucose/time-in-range target
• If hypertension is present, establish blood pressure target
• Diabetes self-management goals
Therapeutic treatment plans
• Lifestyle management
• Pharmacologic therapy: glucose lowering
• Pharmacologic therapy: cardiovascular and renal disease risk factors
• Use of glucose monitoring and insulin delivery devices
• Referral to diabetes education and medical specialists (as needed)

ASCVD, atherosclerotic cardiovascular disease. *Assessment and treatment planning are essential components of initial and all follow-up visits.

not pregnant, but people with chronic conditions such as diabetes are cautioned against taking the live attenuated influenza vaccine and are instead recommended to receive the inactive or recombinant influenza vaccination. For individuals ≥65 years of age, there may be additional benefit from the high-dose quadrivalent inactivated influenza vaccine (20).

Pneumococcal Pneumonia

Like influenza, pneumococcal pneumonia is a common, preventable disease. People with diabetes are at increased risk for the bacteremic form of pneumococcal infection and have been reported to have a high risk of nosocomial bacteremia, with a mortality rate as high as 50% (21). There are two types of vaccines available in the U.S., pneumococcal conjugate vaccines (PCV13, PCV15, and PCV20) and pneumococcal polysaccharide vaccine (PPSV23), with distinct schedules for children and adults.

It is recommended that all children receive a four-dose series of PCV13 or PCV15 by 15 months of age. For children with diabetes who have incomplete series by ages 2–5 years, the CDC recommends a catch-up schedule to ensure that these children have four doses. Children with diabetes between 6 and 18 years of age are also advised to receive one dose of PPSV23, preferably after receipt of PCV13.

Adults aged ≥65 years whose vaccine status is unknown or who have not received pneumococcal vaccine should receive one dose of PCV15 or PCV20. If PCV15 is used, it should be followed by PPSV23.

Adults aged 19–64 years with certain underlying risk factors or other medical conditions whose vaccine status is unknown or who have not received pneumococcal vaccine should receive one dose of PCV15 or PCV20. As for adults aged ≥65 years, if PCV15 is used, it should be followed by PPSV23.

The recommended interval between PCV15 and PPSV23 is ≥1 year. If PPSV23 is the only dose received, PCV15 or PCV20 may be given ≥1 year later.

For adults with immunocompromising conditions, cochlear implant, or cerebrospinal fluid leak, a minimum interval of 8 weeks can be considered for dosing of PCV15 and PPSV23 when PCV15 has been used.

Adults who received PCV13 should follow the previously recommended PPSV23 series. Adults who received only PPSV23 may receive a PCV15 or PCV20 ≥1 year after their last dose.

Table 4.3—Assessment of hypoglycemia risk

Factors that increase risk of treatment-associated hypoglycemia
• Use of insulin or insulin secretagogues (i.e., sulfonylureas, meglitinides)
• Impaired kidney or hepatic function
• Longer duration of diabetes
• Frailty and older age
• Cognitive impairment
• Impaired counterregulatory response, hypoglycemia unawareness
• Physical or intellectual disability that may impair behavioral response to hypoglycemia
• Alcohol use
• Polypharmacy (especially ACE inhibitors, angiotensin receptor blockers, nonselective β-blockers)
• History of severe hypoglycemic event
In addition to individual risk factors, consider use of comprehensive risk prediction models (198).
See references 199–203.

Table 4.4—Referrals for initial care management

• Eye care professional for annual dilated eye exam
• Family planning for individuals of childbearing potential
• Registered dietitian nutritionist for medical nutrition therapy
• Diabetes self-management education and support
• Dentist for comprehensive dental and periodontal examination
• Mental health professional, if indicated
• Audiology, if indicated
• Social worker/community resources, if indicated

Hepatitis B

Compared with the general population, people with type 1 or type 2 diabetes have higher rates of hepatitis B. This may be due to contact with infected blood or through improper equipment use (glucose monitoring devices or infected needles). Because of the higher likelihood of transmission, hepatitis B vaccine is recommended for adults with diabetes aged <60 years. For adults aged ≥60 years, hepatitis B vaccine may be administered at the discretion of the treating clinician

Table 4.5—Highly recommended immunizations for adults with diabetes (Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention)

Vaccination	Age-group recommendations	Frequency	GRADE evidence type*	Reference
Hepatitis B	<60 years of age; ≥60 years of age discuss with health care professionals	Two- or three-dose series	2	Centers for Disease Control and Prevention, Use of Hepatitis B Vaccination for Adults With Diabetes Mellitus: Recommendations of the Advisory Committee on Immunization Practices (ACIP) (204)
Human papilloma virus (HPV)	≤26 years of age; 27–45 years of age may also be vaccinated against HPV after a discussion with health care professionals	Three doses over 6 months	2 for female individuals, 3 for male individuals	Meites et al., Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices (205)
Influenza	All people with diabetes advised not to receive live attenuated influenza vaccine	Annual	—	Demicheli et al., Vaccines for Preventing Influenza in the Elderly (206)
Pneumonia (PPSV23 [Pneumovax])	19–64 years of age, vaccinate with Pneumovax	One dose is recommended for those that previously received PCV13. If PCV15 used, follow with PPSV23 ≥1 year later. PPSV23 is not indicated after PCV20. Adults who received only PPSV23 may receive PCV15 or PCV20 ≥1 year after their last dose.	2	Centers for Disease Control and Prevention, Updated Recommendations for Prevention of Invasive Pneumococcal Disease Among Adults Using the 23-Valent Pneumococcal Polysaccaride Vaccine (PPSV23) (207)
	≥65 years of age	One dose is recommended for those that previously received PCV13. If PCV15 was used, follow with PPSV23 ≥1 year later. PPSV23 is not indicated after PCV20. Adults who received only PPSV23 may receive PCV15 or PCV20 ≥1 year after their last dose.	2	Falkenhorst et al., Effectiveness of the 23-Valent Pneumococcal Polysaccharide Vaccine (PPV23) Against Pneumococcal Disease in the Elderly: Systematic Review and Meta-analysis (208)
PCV20 or PCV15	Adults 19–64 years of age, with an immunocompromising condition (e.g., chronic renal failure), cochlear implant, or cerebrospinal fluid leak	One dose of PCV15 or PCV20 is recommended by the CDC.	3	Kobayashi et al., Use of 15-Valent Pneumococcal Conjugate Vaccine and 20-Valent Pneumococcal Conjugate Vaccine Among U.S. Adults: Updated Recommendations of the Advisory Committee on Immunization Practices—United States, 2022 (22)
	19–64 years of age, immunocompetent	For those who have never received any pneumococcal vaccine, the CDC recommends one dose of PCV15 or PCV20.		
	≥65 years of age, immunocompetent, have shared decision-making discussion with health care professionals	One dose of PCV15 or PCV20. PCSV23 may be given ≥8 weeks after PCV15. PPSV23 is not indicated after PCV20.		
Tetanus, diphtheria, pertussis (TDAP)	All adults; pregnant individuals should have an extra dose	Booster every 10 years	2 for effectiveness, 3 for safety	Havers et al., Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccines: Updated Recommendations of the Advisory Committee on Immunization Practices—United States, 2019 (209)
Zoster	≥50 years of age	Two-dose Shingrix, even if previously vaccinated	1	Dooling et al., Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines (210)

GRADE, Grading of Recommendations Assessment, Development, and Evaluation; PCV13, 13-valent pneumococcal conjugate vaccine; PCV15, 15-valent pneumococcal conjugate vaccine; PCV 20, 20-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine. *Evidence type: 1, randomized controlled trials (RCTs) or overwhelming evidence from observational studies; 2, RCTs with important limitations or exceptionally strong evidence from observational studies; 3, observational studies or RCTs with notable limitations; 4, clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations. For a comprehensive list, refer to the Centers for Disease Control and Prevention (CDC) at cdc.gov/vaccines/.

based on the person's likelihood of acquiring hepatitis B infection.

COVID-19

As of September 2022, the COVID-19 vaccines are recommended for all adults and some children, including people with diabetes, under approval from the U.S. Food and Drug Administration (FDA) (24). The bivalent booster protecting against the omicron variant and original strain has now replaced the monovalent booster for many.

For people 6 months to 17 years of age, most can receive the monovalent Moderna vaccine doses 1 and 2 at least 4–8 weeks apart. For those who are moderately or severely immunocompromised, doses 1 and 2 and doses 2 and 3 should be at least 4 weeks apart.

For the Pfizer-BioNTech monovalent vaccine for most people aged 6 months to 4 years, doses 1 and 2 should be at least 3–8 weeks apart and doses 2 and 3 at least 8 weeks apart. For those aged 6 months to 4 years who are moderately or severely compromised, doses 1 and 2 should be at least 4 weeks apart and doses 2 and 3 at least 4 weeks apart. For most people aged 5–11 years, doses 1 and 2 should be at least 3–8 weeks apart and doses 2 and 3 at least 5 months apart. For those who are moderately or severely immunocompromised, doses 1 and 2 should be at least 3 weeks apart and doses 2 and 3 should be at least 8 weeks apart. For most people aged 12–17 years, doses 1 and 2 should be at least 3–8 weeks apart. For those who are moderately to severely immunocompromised, doses 1 and 2 should be at least 3 weeks apart and doses 2 and 3 should be at least 4 weeks apart.

For the Novavax vaccine, for most people over 12 years of age, doses 1 and 2 should be at least 3–8 weeks apart. For those who are moderately to severely immunocompromised, doses 1 and 2 should be at least 3 weeks apart. For most people aged ≥18 years receiving the Moderna vaccine, doses 1 and 2 should be at least 4–8 weeks apart. For those who are moderately or severely compromised, doses 1 and 2 should be at least 4 weeks apart and doses 2 and 3 at least 4 weeks apart. For most people receiving the Pfizer-BioNTech vaccine, doses 1 and 2 should be at least 3–8 weeks apart. For those who are moderately or severely compromised, doses 1 and 2 should be at least 3 weeks apart and doses 2 and 3 at least 4 weeks apart.

For most people aged ≥18 years receiving Novavax vaccine, doses 1 and 2 should be at least 3–8 weeks apart. For those who are moderately to severely compromised, doses 1 and 2 should be at least 3 weeks apart. The Janssen monovalent vaccine is currently authorized for use in certain limited situations due to safety considerations.

For most people 12–17 years of age who received the Moderna vaccine, the Pfizer-BioNTech bivalent booster may be given at least 8 weeks from doses 2 and 3. For those moderately or severely compromised, doses 3 and 4 should be at least 8 weeks apart.

For most people aged 12–17 years who received the Pfizer-BioNTech vaccine, the Pifzer-BioNTech bivalent booster may be given at least 8 weeks from doses 2 and 3. For those moderately or severely compromised, doses 3 and 4 should be at least 8 weeks apart.

For most people aged ≥12 years receiving the Novavax vaccine, the Pfizer-BioNTech bivalent booster may be given as doses 2 and 3 at least 8 weeks apart. For those moderately to severely immunocompromised, doses 2 and 3 should be given at least 8 weeks apart.

Those ≥18 years of age receiving the Moderna vaccine may be given the Moderna bivalent booster 8 weeks after their last dose. Those ≥18 years of age receiving the Pfizer-BioNTech vaccine may receive the Pfizer-BioNTech bivalent booster 8 weeks after their last dose. Those receiving the Janssen vaccine may receive the Moderna or Pfizer-BioNTech bivalent booster 8 weeks after their last dose. Those receiving the Novavax vaccine aged ≥12 years may receive either the Moderna or Pfizer-BioNTech bivalent booster 8 weeks after their last dose.

ASSESSMENT OF COMORBIDITIES

Besides assessing diabetes-related complications, clinicians and people with diabetes need to be aware of common comorbidities that affect people with diabetes and that may complicate management (25–29). Diabetes comorbidities are conditions that affect people with diabetes more often than age-matched people without diabetes. This section discusses many of the common comorbidities observed in people with diabetes but is not necessarily inclusive of all the conditions that have been reported.

Autoimmune Diseases

Recommendations

4.7 People with type 1 diabetes should be screened for autoimmune thyroid disease soon after diagnosis and periodically thereafter. **B**

4.8 Adults with type 1 diabetes should be screened for celiac disease in the presence of gastrointestinal symptoms, signs, laboratory manifestations, or clinical suspicion suggestive of celiac disease. **B**

People with type 1 diabetes are at increased risk for other autoimmune diseases, with thyroid disease, celiac disease, and pernicious anemia (vitamin B12 deficiency) being among the most common (30). Other associated conditions include autoimmune hepatitis, primary adrenal insufficiency (Addison disease), collagen vascular diseases, and myasthenia gravis (31–34). Type 1 diabetes may also occur with other autoimmune diseases in the context of specific genetic disorders or polyglandular autoimmune syndromes (35). Given the high prevalence, nonspecific symptoms, and insidious onset of primary hypothyroidism, routine screening for thyroid dysfunction is recommended for all people with type 1 diabetes. Screening for celiac disease should be considered in adults with diabetes with suggestive symptoms (e.g., diarrhea, malabsorption, abdominal pain) or signs (e.g., osteoporosis, vitamin deficiencies, iron deficiency anemia) (36,37). Measurement of vitamin B12 levels should be considered for people with type 1 diabetes and peripheral neuropathy or unexplained anemia.

Cancer

Diabetes is associated with increased risk of cancers of the liver, pancreas, endometrium, colon/rectum, breast, and bladder (38). The association may result from shared risk factors between type 2 diabetes and cancer (older age, obesity, and physical inactivity) but may also be due to diabetes-related factors (39), such as underlying disease physiology

or diabetes treatments, although evidence for these links is scarce. People with diabetes should be encouraged to undergo recommended age- and sex-appropriate cancer screenings and to reduce their modifiable cancer risk factors (obesity, physical inactivity, and smoking). New onset of atypical diabetes (lean body habitus, negative family history) in a middle-aged or older person may precede the diagnosis of pancreatic adenocarcinoma (40). However, in the absence of other symptoms (e.g., weight loss, abdominal pain), routine screening of all such individuals is not currently recommended.

Cognitive Impairment/Dementia

Recommendation

4.9 In the presence of cognitive impairment, diabetes treatment plans should be simplified as much as possible and tailored to minimize the risk of hypoglycemia. **B**

Diabetes is associated with a significantly increased risk and rate of cognitive decline and an increased risk of dementia (41,42). A recent meta-analysis of prospective observational studies in people with diabetes showed 73% increased risk of all types of dementia, 56% increased risk of Alzheimer dementia, and 127% increased risk of vascular dementia compared with individuals without diabetes (43). The reverse is also true: people with Alzheimer dementia are more likely to develop diabetes than people without Alzheimer dementia. In a 15-year prospective study of community-dwelling people >60 years of age, the presence of diabetes at baseline significantly increased the age- and sex-adjusted incidence of all-cause dementia, Alzheimer dementia, and vascular dementia compared with rates in those with normal glucose tolerance (44). See Section 13, "Older Adults," for a more detailed discussion regarding screening for cognitive impairment.

Hyperglycemia

In those with type 2 diabetes, the degree and duration of hyperglycemia are related to dementia. More rapid cognitive decline is associated with both increased A1C and longer duration of diabetes (43). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study found that each 1% higher A1C level was associated with lower cognitive function in individuals with type 2 diabetes (45). However, the ACCORD study found no difference in cognitive outcomes in participants randomly assigned to intensive and standard glycemic management, supporting the recommendation that intensive glucose management should not be advised for the improvement of cognitive function in individuals with type 2 diabetes (46).

Hypoglycemia

In type 2 diabetes, severe hypoglycemia is associated with reduced cognitive function, and those with poor cognitive function have more severe hypoglycemia. In a long-term study of older people with type 2 diabetes, individuals with one or more recorded episodes of severe hypoglycemia had a stepwise increase in risk of dementia (47). Likewise, the ACCORD trial found that as cognitive function decreased, the risk of severe hypoglycemia increased (48). This has also been demonstrated in people with type 1 diabetes. Tailoring glycemic therapy may help to prevent hypoglycemia in individuals with cognitive dysfunction (49). See Section 13, "Older Adults," for more detailed discussion of hypoglycemia in older people with type 1 and type 2 diabetes.

Nutrition

In one study, following the Mediterranean diet correlated with improved cognitive function (50). However, a Cochrane review found insufficient evidence to recommend any specific dietary change for the prevention or treatment of cognitive dysfunction (51).

Statins

A systematic review has reported that data do not support an adverse effect of statins on cognition (52). The FDA postmarketing surveillance databases have also revealed a low reporting rate for cognitive function–related adverse events, including cognitive dysfunction or dementia, with statin therapy, similar to rates seen with other commonly prescribed cardiovascular medications (52). Therefore, fear of cognitive decline should not be a barrier to statin use in people with diabetes and a high risk for cardiovascular disease.

Nonalcoholic Fatty Liver Disease

Recommendation

4.10 People with type 2 diabetes or prediabetes with cardiometabolic risk factors, who have either elevated liver enzymes (ALT) or fatty liver on imaging or ultrasound, should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis. **C**

Screening

Nonalcoholic fatty liver disease (NAFLD) is the term used to identify the broad spectrum of the disease ranging from nonalcoholic fatty liver with macrovesicular hepatic steatosis only (or with mild inflammation) to steatohepatitis (nonalcoholic steatohepatitis [NASH]) to cirrhosis. This is in the absence of ongoing or recent consumption of significant amounts of alcohol (defined as ingestion of >21 standard drinks per week in men and >14 standard drinks per week in women over a 2-year period preceding evaluation) or the presence of other secondary causes of fatty liver disease. Diabetes is a major risk factor for developing NASH and for disease progression and worse liver outcomes (53). Recent studies in adults in the U.S. estimate that NAFLD is prevalent in >70% of people with type 2 diabetes (54–56). This is consistent with studies from many other countries (57). NASH is defined histologically as having ≥5% hepatic steatosis and associated with inflammation and hepatocyte injury (hepatocyte ballooning), with or without evidence of liver fibrosis (58). Steatohepatitis is estimated to affect more than half of people with type 2 diabetes with NAFLD (59), and it appears to be a driver for the development of fibrosis. Fibrosis stages are classified histologically as the following: F0, no fibrosis; F1, mild; F2, moderate (significant); F3, severe (advanced); and F4, cirrhosis. In the U.S., between 12% and 20% of people with type 2 diabetes have clinically significant fibrosis (≥F2) (54,55,59), similar to that observed worldwide (53,57). NASH is a leading cause of hepatocellular carcinoma (HCC) (60,61) and of liver transplantation in the U.S.,

with transplant waiting lists being overrepresented by people with type 2 diabetes (62). Still, clinicians underestimate its prevalence and do not consistently implement appropriate screening strategies, thus missing the diagnosis of NAFLD in high-risk groups, such as those having obesity or type 2 diabetes. This pattern of underdiagnosis is compounded by sparse referral to specialists and inadequate prescription of medications with proven efficacy in NASH (63,64).

The goal of screening is not to identify steatosis per se (being already highly prevalent in this population) but rather to use it to identify those on a disease path of future cirrhosis. This risk is higher in people who have obesity and cardiometabolic risk factors or insulin resistance, are >50 years of age, and/or have persistently elevated plasma aminotransferases (AST and/or ALT >30 units/L for more >6 months) (65,66). Some genetic variants that alter hepatocyte triglyceride metabolism may also increase the risk of NASH progression and cirrhosis (67,68), amplifying the impact of obesity, but the role of genetic testing in clinical practice remains to be established.

Individuals with clinically significant fibrosis (≥F2), especially those with type 2 diabetes, have a greater risk of cirrhosis with liver decompensation, HCC, liver transplantation, and all-cause mortality (69–72). Excess mortality associated with NAFLD is attributable not only to cirrhosis and HCC but also to extrahepatic cancer (61), type 2 diabetes (73), and cardiovascular disease (74,75). Their estimated relative impact depends on length of follow-up and population studied, among other factors. Emerging evidence suggests that NAFLD increases the risk of chronic kidney disease, particularly when liver fibrosis is present (76,77), although the association of NAFLD with diabetic retinopathy is less clear (78). Therefore, early diagnosis is essential to prevent future cirrhosis.

A recent meta-analysis reported a prevalence of NAFLD of 22% in people with type 1 diabetes (79). This risk may be linked to the fact that about one-third in the U.S. have obesity (80). However, there was a large variability across studies, and most measured liver fat by ultrasound. In one of the few studies using the gold-standard MRI technique to quantitate liver fat, the prevalence of steatosis in a population with type 1 diabetes with low prevalence of obesity was only 8.8% compared with 68% in people with type 2 diabetes (81). The prevalence of fibrosis was not established. Therefore, screening for fibrosis in people with type 1 diabetes should only be considered in the presence of additional risk factors for NAFLD, such as obesity, incidental hepatic steatosis on imaging, or elevated plasma aminotransferases.

There is consensus that the fibrosis-4 index (FIB-4) is the most cost-effective strategy for the initial screening of people with prediabetes and cardiometabolic risk factors or type 2 diabetes in the primary care and diabetes clinical setting (58,64–66,82–84). See the proposed diagnostic algorithm by an expert group that included ADA representatives in **Fig. 4.2** (64). A screening strategy based on elevated plasma aminotransferases >40 units/L would miss most individuals with NASH in these settings, as clinically significant fibrosis (≥F2) is frequently observed with plasma aminotransferases below the commonly used cutoff of 40 units/L (54–56,59, 85,86). The American College of Gastroenterology considers the upper limit of normal ALT levels to be 29–33 units/L for male individuals and 19–25 units/L for female individuals (87), as higher levels are associated with increased liver-related mortality, even in the absence of identifiable risk factors. The FIB-4 estimates the risk of hepatic cirrhosis and is calculated from the computation of age, plasma aminotransferases (AST and ALT), and platelet count (mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis). A value of <1.3 is considered lower risk, while >2.67 is considered as having a high probability of advanced fibrosis (F3–F4). It also predicts changes over time in hepatic fibrosis (88,89) and allows risk stratification of individuals in terms of future liver-related morbidity and mortality (90,91). FIB-4 has an area under the receiver–operating characteristic curve of only 0.78–0.80 (89,92–95); thus, a confirmatory test is often needed. It has a reasonable specificity and negative predictive value to rule out advanced fibrosis but lacks adequate sensitivity and positive predictive value to establish presence of advanced fibrosis in many cases, which is the reason why people with diabetes often fall in the "indeterminate risk" group for establishing the advanced fibrosis (or intermediate) group (between 1.3 and 2.67). However, its low cost, simplicity, and good specificity make it the initial test of choice (**Fig. 4.2**). Performance is better in a population with higher prevalence of significant fibrosis (i.e., hepatology clinics) compared with primary care settings. FIB-4 has not been

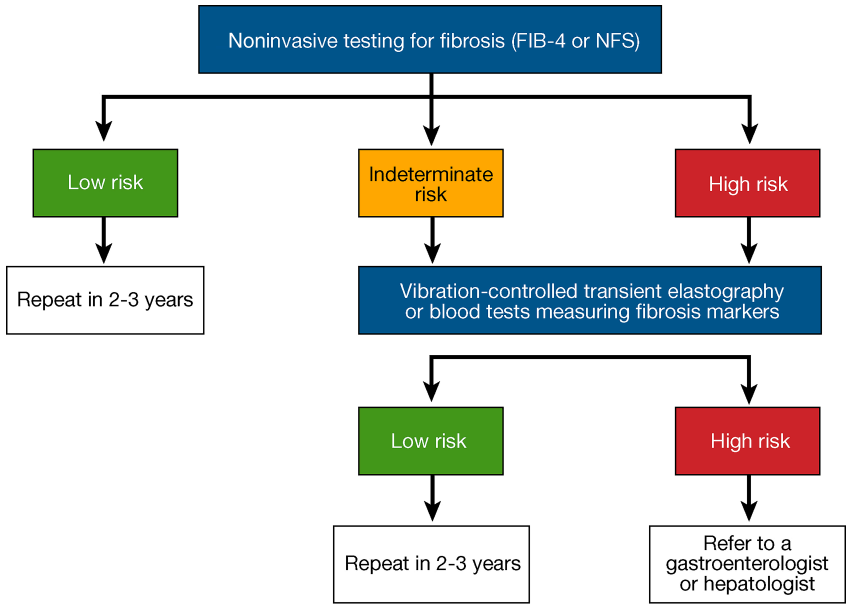

Figure 4.2—A proposed algorithm for risk stratification in individuals with nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH). NFS, NAFLD fibrosis score created by a group of experts that included American Diabetes Association representatives. Reprinted from Kanwal et al. (64).

well validated in pediatric populations and does not perform as well in those aged <35 years. In people with diabetes ≥65 years of age, higher cutoffs for FIB-4 have been recommended (1.9–2.0 rather than >1.3) (96,97).

In people with an indeterminate or high FIB-4, additional risk stratification is required with a liver stiffness measurement (LSM) by transient elastography (**Fig. 4.2**) or, if unavailable, by commercial blood fibrosis biomarkers such as the Enhanced Liver Fibrosis (ELF) test (98) or others. Use of a second nonproprietary diagnostic panel is not recommended (i.e., NAFLD fibrosis score, others), as they generally do not perform better than FIB-4 (56,92). Transient elastography (LSM) is the best-validated imaging technique for fibrosis risk stratification, and it predicts future cirrhosis and all-cause mortality in NAFLD (58,65,99). An LSM value of <8.0 kPa has a good negative predictive value to exclude advanced fibrosis (≥F3–F4) (100–102) and indicates low risk for clinically significant fibrosis. Such individuals with diabetes can be followed in nonspecialty clinics with repeat surveillance testing every ≥2 years. If the LSM is >12 kPa, the risk for advanced fibrosis is high and people with diabetes should be referred to the hepatologist (100). FIB-4 followed by LSM helps stratify people with diabetes by risk level and minimize referrals to the specialist (91,94,99,103,104) (**Fig. 4.2**).

Specialists may order additional tests for fibrosis risk stratification (64–66,84, 99), with magnetic resonance elastography having the best overall performance (particularly for early fibrosis stages). Finally, liver biopsy remains the gold standard for the diagnosis of NASH, and its indication is reserved to the discretion of the specialist within a multidisciplinary team approach.

The American Gastroenterological Association convened an international conference, including representatives of the ADA, to review and discuss published literature on the burden, screening, risk stratification, diagnosis, and management of individuals with NAFLD (64). See **Fig. 4.2**, which is reproduced from this special report (64). A Clinical Care Pathway summarized the diagnosis and management of NAFLD in a subsequent publication (66). Consensus is emerging to start screening with FIB-4 followed by LSM and/or patented biomarkers for the noninvasive fibrosis risk stratification of individuals with NAFLD in primary care and diabetes clinics (58,64–66,82–84).

After initial risk stratification (i.e., FIB-4, LSM, and/or patented biomarkers), people with diabetes at indeterminate or high risk of fibrosis should be referred, based on practice setting, to a gastroenterologist or hepatologist for further workup within the framework of a multidisciplinary team (64,105,106).

Management

While steatohepatitis and cirrhosis occur in lean people with diabetes and are believed to be linked to genetic predisposition, insulin resistance, and environmental factors (107–109), there is ample evidence to implicate excess adiposity in people with overweight and obesity in the pathogenesis of the disease (110,111). Obesity in the setting of type 2 diabetes worsens insulin resistance and steatohepatitis, promoting the development of cirrhosis (112). Therefore, clinicians should recommend lifestyle changes in people with overweight or obesity and NAFLD. A minimum weight loss goal of 5%, preferably ≥10% (113,114), is needed to improve liver histology, with fibrosis requiring the larger weight reduction to change (114–116). Individualized, structured weight loss and exercise programs offer greater benefit than standard counseling in people with NAFLD (107,117).

Dietary recommendations to induce an energy deficit are not different than those for people with diabetes with obesity without NAFLD and should include a reduction of macronutrient content, limiting saturated fat, starch, and added sugar, with adoption of healthier eating patterns. The Mediterranean diet has the best evidence for improving liver and cardiometabolic health (58,65,82,83,117–121). Both aerobic and resistance training improve NAFLD in proportion to treatment engagement and intensity of the program (122–124).

Obesity pharmacotherapy may assist with weight loss in the context of lifestyle modification if not achieved by lifestyle modification alone.

Bariatric surgery improves NASH and cardiometabolic health, altering the natural history of the disease (125). Meta-analyses report that 70–80% of people have improvement in hepatic steatosis, 50–75% in inflammation and hepatocyte ballooning (necrosis), and 30–40% in fibrosis (126,127). It may also reduce the risk of HCC (127). Bariatric surgery should be used with caution in individuals with compensated cirrhosis, but in experienced hands the risk of hepatic decompensation is similar to that for those with less advanced liver disease. Because of the paucity of safety and outcome data, bariatric surgery is not recommended in individuals with decompensated cirrhosis who also have a much higher risk of postoperative liver-related complications (encephalopathy, variceal bleeding, or ascites) (58,65,66).

At present, there are no FDA-approved drugs for the treatment of NASH. Therefore, treatment for people with type 2 diabetes and NASH is centered on the dual purpose of treating hyperglycemia and obesity, especially if clinically significant fibrosis (≥F2) is present. The rationale for the treatment of people with type 2 diabetes is based on their high prevalence of NASH with significant fibrosis (10–15% of people with type 2 diabetes) (54,55,57), their higher risk of disease progression and liver-related mortality (53,72,128), and the lack of pharmacological treatments once cirrhosis is established (129). Therefore, early diagnosis and treatment of NAFLD offers the best opportunity for cirrhosis prevention. Pioglitazone and some glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have been shown to be effective to treat steatohepatitis (64,65,130–132) and may slow fibrosis progression (133–135) and decrease cardiovascular disease (65,131), which is the number one cause of death in people with type 2 diabetes and NAFLD (74).

Pioglitazone improves glucose and lipid metabolism and reverses steatohepatitis in people with prediabetes, type 2 diabetes (136,137), or even without diabetes (138–140). Fibrosis also improved in some trials (137,139). A meta-analysis (133) concluded that pioglitazone treatment results in resolution of NASH and may improve fibrosis. Pioglitazone may halt the accelerated pace of fibrosis progression observed in people with type 2 diabetes (134) and is overall cost-effective for the treatment of NASH (141,142). Vitamin E may be beneficial for the treatment of NASH in people without diabetes (138). However, in people with type 2 diabetes,

treatment in a small randomized controlled trial (RCT) was largely negative as monotherapy (134), and when added to pioglitazone, it did not seem to enhance pioglitazone's efficacy, as reported in an earlier trial in this population (137). Pioglitazone causes dose-dependent weight gain (15 mg/day, mean of 1–2%; 45 mg/day, 3–5%), increases fracture risk, may promote heart failure if used in individuals with preexisting congestive heart failure, and may increase the risk of bladder cancer, although this remains controversial (64,65,131, 132).

GLP-1 RAs are effective in inducing weight loss and ameliorating elevated plasma aminotransferases and steatosis (130). However, there are only two RCTs in biopsy-proven individuals with NASH. A small RCT reported that liraglutide improved some features of NASH and, of particular relevance, delayed the progression of fibrosis (143). More recently, once-daily subcutaneous semaglutide in 320 people with biopsy-proven NASH (62% having type 2 diabetes) reported resolution of steatohepatitis in 59% at the higher dose (equivalent to 2.4 mg/week semaglutide) compared with 17% in the placebo group ($P < 0.001$) (135). Cumulatively, semaglutide did not significantly affect the stage of liver fibrosis in this group of people (70% of whom had F2 or F3 at baseline), but it significantly slowed over 72 weeks the progression of liver fibrosis (4.9% with the GLP-1 RA at the highest dose compared with 18.8% on placebo). Tirzepatide (144), sodium–glucose cotransporter inhibitors (145–147), and insulin (132) reduce hepatic steatosis, but their effects on steatohepatitis remain unknown.

Obstructive Sleep Apnea

Age-adjusted rates of obstructive sleep apnea, a risk factor for cardiovascular disease, are significantly higher (4- to 10-fold) with obesity, especially with central obesity (148). The prevalence of obstructive sleep apnea in the population with type 2 diabetes may be as high as 23%, and the prevalence of any sleep-disordered breathing may be as high as 58% (149,150). In participants with obesity enrolled in the Action for Health in Diabetes (Look AHEAD) trial, it exceeded 80% (151). Individuals with symptoms suggestive of obstructive sleep apnea (e.g., excessive daytime sleepiness, snoring, witnessed apnea) should be considered for screening (152). Sleep apnea treatment (lifestyle modification, continuous positive airway pressure, oral appliances, and surgery) significantly improves quality of life and blood pressure management. The evidence for a treatment effect on glycemic control is mixed (153).

Periodontal Disease

Periodontal disease is more severe, and may be more prevalent, in people with diabetes than in those without and has been associated with higher A1C levels (154–156). Longitudinal studies suggest that people with periodontal disease have higher rates of incident diabetes. Current evidence suggests that periodontal disease adversely affects diabetes outcomes, although evidence for treatment benefits remains controversial (29,157). In an RCT, intensive periodontal treatment was associated with better glycemic outcomes (A1C 8.3% vs. 7.8% in control subjects and the intensive-treatment group, respectively) and reduction in inflammatory markers after 12 months of follow-up (158).

DIABETES AND COVID-19

Recommendations

4.11 Health care professionals should help people with diabetes aim to achieve individualized targeted glycemic control to reduce the risk of macrovascular and microvascular risk as well as reduce the risk of COVID-19 and its complications. **B**

4.12 As we move into the recovery phase, diabetes health care services and practitioners should address the impact of the pandemic in higher-risk groups, including ethnic minority, deprived, and older populations. **B**

4.13 People who have been infected with SARS-CoV-2 should be followed up in the longer term to assess for complications and symptoms of long COVID. **E**

4.14 People with new-onset diabetes need to be followed up regularly in routine clinical practice to determine if diabetes is transient. **B**

4.15 Health care professionals need to carefully monitor people with diabetes for diabetic ketoacidosis during the COVID-19 pandemic. **C**

4.16 People with diabetes and their families/caregivers should be monitored for psychological well-being and offered support or referrals as needed, including mental/behavioral health care, self-management education and support, and resources to address related risk factors. **E**

4.17 Health care systems need to ensure that the vulnerable populations are not disproportionately disadvantaged by use of technological methods of consultations. **E**

4.18 There is no clear indication to change prescribing of glucose-lowering therapies in people with diabetes infected by the SARS-CoV-2 virus. **B**

4.19 People with diabetes should be prioritized and offered SARS-CoV-2 vaccines. **B**

SARS-CoV-2, the virus that causes the clinical disease COVID-19, was first reported in December 2019 in China and has disproportionately impacted certain groups, including men, older people, ethnic minority populations, and people with certain chronic conditions, including diabetes, cardiovascular disease, kidney disease, and certain respiratory diseases. COVID-19 has now been recognized as a complex multisystem disease including widespread insulin resistance, endothelial dysfunction, hematological disorders, and hyperimmune responses (159). There is now evidence of not only direct but also indirect adverse effects of COVID-19 in people with diabetes. Many people with multiple long-term conditions have diabetes, which has also been associated with worse outcomes in people with COVID-19 (160). The association with BMI and COVID-19 mortality is U-shaped in both type 1 and type 2 diabetes (161).

COVID-19 has disproportionately affected certain groups, such as older people and those from some ethnic populations who are known to have high prevalence of chronic conditions such as diabetes, cardiovascular disease, kidney disease, and certain respiratory diseases (162). People with chronic

conditions have experienced some of the worst COVID-19 outcomes, including hospital admission and mortality (163). In people with diabetes, higher blood glucose levels both prior to and during COVID-19 admission have been associated with poor outcomes, including mortality (164). Type 1 diabetes has been associated with higher risk of COVID-19 mortality than type 2 diabetes (165). One whole-population-level study of over 61 million people in England in the first wave of the pandemic reported that after adjustment for age, sex, ethnicity, deprivation, and geographical region, the odds ratios for in-hospital COVID-19–related deaths were 3.51 (95% CI 3.16–3.90) in people with type 1 diabetes and 2.03 (1.97–2.09) in people with type 2 diabetes compared with the general population (166). There were also excess deaths in the first wave by 59.1% in people with type 1 diabetes and 64.3% in people with type 2 diabetes compared with death rates in the same time period for the previous 3 years (161). The largest study of people with diabetes to date, using whole-population data from England with over 3 million people, reported a higher association for mortality in people with type 1 diabetes than type 2 diabetes (161). Male sex, older age, renal impairment, non-White ethnicity, socioeconomic deprivation, and previous stroke and heart failure were associated with increased COVID-19–related mortality in both type 1 and type 2 diabetes (161).

Much of the evidence for recommendations is from a recent systematic review that was commissioned by the World Health Organization on the latest research evidence on the impact of COVID-19 on people with diabetes (165). Data were summarized from 112 systematic reviews that were narratively synthesized. The review reported that there are no appropriate data to determine whether diabetes is a risk factor for acquiring SARS-CoV-2 infection. Diabetes is a risk factor for severe disease and death from COVID-19.

Reasons for the higher rates of COVID-19 and severity in minority ethnic groups are complex and could be due to higher prevalence of comorbid conditions (e.g., diabetes), differences in exposure risk (e.g., overcrowded living conditions, essential worker jobs), and access to treatment (e.g., health insurance status, specialist services, and medications), which all relate to long-standing structural inequities that vary by ethnicity (167).

There is now overwhelming evidence that approximately 30–40% of people who are infected with COVID-19 get persistent and sometimes relapsing and remitting symptoms 4 weeks after infection, which has been termed post-acute sequelae of COVID-19, post-COVID-19 condition, post-acute COVID-19 syndrome, or long COVID (168,169). Currently, data on long COVID specifically in people with diabetes are lacking, and people who have been infected with SARS-CoV-2 should be followed up in the longer term.

There have also been recent reports of development of new-onset diabetes in people who have had COVID-19. There are conflicting reports of new-onset diabetes, with publications from a number of countries. The precise mechanisms for new-onset diabetes in people with COVID-19 are not known but may include previously undiagnosed diabetes presenting early or later in the disease trajectory, stress hyperglycemia, steroid-induced hyperglycemia, and possibly direct or indirect effects of SARS-CoV-2 on the β-cell (170). Whether new-onset diabetes is likely to remain permanent or is more aggressive is not known, and it will be important for health care professionals to monitor these people in the longer term. One large U.S. retrospective study of over 27 million people reported that COVID-19 was associated with significantly increased risk of new-onset type 1 diabetes and a disproportionately higher risk in ethnic minority people (171). Another recent cross-sectional population–based Canadian study observed a slightly higher but nonsignificant increase in diabetes incidence in children during the pandemic, suggesting this resulted from delays in diagnosis early during the pandemic with a catch-up effect (172). Whether COVID-19 leads to new-onset diabetes is not known.

There have been several publications on the risk of diabetic ketoacidosis (DKA) during the pandemic. A German diabetes prospective study using registry data of children and adolescents found an increase in type 1 diabetes in the first 3 months of the first wave, and the frequency of DKA at presentation was significantly higher than those for 2019 (44.7% vs. 24.5%, adjusted risk ratio 1.84) and 2018 (vs. 24.1%, adjusted risk ratio 1.85) as well as the proportion with severe DKA (173). A larger study using national data in England during the first two waves found that rates of DKA were higher than those for preceding years across all pandemic periods studied (174). The study reported lower DKA hospital admissions in people with type 1 diabetes but higher rates of DKA in people with type 1 diabetes and those newly diagnosed with diabetes.

There is also evidence of adverse effects of COVID-19 on mental health (175) and health-promoting lifestyles during the pandemic. Some small studies in people with diabetes have reported longer-term psychological impact of SARS-CoV-2 infection in people with diabetes, including fatigue and risk of suicide (176). Longitudinal follow-up of the Look AHEAD study of older adults with type 2 diabetes reported a 1.6-fold higher prevalence for depressive symptoms and 1.8-fold higher prevalence for loneliness during the pandemic compared with prepandemic levels (177). Furthermore, people with diabetes remain fearful of attending face-to-face contact due to the possible threat from mutant strains of coronavirus (178). Negative emotions due to the pandemic, including lockdowns, have been associated with reduced motivation, physical inactivity, and sedentary behavior (179). Higher levels of pandemic-related distress have been linked to higher A1C (180). Greater pandemic-related life disruptions have been related to higher distress in parents of youth with diabetes, which may have impacted families from racial and ethnic minority groups to a greater degree than non-Hispanic White families (181). On the other hand, for some youth with type 1 diabetes, increased time at home during the early phases of the COVID-19 pandemic provided opportunities for enhanced family support for diabetes self-management and reduced diabetes-related distress (182).

Recurrent lockdowns and other public health measures due to the pandemic have restricted access to routine diabetes care and have affected self-management, care-seeking behavior, and access to medications (183). This has resulted in compromised routine care and management of risk factors (184,185). There have been reductions in diagnosis of

type 2 diabetes and reductions in new prescriptions of metformin during the pandemic (186). Due to unemployment or lost income during the pandemic, people living with diabetes have experienced financial hardships that may have reduced their affordability for medications in countries where costs for medications are out of pocket (184). Many individuals with diabetes have avoided or delayed seeking medical attention for routine non-COVID-19–related problems due to fear of infection and/or to reduce strain on health care services (187). Disruptions in care delivery and completion of care processes have been associated with an increased risk of non-COVID-19–related deaths in people with diabetes (188).

Direct contact will still be necessary if blood tests or physical examinations are required. However, it will be important to ensure that disparities are not widened for vulnerable groups such as the elderly and socieconomically challenged and ethnic minority groups due to access to literacy.

As we recover from the pandemic, it is essential that we prioritize the highest-risk groups for their routine review and assessment as well as management of their mental/behavioral health and risk factors. Diabetes professional bodies in some countries have published guidance on risk stratification and who to prioritize for diabetes review (189,190). Factors to consider for prioritization should include demographics, socioeconomical status, education levels, established complications, comorbidities, and modifiable risk factors, which are associated with high risk of progression of diabetes-related complications.

In many countries, health care professionals have reduced face-to-face contact and adapted technological methods of delivering routine diabetes care. One small RCT in adults with type 2 diabetes with follow-up to 16 weeks showed that remote consultations during the pandemic reduced the prevalence of mental health- and diabetes-related emotional distress (191). The number of face-to-face appointments is now increasing, and hybrid models with both virtual and face-to-face consultations are likely to remain (192). Technological interventions such as telehealth in people with diabetes may be a solution to improve care and clinical outcomes (193). However, such technological interventions may further widen disparities in vulnerable populations such as the elderly, ethnic minority groups, frail populations, and those from deprived communities (194).

Several pharmacoepidemiological studies have examined the association between glucose-lowering medications and risk of COVID-19 and have reported conflicting findings, although most studies showed a lower risk of mortality with metformin and a higher risk in people on insulin. However, the absolute differences in the risks have been small, and these findings could be due to confounding by indication (195). The gold standard for assessing the effects of therapies is by RCT, and only one RCT, the Dapagliflozin in Patients with Cardiometabolic Risk Factors Hospitalized with COVID-19 (DARE-19), a double-blind, placebo-controlled RCT in people with and without type 2 diabetes with at least one cardiovascular risk factor, has been reported (196). In this study, dapagliflozin was well tolerated and resulted in fewer events of organ dysfunction, but results were not statistically significant for the dual primary outcome of prevention (time to new or worsening organ dysfunction or death) and the hierarchical composite outcome of recovery by 30 days.

Great progress has been made globally to develop vaccines against SARS-CoV-2, and RCT data and real-world data show that vaccines have led to reduced infections, transmission, hospitalization, and mortality. It is therefore important that people with diabetes have regular SARS-CoV-2 vaccines (see IMMUNIZATIONS, above, for detailed information on COVID-19 vaccines).

It is unclear currently how often people with diabetes will require booster vaccines. Though limited data are available on COVID-19 vaccination attitudes or uptake in people with diabetes in the U.S. (197), diabetes health care professionals may be in a position to address questions and concerns among people with diabetes and encourage vaccination.

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5. Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Building positive health behaviors and maintaining psychological well-being are foundational for achieving diabetes treatment goals and maximizing quality of life (1,2). Essential to achieving these goals are diabetes self-management education and support (DSMES), medical nutrition therapy (MNT), routine physical activity, tobacco cessation counseling when needed, health behavior counseling, and psychosocial care. Following an initial comprehensive medical evaluation (see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities"), people with diabetes and health care professionals are encouraged to engage in person-centered collaborative care (3–6), which is guided by shared decision-making in treatment plan selection; facilitation of obtaining medical, behavioral, psychosocial, and technology resources as needed; and shared monitoring of agreed-upon treatment plans and behavioral goals (7,8). Reevaluation during routine care should include assessment of medical, behavioral, and mental health outcomes, especially during times of change in health and well-being.

DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT

Recommendations

5.1 All people with diabetes should participate in diabetes self-management education and support to facilitate the knowledge, decision-making, and skills mastery for diabetes self-care. **A**

5.2 There are four critical times to evaluate the need for diabetes self-management education and support to promote skills acquisition to aid treatment plan implementation, medical nutrition therapy, and well-being: at diagnosis, annually

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and/or when not meeting treatment targets, when complicating factors develop (medical, physical, psychosocial), and when transitions in life and care occur. **E**

5.3 Clinical outcomes, health status, and well-being are key goals of diabetes self-management education and support that should be measured as part of routine care. **C**

5.4 Diabetes self-management education and support should be person-centered, may be offered in group or individual settings, and should be communicated with the entire diabetes care team. **A**

5.5 Digital coaching and digital self-management interventions can be effective methods to deliver diabetes self-management education and support. **B**

5.6 Reimbursement by third-party payers is recommended **C** because diabetes self-management education and support can improve outcomes and reduce costs. **B**

5.7 Identify and address barriers to diabetes self-management education and support that exist at the health system, payer, health care professional, and individual levels. **E**

5.8 Include social determinants of health of the target population in guiding design and delivery of diabetes self-management education and support **C** with the ultimate goal of health equity across all populations.

5.9 Consider addressing barriers to diabetes self-management education and support access through telehealth delivery of care **B** and other digital health solutions. **C**

The overall objectives of diabetes self-management education and support (DSMES) are to support informed decision-making, self-care behaviors, problem-solving, and active collaboration with the health care team to improve clinical outcomes, health status, and well-being in a cost-effective manner (2). DSMES services facilitate the knowledge, decision-making, and skills mastery necessary for optimal diabetes self-care and incorporate the needs, goals, and life experiences of the person with diabetes. Health care professionals are encouraged to consider the burden of treatment (9) and the person's level of confidence and self-efficacy for management behaviors as well as the level of social and family support when providing DSMES. An individual's engagement in self-management behaviors and the effects on clinical outcomes, health status, and quality of life, as well as the psychosocial factors impacting the person's ability to self-manage, should be monitored as part of routine clinical care. A randomized controlled trial (RCT) testing a decision-making education and skill-building program (10) showed that addressing these targets improved health outcomes in a population in need of health care resources. Furthermore, following a DSMES curriculum improves quality of care (11).

Additionally, in response to the growing body of evidence that associates potentially judgmental words with increased feelings of shame and guilt, health care professionals are encouraged to consider the impact that language has on building therapeutic relationships and to choose positive, strength-based words and phrases that put people first (4,12). Please see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities," for more on use of language.

In accordance with the national standards for DSMES (13), all people with diabetes should participate in DSMES as it helps people with diabetes to identify and implement effective self-management strategies and cope with diabetes (2). Ongoing DSMES helps people with diabetes to maintain effective self-management throughout the life course as they encounter new challenges and as advances in treatment become available (14).

There are four critical time points when the need for DSMES should be evaluated by the health care professional and/or multidisciplinary team, with referrals made as needed (2):

1. At diagnosis
2. Annually and/or when not meeting treatment targets
3. When complicating factors (health conditions, physical limitations, emotional factors, or basic living needs) develop that influence self-management
4. When transitions in life and care occur

DSMES focuses on empowering individuals with diabetes by providing people with diabetes the tools to make informed self-management decisions (15). DSMES should be person-centered. This is an approach that places the person with diabetes and their family and/or support system at the center of the care model, working in collaboration with health care professionals. Person-centered care is respectful of and responsive to individual preferences, needs, and values. It ensures that the values of the person with diabetes guide all decision-making (16).

Evidence for the Benefits

DSMES is associated with improved diabetes knowledge and self-care behaviors (17), lower A1C (17–21), lower self-reported weight (22), improved quality of life (19,23,24), reduced all-cause mortality risk (25), positive coping behaviors (5,26), and reduced health care costs (27–29). DSMES is associated with an increased use of primary care and preventive services (27,30,31) and less frequent use of acute care and inpatient hospital services (22). People with diabetes who participate in DSMES are more likely to follow best practice treatment recommendations, particularly those with Medicare, and have lower Medicare and insurance claim costs (28,31). Better outcomes were reported for DSMES interventions that were more than 10 h over the course of 6–12 months (20), included ongoing support (14,32), were culturally (33–35) and age appropriate (36,37), were tailored to individual needs and preferences, addressed psychosocial issues, and incorporated behavioral strategies (15,26,38,39). Individual and group approaches are effective (40–42), with a slight benefit realized by those who engage in both (20). Strong evidence now exists on the benefits of virtual, telehealth, or internet-based DSMES services for diabetes prevention and management in a wide variety of populations (43–54).

Technologies such as mobile apps, simulation tools, digital coaching, and digital self-management interventions can also be used to deliver DSMES (55–60). These methods provide comparable or even improved outcomes compared with traditional in-person care (61). Greater A1C reductions are demonstrated with

increased patient engagement (62), although data from trials are considerably heterogeneous.

Technology-enabled diabetes self-management solutions improve A1C most effectively when there is two-way communication between the person with diabetes and the health care team, individualized feedback, use of person-generated health data, and education (46). Continuous glucose monitoring, when combined with individualized diabetes education or behavioral interventions, has demonstrated greater improvement on glycemic and psychosocial outcomes compared with continuous glucose monitoring alone (63,64). Incorporating a systematic approach for technology assessment, adoption, and integration into the care plan may help ensure equity in access and standardized application of technology-enabled solutions (8, 30,65–67).

Research supports diabetes care and education specialists (DCES), including nurses, registered dietitian nutritionists (RDNs), and pharmacists as providers of DSMES who may also tailor curriculum to the person's needs (68–70). Many other health disciplines can also become DCES. Members of the DSMES team should have specialized clinical knowledge in diabetes and behavior change principles. In addition, a DCES needs to be knowledgeable about technology-enabled services and may serve as a technology champion within their practice (65). Certification as a DCES (cbdce.org/) and/or board certification in advanced diabetes management (diabeteseducator.org/education/certification/bc_adm) demonstrates an individual's specialized training in and understanding of diabetes management and support (43), and engagement with qualified professionals has been shown to improve disease-related outcomes. Additionally, there is growing evidence for the role of community health workers (71,72), as well as peer (71–76) and lay leaders (77), in providing ongoing support.

Given individual needs and access to resources, a variety of culturally adapted DSMES programs need to be offered in a variety of settings. The use of technology to facilitate access to DSMES services, support self-management decisions, and decrease therapeutic inertia suggests that these approaches need broader adoption (78). Additionally, it is important to include social determinants of health (SDOH) of the target population in guiding design and delivery of DSMES. The DSMES team should take into account demographic characteristics such as race, ethnic/cultural background, sex/gender, age, geographic location, technology access, education, literacy, and numeracy (43,79).

Despite the benefits of DSMES, reports indicate that only 5–7% of individuals eligible for DSMES through Medicare or a private insurance plan actually receive it (80,81). Barriers to DSMES exist at the health system, payer, health care professional, and individual levels. This low participation may be due to lack of referral or other identified barriers, such as logistical issues (accessibility, timing, costs) and the lack of a perceived benefit (81). Health system, programmatic, and payer barriers include lack of administrative leadership support, limited numbers of DSMES professionals, not having referral to DSMES services effectively embedded in the health system service structure, and limited reimbursement rates (82). Thus, in addition to educating referring health care professionals about the benefits of DSMES and the critical times to refer, efforts need to be made to identify and address all of the various potential barriers (2). Support from institutional leadership is foundational for the success of DSMES services. Expert stakeholders should also support DSMES by providing input and advocacy (43). Alternative and innovative models of DSMES delivery (56) need to be explored and evaluated, including the integration of technology-enabled diabetes and cardiometabolic health services (8,65). Barriers to equitable access to DSMES may be addressed through telehealth delivery of care and other digital health solutions (43).

Reimbursement

Medicare reimburses DSMES when that service meets the national standards (2,43) and is recognized by the American Diabetes Association (ADA) through the Education Recognition Program (professional.diabetes.org/diabetes-education) or Association of Diabetes Care & Education Specialists (diabeteseducator.org/practice/diabetes-education-accreditation-program). DSMES is also covered by most health insurance plans. Ongoing support has been shown to be instrumental for improving outcomes when it is implemented after the completion of education services. DSMES is frequently reimbursed when performed in person. However, although DSMES can also be provided via phone calls and telehealth, these remote versions may not always be reimbursed (13). Medicare reimburses remote physiologic monitoring for glucose and other cardiometabolic data if certain conditions are met (83).

Changes in reimbursement policies that increase DSMES access and utilization will result in a positive impact to beneficiaries' clinical outcomes, quality of life, health care utilization, and costs (13,84–86). During the time of the coronavirus disease 2019 (COVID-19) pandemic, reimbursement policies were revised (professional.diabetes.org/content-page/dsmes-and-mnt-during-covid-19-national-pandemic), and these changes may provide a new reimbursement paradigm for future provision of DSMES through telehealth channels.

MEDICAL NUTRITION THERAPY

Please refer to the ADA consensus report "Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report" for more information on nutrition therapy (70). Despite agreement in nutrition recommendations from large scientific bodies, including the American Heart Association, American College of Lifestyle Medicine, and the U.S. Dietary Guidelines (87–93), confusion and controversy remain. For many individuals with diabetes, the most challenging part of the treatment plan is determining what to eat. There is not a "one-size-fits-all" eating pattern for individuals with diabetes, and meal planning should be individualized. Nutrition therapy plays an integral role in overall diabetes management, and each person with diabetes should be actively engaged in education, self-management, and treatment planning with the health care team, including the collaborative development of an individualized eating plan (70,94). All health care professionals should refer people with diabetes for individualized MNT provided by an RDN who is knowledgeable and skilled in providing diabetes-specific MNT (21,95,96) at diagnosis and as needed throughout the life span, similar to DSMES. MNT delivered by an RDN is associated with A1C absolute decreases of 1.0–1.9% for people

with type 1 diabetes (97) and 0.3–2.0% for people with type 2 diabetes (97). See **Table 5.1** for specific nutrition recommendations. Because of the progressive nature of type 2 diabetes, behavior modification alone may not be adequate to maintain euglycemia over time. However, after medication is initiated, nutrition therapy continues to be an important component, and RDNs providing MNT in diabetes care should assess and monitor medication changes in relation to the nutrition care plan (70,94).

Goals of Nutrition Therapy for Adults With Diabetes

1. To promote and support healthful eating patterns, emphasizing a variety of nutrient-dense foods in appropriate portion sizes, to improve overall health and:
   - achieve and maintain body weight goals
   - attain individualized glycemic, blood pressure, and lipid goals
   - delay or prevent the complications of diabetes
2. To address individual nutrition needs based on personal and cultural preferences, health literacy and numeracy, access to healthful foods, willingness and ability to make behavioral changes, and existing barriers to change
3. To maintain the pleasure of eating by providing nonjudgmental messages about food choices while limiting food choices only when indicated by scientific evidence
4. To provide an individual with diabetes the practical tools for developing healthy eating patterns rather than focusing on individual macronutrients, micronutrients, or single foods

Weight Management

Management and reduction of weight is important for people with type 1 diabetes, type 2 diabetes, or prediabetes with overweight or obesity. To support weight loss and improve A1C, cardiovascular disease (CVD) risk factors, and well-being in adults with overweight/obesity and prediabetes or diabetes, MNT and DSMES services should include an individualized eating plan in a format that results in an energy deficit in combination with enhanced physical activity (70). Lifestyle intervention programs should be intensive and have frequent follow-up to achieve significant reductions in excess body weight and improve clinical indicators. There is strong and consistent evidence that modest, sustained weight loss can delay the progression from prediabetes to type 2 diabetes (97–99) (see Section 3, "Prevention or Delay of Type 2 Diabetes and Associated Comorbidities") and is beneficial for the management of type 2 diabetes (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes").

In prediabetes, the weight loss goal is 7–10% for preventing progression to type 2 diabetes (100). In conjunction with support for healthy lifestyle behaviors, medication-assisted weight loss can be considered for people at risk for type 2 diabetes when needed to achieve and sustain 7–10% weight loss (101,102) (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes"). People with prediabetes at a healthy weight should also be considered for behavioral interventions to help establish routine aerobic and resistance exercise (100,103,104) as well as to establish healthy eating patterns. Services delivered by practitioners familiar with diabetes and its management, such as an RDN, have been found to be effective (95).

For many individuals with overweight and obesity with type 2 diabetes, 5% weight loss is needed to achieve beneficial outcomes in glycemic control, lipids, and blood pressure (105). It should be noted, however, that the clinical benefits of weight loss are progressive, and more intensive weight loss goals (i.e., 15%) may be appropriate to maximize benefit depending on need, feasibility, and safety (106,107). Long-term durability of weight loss remains a challenge; however, newer medications (beyond metabolic surgery) may have potential for sustainability, impact on cardiovascular outcomes, and weight reduction beyond 10–15% (108–111).

In select individuals with type 2 diabetes, an overall healthy eating plan that results in energy deficit in conjunction with weight loss medications and/or metabolic surgery should be considered to help achieve weight loss and maintenance goals, lower A1C, and reduce CVD risk (101,112,113). Overweight and obesity are also increasingly prevalent in people with type 1 diabetes and present clinical challenges regarding diabetes treatment and CVD risk factors (114,115). Sustaining weight loss can be challenging (105,116) but has long-term benefits; maintaining weight loss for 5 years is associated with sustained improvements in A1C and lipid levels (117). MNT guidance from an RDN with expertise in diabetes and weight management throughout the course of a structured weight loss plan is strongly recommended.

Along with routine medical management visits, people with diabetes and prediabetes should be screened during DSMES and MNT encounters for a history of dieting and past or current disordered eating behaviors. Nutrition therapy should be individualized to help address maladaptive eating behavior (e.g., purging) or compensatory changes in medical treatment plan (e.g., overtreatment of hypoglycemic episodes, reduction in medication dosing to reduce hunger) (70) (see DISORDERED EATING BEHAVIOR, below). Disordered eating, eating disorders, and/or disrupted eating can increase challenges for weight and diabetes management. For example, caloric restriction may be essential for glycemic management and weight maintenance, but rigid meal plans may be contraindicated for individuals who are at increased risk of clinically significant maladaptive eating behaviors (118). If eating disorders are identified during screening with diabetes-specific questionnaires, individuals should be referred to a qualified mental health professional (1).

Studies have demonstrated that a variety of eating plans, varying in macronutrient composition, can be used effectively and safely in the short term (1–2 years) to achieve weight loss in people with diabetes. These plans include structured low-calorie meal plans with meal replacements (106,117,119), a Mediterranean eating pattern (120), and low-carbohydrate meal plans with additional support (121,122). However, no single approach has been proven to be consistently superior (70,123–125), and more data are needed to identify and validate those meal plans that are optimal with respect to long-term outcomes and acceptability. The importance of providing guidance on an individualized meal plan containing nutrient-dense foods, such as vegetables, fruits, legumes, dairy, lean sources of protein (including plant-based sources as well as lean meats, fish, and poultry), nuts, seeds, and whole grains, cannot be overemphasized (124), as well as guidance on achieving the

Table 5.1—Medical nutrition therapy recommendations

	Recommendations
Effectiveness of nutrition therapy	**5.10** An individualized medical nutrition therapy program as needed to achieve treatment goals, provided by a registered dietitian nutritionist, preferably one who has comprehensive knowledge and experience in diabetes care, is recommended for all people with type 1 or type 2 diabetes, prediabetes, and gestational diabetes mellitus. **A** **5.11** Because diabetes medical nutrition therapy can result in cost savings **B** and improved cardiometabolic outcomes **A**, medical nutrition therapy should be adequately reimbursed by insurance and other payers. **E**
Energy balance	**5.12** For all people with overweight or obesity, behavioral modification to achieve and maintain a minimum weight loss of 5% is recommended. **A**
Eating patterns and macronutrient distribution	**5.13** There is no ideal macronutrient pattern for people with diabetes; meal plans should be individualized while keeping nutrient quality, total calorie, and metabolic goals in mind. **E** **5.14** A variety of eating patterns can be considered for the management of type 2 diabetes and to prevent diabetes in individuals with prediabetes. **B** **5.15** Reducing overall carbohydrate intake for individuals with diabetes has demonstrated the most evidence for improving glycemia and may be applied to a variety of eating patterns that meet individual needs and preferences. **B**
Carbohydrates	**5.16** Carbohydrate intake should emphasize nutrient-dense carbohydrate sources that are high in fiber (at least 14 g fiber per 1,000 kcal) and minimally processed. Eating plans should emphasize nonstarchy vegetables, fruits, legumes, and whole grains, as well as dairy products, with minimal added sugars. **B** **5.17** People with diabetes and those at risk are advised to replace sugar-sweetened beverages (including fruit juices) with water or low calorie, no calorie beverages as much as possible to manage glycemia and reduce risk for cardiometabolic disease **B** and minimize consumption of foods with added sugar that have the capacity to displace healthier, more nutrient-dense food choices. **A** **5.18** When using a flexible insulin therapy program, education on the glycemic impact of carbohydrate **A**, fat, and protein **B** should be tailored to an individual's needs and preferences and used to optimize mealtime insulin dosing. **5.19** When using fixed insulin doses, individuals should be provided with education about consistent patterns of carbohydrate intake with respect to time and amount while considering the insulin action time, as it can result in improved glycemia and reduce the risk for hypoglycemia. **B**
Protein	**5.20** In individuals with type 2 diabetes, ingested protein appears to increase insulin response without increasing plasma glucose concentrations. Therefore, carbohydrate sources high in protein should be avoided when trying to treat or prevent hypoglycemia. **B**
Dietary fat	**5.21** An eating plan emphasizing elements of a Mediterranean eating pattern rich in monounsaturated and polyunsaturated fats may be considered to improve glucose metabolism and lower cardiovascular disease risk. **B** **5.22** Eating foods rich in long-chain n-3 fatty acids, such as fatty fish (EPA and DHA) and nuts and seeds (ALA), is recommended to prevent or treat cardiovascular disease. **B**
Micronutrients and herbal supplements	**5.23** There is no clear evidence that dietary supplementation with vitamins, minerals (such as chromium and vitamin D), herbs, or spices (such as cinnamon or aloe vera) can improve outcomes in people with diabetes who do not have underlying deficiencies, and they are not generally recommended for glycemic control. **C** There may be evidence of harm for certain individuals with β carotene supplementation. **B**
Alcohol	**5.24** Adults with diabetes who drink alcohol should do so in moderation (no more than one drink per day for adult women and no more than two drinks per day for adult men). **C** **5.25** Educating people with diabetes about the signs, symptoms, and self-management of delayed hypoglycemia after drinking alcohol, especially when using insulin or insulin secretagogues, is recommended. The importance of glucose monitoring after drinking alcoholic beverages to reduce hypoglycemia risk should be emphasized. **B**
Sodium	**5.26** Sodium consumption should be limited to <2,300 mg/day. **B**
Nonnutritive sweeteners	**5.27** The use of nonnutritive sweeteners as a replacement for sugar-sweetened products may reduce overall calorie and carbohydrate intake as long as there is not a compensatory increase in energy intake from other sources. There is evidence that low- and no-calorie sweetened beverages are a viable alternative to water. **B**

desired energy deficit (126–129). Any approach to meal planning should be individualized, considering the health status, personal preferences, and ability of the person with diabetes to sustain the recommendations in the plan.

Eating Patterns and Meal Planning

Evidence suggests that there is not an ideal percentage of calories from carbohydrate, protein, and fat for people with diabetes. Therefore, macronutrient distribution should be based on an individualized assessment of current eating patterns, preferences, and metabolic goals. Dietary guidance should emphasize the importance of a healthy dietary pattern as a whole rather than focusing on individual nutrients, foods, or food groups, given that individuals rarely eat foods in isolation. Personal preferences (e.g., tradition, culture, religion, health beliefs and goals, economics), as well as metabolic goals, need to be considered when working with individuals to determine the best eating pattern (70,97,130). Members of the health care team should complement MNT by providing evidence-based guidance that helps people with diabetes make healthy food choices that meet their individualized needs and improve overall health. A variety of eating patterns are acceptable for the management of diabetes (70,97,131,132). Health care professionals should focus on the core dimensions common among the patterns: *1*) emphasize nonstarchy vegetables, *2*) minimize added sugars and refined grains, and *3*) choose whole foods over highly processed foods to the extent possible (70). An individualized eating pattern also considers the individual's health status, food and numeracy skills, resources, food preferences, health goals, and food access. Any member of the health care team can screen for food insecurity using The Hunger Vital Sign. Households are considered at risk if they answer either or both of the following statements as "often true" or "sometimes true" (compared with "never true") (133):

- "Within the past 12 months, we worried whether our food would run out before we got money to buy more."
- "Within the past 12 months, the food we bought just didn't last, and we didn't have money to get more."

Referral to an RDN is essential to assess the overall nutrition status of, and to work collaboratively with, the person with diabetes to create a personalized meal plan that coordinates and aligns with the overall treatment plan, including physical activity and medication use. The Mediterranean (130,134–136), low-carbohydrate (137–139), and vegetarian or plant-based (135,136,140,141) eating patterns are all examples of healthful eating patterns that have shown positive results in research for individuals with type 2 diabetes, but individualized meal planning should focus on personal preferences, needs, and goals. There is currently inadequate research in type 1 diabetes to support one eating pattern over another. Moreover, there is a paucity of evidence and agreement as it relates to nutrition management among children and adolescents with type 1 diabetes. There remains a significant gap in the literature as it relates to the efficacy and long-term management implications of nutrition interventions for young children with type 1 diabetes (142).

For individuals with type 2 diabetes not meeting glycemic targets or for whom reducing glucose-lowering drugs is a priority, reducing overall carbohydrate intake with a low- or very-low-carbohydrate eating pattern is a viable option (137–139). As research studies on low-carbohydrate eating plans generally indicate challenges with long-term sustainability (143), it is important to reassess and individualize meal plan guidance regularly for those interested in this approach. In response to questions regarding implementation of low-carbohydrate and very-low-carbohydrate eating patterns, the ADA has developed a guide for health care professionals that may assist in the practical implementation of these eating patterns (144). Most individuals with diabetes report a moderate intake of carbohydrates (44–46% of total calories) (97,144). Efforts to modify habitual eating patterns are often unsuccessful in the long term; people generally go back to their usual macronutrient distribution (97). Thus, the recommended approach is to individualize meal plans with a macronutrient distribution that is more consistent with personal preference and usual intake to increase the likelihood for long-term maintenance.

An RCT found that two meal-planning approaches (diabetes plate method and carbohydrate counting) were effective in helping achieve improved A1C (145). The diabetes plate method is a commonly used visual approach for providing basic meal planning guidance. This simple graphic (featuring a 9-inch plate) shows how to portion foods (1/2 of the plate for nonstarchy vegetables, 1/4 of the plate for protein, and 1/4 of the plate for carbohydrates). Carbohydrate counting is a more advanced skill that helps plan for and track how much carbohydrate is consumed at meals and snacks. Meal planning approaches should be customized to the individual, including their numeracy (145) and food literacy level. Food literacy generally describes proficiency in food-related knowledge and skills that ultimately impact health, although specific definitions vary across initiatives (146,147).

There has been an increased interest in time-restricted eating and intermittent fasting as strategies for weight management. Intermittent fasting is an umbrella term which includes three main forms of restricted eating: alternate-day fasting (energy restriction of 500–600 calories on alternate days), the 5:2 diet (energy restriction of 500–600 calories on consecutive or nonconsecutive days) with usual intake the other five, and time-restricted eating (daily calorie restriction based on window of time of 8–15 h). Each produces mild to moderate weight loss (3–8% loss from baseline) over short durations (8–12 weeks) with no significant differences in weight loss when compared with continuous calorie restriction (148–151). A few studies have extended up to 52 weeks and show similar findings (152–155). Time-restricted eating (shortening the eating window) is generally easier to follow compared with alternative-day fasting or the 5:2 plan, largely due to ease, no need to count calories, sustainability, and feasibility. This may have implications as people with diabetes are looking for practical eating management tools.

Carbohydrates

Studies examining the ideal amount of carbohydrate intake for people with diabetes are inconclusive, although monitoring carbohydrate intake and considering the blood glucose response to dietary carbohydrate are key for improving postprandial glucose management

(156,157). The literature concerning glycemic index and glycemic load in individuals with diabetes is complex, often with varying definitions of low- and high-glycemic-index foods (158,159). The glycemic index ranks carbohydrate foods on their postprandial glycemic response, and glycemic load takes into account both the glycemic index of foods and the amount of carbohydrate eaten. Studies have found mixed results regarding the effect of glycemic index and glycemic load on fasting glucose levels and A1C, with one systematic review finding no significant impact on A1C (160) while others demonstrated A1C reductions of 0.15% (158) to 0.5% (161,162).

Reducing overall carbohydrate intake for individuals with diabetes has demonstrated evidence for improving glycemia and may be applied in a variety of eating patterns that meet individual needs and preferences (70). For people with type 2 diabetes, low-carbohydrate and very-low-carbohydrate eating patterns in particular have been found to reduce A1C and the need for antihyperglycemic medications (70,130,143,163–165). Systematic reviews and meta-analyses of RCTs found carbohydrate-restricted eating patterns, particularly those considered low carbohydrate (<26% total energy), were effective in reducing A1C in the short term (<6 months), with less difference in eating patterns beyond 1 year (125,126, 137,138,164). Questions still remain about the optimal degree of carbohydrate restriction and the long-term effects of those meal patterns on cardiovascular disease. A systematic review and meta-analysis of RCTs investigating the dose-dependent effect of carbohydrate restriction on metabolic control found each 10% decrease in carbohydrate intake had reductions in levels of A1C, fasting plasma glucose, body weight, lipids, and systolic blood pressure at 6 months, but favorable effects diminished and were not maintained at follow-up or at greater than 12 months. This systematic review highlights the metabolic complexity of response to dietary intervention in type 2 diabetes as well as the need to better understand longer-term sustainability and results (166). Part of the challenge in interpreting low-carbohydrate research has been due to the wide range of definitions for a low-carbohydrate eating plan (139,161). Weight reduction was also a goal in many low-carbohydrate studies, which further complicates evaluating the distinct contribution of the eating pattern (47,121,125,167).

The quality of carbohydrate and/or what is absent from the diet may contribute to confounding results. However, when core dimensions of the comparative diets are similar, there is little difference in outcome measures. When Gardner et al. (168) tested a low-carbohydrate ketogenic diet and a low-carbohydrate Mediterranean diet, in a randomized crossover design, metabolic improvements were seen in both diets without significant differences between them. Each of the interventions avoided added sugars and refined grains and included nonstarchy vegetables. Legumes, fruits, and whole intact grains were included in the Mediterranean but not in the ketogenic diet. The improvements (fasting glucose, insulin, HDL cholesterol, and A1C) were likely due to the nutritional quality of both interventions. However, the ketogenic plan led to a greater decrease in triglycerides (168) but also a greater increase in LDL cholesterol.

As studies on low-carbohydrate eating plans generally indicate challenges with long-term sustainability (143), it is important to reassess and individualize meal plan guidance regularly for those interested in this approach. Health care professionals should maintain consistent medical oversight and recognize that insulin and other diabetes medications may need to be adjusted to prevent hypoglycemia, and blood pressure will need to be monitored. In addition, very-low-carbohydrate eating plans are not currently recommended for individuals who are pregnant or lactating, children, people who have renal disease, or people with or at risk for disordered eating, and these plans should be used with caution in those taking sodium–glucose cotransporter 2 inhibitors because of the potential risk of ketoacidosis (169,170).

Regardless of amount of carbohydrate in the meal plan, focus should be placed on high-quality, nutrient-dense carbohydrate sources that are high in fiber and minimally processed. The addition of dietary fiber modulates composition of gut microbiota and increases gut microbial diversity. Although there is still much to be elucidated with the gut microbiome and chronic disease, higher-fiber diets are advantageous (171). Both children and adults with diabetes are encouraged to minimize intake of refined carbohydrates with added sugars, fat, and sodium and instead focus on carbohydrates from vegetables, legumes, fruits, dairy (milk and yogurt), and whole grains. People with diabetes and those at risk for diabetes are encouraged to consume a minimum of 14 g of fiber/1,000 kcal, with at least half of grain consumption being whole, intact grains, according to the Dietary Guidelines for Americans (172). Regular intake of sufficient dietary fiber is associated with lower all-cause mortality in people with diabetes (173,174), and prospective cohort studies have found dietary fiber intake is inversely associated with risk of type 2 diabetes (175–177). The consumption of sugar-sweetened beverages and processed food products with large amounts of refined grains and added sugars is strongly discouraged (172,178,179), as these have the capacity to displace healthier, more nutrient-dense food choices.

Individuals with type 1 or type 2 diabetes taking insulin at mealtime should be offered intensive and ongoing education on the need to couple insulin administration with carbohydrate intake. For people whose meal schedule or carbohydrate consumption is variable, regular education to increase understanding of the relationship between carbohydrate intake and insulin needs is important. In addition, education on using insulin-to-carbohydrate ratios for meal planning can assist individuals with effectively modifying insulin dosing from meal to meal to improve glycemic management (97,156,180–183). Studies have shown that dietary fat and protein can impact early and delayed postprandial glycemia (184–187), and it appears to have a dose-dependent response (188–191). Results from high-fat, high-protein meal studies highlight the need for additional insulin to cover these meals; however, more studies are needed to determine the optimal insulin dose and delivery strategy. The results from these studies also point to individual differences in postprandial glycemic response; therefore, a cautious approach to increasing insulin doses for high-fat and/or high-protein mixed meals is recommended to address delayed hyperglycemia that may occur 3 h or more after eating (70). If using an insulin pump, a split bolus feature (part of the bolus delivered immediately, the remainder over a programmed duration of time) may provide

better insulin coverage for high-fat and/or high-protein mixed meals (185,192).

The effectiveness of insulin dosing decisions should be confirmed with a structured approach to blood glucose monitoring or continuous glucose monitoring to evaluate individual responses and guide insulin dose adjustments. Checking glucose 3 h after eating may help to determine if additional insulin adjustments are required (i.e., increasing or stopping bolus) (185,192,193). Refining insulin doses to account for high-fat and/or -protein meals requires determination of anticipated nutrient intake to calculate the mealtime dose. Food literacy, numeracy, interest, and capability should be evaluated (70). For individuals on a fixed daily insulin schedule, meal planning should emphasize a relatively fixed carbohydrate consumption pattern with respect to both time and amount while considering insulin action. Attention to resultant hunger and satiety cues will also help with nutrient modifications throughout the day (70,194).

Protein

There is no evidence that adjusting the daily level of protein intake (typically 1–1.5 g/kg body wt/day or 15–20% total calories) will improve health, and research is inconclusive regarding the ideal amount of dietary protein to optimize either glycemic management or CVD risk (159,195). Therefore, protein intake goals should be individualized based on current eating patterns. Some research has found successful management of type 2 diabetes with meal plans including slightly higher levels of protein (20–30%), which may contribute to increased satiety (196).

Historically, low-protein eating plans were advised for individuals with diabetic kidney disease (DKD) (with albuminuria and/or reduced estimated glomerular filtration rate); however, current evidence does not suggest that people with DKD need to restrict protein to less than the generally recommended protein intake (70). Reducing the amount of dietary protein below the recommended daily allowance of 0.8 g/kg is not recommended because it does not alter glycemic measures, cardiovascular risk measures, or the rate at which glomerular filtration rate declines and may increase risk for malnutrition (197,198).

In individuals with type 2 diabetes, protein intake may enhance or increase the insulin response to dietary carbohydrates (199). Therefore, use of carbohydrate sources high in protein (e.g., nuts) to treat or prevent hypoglycemia should be avoided due to the potential concurrent rise in endogenous insulin. Health care professionals should counsel patients to treat hypoglycemia with pure glucose (i.e., glucose tablets) or carbohydrate-containing foods at the hypoglycemia alert value of $<$70 mg/dL. See Section 6, "Glycemic Targets," for more information.

Fats

Evidence suggests that there is not an ideal percentage of calories from fat for people with or at risk for diabetes and that macronutrient distribution should be individualized according to the patient's eating patterns, preferences, and metabolic goals (70). The type of fats consumed is more important than total amount of fat when looking at metabolic goals and CVD risk, and it is recommended that the percentage of total calories from saturated fats should be limited (120,172,200–202). Multiple RCTs including people with type 2 diabetes have reported that a Mediterranean eating pattern (120,203–208) can improve both glycemic management and blood lipids. The Mediterranean eating pattern is based on the traditional eating habits in the countries bordering the Mediterranean Sea. Although eating styles vary, they share a number of common features, including consumption of fresh fruits and vegetables, whole grains, beans, and nuts/seeds; olive oil as the primary fat source; low to moderate amounts of fish, eggs, and poultry; and limited added sugars, sugary beverages, sodium, highly processed foods, refined carbohydrates, saturated fats, and fatty or processed meats.

Evidence does not conclusively support recommending n-3 (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) supplements for all people with diabetes for the prevention or treatment of cardiovascular events (70,209,210). In individuals with type 2 diabetes, two systematic reviews with n-3 and n-6 fatty acids concluded that the dietary supplements did not improve glycemic management (159,211). In the ASCEND trial (A Study of Cardiovascular Events iN Diabetes), when compared with placebo, supplementation with n-3 fatty acids at the dose of 1 g/day did not lead to cardiovascular benefit in people with diabetes without evidence of CVD (212). However, results from the Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial (REDUCE-IT) found that supplementation with 4 g/day of pure EPA significantly lowered the risk of adverse cardiovascular events. This trial of 8,179 participants, in which over 50% had diabetes, found a 5% absolute reduction in cardiovascular events for individuals with established atherosclerotic CVD taking a preexisting statin with residual hypertriglyceridemia (135–499 mg/dL) (213). See Section 10, "Cardiovascular Disease and Risk Management," for more information. People with diabetes should be advised to follow the guidelines for the general population for the recommended intakes of saturated fat, dietary cholesterol, and *trans* fat (172). *Trans* fats should be avoided. In addition, as saturated fats are progressively decreased in the diet, they should be replaced with unsaturated fats and not with refined carbohydrates (207).

Sodium

As for the general population, people with diabetes are advised to limit their sodium consumption to $<$2,300 mg/day (70). Restriction to $<$1,500 mg, even for those with hypertension, is generally not recommended (214–216). Sodium recommendations should take into account palatability, availability, affordability, and the difficulty of achieving low-sodium recommendations in a nutritionally adequate diet (217).

Micronutrients and Supplements

There continues to be no clear evidence of benefit from herbal or nonherbal (i.e., vitamin or mineral) supplementation for people with diabetes without underlying deficiencies (70). Metformin is associated with vitamin B12 deficiency per a report from the Diabetes Prevention Program Outcomes Study (DPPOS), suggesting that periodic testing of vitamin B12 levels should be considered in people taking metformin, particularly in those with anemia or peripheral neuropathy (218). Routine supplementation with antioxidants, such as vitamins E and C, is not advised due to lack of evidence of efficacy and

concern related to long-term safety. Based on the recent U.S. Preventative Services Task Force statement, the harms of β-carotene outweigh the benefits for the prevention of CVD or cancer. β-Carotene was significantly associated with increased lung cancer and cardiovascular mortality risk (219).

In addition, there is insufficient evidence to support the routine use of herbal supplements and micronutrients, such as cinnamon (220), curcumin, vitamin D (221), aloe vera, or chromium, to improve glycemia in people with diabetes (70,222).

Although the Vitamin D and Type 2 Diabetes Study (D2d) prospective RCT showed no significant benefit of vitamin D versus placebo on the progression to type 2 diabetes in individuals at high risk (223), post hoc analyses and meta-analyses suggest a potential benefit in specific populations (223–226). Further research is needed to define individual characteristics and clinical indicators where vitamin D supplementation may be of benefit.

For special populations, including pregnant or lactating individuals, older adults, vegetarians, and people following very-low-calorie or low-carbohydrate diets, a multivitamin may be necessary.

Alcohol

Moderate alcohol intake does not have major detrimental effects on long-term blood glucose management in people with diabetes. Risks associated with alcohol consumption include hypoglycemia and/or delayed hypoglycemia (particularly for those using insulin or insulin secretagogue therapies), weight gain, and hyperglycemia (for those consuming excessive amounts) (70,222). People with diabetes should be educated about these risks and encouraged to monitor glucose frequently after drinking alcohol to minimize such risks. People with diabetes can follow the same guidelines as those without diabetes. For women, no more than one drink per day, and for men, no more than two drinks per day is recommended (one drink is equal to a 12-oz beer, a 5-oz glass of wine, or 1.5 oz of distilled spirits).

Nonnutritive Sweeteners

The U.S. Food and Drug Administration has approved many nonnutritive sweeteners for consumption by the general public, including people with diabetes (70,227). For some people with diabetes who are accustomed to regularly consuming sugar-sweetened products, nonnutritive sweeteners (containing few or no calories) may be an acceptable substitute for nutritive sweeteners (those containing calories, such as sugar, honey, and agave syrup) when consumed in moderation (228,229). Nonnutritive sweeteners do not appear to have a significant effect on glycemic management (97,230,231), and they can reduce overall calorie and carbohydrate intake (97,228) as long as individuals are not compensating with additional calories from other food sources (70,232). There is mixed evidence from systematic reviews and meta-analyses for nonnutritive sweetener use with regard to weight management, with some finding benefit in weight loss (233–235) while other research suggests an association with weight gain (236,237). This may be explained by reverse causality and residual confounding variables (237). The addition of nonnutritive sweeteners to diets poses no benefit for weight loss or reduced weight gain without energy restriction (238). In a recent systematic review and meta-analysis using low-calorie and no-calorie sweetened beverages as an intended substitute for sugar-sweetened beverages, a small improvement in body weight and cardiometabolic risk factors was seen without evidence of harm and had a direction of benefit similar to that seen with water. Health care professionals should continue to recommend water, but people with overweight or obesity and diabetes may also have a variety of no-calorie or low-calorie sweetened products so that they do not feel deprived (239).

PHYSICAL ACTIVITY

Recommendations

5.28 Children and adolescents with type 1 diabetes **C** or type 2 diabetes or prediabetes **B** should engage in 60 min/day or more of moderate- or vigorous-intensity aerobic activity, with vigorous muscle-strengthening and bone-strengthening activities at least 3 days/week.

5.29 Most adults with type 1 diabetes **C** and type 2 diabetes **B** should engage in 150 min or more of moderate- to vigorous-intensity aerobic activity per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity. Shorter durations (minimum 75 min/week) of vigorous-intensity or interval training may be sufficient for younger and more physically fit individuals.

5.30 Adults with type 1 diabetes **C** and type 2 diabetes **B** should engage in 2–3 sessions/week of resistance exercise on nonconsecutive days.

5.31 All adults, and particularly those with type 2 diabetes, should decrease the amount of time spent in daily sedentary behavior. **B** Prolonged sitting should be interrupted every 30 min for blood glucose benefits. **C**

5.32 Flexibility training and balance training are recommended 2–3 times/week for older adults with diabetes. Yoga and tai chi may be included based on individual preferences to increase flexibility, muscular strength, and balance. **C**

5.33 Evaluate baseline physical activity and sedentary time. Promote increase in nonsedentary activities above baseline for sedentary individuals with type 1 diabetes **E** and type 2 diabetes. **B** Examples include walking, yoga, housework, gardening, swimming, and dancing.

Physical activity is a general term that includes all movement that increases energy use and is an important part of the diabetes management plan. Exercise is a more specific form of physical activity that is structured and designed to improve physical fitness. Both physical activity and exercise are important. Exercise has been shown to improve blood glucose levels, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being (240). Physical activity is as important for those with type 1 diabetes as it is for the general population, but its specific role in the prevention of diabetes complications and the management of blood glucose is not as clear as it is for those with type 2 diabetes. Many individuals with type 2 diabetes do not meet the recommended exercise level per week (150 min).

Objective measurement by accelerometer in 871 individuals with type 2 diabetes showed that 44.2%, 42.6%, and 65.1% of White, African American, and Hispanic individuals, respectively, met the recommended threshold of exercise (241). An RCT in 1,366 individuals with prediabetes combined a physical activity intervention with text messaging and telephone support, which showed improvement in daily step count at 12 months compared with the control group. Unfortunately, this was not sustained at 48 months (242). Another RCT, including 324 individuals with prediabetes, showed increased physical activity at 8 weeks with supportive text messages, but by 12 weeks there was no difference between groups (243). It is important for diabetes care management teams to understand the difficulty that many people have reaching recommended treatment targets and to identify individualized approaches to improve goal achievement, which may need to change over time.

Moderate to high volumes of aerobic activity are associated with substantially lower cardiovascular and overall mortality risks in both type 1 and type 2 diabetes (244). A prospective observational study of adults with type 1 diabetes suggested that higher amounts of physical activity led to reduced cardiovascular mortality after a mean follow-up time of 11.4 years for people with and without chronic kidney disease (245). Additionally, structured exercise interventions of at least 8 weeks' duration have been shown to lower A1C by an average of 0.66% in people with type 2 diabetes, even without a significant change in BMI (246). There are also considerable data for the health benefits (e.g., increased cardiovascular fitness, greater muscle strength, improved insulin sensitivity) of regular exercise for those with type 1 diabetes (247). Exercise training in type 1 diabetes may also improve several important markers such as triglyceride level, LDL cholesterol, waist circumference, and body mass (248). In adults with type 2 diabetes, higher levels of exercise intensity are associated with greater improvements in A1C and in cardiorespiratory fitness (249); sustained improvements in cardiorespiratory fitness and weight loss have also been associated with a lower risk of heart failure (250). Other benefits include slowing the decline in mobility among overweight people with diabetes (251). The ADA position statement "Physical Activity/Exercise and Diabetes" reviews the evidence for the benefits of exercise in people with type 1 and type 2 diabetes and offers specific recommendations (252). Increased physical activity (soccer training) has also been shown to be beneficial for improving overall fitness in Latino men with obesity, demonstrating feasible methods to increase physical activity in an often hard-to-engage population (253). Physical activity and exercise should be recommended and prescribed to all individuals who are at risk for or with diabetes as part of management of glycemia and overall health. Specific recommendations and precautions will vary by the type of diabetes, age, activity, and presence of diabetes-related health complications. Recommendations should be tailored to meet the specific needs of each individual (252).

Exercise and Children

All children, including children with diabetes or prediabetes, should be encouraged to engage in regular physical activity. Children should engage in at least 60 min of moderate to vigorous aerobic activity every day, with muscle- and bone-strengthening activities at least 3 days per week (254). In general, youth with type 1 diabetes benefit from being physically active, and an active lifestyle should be recommended to all (255). Youth with type 1 diabetes who engage in more physical activity may have better health outcomes and health-related quality of life (256,257). See Section 14, "Children and Adolescents," for details.

Frequency and Type of Physical Activity

People with diabetes should perform aerobic and resistance exercise regularly (209). Aerobic activity bouts should ideally last at least 10 min, with the goal of ~30 min/day or more most days of the week for adults with type 2 diabetes. Daily exercise, or at least not allowing more than 2 days to elapse between exercise sessions, is recommended to decrease insulin resistance, regardless of diabetes type (258,259). A study in adults with type 1 diabetes found a dose-response inverse relationship between self-reported bouts of physical activity per week and A1C, BMI, hypertension, dyslipidemia, and diabetes-related complications such as hypoglycemia, diabetic ketoacidosis, retinopathy, and microalbuminuria (260). Over time, activities should progress in intensity, frequency, and/or duration to at least 150 min/week of moderate-intensity exercise. Adults able to run at 6 miles/h (9.7 km/h) for at least 25 min can benefit sufficiently from shorter-intensity activity (75 min/week) (252). Many adults, including most with type 2 diabetes, may be unable or unwilling to participate in such intense exercise and should engage in moderate exercise for the recommended duration. Adults with diabetes should engage in 2–3 sessions/week of resistance exercise on nonconsecutive days (261). Although heavier resistance training with free weights and weight machines may improve glycemic control and strength (262), resistance training of any intensity is recommended to improve strength, balance, and the ability to engage in activities of daily living throughout the life span. Health care professionals should help people with diabetes set stepwise goals toward meeting the recommended exercise targets. As individuals intensify their exercise program, medical monitoring may be indicated to ensure safety and evaluate the effects on glucose management. (See PHYSICAL ACTIVITY AND GLYCEMIC CONTROL, below.)

Evidence supports that all individuals, including those with diabetes, should be encouraged to reduce the amount of time spent being sedentary—waking behaviors with low energy expenditure (e.g., working at a computer, watching television)—by breaking up bouts of sedentary activity (>30 min) by briefly standing, walking, or performing other light physical activities (263,264). Participating in leisure-time activity and avoiding extended sedentary periods may help prevent type 2 diabetes for those at risk (265,266) and may also aid in glycemic management for those with diabetes.

A systematic review and meta-analysis found higher frequency of regular leisure-time physical activity was more effective in reducing A1C levels (267). A wide range of activities, including yoga, tai chi, and other types, can have significant impacts on A1C, flexibility, muscle strength, and balance (240,268–270). Flexibility and balance exercises may be particularly important in older adults with diabetes to maintain range of motion, strength, and balance (252) (**Fig. 5.1**).

Physical Activity and Glycemic Management

Clinical trials have provided strong evidence for the A1C-lowering value of resistance training in older adults with type 2 diabetes (252) and for an additive benefit of combined aerobic and resistance exercise in adults with type 2 diabetes (271). If not contraindicated, people with type 2 diabetes should be encouraged to do at least two weekly sessions of resistance exercise (exercise with free weights or weight machines), with each session consisting of at least one set (group of consecutive repetitive exercise motions) of five or more different resistance exercises involving the large muscle groups (272).

For people with type 1 diabetes, although exercise, in general, is associated with improvement in disease status, care needs to be taken in titrating exercise with respect to glycemic management. Each individual with type 1 diabetes has a variable glycemic response to exercise. This variability should be taken into consideration when recommending the type and duration of exercise for a given individual (247).

Individuals of childbearing potential with preexisting diabetes, particularly type 2 diabetes, and those at risk for or presenting with gestational diabetes mellitus should be advised to engage in regular moderate physical activity prior to and during their pregnancies as tolerated (252).

Pre-exercise Evaluation

As discussed more fully in Section 10, "Cardiovascular Disease and Risk Management," the best protocol for assessing asymptomatic people with diabetes for coronary artery disease remains unclear. The ADA consensus report "Screening for Coronary Artery Disease in Patients With Diabetes" (273) concluded that routine testing is not recommended. However, health care professionals should perform a careful history, assess cardiovascular risk factors, and be aware of the atypical presentation of coronary artery disease, such as recent reported or tested decrease in exercise tolerance in people with diabetes. Certainly, those with high risk should be encouraged to start with short periods of low-intensity exercise and slowly increase the intensity and duration as tolerated. Health care professionals should assess for conditions that might contraindicate certain types of exercise or predispose to injury, such as uncontrolled hypertension, untreated proliferative retinopathy, autonomic neuropathy, peripheral neuropathy, and a history of foot ulcers or Charcot foot. Age and previous physical activity level should be considered when customizing the exercise plan to the individual's needs. Those with complications may need a more thorough evaluation prior to starting an exercise program (247).

Hypoglycemia

In individuals taking insulin and/or insulin secretagogues, physical activity may cause hypoglycemia if the medication dose or carbohydrate consumption is not adjusted for the exercise bout and postbout impact on glucose. Individuals on these therapies may need to ingest some added carbohydrate if pre-exercise glucose levels are $<$90 mg/dL (5.0 mmol/L), depending on whether they are able to lower insulin doses during the workout (such as with an insulin pump or reduced pre-exercise insulin dosage), the time of day exercise is done, and the intensity and duration of the activity (247). In some people with diabetes, hypoglycemia after exercise may occur and last for several hours due to increased insulin sensitivity. Hypoglycemia is less common in those who are not treated with insulin or insulin secretagogues, and no routine preventive measures for hypoglycemia are usually advised in these cases. Intense activities may actually raise blood glucose levels instead of lowering them, especially if pre-exercise glucose levels are elevated (247). Because of the variation in glycemic response to exercise bouts, people with diabetes need to be educated to check blood glucose levels before and after periods of exercise and about the potential prolonged effects (depending on intensity and duration).

Exercise in the Presence of Microvascular Complications

See Section 11, "Chronic Kidney Disease and Risk Management," and Section 12, "Retinopathy, Neuropathy, and Foot Care," for more information on these long-term complications.

Retinopathy

If proliferative diabetic retinopathy or severe nonproliferative diabetic retinopathy is present, then vigorous-intensity aerobic or resistance exercise may be contraindicated because of the risk of triggering vitreous hemorrhage or retinal detachment (274). Consultation with an ophthalmologist prior to engaging in an intense exercise plan may be appropriate.

Peripheral Neuropathy

Decreased pain sensation and a higher pain threshold in the extremities can result in an increased risk of skin breakdown, infection, and Charcot joint destruction with some forms of exercise. Therefore, a thorough assessment should be done to ensure that neuropathy does not alter kinesthetic or proprioceptive sensation during physical activity, particularly in those with more severe neuropathy. Studies have shown that moderate-intensity walking may not lead to an increased risk of foot ulcers or reulceration in those with peripheral neuropathy who use proper footwear (275). In addition, 150 min/week of moderate exercise was reported to improve outcomes in people with prediabetic neuropathy (276). All individuals with peripheral neuropathy should wear proper footwear and examine their feet daily to detect lesions early. Anyone with a foot injury or open sore should be restricted to non–weight-bearing activities.

Autonomic Neuropathy

Autonomic neuropathy can increase the risk of exercise-induced injury or adverse events through decreased cardiac responsiveness to exercise, postural hypotension, impaired thermoregulation, impaired night vision due to impaired papillary reaction, and greater susceptibility to hypoglycemia (277). Cardiovascular autonomic neuropathy is also an independent risk factor for cardiovascular death and silent myocardial ischemia (278). Therefore, individuals with diabetic autonomic neuropathy should undergo cardiac investigation before beginning physical activity more intense than that to which they are accustomed.

Diabetic Kidney Disease

Physical activity can acutely increase urinary albumin excretion. However, there is no evidence that vigorous-intensity exercise accelerates the rate of progression of DKD, and there appears to be no need for specific exercise restrictions for people with DKD in general (274).

SMOKING CESSATION: TOBACCO AND E-CIGARETTES

Recommendations

5.34 Advise all individuals not to use cigarettes and other tobacco products or e-cigarettes. **A**

5.35 After identification of tobacco or e-cigarette use, include smoking cessation counseling and other forms of treatment as a routine component of diabetes care. **A**

5.36 Address smoking cessation as part of diabetes education programs for those in need. **B**

Results from epidemiologic, case-control, and cohort studies provide convincing evidence to support the causal link between cigarette smoking and health risks (279). Data show tobacco use is higher among adults with chronic conditions (280) as well as in adolescents and young adults with diabetes (281). People with diabetes who smoke (and people with diabetes exposed to second-hand smoke) have a heightened risk of CVD, premature death, microvascular complications, and worse glycemic outcomes when compared with those who do not smoke (282–284). Smoking may have a role in the development of type 2 diabetes (285–287).

The routine and thorough assessment of tobacco use is essential to prevent smoking or encourage cessation. Numerous large RCTs have demonstrated the efficacy and cost-effectiveness of brief counseling in smoking cessation, including the use of telephone quit lines, in reducing tobacco use. Pharmacologic therapy to assist with smoking cessation in people with diabetes has been shown to be effective (288), and for people who are motivated to quit, the addition of pharmacologic therapy to counseling is more effective than either treatment alone (289). Special considerations should include assessment of level of nicotine dependence, which is associated with difficulty in quitting and relapse (290). Although some people may gain weight in the period shortly after smoking cessation (291), recent research has demonstrated that this weight gain does not diminish the substantial CVD benefit realized from smoking cessation (292). One study in people who smoke who had newly diagnosed type 2 diabetes found that smoking cessation was associated with amelioration of metabolic parameters and reduced blood pressure and albuminuria at 1 year (293).

In recent years, e-cigarettes have gained public awareness and popularity because of perceptions that e-cigarette use is less harmful than regular cigarette smoking (294,295). However, in light of recent Centers for Disease Control and Prevention evidence (296) of deaths related to e-cigarette use, no individuals should be advised to use e-cigarettes, either as a way to stop smoking tobacco or as a recreational drug.

Diabetes education programs offer potential to systematically reach and engage individuals with diabetes in smoking cessation efforts. A cluster randomized trial found statistically significant increases in quit rates and long-term abstinence rates (>6 months) when smoking cessation interventions were offered through diabetes education clinics, regardless of motivation to quit at baseline (297).

SUPPORTING POSITIVE HEALTH BEHAVIORS

Recommendation

5.37 Behavioral strategies should be used to support diabetes self-management and engagement in health behaviors (e.g., taking medications, using diabetes technologies, physical activity, healthy eating) to promote optimal diabetes health outcomes. **A**

Given associations with glycemic outcomes and risk for future complications (298,299), it is important for diabetes care professionals to support people with diabetes to engage in health-promoting behaviors (preventive, treatment, and maintenance), including blood glucose monitoring, taking insulin and medications, using diabetes technologies, engaging in physical activity, and making nutritional changes. Evidence supports using a variety of behavioral strategies and multicomponent interventions to help people with diabetes and their caregivers or family members develop health behavior routines and overcome barriers to self-management behaviors (300–302). Behavioral strategies with empirical support include motivational interviewing (303–305), patient activation (306), goal setting and action planning (305,307–309), problem-solving (308,310), tracking or self-monitoring health behaviors with or without feedback from a health care professional (305,307–309), and facilitating opportunities for social support (305,308,309). Multicomponent intervention packages have the highest efficacy for behavioral and glycemic outcomes (300,309,311). For youth with diabetes, family-based behavioral intervention packages and multisystem interventions that facilitate health behavior change demonstrate benefit for increasing management behaviors and improving glycemic outcomes (301). Health behavior change strategies may be delivered by mental health professionals, DCES, or other trained health care professionals (307,312–314) or qualified community health workers (307,308). These approaches may be delivered via digital health tools (309,313,315).

PSYCHOSOCIAL CARE

Recommendations

5.38 Psychosocial care should be provided to all people with diabetes, with the goal of optimizing health-related quality of life and health outcomes. Such care should be integrated with routine medical care and delivered by trained health care professionals using a collaborative, person-centered, culturally informed approach. **A** When indicated and available, qualified mental health professionals should provide additional targeted mental health care. **B**

5.39 Diabetes care teams should implement psychosocial screening protocols that may include but are not limited to attitudes about diabetes, expectations for treatment and outcomes, general and diabetes-related mood, stress and/or quality of life, available resources (financial, social, family, and emotional), and/or psychiatric history. Screening should occur at periodic intervals and when there is a change in disease, treatment, or life circumstances. **C**

5.40 When indicated, refer to mental health professionals or other trained health care professionals for further assessment and

treatment for symptoms of diabetes distress, depression, suicidality, anxiety, treatment-related fear of hypoglycemia, disordered eating, and/or cognitive capacities. Such specialized psychosocial care should use age-appropriate standardized and validated tools and treatment approaches. **B**

5.41 Consider screening older adults (aged ≥65 years) with diabetes for cognitive impairment, frailty, and depressive symptoms. Monitoring of cognitive capacity, i.e., the ability to actively engage in decision-making regarding treatment plan behaviors, is advised. **B**

Please refer to the ADA position statement "Psychosocial Care for People With Diabetes" for a list of assessment tools and additional details (1) and the ADA Mental Health Toolkit for assessment questionnaires and surveys (professional.diabetes.org/mental-health-toolkit).

Complex environmental, social, family, behavioral, and emotional factors, known as psychosocial factors, influence living with diabetes, both type 1 and type 2, and achieving optimal health outcomes and psychological well-being. Thus, individuals with diabetes and their families are challenged with complex, multifaceted issues when integrating diabetes care into daily life (183). Clinically significant mental health diagnoses are considerably more prevalent in people with diabetes than in those without (316,317). Emotional well-being is an important part of diabetes care and self-management. Psychological and social problems can impair the individual's (43,318–322) or family's (321) ability to carry out diabetes care tasks and, therefore, potentially compromise health status. Therefore, psychological symptoms, both clinical and subclinical, must be addressed. In addition to impacting a person's ability to carry out self-management and the association of mental health diagnosis with poorer short-term glycemic stability, symptoms of emotional distress are associated with mortality risk (316,323).

There are opportunities for diabetes health care professionals to routinely monitor and screen psychosocial status in a timely and efficient manner for referral to appropriate services (324,325). Various health care professionals working with people with diabetes may contribute to psychosocial care in different ways based on training, experience, need, and availability (313,326,327). Ideally, qualified mental health professionals with specialized training and experience in diabetes should be integrated with or provide collaborative care as part of diabetes care teams (328–331), or referrals for in-depth assessment and treatment for psychosocial concerns should be made to such mental health professionals when indicated (314,332,333). A systematic review and meta-analysis showed that psychosocial interventions modestly but significantly improved A1C (standardized mean difference –0.29%) and mental health outcomes (334). There was a limited association between the effects on A1C and mental health, and no intervention characteristics predicted benefit on both outcomes. However, cost analyses have shown that behavioral health interventions are both effective and cost-efficient approaches to the prevention of diabetes (335).

Screening

Health care teams should develop and implement psychosocial screening protocols to ensure routine monitoring of psychosocial well-being and concerns among people with diabetes, following published guidance and recommendations (336–340). Topics to screen for may include, but are not limited to, attitudes about diabetes, expectations for treatment and outcomes (especially related to starting a new treatment or technology), general and diabetes-related mood, stress, and/or quality of life (e.g., diabetes distress, depressive symptoms, anxiety symptoms, and/or fear of hypoglycemia), available resources (financial, social, family, and emotional), and/or psychiatric history. A list of age-appropriate screening and evaluation measures is provided in the ADA position statement "Psychosocial Care for People with Diabetes" (1). Key opportunities for psychosocial screening occur at diabetes diagnosis, during regularly scheduled management visits, during hospitalizations, with new onset of complications, during significant transitions in care such as from pediatric to adult care teams (341), at the time of medical treatment changes, or when problems with achieving A1C goals, quality of life, or self-management are identified. People with diabetes are likely to exhibit psychological vulnerability at diagnosis, when their medical status changes (e.g., end of the honeymoon period), when the need for intensified treatment is evident, and when complications are discovered. Significant changes in life circumstances and SDOH are known to considerably affect a person's ability to self-manage their condition. Thus, screening for SDOH (e.g., loss of employment, birth of a child, or other family-based stresses) should also be incorporated into routine care (342). In circumstances where individuals other than the person with diabetes are significantly involved in diabetes management (e.g., caregivers or family members), these issues should be monitored and treated by appropriate professionals (341,343,344).

Standardized, validated, age-appropriate tools for psychosocial monitoring and screening can also be used (1). Health care professionals may also use informal verbal inquires, for example, by asking whether there have been persistent changes in mood during the past 2 weeks or since the individual's last appointment and whether the person can identify a triggering event or change in circumstances. Diabetes care professionals should also ask whether there are new or different barriers to treatment and self-management, such as feeling overwhelmed or stressed by having diabetes (see DIABETES DISTRESS, below), changes in finances, or competing medical demands (e.g., the diagnosis of a comorbid condition).

Psychological Assessment and Treatment

When psychosocial concerns are identified, referral to a qualified behavioral and/or mental health professional, ideally one specializing in diabetes, should be made for comprehensive evaluation, diagnosis, and treatment (313,314,332,333). Indications for referral may include positive screening for overall stress related to work-life balance, diabetes distress, diabetes management difficulties, depression, anxiety, disordered eating, and cognitive dysfunction (see **Table 5.2** for a complete list). It is preferable to incorporate psychosocial assessment and treatment into routine care rather than waiting for a specific problem or deterioration in metabolic or psychological status to occur (38,321).

Table 5.2—Situations that warrant referral of a person with diabetes to a qualified behavioral or mental health professional for evaluation and treatment

• A positive screen on a validated screening tool for depressive symptoms, diabetes distress, anxiety, fear of hypoglycemia, or cognitive impairment
• The presence of symptoms or suspicions of disordered eating behavior, an eating disorder, or disrupted patterns of eating
• Intentional omission of insulin or oral medication to cause weight loss is identified
• A serious mental illness is suspected
• In youth and families with behavioral self-care difficulties, repeated hospitalizations for diabetic ketoacidosis, failure to achieve expected developmental milestones, or significant distress
• Declining or impaired ability to perform diabetes self-care behaviors
• Before undergoing bariatric or metabolic surgery and after surgery, if assessment reveals an ongoing need for adjustment support

Health care professionals should identify behavioral and mental health professionals, knowledgeable about diabetes treatment and the psychosocial aspects of diabetes, to whom they can refer patients. The ADA provides a list of mental health professionals who have specialized expertise or who have received education about psychosocial and behavioral issues related to diabetes in the ADA Mental Health Professional Directory Listing (professional.diabetes.org/mhp_listing). Ideally, mental health professionals should be embedded in diabetes care settings. In recognition of limited behavioral health resources and to optimize availability, other health care professionals who have been trained in behavioral and mental health interventions may also provide this specialized psychosocial care (326,329,345,346). Although some health care professionals may not feel qualified to treat psychological problems (347), optimizing the relationship between a person with diabetes and health care professional may increase the likelihood of the individual accepting referral for other services. Collaborative care interventions and a team approach have demonstrated efficacy in diabetes self-management, outcomes of depression, and psychosocial functioning (5,6).

Evidence supports interventions for people with diabetes and psychosocial concerns, including issues that affect mental and behavioral health. Successful therapeutic approaches include cognitive behavioral (330,332,348,349) and mindfulness-based therapies (346,350,351). See the sections below for details about interventions for specific psychological concerns. Behavioral interventions may also be indicated in a preventive manner even in the absence of positive psychosocial screeners, such as resilience-promoting interventions to prevent diabetes distress in adolescence (352,353) and behavioral family interventions to promote collaborative family diabetes management in early adolescence (354,355) or to support adjustment to a new treatment plan or technology (64). Psychosocial interventions can be delivered via digital health platforms (356). Group-based or shared diabetes appointments that address both medical and psychosocial issues relevant to living with diabetes are a promising model to consider (327,357).

Although efficacy has been demonstrated with psychosocial interventions, there has been varying success regarding sustained increases in engagement in health behaviors and improved glycemic outcomes associated with behavioral and mental health issues. Thus, health care professionals should systematically monitor these outcomes following implementation of current evidence-based psychosocial treatments to determine ongoing needs.

Diabetes Distress

Recommendation

5.42 Routinely monitor people with diabetes, caregivers, and family members for diabetes distress, particularly when treatment targets are not met and/or at the onset of diabetes complications. Refer to a qualified mental health professional or other trained health care professional for further assessment and treatment if indicated. **B**

Diabetes distress is very common (321, 358–360). While it shares some features with depression, diabetes distress is distinct and has unique relationships with glycemic and other outcomes (359,361). Diabetes distress refers to significant negative psychological reactions related to emotional burdens and worries specific to an individual's experience in having to manage a severe, complicated, and demanding chronic condition such as diabetes (358,359,362). The constant behavioral demands of diabetes self-management (medication dosing, frequency, and titration; monitoring of glucose, food intake, eating patterns, and physical activity) and the potential or actuality of disease progression are directly associated with reports of diabetes distress (358). The prevalence of diabetes distress is reported to be 18–45%, with an incidence of 38–48% over 18 months in people with type 2 diabetes (362). In the second Diabetes Attitudes, Wishes, and Needs (DAWN2) study, significant diabetes distress was reported by 45% of the participants, but only 24% reported that their health care teams asked them how diabetes affected their lives (321). Similar rates have been identified among adolescents with type 1 diabetes (360) and in parents of youth with type 1 diabetes. High levels of diabetes distress significantly impact medication-taking behaviors and are linked to higher A1C, lower self-efficacy, and less optimal eating and exercise behaviors (5,358,362). Diabetes distress is also associated with symptoms of anxiety, depression, and reduced health-related quality of life (363).

Diabetes distress should be routinely monitored (364) using diabetes-specific validated measures (1). If diabetes

distress is identified, it should be acknowledged and addressed. If indicated, the person should be referred for follow-up care (333). This may include specific diabetes education to address areas of diabetes self-care causing distress and impacting clinical management and/or behavioral intervention from a qualified mental health professional, ideally with expertise in diabetes, or from another trained health care professional. Several educational and behavioral intervention strategies have demonstrated benefits for diabetes distress and, to a lesser degree, glycemic outcomes, including education, psychological therapies such as cognitive behavioral therapy and mindfulness-based therapies, and health behavior change approaches such as motivational interviewing (348,349,365,366). Data support diabetes distress interventions delivered using technology (356). DSMES has been shown to reduce diabetes distress (5) and may also benefit A1C when combined with peer support (367). It may be helpful to provide counseling regarding expected diabetes-related versus generalized psychological distress, both at diagnosis and when disease state or treatment changes occur (368). A multisite RCT with adults with type 1 diabetes and elevated diabetes distress and A1C demonstrated large improvements in diabetes distress and small reductions in A1C through two 3-month intervention approaches: a diabetes education intervention with goal setting and a psychological intervention that included emotion regulation skills, motivational interviewing, and goal setting (369). Among adults with type 2 diabetes in the Veterans Affairs system, an RCT demonstrated benefits of integrating a single session of mindfulness intervention into DSMES, followed by a booster session and mobile app-based home practice over 24 weeks, with the strongest effects on diabetes distress (370). An RCT of cognitive behavioral therapy demonstrated positive benefits for diabetes distress, A1C, and depressive symptoms for up to 1 year among adults with type 2 diabetes and elevated symptoms of distress or depression (371). An RCT among people with type 1 and type 2 diabetes found mindful self-compassion training increased self-compassion, reduced depression and diabetes distress, and improved A1C (372). An RCT of a resilience-focused cognitive behavioral and social problem-solving intervention compared with diabetes education (353) in teens with type 1 diabetes showed that diabetes distress and depressive symptoms were significantly reduced for up to 3 years post-intervention, though neither A1C nor self-management behaviors improved over time. These recent studies support that a combination of educational, behavioral, and psychological intervention approaches is needed to address distress, depression, and A1C.

As with treatment of other diabetes-associated behavioral and psychosocial factors affecting disease outcomes, there is little outcome data on long-term systematic treatment of diabetes distress integrated into routine care. As the diabetes disease course and its management are fluid, it can be expected that related distress may fluctuate and may need different methods of remediation at different points in the life course and as disease progression occurs.

Anxiety

Recommendations

5.43 Consider screening people with diabetes for anxiety symptoms or diabetes-related worries. Health care professionals can discuss diabetes-related worries and may refer to a qualified mental health professional for further assessment and treatment if anxiety symptoms indicate interference with diabetes self-management behaviors or quality of life. **B**

5.44 Refer people with hypoglycemia unawareness, which can co-occur with fear of hypoglycemia, to a trained professional to receive evidence-based intervention to help re-establish awareness of symptoms of hypoglycemia and reduce fear of hypoglycemia. **A**

Anxiety symptoms and diagnosable disorders (e.g., generalized anxiety disorder, body dysmorphic disorder, obsessive compulsive disorder, specific phobias, and posttraumatic stress disorder) are common in people with diabetes (373). The Behavioral Risk Factor Surveillance System estimated the lifetime prevalence of generalized anxiety disorder to be 19.5% in people with either type 1 or type 2 diabetes (374). A common diabetes-specific concern is fears related to hypoglycemia (375,376), which may explain avoidance of behaviors associated with lowering glucose, such as increasing insulin doses or frequency of monitoring. Other common sources of diabetes-related anxiety include not meeting blood glucose targets (373), insulin injections or infusion (377), and onset of complications (1). People with diabetes who exhibit excessive diabetes self-management behaviors well beyond what is prescribed or needed to achieve glycemic targets may be experiencing symptoms of obsessive-compulsive disorder (378). General anxiety is a predictor of injection-related anxiety and is associated with fear of hypoglycemia (376,379).

Psychological and behavioral care can be helpful to address symptoms of anxiety in people with diabetes. Among adults with type 2 diabetes and elevated depressive symptoms, an RCT of collaborative care demonstrated benefits on anxiety symptoms for up to 1 year (380). Fear of hypoglycemia and hypoglycemia unawareness often co-occur, so interventions aimed at treating one often benefit both (381). If fear of hypoglycemia is identified and a person does not have symptoms of hypoglycemia, a structured program of blood glucose awareness training delivered in routine clinical practice can improve A1C, reduce the rate of severe hypoglycemia, and restore hypoglycemia awareness (382,383). If not available within the practice setting, a structured program targeting both fear of hypoglycemia and unawareness should be sought out and implemented by a qualified behavioral practitioner (381,383–385). An RCT comparing blood glucose awareness training with a cognitively focused psychoeducation program in adults with type 1 diabetes and impaired awareness of hypoglycemia that has been treatment resistant suggested that both approaches were beneficial for reducing hypoglycemia (386). Thus, specialized behavioral intervention from a trained health care professional is needed to treat hypoglycemia-related anxiety and unawareness.

Depression

Recommendations

5.45 Consider at least annual screening of depressive symptoms in

all people with diabetes, especially those with a self-reported history of depression. Use age-appropriate, validated depression screening measures, recognizing that further evaluation will be necessary for individuals who have a positive screen. **B**

5.46 Beginning at diagnosis of complications or when there are significant changes in medical status, consider assessment for depression. **B**

5.47 Refer to qualified mental health professionals or other trained health care professionals with experience using evidence-based treatment approaches for depression in conjunction with collaborative care with the diabetes treatment team. **A**

History of depression, current depression, and antidepressant medication use are risk factors for the development of type 2 diabetes, especially if the individual has other risk factors such as obesity and family history of type 2 diabetes (387–389). Elevated depressive symptoms and depressive disorders affect one in four people with type 1 or type 2 diabetes (320). Thus, routine screening for depressive symptoms is indicated in this high-risk population, including people with type 1 or type 2 diabetes, gestational diabetes mellitus, and postpartum diabetes. Regardless of diabetes type, women have significantly higher rates of depression than men (390).

Routine monitoring with age-appropriate validated measures (1) can help to identify if referral is warranted (333,339). Multisite studies have demonstrated feasibility of implementing depressive symptom screening protocols in diabetes clinics and published practical guides for implementation (336–339,391). Adults with a history of depressive symptoms need ongoing monitoring of depression recurrence within the context of routine care (387). Integrating mental and physical health care can improve outcomes. When a person with diabetes is receiving psychological therapy, the mental/behavioral health professional should be incorporated into or collaborate with the diabetes treatment team (392). As with DSMES, person-centered collaborative care approaches have been shown to improve both depression and medical outcomes (392). Depressive symptoms may also be a manifestation of reduced quality of life secondary to disease burden (also see DIABETES DISTRESS, above) and resultant changes in resource allocation impacting the person and their family. When depressive symptoms are identified, it is important to query origins, both diabetes-specific and due to other life circumstances (363,393).

Trials have shown consistent evidence of improvements in depressive symptoms and variable benefits for A1C when depression is simultaneously treated (331,392,394), whether through pharmacological treatment, group therapy, psychotherapy, or collaborative care (328,348,349,395,396). Psychological interventions targeting depressive symptoms have shown efficacy when delivered via digital technologies (397). Physical activity interventions also demonstrate benefits for depressive symptoms and A1C (398). It is important to note that medical treatment plan should also be monitored in response to reduction in depressive symptoms. People may agree to or adopt previously refused treatment strategies (improving ability to follow recommended treatment behaviors), which may include increased physical activity and intensification of treatment plan behaviors and monitoring, resulting in changed glucose profiles.

Disordered Eating Behavior

Recommendations

5.48 Consider screening for disordered or disrupted eating using validated screening measures when hyperglycemia and weight loss are unexplained based on self-reported behaviors related to medication dosing, meal plan, and physical activity. In addition, a review of the medical treatment plan is recommended to identify potential treatment-related effects on hunger/caloric intake. **B**

5.49 Consider reevaluating the treatment plan of people with diabetes who present with symptoms of disordered eating behavior, an eating disorder, or disrupted patterns of eating, in consultation with a qualified professional as available. Key qualifications include familiarity with the diabetes disease physiology, treatments for diabetes and disordered eating behaviors, and weight-related and psychological risk factors for disordered eating behaviors. **B**

Estimated prevalence of disordered eating behavior and diagnosable eating disorders in people with diabetes varies (399–401). For people with type 1 diabetes, insulin omission causing glycosuria in order to lose weight is the most commonly reported disordered eating behavior (402,403); in people with type 2 diabetes, bingeing (excessive food intake with an accompanying sense of loss of control) is most commonly reported. For people with type 2 diabetes treated with insulin, intentional omission is also frequently reported (404). People with diabetes and diagnosable eating disorders have high rates of comorbid psychiatric disorders (405). People with type 1 diabetes and eating disorders have high rates of diabetes distress and fear of hypoglycemia (406).

Diabetes care professionals should monitor for disordered eating behaviors using validated measures (407). When evaluating symptoms of disordered or disrupted eating (when the individual exhibits eating behaviors that appear maladaptive but are not volitional, such as bingeing caused by loss of satiety cues), etiology and motivation for the behavior should be evaluated (401,408). Mixed intervention results point to the need for treatment of eating disorders and disordered eating behavior in the context of the disease and its treatment. Given the complexities of treating disordered eating behaviors and disrupted eating patterns in people with diabetes, it is recommended that multidisciplinary care teams include or collaborate with a health professional trained to identify and treat eating behaviors with expertise in disordered eating and diabetes (409). Key qualifications for such professionals include familiarity with the diabetes disease physiology, weight-related and psychological risk factors for disordered eating behaviors, and treatments for diabetes and disordered eating behaviors. More rigorous methods to identify underlying mechanisms of action that drive change in eating and treatment behaviors, as well as associated mental distress, are

needed (410). Health care teams may consider the appropriateness of technology use among people with diabetes and disordered eating behaviors, although more research on the risks and benefits is needed (411). Caution should be taken in labeling individuals with diabetes as having a diagnosable psychiatric disorder, i.e., an eating disorder, when disordered or disrupted eating patterns are found to be associated with the disease and its treatment. In other words, patterns of maladaptive food intake that appear to have a psychological origin may be driven by physiologic disruption in hunger and satiety cues, metabolic perturbations, and/or secondary distress because of the individual's inability to control their hunger and satiety (401,408).

The use of incretin therapies may have potential implications and relevance for the treatment of disrupted or disordered eating (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes"). These medications promote substantial weight loss and maintenance of lost weight beyond conventional nutrition therapies (412), which may improve quality of life. Incretin therapies work in the appetite and reward circuitries to modulate food intake and energy balance, reducing uncontrollable hunger, overeating, and bulimic symptoms (413), although mechanisms are not completely understood. Health care professionals may see expanded use of these medications as data become available (401). This therapy has the potential to improve psychosocial outcomes and control overeating behaviors in people with diabetes, which may ultimately benefit engagement with medical nutrition therapy recommendations (414). More research is needed about adjunctive use of incretins and other medications affecting physiologically based eating behavior in people with diabetes.

Serious Mental Illness

Recommendations

5.50 Provide an increased level of support for people with diabetes and serious mental illness through enhanced monitoring of and assistance with diabetes self-management behaviors. **B**

5.51 In people who are prescribed atypical antipsychotic medications, screen for prediabetes and diabetes 4 months after medication initiation and sooner if clinically indicated, at least annually. **B**

5.52 If a second-generation antipsychotic medication is prescribed for adolescents or adults with diabetes, changes in weight, glycemia, and cholesterol levels should be carefully monitored, and the treatment plan should be reassessed accordingly. **C**

Studies of individuals with serious mental illness, particularly schizophrenia and other thought disorders, show significantly increased rates of type 2 diabetes (415). People with schizophrenia should be monitored for type 2 diabetes because of the known comorbidity. Disordered thinking and judgment can be expected to make it difficult to engage in behavior that reduces risk factors for type 2 diabetes, such as restrained eating for weight management. Further, people with serious mental health disorders and diabetes frequently experience moderate psychological distress, suggesting pervasive intrusion of mental health issues into daily functioning (416).

Coordinated management of diabetes or prediabetes and serious mental illness is recommended to achieve diabetes treatment targets. The diabetes care team, in collaboration with other care professionals, should work to provide an enhanced level of care and self-management support for people with diabetes and serious mental illness based on individual capacity and needs. Such care may include remote monitoring, facilitating health care aides, and providing diabetes training for family members, community support personnel, and other caregivers. Qualitative research suggests that educational and behavioral intervention may provide benefit via group support, accountability, and assistance with applying diabetes knowledge (417). In addition, those taking second-generation (atypical) antipsychotics, such as olanzapine, require greater monitoring because of an increase in risk of type 2 diabetes associated with this medication (418–420). Because of this increased risk, people should be screened for prediabetes or diabetes 4 months after medication initiation and at least annually thereafter. Serious mental illness is often associated with the inability to evaluate and utilize information to make judgments about treatment options. When a person has an established diagnosis of a mental illness that impacts judgment, activities of daily living, and ability to establish a collaborative relationship with care professionals, it is wise to include a nonmedical caretaker in decision-making regarding the medical treatment plan. This person can help improve the patient's ability to follow the agreed-upon treatment plan through both monitoring and caretaking functions (421).

Cognitive Capacity/Impairment

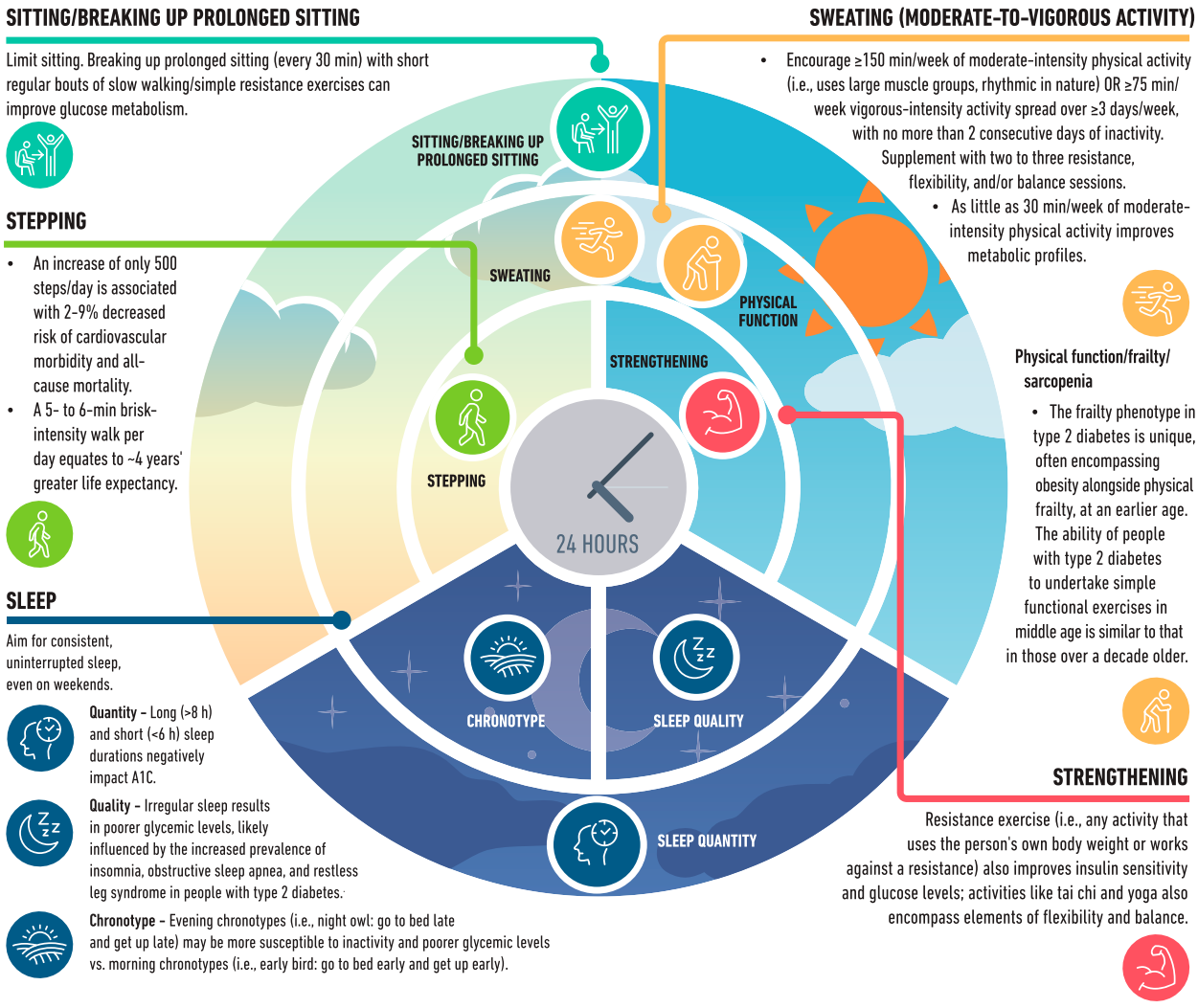
Recommendations

5.53 Cognitive capacity should be monitored throughout the life span for all individuals with diabetes, particularly in those who have documented cognitive disabilities, those who experience severe hypoglycemia, very young children, and older adults. **B**

5.54 If cognitive capacity changes or appears to be suboptimal for patient decision-making and/or behavioral self-management, referral for a formal assessment should be considered. **E**

Cognitive capacity is generally defined as attention, memory, logic and reasoning, and auditory and visual processing, all of which are involved in diabetes self-management behavior (422). Having diabetes over decades—type 1 and type 2—has been shown to be associated with cognitive decline (423–425). Declines have been shown to impact executive function and information processing speed; they are not consistent between people, and evidence is lacking regarding a known course of decline (426). Diagnosis of dementia is also more prevalent among people with diabetes, both type 1 and type 2 (427). Thus, monitoring of cognitive capacity of individuals is recommended, particularly regarding their ability to self-monitor and make judgments about their symptoms, physical status, and needed alterations to their self-management behaviors, all of which are mediated by executive function (427). As with other disorders affecting mental capacity (e.g., major psychiatric disorders), the key issue is

IMPORTANCE OF 24-HOUR PHYSICAL BEHAVIORS FOR TYPE 2 DIABETES



	Glucose/insulin	Blood pressure	A1C	Lipids	Physical function	Depression	Quality of life
SITTING/BREAKING UP PROLONGED SITTING	↓	↓	↓	↓	↑	↓	↑
STEPPING	↓	↓	↓	↓	↑	↓	↑
SWEATING (MODERATE-TO-VIGOROUS ACTIVITY)	↓	↓	↓	↓	↑	↓	↑
STRENGTHENING	↓	↓	↓	↓	↑	↓	↑
ADEQUATE SLEEP DURATION	↓	↓	↓	↓	?	↓	↑
GOOD SLEEP QUALITY	↓	↓	↓	↓	?	↓	↑
CHRONOTYPE/CONSISTENT TIMING	↓	?	↓	?	?	↓	?

IMPACT OF PHYSICAL BEHAVIORS ON CARDIOMETABOLIC HEALTH IN PEOPLE WITH TYPE 2 DIABETES

↑ **Higher levels/improvement** (physical function, quality of life); ↓ **Lower levels/improvement** (glucose/insulin, blood pressure, A1C, lipids, depression); ? no data available; ↑ Green arrows = **strong evidence**; ↑ Yellow arrows = **medium-strength evidence**; ↑ Red arrows = **limited evidence**.

Figure 5.1—Importance of 24-h physical behaviors for type 2 diabetes. Reprinted from Davies et al. (88).

whether the person can collaborate with the care team to achieve optimal metabolic outcomes and prevent complications, both short and long term (416). When this ability is shown to be altered, declining, or absent, a lay care professional should be introduced into the care team who serves in the capacities of day-to-day monitoring as well as a liaison with the rest of the care team (1). Cognitive capacity also contributes to ability to benefit from diabetes education and

may indicate the need for alternative teaching approaches as well as remote monitoring. Youth will need second-party monitoring (e.g., parents and adult caregivers) until they are developmentally able to evaluate necessary information for self-management decisions and to inform resultant behavior changes.

Episodes of severe hypoglycemia are independently associated with decline, as well as the more immediate symptoms of mental confusion (428). Early-onset type 1 diabetes has been shown to be associated with potential deficits in intellectual abilities, especially in the context of repeated episodes of severe hypoglycemia (429). (See Section 14, "Children and Adolescents," for information on early-onset diabetes and cognitive abilities and the effects of severe hypoglycemia on children's cognitive and academic performance.) Thus, for myriad reasons, cognitive capacity should be assessed during routine care to ascertain the person's ability to maintain and adjust self-management behaviors, such as dosing of medications, remediation approaches to glycemic excursions, etc., and to determine whether to enlist a caregiver in monitoring and decision-making regarding management behaviors. If cognitive capacity to carry out self-maintenance behaviors is questioned, an age-appropriate test of cognitive capacity is recommended (1). Cognitive capacity should be evaluated in the context of the person's age, for example, in very young children who are not expected to manage their disease independently and in older adults who may need active monitoring of treatment plan behaviors.

Sleep Health

Recommendation

5.55 Consider screening for sleep health in people with diabetes, including symptoms of sleep disorders, disruptions to sleep due to diabetes symptoms or management needs, and worries about sleep. Refer to sleep medicine and/or a qualified behavioral health professional as indicated. **B**

The associations between sleep problems and diabetes are complex: sleep disorders are a risk factor for developing type 2 diabetes (430,431) and possibly gestational diabetes mellitus (432,433). Moreover, sleep disturbances are associated with less engagement in diabetes self-management and may interfere with the achievement of glycemic targets among people with type 1 and type 2 diabetes (434–439). Disrupted sleep and sleep disorders, including obstructive sleep apnea (440), insomnia, and sleep disturbances (435), are common among people with diabetes. In type 1 diabetes, estimates of poor sleep range from 30% to 50% (441), and estimates of moderate to severe obstructive sleep apnea are >50% (436). In type 2 diabetes, 24–86% of people are estimated to have obstructive sleep apnea (442), 39% to have insomnia, and 8–45% to have restless leg syndrome (439). Risk of hypoglycemia poses specific challenges for sleep in people with type 1 diabetes and may require targeted assessment and treatment approaches (443). People with diabetes and their family members also describe diabetes management needs interfering with sleep and experiencing worries about poor sleep; technology has been described as both a help and challenge in relation to sleep (444). Cognitive behavioral therapy shows benefits for sleep in people with diabetes (348), including cognitive behavioral therapy for insomnia, which demonstrates improvements in sleep outcomes and possible small improvements in A1C and fasting glucose (445). There is also evidence that sleep extension and pharmacological treatments for sleep can improve sleep outcomes and possibly insulin resistance (443,445). Thus, referral to sleep specialists to address the medical and behavioral aspects of sleep is recommended, ideally in collaboration with the diabetes care professional (**Fig. 5.1**).

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6. Glycemic Targets: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

ASSESSMENT OF GLYCEMIC CONTROL

Glycemic control is assessed by the A1C measurement, continuous glucose monitoring (CGM) using time in range (TIR) and/or glucose management indicator (GMI), and blood glucose monitoring (BGM). A1C is the metric used to date in clinical trials demonstrating the benefits of improved glycemic control. Individual glucose monitoring (discussed in detail in Section 7, "Diabetes Technology") is a useful tool for diabetes self-management, which includes meals, physical activity, and medication adjustment, particularly in individuals taking insulin. CGM serves an increasingly important role in the management of the effectiveness and safety of treatment in many people with type 1 diabetes and in selected people with type 2 diabetes. Individuals on a variety of insulin treatment plans can benefit from CGM with improved glucose control, decreased hypoglycemia, and enhanced self-efficacy (Section 7, "Diabetes Technology") (1).

Glycemic Assessment

Recommendations

6.1 Assess glycemic status (A1C or other glycemic measurement such as time in range or glucose management indicator) *at least* two times a year in patients who are meeting treatment goals (and who have stable glycemic control). **E**

6.2 Assess glycemic status at least quarterly and as needed in patients whose therapy has recently changed and/or who are not meeting glycemic goals. **E**

A1C reflects average glycemia over approximately 3 months. The performance of the test is generally excellent for National Glycohemoglobin Standardization Program

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(NGSP)-certified assays (ngsp.org). The test is the primary tool for assessing glycemic control and has a strong predictive value for diabetes complications (2–4). Thus, A1C testing should be performed routinely in all people with diabetes at initial assessment and as part of continuing care. Measurement approximately every 3 months determines whether patients' glycemic targets have been reached and maintained. A 14-day CGM assessment of TIR and GMI can serve as a surrogate for A1C for use in clinical management (5–9). The frequency of A1C testing should depend on the clinical situation, the treatment plan, and the clinician's judgment. The use of point-of-care A1C testing or CGM-derived TIR and GMI may provide an opportunity for more timely treatment changes during encounters between patients and health care professionals. People with type 2 diabetes with stable glycemia well within target may do well with A1C testing or other glucose assessment only twice per year. Unstable or intensively managed patients or people not at goal with treatment adjustments may require testing more frequently (every 3 months with interim assessments as needed for safety) (10). CGM parameters can be tracked in the clinic or via telehealth to optimize diabetes management.

A1C Limitations

The A1C test is an indirect measure of average glycemia and, as such, is subject to limitations. As with any laboratory test, there is variability in the measurement of A1C. Although A1C variability is lower on an intraindividual basis than that of blood glucose measurements, clinicians should exercise judgment when using A1C as the sole basis for assessing glycemic control, particularly if the result is close to the threshold that might prompt a change in medication therapy. For example, conditions that affect red blood cell turnover (hemolytic and other anemias, glucose-6-phosphate dehydrogenase deficiency, recent blood transfusion, use of drugs that stimulate erythropoiesis, end-stage kidney disease, and pregnancy) may result in discrepancies between the A1C result and the patient's true mean glycemia (11). Hemoglobin variants must be considered, particularly when the A1C result does not correlate with the patient's CGM or BGM levels. However, most assays in use in the U.S. are accurate in individuals who are heterozygous for the most common variants (ngsp.org/interf.asp). Other measures of average glycemia such as fructosamine and 1,5-anhydroglucitol are available, but their translation into average glucose levels and their prognostic significance are not as clear as for A1C and CGM. Though some variability in the relationship between average glucose levels and A1C exists among different individuals, in general the association between mean glucose and A1C within an individual correlates over time (12).

A1C does not provide a measure of glycemic variability or hypoglycemia. For patients prone to glycemic variability, especially people with type 1 diabetes or type 2 diabetes with severe insulin deficiency, glycemic control is best evaluated by the combination of results from BGM/CGM and A1C. Discordant results between BGM/CGM and A1C can be the result of the conditions outlined above or glycemic variability, with BGM missing the extremes.

Correlation Between BGM and A1C

Table 6.1 shows the correlation between A1C levels and mean glucose levels based on the international A1C-Derived Average Glucose (ADAG) study, which assessed the correlation between A1C and frequent BGM and CGM in 507 adults (83% non-Hispanic White) with type 1, type 2, and no diabetes (13), and an empirical study of the average blood glucose levels at premeal, postmeal, and bedtime associated with specified A1C levels using data from the ADAG trial (14). The American Diabetes Association (ADA) and the American Association for Clinical Chemistry have determined that the correlation (r = 0.92) in the ADAG trial is strong enough to justify reporting both the A1C result and the estimated average glucose (eAG) result when a clinician orders the A1C test. Clinicians should note that the mean plasma glucose numbers in **Table 6.1** are based on ∼2,700 readings per A1C measurement in the ADAG trial. In a report, mean glucose measured with CGM versus central laboratory–measured A1C in 387 participants in three randomized trials demonstrated that A1C may underestimate or overestimate mean glucose in individuals (12). Thus, as suggested, a patient's BGM or CGM profile has considerable potential for optimizing their glycemic management (13).

Table 6.1—Estimated average glucose (eAG)

A1C (%)	mg/dL*	mmol/L
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)

Data in parentheses are 95% CI. A calculator for converting A1C results into eAG, in either mg/dL or mmol/L, is available at professional.diabetes.org/eAG. *These estimates are based on ADAG data of ∼2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, or no diabetes. The correlation between A1C and average glucose was 0.92 (13,14). Adapted from Nathan et al. (13).

A1C Differences in Ethnic Populations and Children

In the ADAG study, there were no significant differences among racial and ethnic groups in the regression lines between A1C and mean glucose, although the study was underpowered to detect a difference and there was a trend toward a difference between the African and African American and the non-Hispanic White cohorts, with higher A1C values observed in the African and African American cohorts compared with non-Hispanic White cohorts for a given mean glucose. Other studies have also demonstrated higher A1C levels in African American participants than in White participants at a given mean glucose concentration (15,16). In contrast, a recent report in Afro-Caribbean individuals found lower A1C relative to glucose values (17). Taken together, A1C and glucose parameters are essential for the optimal assessment of glycemic status.

A1C assays are available that do not demonstrate a statistically significant difference in individuals with hemoglobin variants. Other assays have statistically significant interference, but the difference is not clinically significant. Use of an assay with such statistically significant interference may explain a report that

Table 6.2—Standardized CGM metrics for clinical care

1. Number of days CGM device is worn (recommend 14 days)	
2. Percentage of time CGM device is active (recommend 70% of data from 14 days)	
3. Mean glucose	
4. Glucose management indicator	
5. Glycemic variability (%CV) target ≤36%*	
6. TAR: % of readings and time >250 mg/dL (>13.9 mmol/L)	Level 2 hyperglycemia
7. TAR: % of readings and time 181–250 mg/dL (10.1–13.9 mmol/L)	Level 1 hyperglycemia
8. TIR: % of readings and time 70–180 mg/dL (3.9–10.0 mmol/L)	In range
9. TBR: % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1 hypoglycemia
10. TBR: % of readings and time <54 mg/dL (<3.0 mmol/L)	Level 2 hypoglycemia

CGM, continuous glucose monitoring; CV, coefficient of variation; TAR, time above range; TBR, time below range; TIR, time in range. *Some studies suggest that lower %CV targets (<33%) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas. Adapted from Battelino et al. (35).

for any level of mean glycemia, African American individuals heterozygous for the common hemoglobin variant HbS had lower A1C by about 0.3 percentage points when compared with those without the trait (18,19). Another genetic variant, X-linked glucose-6-phosphate dehydrogenase G202A, carried by 11% of African American individuals, was associated with a decrease in A1C of about 0.8% in hemizygous men and 0.7% in homozygous women compared with those without the trait (20).

A small study comparing A1C to CGM data in children with type 1 diabetes found a highly statistically significant correlation between A1C and mean blood glucose, although the correlation (r = 0.7) was significantly lower than that in the ADAG trial (21). Whether there are clinically meaningful differences in how A1C relates to average glucose in children or in different ethnicities is an area for further study (15,22,23). Until further evidence is available, it seems prudent to establish A1C goals in these populations with consideration of individualized CGM, BGM, and A1C results. Limitations in perfect alignment between glycemic measurements do not interfere with the usefulness of BGM/CGM for insulin dose adjustments.

Glucose Assessment by Continuous Glucose Monitoring

Recommendations

6.3 Standardized, single-page glucose reports from continuous glucose monitoring (CGM) devices with visual cues, such as the ambulatory glucose profile, should be considered as a standard summary for all CGM devices. **E**

6.4 Time in range is associated with the risk of microvascular complications and can be used for assessment of glycemic control. Additionally, time below range and time above range are useful parameters for the evaluation of the treatment plan (**Table 6.2**). **C**

CGM is rapidly improving diabetes management. As stated in the recommendations, time in range (TIR) is a useful metric of glycemic control and glucose patterns, and it correlates well with A1C in most studies (24–29). New data support the premise that increased TIR correlates with the risk of complications. The studies supporting this assertion are reviewed in more detail in Section 7, "Diabetes Technology"; they include cross-sectional data and cohort studies (30–32) demonstrating TIR as an acceptable end point for clinical trials moving forward and that it can be used for assessment of glycemic control. Additionally, time below range (<70 and <54 mg/dL [3.9 and 3.0 mmol/L]) and time above range (>180 mg/dL [10.0 mmol/L]) are useful parameters for insulin dose adjustments and reevaluation of the treatment plan.

For many people with diabetes, glucose monitoring is key for achieving glycemic targets. Major clinical trials of insulin-treated patients have included BGM as part of multifactorial interventions to demonstrate the benefit of intensive glycemic control on diabetes complications (33). BGM is thus an integral component of effective therapy of patients taking insulin. In recent years, CGM has become a standard method for glucose monitoring for most adults with type 1 diabetes (34). Both approaches to glucose monitoring allow patients to evaluate individual responses to therapy and assess whether glycemic targets are being safely achieved. The international consensus on TIR provides guidance on standardized CGM metrics (**Table 6.2**) and considerations for clinical interpretation and care (35). To make these metrics more actionable, standardized reports with visual cues, such as the ambulatory glucose profile (**Fig 6.1**), are recommended (35) and may help the patient and the health care professional better interpret the data to guide treatment decisions (24,27). BGM and CGM can be useful to guide medical nutrition therapy and physical activity, prevent hypoglycemia, and aid medication management. While A1C is currently the primary measure to guide glucose management and a valuable risk marker for developing diabetes complications, the CGM metrics TIR (with time below range and time above range) and GMI provide the insights for a more personalized diabetes management plan. The incorporation of these metrics into clinical practice is in evolution, and remote access to these data can be critical for telehealth. A rapid optimization and harmonization of CGM terminology and remote access is occurring to meet patient and health care professional needs (36–38). The patient's specific needs and goals should dictate BGM frequency and timing and consideration of CGM use. Please refer to Section 7, "Diabetes Technology," for a more complete discussion of the use of BGM and CGM.

With the advent of new technology, CGM has evolved rapidly in both accuracy and affordability. As such, many patients have these data available to assist with self-management and their health care professionals' assessment of glycemic status. Reports can be generated from CGM that will allow the health care professional and person with diabetes to determine TIR, calculate GMI, and

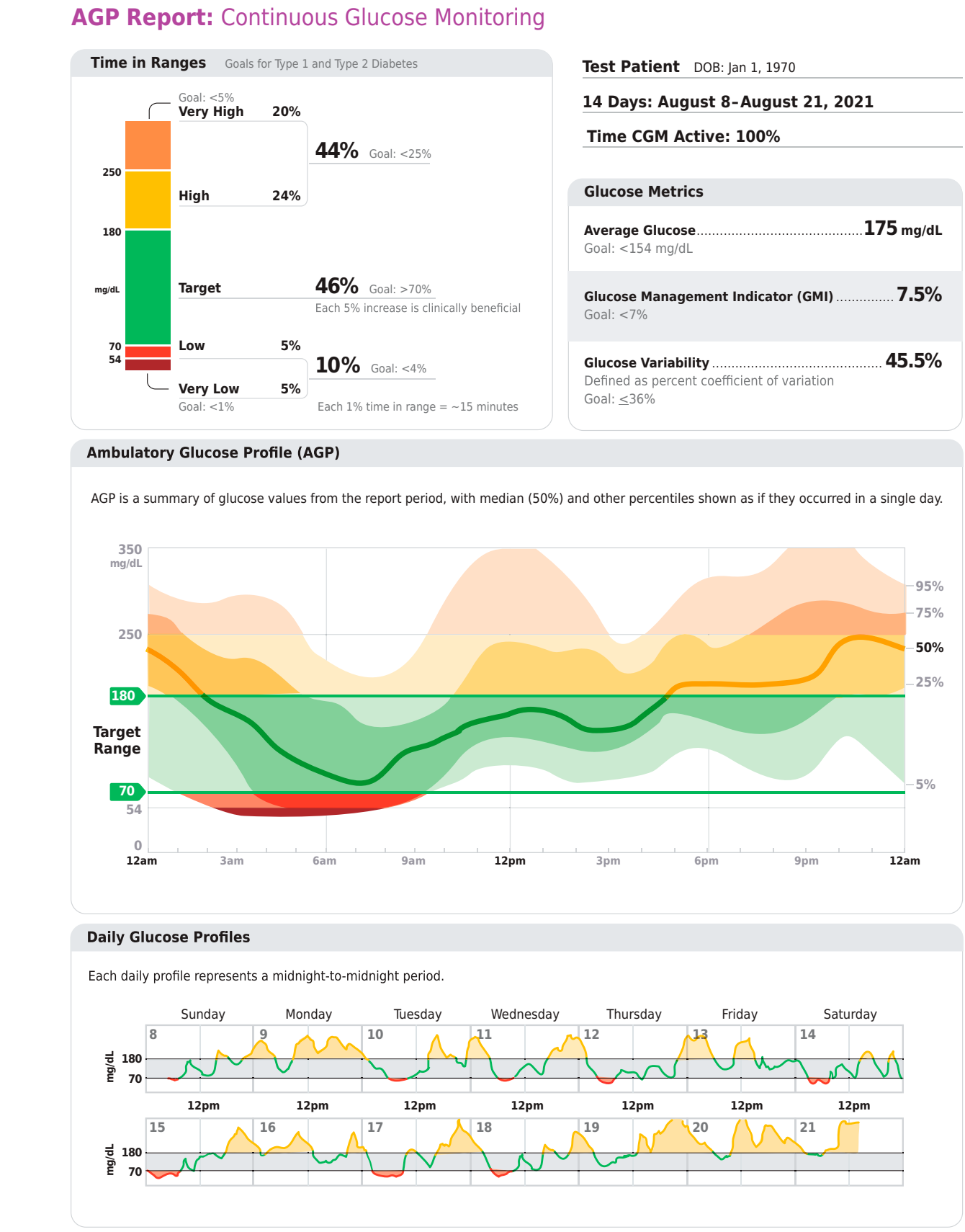

Figure 6.1—Key points included in standard ambulatory glucose profile (AGP) report. Reprinted from Holt et al. (34).

assess hypoglycemia, hyperglycemia, and glycemic variability. As discussed in a recent consensus document, a report formatted as shown in **Fig. 6.1** can be generated (35). Published data from two retrospective studies suggest a strong correlation between TIR and A1C, with a goal of 70% TIR aligning with an A1C of ~7% (8,26). Note the goals of therapy next to each metric in **Fig. 6.1** (e.g., low, <4%; very low, <1%) as values to guide changes in therapy.

GLYCEMIC GOALS

For glycemic goals in older adults, please refer to Section 13, "Older Adults." For glycemic goals in children, please refer to Section 14, "Children and Adolescents." For glycemic goals during pregnancy, please refer to Section 15, "Management of Diabetes in Pregnancy." Overall, regardless of the population being served, it is critical for the glycemic targets to be woven into the overall person-centered strategy. For example, in a very young child, safety and simplicity may outweigh the need for glycemic stability in the short run. Simplification may decrease parental anxiety and build trust and confidence, which could support further strengthening of glycemic targets and self-efficacy. In healthy older adults, there is no empiric need to loosen control; however, less stringent A1C goals may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits (39,40).

However, the health care professional needs to work with an individual and should consider adjusting targets for simplifying the treatment plan if this change is needed to improve safety and medication-taking behavior. Setting goals by face-to-face or remote consultations has been shown to be more effective than usual care for glycemic control in type 2 diabetes for fasting plasma glucose and glycated hemoglobin (41).

Recommendations

6.5a An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate. **A**

6.5b If using ambulatory glucose profile/glucose management indicator to assess glycemia, a parallel goal for many nonpregnant adults is time in range of >70% with time below range <4% and time <54 mg/dL <1%. For those with frailty or at high risk of hypoglycemia, a target of >50% time in range with <1% time below range is recommended. (See **Fig. 6.1** and **Table 6.2**.) **B**

6.6 On the basis of health care professional judgment and patient preference, achievement of lower A1C levels than the goal of 7% may be acceptable and even beneficial if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. **B**

6.7 Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits. Health care professionals should consider deintensification of therapy if appropriate to reduce the risk of hypoglycemia in patients with inappropriate stringent A1C targets. **B**

6.8 Reassess glycemic targets based on the individualized criteria in **Fig. 6.2**. **E**

6.9 Setting a glycemic goal during consultations is likely to improve patient outcomes. **E**

A1C and Microvascular Complications

Hyperglycemia defines diabetes, and glycemic control is fundamental to diabetes management. The Diabetes Control and Complications Trial (DCCT) (33), a prospective randomized controlled trial of intensive (mean A1C about 7% [53 mmol/mol]) versus standard (mean A1C about 9% [75 mmol/mol]) glycemic control in people with type 1 diabetes, showed definitively that better glycemic control is associated with 50–76% reductions in rates of development and progression of microvascular (retinopathy, neuropathy, and diabetic kidney disease) complications. Follow-up of the DCCT cohorts in the Epidemiology of Diabetes Interventions and Complications (EDIC) study (42,43) demonstrated persistence of these microvascular benefits over two decades despite the fact that the glycemic separation between the treatment groups diminished and disappeared during follow-up.

The Kumamoto Study (44) and UK Prospective Diabetes Study (UKPDS) (45,46) confirmed that intensive glycemic control significantly decreased rates of microvascular complications in people with short-duration type 2 diabetes. Long-term follow-up of the UKPDS cohorts showed enduring effects of early glycemic control on most microvascular complications (47).

Therefore, achieving A1C targets of <7% (53 mmol/mol) has been shown to reduce microvascular complications of type 1 and type 2 diabetes when instituted early in the course of disease (2,48). Findings from the DCCT (33) and UKPDS (49) studies demonstrate a curvilinear relationship between A1C and microvascular complications. Such analyses suggest that, on a population level, the greatest number of complications will be averted by taking patients from very poor control to fair/good control. These analyses also suggest that further lowering of A1C from 7 to 6% (53 mmol/mol to 42 mmol/mol) is associated with further reduction in the risk of microvascular complications, although the absolute risk reductions become much smaller. The implication of these findings is that there is no need to deintensify therapy for an individual with an A1C between 6 and 7% in the setting of low hypoglycemia risk with a long life expectancy. There are now newer agents that do not cause hypoglycemia, making it possible to maintain glucose control without the risk of hypoglycemia (see Section 9, "Pharmacologic Approaches to Glycemic Treatment").

Given the substantially increased risk of hypoglycemia in type 1 diabetes and with polypharmacy in type 2 diabetes, the risks of lower glycemic targets may outweigh the potential benefits on microvascular complications. Three landmark trials (Action to Control Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE], and Veterans Affairs Diabetes Trial [VADT]) were conducted to test the effects of near normalization of blood glucose on cardiovascular outcomes in individuals with long-standing type 2 diabetes and either known cardiovascular disease (CVD) or high cardiovascular

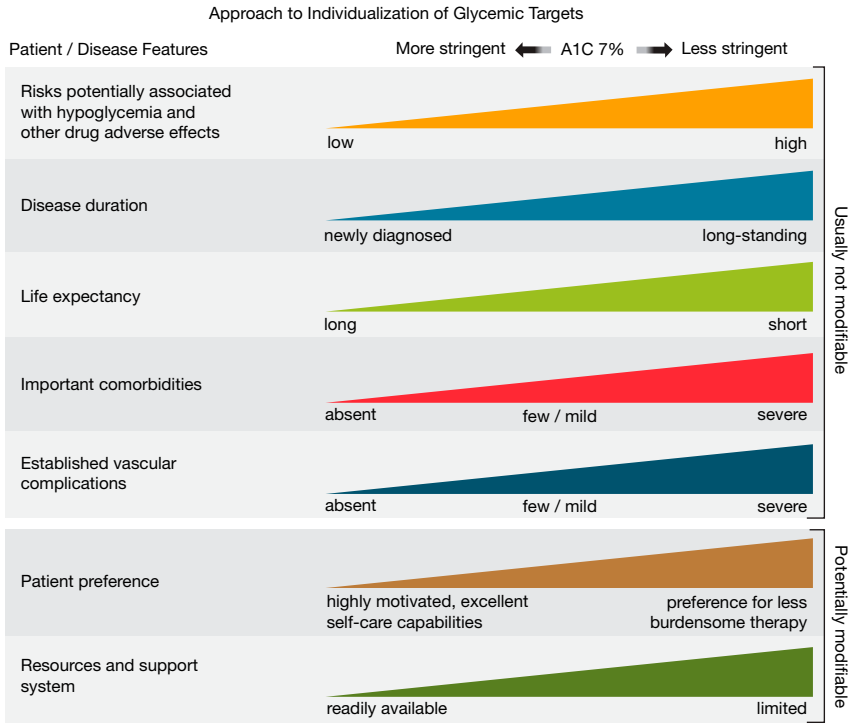

Figure 6.2—Patient and disease factors used to determine optimal glycemic targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. A1C 7% = 53 mmol/mol. Adapted with permission from Inzucchi et al. (71).

risk. These trials showed that lower A1C levels were associated with reduced onset or progression of some microvascular complications (50–52).

The concerning mortality findings in the ACCORD trial discussed below and the relatively intense efforts required to achieve near euglycemia should also be considered when setting glycemic targets for individuals with long-standing diabetes, such as those populations studied in ACCORD, ADVANCE, and VADT. Findings from these studies suggest caution is needed in treating diabetes to near-normal A1C goals in people with long-standing type 2 diabetes with or at significant risk of CVD.

These landmark studies need to be considered with an important caveat; glucagon-like peptide 1 (GLP-1) receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors were not approved at the time of these trials. As such, these agents with established cardiovascular and renal benefits appear to be safe and beneficial in this group of individuals at high risk for cardiorenal complications. Randomized clinical trials examining these agents for cardiovascular safety were not designed to test higher versus lower A1C; therefore, beyond post hoc analysis of these trials, we do not have evidence that it is the glucose lowering by these agents that confers the CVD and renal benefit (53). As such, based on clinician judgment and patient preferences, select patients, especially those with little comorbidity and a long life expectancy, may benefit from adopting more intensive glycemic targets if they can achieve them safely and without hypoglycemia or significant therapeutic burden.

A1C and Cardiovascular Disease Outcomes

Cardiovascular Disease and Type 1 Diabetes

CVD is a more common cause of death than microvascular complications in populations with diabetes. There is evidence for a cardiovascular benefit of intensive glycemic control after long-term follow-up of cohorts treated early in the course of type 1 diabetes. In the DCCT, there was a trend toward lower risk of CVD events with intensive control. In the 9-year post-DCCT follow-up of the EDIC cohort, participants previously randomized to the intensive arm had a significant 57% reduction in the risk of nonfatal myocardial infarction (MI), stroke, or cardiovascular death compared with those previously randomized to the standard arm (54). The benefit of intensive glycemic control in this cohort with type 1 diabetes has been shown to persist for several decades (55) and to be associated with a modest reduction in all-cause mortality (56).

Cardiovascular Disease and Type 2 Diabetes

In type 2 diabetes, there is evidence that more intensive treatment of glycemia in newly diagnosed patients may reduce long-term CVD rates. In addition, data from the Swedish National Diabetes Registry (56) and the Joint Asia Diabetes Evaluation (JADE) demonstrate greater proportions of people with diabetes being diagnosed at <40 years of age and a demonstrably increased burden of heart disease and years of life lost in people diagnosed at a younger age (57–60). Thus, to prevent both microvascular and macrovascular complications of diabetes, there is a major call to overcome therapeutic inertia and treat to target for an individual patient (60,61). During the UKPDS, there was a 16% reduction in CVD events (combined fatal or nonfatal MI and sudden death) in the intensive glycemic control arm that did not reach statistical significance (P = 0.052), and there was no suggestion of benefit on other CVD outcomes (e.g., stroke). Similar to the DCCT/EDIC, after 10 years of observational follow-up, those originally randomized to intensive glycemic control had significant long-term reductions in MI (15% with sulfonylurea or insulin as initial pharmacotherapy, 33% with metformin as initial pharmacotherapy) and in all-cause mortality (13% and 27%, respectively) (47).

ACCORD, ADVANCE, and VADT suggested no significant reduction in CVD outcomes with intensive glycemic control in participants followed for shorter durations (3.5–5.6 years) and who had more advanced type 2 diabetes and CVD risk than the UKPDS participants. All three trials were conducted in relatively older participants with a longer known duration of diabetes (mean duration 8–11 years) and either CVD or multiple cardiovascular risk factors. The target A1C among intensive-control participants was <6% (42 mmol/mol) in ACCORD, <6.5% (48 mmol/mol) in ADVANCE,

and a 1.5% reduction in A1C compared with control participants in VADT, with achieved A1C of 6.4% vs. 7.5% (46 mmol/mol vs. 58 mmol/mol) in ACCORD, 6.5% vs. 7.3% (48 mmol/mol vs. 56 mmol/mol) in ADVANCE, and 6.9% vs. 8.4% (52 mmol/mol vs. 68 mmol/mol) in VADT. Details of these studies are reviewed extensively in the joint ADA position statement "Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials" (61).

The glycemic control comparison in ACCORD was halted early due to an increased mortality rate in the intensive compared with the standard treatment arm (1.41% vs. 1.14% per year; hazard ratio 1.22 [95% CI 1.01–1.46]), with a similar increase in cardiovascular deaths. Analysis of the ACCORD data did not identify a clear explanation for the excess mortality in the intensive treatment arm (62).

Longer-term follow-up has shown no evidence of cardiovascular benefit, or harm, in the ADVANCE trial (63). The end-stage renal disease rate was lower in the intensive treatment group over follow-up. However, 10-year follow-up of the VADT cohort (64) did demonstrate a reduction in the risk of cardiovascular events (52.7 [control group] vs. 44.1 [intervention group] events per 1,000 person-years) with no benefit in cardiovascular or overall mortality. Heterogeneity of mortality effects across studies was noted, which may reflect differences in glycemic targets, therapeutic approaches, and, importantly, population characteristics (65).

Mortality findings in ACCORD (62) and subgroup analyses of VADT (66) suggest that the potential risks of intensive glycemic control may outweigh its benefits in higher-risk individuals. In all three trials, severe hypoglycemia was significantly more likely in participants who were randomly assigned to the intensive glycemic control arm. Individuals with a long duration of diabetes, a known history of hypoglycemia, advanced atherosclerosis, or advanced age/frailty may benefit from less aggressive targets (67,68).

As discussed further below, severe hypoglycemia is a potent marker of high absolute risk of cardiovascular events and mortality (69). Therefore, health care professionals should be vigilant in preventing hypoglycemia and should not aggressively attempt to achieve near-normal A1C levels in people in whom such targets cannot be safely and reasonably achieved. As discussed in Section 9, "Pharmacologic Approaches to Glycemic Treatment," addition of specific SGLT2 inhibitors or GLP-1 receptor agonists that have demonstrated CVD benefit is recommended in patients with established CVD, chronic kidney disease, and heart failure. As outlined in more detail in Section 9, "Pharmacologic Approaches to Glycemic Treatment," and Section 10, "Cardiovascular Disease and Risk Management," the cardiovascular benefits of SGLT2 inhibitors or GLP-1 receptor agonists are not contingent upon A1C lowering; therefore, initiation can be considered in people with type 2 diabetes and CVD independent of the current A1C or A1C goal or metformin therapy. Based on these considerations, the following two strategies are offered (70):

1. If already on dual therapy or multiple glucose-lowering therapies and not on an SGLT2 inhibitor or GLP-1 receptor agonist, consider switching to one of these agents with proven cardiovascular benefit.
2. Introduce SGLT2 inhibitors or GLP-1 receptor agonists in people with CVD at A1C goal (independent of metformin) for cardiovascular benefit, independent of baseline A1C or individualized A1C target.

Setting and Modifying A1C Goals

Numerous factors must be considered when setting glycemic targets. The ADA proposes general targets appropriate for many people but emphasizes the importance of individualization based on key patient characteristics. Glycemic targets must be individualized in the context of shared decision-making to address individual needs and preferences and consider characteristics that influence risks and benefits of therapy; this approach may optimize engagement and self-efficacy.

The factors to consider in individualizing goals are depicted in **Fig. 6.2**. This figure is not designed to be applied rigidly but to be used as a broad construct to guide clinical decision-making (71) and engage people with type 1 and type 2 diabetes in shared decision-making. More aggressive targets may be recommended if they can be achieved safely and with an acceptable burden of therapy and if life expectancy is sufficient to reap the benefits of stringent targets. Less stringent targets (A1C up to 8% [64 mmol/mol]) may be recommended if the patient's life expectancy is such that the benefits of an intensive goal may not be realized, or if the risks and burdens outweigh the potential benefits. Severe or frequent hypoglycemia is an absolute indication for the modification of treatment plans, including setting higher glycemic goals.

Diabetes is a chronic disease that progresses over decades. Thus, a goal that might be appropriate for an individual early in the course of their diabetes may change over time. Newly diagnosed patients and/or those without comorbidities that limit life expectancy may benefit from intensive control proven to prevent microvascular complications. Both DCCT/EDIC and UKPDS demonstrated metabolic memory, or a legacy effect, in which a finite period of intensive control yielded benefits that extended for decades after that control ended. Thus, a finite period of intensive control to near-normal A1C may yield enduring benefits even if control is subsequently deintensified as patient characteristics change. Over time, comorbidities may emerge, decreasing life expectancy and thereby decreasing the potential to reap benefits from intensive control. Also, with longer disease duration, diabetes may become more difficult to control, with increasing risks and burdens of therapy. Thus, A1C targets should be reevaluated over time to balance the risks and benefits as patient factors change.

Recommended glycemic targets for many nonpregnant adults are shown in **Table 6.3**. The recommendations include blood glucose levels that appear to correlate with achievement of an A1C of $<7\%$ (53 mmol/mol). Pregnancy recommendations are discussed in more detail in Section 15, "Management of Diabetes in Pregnancy."

The issue of preprandial versus postprandial BGM targets is complex (72,73). Elevated postchallenge (2-h oral glucose tolerance test) glucose values have been associated with increased cardiovascular risk independent of fasting plasma glucose in some epidemiologic studies, whereas intervention trials have not

Table 6.3—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0% (53 mmol/mol)*#
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients. #CGM may be used to assess glycemic target as noted in Recommendation 6.5b and **Fig. 6.1**. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations (as per **Fig. 6.2**). †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in people with diabetes.

shown postprandial glucose to be a cardiovascular risk factor independent of A1C. In people with diabetes, surrogate measures of vascular pathology, such as endothelial dysfunction, are negatively affected by postprandial hyperglycemia. It is clear that postprandial hyperglycemia, like preprandial hyperglycemia, contributes to elevated A1C levels, with its relative contribution being greater at A1C levels that are closer to 7% (53 mmol/mol). However, outcome studies have shown A1C to be the primary predictor of complications, and landmark trials of glycemic control such as the DCCT and UKPDS relied overwhelmingly on preprandial BGM. Additionally, a randomized controlled trial in patients with known CVD found no CVD benefit of insulin treatment plans targeting postprandial glucose compared with those targeting preprandial glucose (73). Therefore, it is reasonable to check postprandial glucose in individuals who have premeal glucose values within target but A1C values above target. In addition, when intensifying insulin therapy, measuring postprandial plasma glucose 1–2 h after the start of a meal (using BGM or CGM) and using treatments aimed at reducing postprandial plasma glucose values to <180 mg/dL (10.0 mmol/L) may help to lower A1C.

An analysis of data from 470 participants in the ADAG study (237 with type 1 diabetes and 147 with type 2 diabetes) found that the glucose ranges highlighted in **Table 6.1** are adequate to meet targets and decrease hypoglycemia (14). These findings support that premeal glucose targets may be relaxed without undermining overall glycemic control as measured by A1C. These data prompted the revision in the ADA-recommended premeal glucose target to 80–130 mg/dL (4.4–7.2 mmol/L) but did not affect the definition of hypoglycemia.

HYPOGLYCEMIA

Recommendations

6.10 Occurrence and risk for hypoglycemia should be reviewed at every encounter and investigated as indicated. Awareness of hypoglycemia should be considered using validated tools. **C**

6.11 Glucose (approximately 15–20 g) is the preferred treatment for the conscious individual with blood glucose <70 mg/dL (3.9 mmol/L), although any form of carbohydrate that contains glucose may be used. Fifteen minutes after treatment, if blood glucose monitoring (BGM) shows continued hypoglycemia, the treatment should be repeated. Once the BGM or glucose pattern is trending up, the individual should consume a meal or snack to prevent recurrence of hypoglycemia. **B**

6.12 Glucagon should be prescribed for all individuals at increased risk of level 2 or 3 hypoglycemia, so that it is available should it be needed. Caregivers, school personnel, or family members providing support to these individuals should know where it is and when and how to administer it. Glucagon administration is not limited to health care professionals. **E**

6.13 Hypoglycemia unawareness or one or more episodes of level 3 hypoglycemia should trigger hypoglycemia avoidance education and reevaluation and adjustment of the treatment plan to decrease hypoglycemia. **E**

6.14 Insulin-treated patients with hypoglycemia unawareness, one level 3 hypoglycemic event, or a pattern of unexplained level 2 hypoglycemia should be advised to raise their glycemic targets to strictly avoid hypoglycemia for at least several weeks in order to partially reverse hypoglycemia unawareness and reduce risk of future episodes. **A**

6.15 Ongoing assessment of cognitive function is suggested with increased vigilance for hypoglycemia by the clinician, patient, and caregivers if impaired or declining cognition is found. **B**

Hypoglycemia is the major limiting factor in the glycemic management of type 1 and type 2 diabetes. Recommendations regarding the classification of hypoglycemia are outlined in **Table 6.4** (74–83). Level 1 hypoglycemia is defined as a measurable glucose concentration <70 mg/dL (3.9 mmol/L) but ≥54 mg/dL (3.0 mmol/L). A blood glucose concentration of 70 mg/dL (3.9 mmol/L) has been recognized as a threshold for neuroendocrine responses to falling glucose in people without diabetes. Because many people with diabetes demonstrate impaired counterregulatory responses to hypoglycemia and/or experience hypoglycemia unawareness, a measured glucose level <70 mg/dL (3.9 mmol/L) is considered clinically important (independent of the severity of acute hypoglycemic symptoms). Level 2 hypoglycemia (defined as a blood glucose concentration <54 mg/dL [3.0 mmol/L]) is the threshold at which neuroglycopenic symptoms begin to occur and requires immediate action to resolve the hypoglycemic event. If a patient has level 2 hypoglycemia without adrenergic or neuroglycopenic symptoms, they likely have hypoglycemia unawareness (discussed further below). This clinical scenario warrants investigation and review of the treatment plan (75,79). Use Clarke score, Gold score, or Pedersen-Bjergaard score to assess impaired awareness (76). Lastly, level 3 hypoglycemia is defined as a severe

Table 6.4—Classification of hypoglycemia

	Glycemic criteria/description
Level 1	Glucose <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L)
Level 2	Glucose <54 mg/dL (3.0 mmol/L)
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia

Reprinted from Agiostratidou et al. (74).

event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery.

Symptoms of hypoglycemia include, but are not limited to, shakiness, irritability, confusion, tachycardia, and hunger. Hypoglycemia may be inconvenient or frightening to people with diabetes. Level 3 hypoglycemia may be recognized or unrecognized and can progress to loss of consciousness, seizure, coma, or death. Hypoglycemia is reversed by administration of rapid-acting glucose or glucagon. Hypoglycemia can cause acute harm to the person with diabetes or others, especially if it causes falls, motor vehicle accidents, or other injury. Recurrent level 2 hypoglycemia and/or level 3 hypoglycemia is an urgent medical issue and requires intervention with medical treatment plan adjustment, behavioral intervention, and, in some cases, use of technology to assist with hypoglycemia prevention and identification (76,79–82). A large cohort study suggested that among older adults with type 2 diabetes, a history of level 3 hypoglycemia was associated with greater risk of dementia (84). Conversely, in a substudy of the ACCORD trial, cognitive impairment at baseline or decline in cognitive function during the trial was significantly associated with subsequent episodes of level 3 hypoglycemia (85). Evidence from DCCT/EDIC, which involved adolescents and younger adults with type 1 diabetes, found no association between frequency of level 3 hypoglycemia and cognitive decline (86).

Studies of rates of level 3 hypoglycemia that rely on claims data for hospitalization, emergency department visits, and ambulance use substantially underestimate rates of level 3 hypoglycemia (87) yet reveal a high burden of hypoglycemia in adults over 60 years of age in the community (88). African American individuals are at substantially increased risk of level 3 hypoglycemia (88,89). In addition to age and race, other important risk factors found in a community-based epidemiologic cohort of older adults with type 2 diabetes include insulin use, poor or moderate versus good glycemic control, albuminuria, and poor cognitive function (88). Level 3 hypoglycemia was associated with mortality in participants in both the standard and the intensive glycemia arms of the ACCORD trial, but the relationships between hypoglycemia, achieved A1C, and treatment intensity were not straightforward. An association of level 3 hypoglycemia with mortality was also found in the ADVANCE trial (90). An association between self-reported level 3 hypoglycemia and 5-year mortality has also been reported in clinical practice (91). Glucose variability is also associated with an increased risk for hypoglycemia (92).

Young children with type 1 diabetes and the elderly, including those with type 1 and type 2 diabetes (84,93), are noted as particularly vulnerable to hypoglycemia because of their reduced ability to recognize hypoglycemic symptoms and effectively communicate their needs. Individualized glucose targets, patient education, nutrition intervention (e.g., bedtime snack to prevent overnight hypoglycemia when specifically needed to treat low blood glucose), physical activity management, medication adjustment, glucose monitoring, and routine clinical surveillance may improve patient outcomes (94). CGM with automated low glucose suspend and hybrid closed-loop systems have been shown to be effective in reducing hypoglycemia in type 1 diabetes (95). For people with type 1 diabetes with level 3 hypoglycemia and hypoglycemia unawareness that persists despite medical treatment, human islet transplantation may be an option, but the approach remains experimental (96,97).

In 2015, the ADA changed its preprandial glycemic target from 70–130 mg/dL (3.9–7.2 mmol/L) to 80–130 mg/dL (4.4–7.2 mmol/L). This change reflects the results of the ADAG study, which demonstrated that higher glycemic targets corresponded to A1C goals (14). An additional goal of raising the lower range of the glycemic target was to limit overtreatment and provide a safety margin in patients titrating glucose-lowering drugs such as insulin to glycemic targets.

Hypoglycemia Treatment

Health care professionals should continue to counsel patients to treat hypoglycemia with fast-acting carbohydrates at the hypoglycemia alert value of 70 mg/dL (3.9 mmol/L) or less. This should be reviewed at each patient visit. Hypoglycemia treatment requires ingestion of glucose- or carbohydrate-containing foods (98–100). The acute glycemic response correlates better with the glucose content of food than with the carbohydrate content of food. Pure glucose is the preferred treatment, but any form of carbohydrate that contains glucose will raise blood glucose. Added fat may retard and then prolong the acute glycemic response. In type 2 diabetes, ingested protein may increase insulin response without increasing plasma glucose concentrations (101). Therefore, carbohydrate sources high in protein should not be used to treat or prevent hypoglycemia. Ongoing insulin activity or insulin secretagogues may lead to recurrent hypoglycemia unless more food is ingested after recovery. Once the glucose returns to normal, the individual should be counseled to eat a meal or snack to prevent recurrent hypoglycemia.

Glucagon

The use of glucagon is indicated for the treatment of hypoglycemia in people unable or unwilling to consume carbohydrates by mouth. Those in close contact with, or having custodial care of, people with hypoglycemia-prone diabetes (family members, roommates, school personnel, childcare professionals, correctional institution staff, or coworkers) should be instructed on the use of glucagon, including where the glucagon product is kept and when and how to administer it. An individual does not need to be a health care professional to safely

administer glucagon. In addition to traditional glucagon injection powder that requires reconstitution prior to injection, intranasal glucagon and ready-to-inject glucagon preparations for subcutaneous injection are available and may be beneficial in view of safety, efficacy, and ease of use. Care should be taken to ensure that glucagon products are not expired (102).

Hypoglycemia Prevention

Hypoglycemia prevention is a critical component of diabetes management. BGM and, for some individuals, CGM are essential tools to assess therapy and detect incipient hypoglycemia. People with diabetes should understand situations that increase their risk of hypoglycemia, such as when fasting for laboratory tests or procedures, when meals are delayed, during and after the consumption of alcohol, during and after intense physical activity, and during sleep. Hypoglycemia may increase the risk of harm to self or others, such as when driving. Teaching people with diabetes to balance insulin use and carbohydrate intake and physical activity are necessary, but these strategies are not always sufficient for prevention (77, 103–105). Formal training programs to increase awareness of hypoglycemia and to develop strategies to decrease hypoglycemia have been developed, including the Blood Glucose Awareness Training Program, Dose Adjusted for Normal Eating (DAFNE), and DAFNEplus. Conversely, some individuals with type 1 diabetes or type 2 diabetes and hypoglycemia who have a fear of hyperglycemia are resistant to relaxation of glycemic targets (74–83). Regardless of the factors contributing to hypoglycemia and hypoglycemia unawareness, this represents an urgent medical issue requiring intervention.

In type 1 diabetes and severely insulin-deficient type 2 diabetes, hypoglycemia unawareness (or hypoglycemia-associated autonomic failure) can severely compromise stringent diabetes control and quality of life. This syndrome is characterized by deficient counterregulatory hormone release, especially in older adults, and a diminished autonomic response, which are both risk factors for and caused by hypoglycemia. A corollary to this "vicious cycle" is that several weeks of avoidance of hypoglycemia has been demonstrated to improve counterregulation and hypoglycemia awareness in many people with diabetes (106). Hence, individuals with one or more episodes of clinically significant hypoglycemia may benefit from at least short-term relaxation of glycemic targets and availability of glucagon (107). Any person with recurrent hypoglycemia or hypoglycemia unawareness should have their glucose management treatment plan adjusted.

Use of CGM Technology in Hypoglycemia Prevention

With the advent of sensor-augmented CGM and CGM-assisted pump therapy, there has been a promise of alarm-based prevention of hypoglycemia (108,109). To date, there have been a number of randomized controlled trials in adults with type 1 diabetes and studies in adults and children with type 1 diabetes using real-time CGM (see Section 7, "Diabetes Technology"). These studies had differing A1C at entry and differing primary end points and thus must be interpreted carefully. Real-time CGM studies can be divided into studies with elevated A1C with the primary end point of A1C reduction and studies with A1C near target with the primary end point of reduction in hypoglycemia (98, 109–124). In people with type 1 and type 2 diabetes with A1C above target, CGM improved A1C between 0.3 and 0.6%. For studies targeting hypoglycemia, most studies demonstrated a significant reduction in time spent between 54 and 70 mg/dL. A report in people with type 1 diabetes over the age of 60 years revealed a small but statistically significant decrease in hypoglycemia (125). No study to date has reported a decrease in level 3 hypoglycemia. In a single study using intermittently scanned CGM, adults with type 1 diabetes with A1C near goal and impaired awareness of hypoglycemia demonstrated no change in A1C and decreased level 2 hypoglycemia (115). For people with type 2 diabetes, studies examining the impact of CGM on hypoglycemic events are limited; a recent meta-analysis does not reflect a significant impact on hypoglycemic events in type 2 diabetes (126), whereas improvements in A1C were observed in most studies (126–132). Overall, real-time CGM appears to be a useful tool for decreasing time spent in a hypoglycemic range in people with impaired awareness. For people with type 2 diabetes, other strategies to assist them with insulin dosing can improve A1C with minimal hypoglycemia (133,134).

INTERCURRENT ILLNESS

For further information on management of individuals with hyperglycemia in the hospital, see Section 16, "Diabetes Care in the Hospital."

Stressful events (e.g., illness, trauma, surgery) may worsen glycemic control and precipitate diabetic ketoacidosis or nonketotic hyperglycemic hyperosmolar state, life-threatening conditions that require immediate medical care to prevent complications and death. Any condition leading to deterioration in glycemic control necessitates more frequent monitoring of blood glucose; ketosis-prone patients also require urine or blood ketone monitoring. If accompanied by ketosis, vomiting, or alteration in the level of consciousness, marked hyperglycemia requires temporary adjustment of the treatment plan and immediate interaction with the diabetes care team. The patient treated with noninsulin therapies or medical nutrition therapy alone may require insulin. Adequate fluid and caloric intake must be ensured. Infection or dehydration are more likely to necessitate hospitalization of individuals with diabetes versus those without diabetes.

A clinician with expertise in diabetes management should treat the hospitalized patient. For further information on the management of diabetic ketoacidosis and the nonketotic hyperglycemic hyperosmolar state, please refer to the ADA consensus report "Hyperglycemic Crises in Adult Patients With Diabetes" (134).

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7. Diabetes Technology: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Diabetes technology is the term used to describe the hardware, devices, and software that people with diabetes use to assist with self-management, ranging from lifestyle modifications to glucose monitoring and therapy adjustments. Historically, diabetes technology has been divided into two main categories: insulin administered by syringe, pen, or pump (also called continuous subcutaneous insulin infusion), and glucose as assessed by blood glucose monitoring (BGM) or continuous glucose monitoring (CGM). Diabetes technology has expanded to include automated insulin delivery (AID) systems, where CGM-informed algorithms modulate insulin delivery, as well as diabetes self-management support software serving as medical devices. Diabetes technology, when coupled with education, follow-up, and support, can improve the lives and health of people with diabetes; however, the complexity and rapid evolution of the diabetes technology landscape can also be a barrier to implementation for both people with diabetes and the health care team.

GENERAL DEVICE PRINCIPLES

Recommendations

7.1 The type(s) and selection of devices should be individualized based on a person's specific needs, preferences, and skill level. In the setting of an individual whose diabetes is partially or wholly managed by someone else (e.g., a young child or a person with cognitive impairment or dexterity, psychosocial, and/or physical limitations), the caregiver's skills and preferences are integral to the decision-making process. **E**

7.2 When prescribing a device, ensure that people with diabetes/caregivers receive initial and ongoing education and training, either in-person or remotely, and ongoing evaluation of technique, results, and their ability to utilize data, including uploading/sharing data (if applicable), to monitor and adjust therapy. **C**

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7.3 People with diabetes who have been using continuous glucose monitoring, continuous subcutaneous insulin infusion, and/or automated insulin delivery for diabetes management should have continued access across third-party payers, regardless of age or A1C levels. **E**

7.4 Students should be supported at school in the use of diabetes technology, such as continuous glucose monitoring systems, continuous subcutaneous insulin infusion, connected insulin pens, and automated insulin delivery systems, as prescribed by their health care team. **E**

7.5 Initiation of continuous glucose monitoring, continuous subcutaneous insulin infusion, and/or automated insulin delivery early in the treatment of diabetes can be beneficial depending on a person's/caregiver's needs and preferences. **C**

Technology is rapidly changing, but there is no "one-size-fits-all" approach to technology use in people with diabetes. Insurance coverage can lag behind device availability, patient interest in devices and willingness for adoption can vary, and health care teams may have challenges keeping up with newly released technology. An American Diabetes Association resource, which can be accessed at consumerguide.diabetes.org, can help health care professionals and people with diabetes make decisions as to the initial choice of devices. Other sources, including health care professionals and device manufacturers, can help people troubleshoot when difficulties arise.

Education and Training

In general, no device used in diabetes management works optimally without education, training, and ongoing support. There are multiple resources for online tutorials and training videos as well as written material on the use of devices. People with diabetes vary in comfort level with technology, and some prefer in-person training and support. Those with more education regarding device use have better outcomes (1,2); therefore, the need for additional education should be periodically assessed, particularly if outcomes are not being met.

Use in Schools

Instructions for device use should be outlined in the student's diabetes medical management plan (DMMP). A backup plan should be included in the DMMP for potential device failure (e.g., BGM, CGM, and/or insulin delivery devices). School nurses and designees should complete training to stay up to date on diabetes technologies prescribed for use in the school setting. Updated resources to support diabetes care at school, including training materials and a DMMP template, can be found online at diabetes.org/safeatschool.

Initiation of Device Use

The use of CGM devices should be considered from the outset of the diagnosis of diabetes that requires insulin management (3,4). This allows for close tracking of glucose levels with adjustments of insulin dosing and lifestyle modifications and removes the burden of frequent BGM. In addition, early CGM initiation after diagnosis of type 1 diabetes in youth has been shown to decrease A1C and is associated with high parental satisfaction and reliance on this technology for diabetes management (5,6). In appropriate individuals, early use of AID systems or insulin pumps may be considered. Interruption of access to CGM is associated with a worsening of outcomes (7,8); therefore, it is important for individuals on CGM to have consistent access to devices.

BLOOD GLUCOSE MONITORING

Recommendations

7.6 People with diabetes should be provided with blood glucose monitoring devices as indicated by their circumstances, preferences, and treatment. People using continuous glucose monitoring devices must also have access to blood glucose monitoring at all times. **A**

7.7 People who are on insulin using blood glucose monitoring should be encouraged to check their blood glucose levels when appropriate based on their insulin therapy. This may include checking when fasting, prior to meals and snacks, after meals, at bedtime, prior to exercise, when hypoglycemia is suspected, after treating low blood glucose levels until they are normoglycemic, when hyperglycemia is suspected, and prior to and while performing critical tasks such as driving. **B**

7.8 Health care professionals should be aware of the differences in accuracy among blood glucose meters—only meters approved by the U.S. Food and Drug Administration (or comparable regulatory agencies for other geographical locations) with proven accuracy should be used, with unexpired strips purchased from a pharmacy or licensed distributor. **E**

7.9 Although blood glucose monitoring in individuals on noninsulin therapies has not consistently shown clinically significant reductions in A1C, it may be helpful when altering nutrition plan, physical activity, and/or medications (particularly medications that can cause hypoglycemia) in conjunction with a treatment adjustment program. **E**

7.10 Health care professionals should be aware of medications and other factors, such as high-dose vitamin C and hypoxemia, that can interfere with glucose meter accuracy and provide clinical management as indicated. **E**

Major clinical trials of insulin-treated people with diabetes have included BGM as part of multifactorial interventions to demonstrate the benefit of intensive glycemic management on diabetes complications (9). BGM is thus an integral component of effective therapy of individuals taking insulin. In recent years, CGM has emerged as a method for the assessment of glucose levels (discussed below). Glucose monitoring allows people with diabetes to evaluate their individual response to therapy and assess whether glycemic targets are being safely achieved. Integrating results into diabetes management can be a useful tool for guiding medical nutrition therapy and physical activity, preventing hypoglycemia, or adjusting medications (particularly

prandial insulin doses). The specific needs and goals of the person with diabetes should dictate BGM frequency and timing or the consideration of CGM use. As recommended by the device manufacturers and the U.S. Food and Drug Administration (FDA), people with diabetes using CGM must have access to BGM for multiple reasons, including whenever there is suspicion that the CGM is inaccurate, while waiting for warm-up, for calibration (some sensors) or if a warning message appears, and in any clinical setting where glucose levels are changing rapidly (>2 mg/dL/min), which could cause a discrepancy between CGM and blood glucose.

Meter Standards

Glucose meters meeting FDA guidance for meter accuracy provide the most reliable data for diabetes management. There are several current standards for the accuracy of blood glucose meters, but the two most used are those of the International Organization for Standardization (ISO) (ISO 15197:2013) and the FDA. The current ISO and FDA standards are compared in **Table 7.1**. In Europe, currently marketed meters must meet current ISO standards. In the U.S., currently marketed meters must meet the standard under which they were approved, which may not be the current standard. Moreover, the monitoring of current accuracy post-marketing is left to the manufacturer and not routinely checked by an independent source.

People with diabetes assume their glucose meter is accurate because it is FDA cleared, but that may not be the case. There is substantial variation in the accuracy of widely used BGM systems (10,11). The Diabetes Technology Society Blood Glucose Monitoring System Surveillance Program provides information on the performance of devices used for BGM (diabetestechnology.org/surveillance/). In one analysis, 6 of the top 18 glucose meters met the accuracy standard (12). In a subsequent analysis with updated glucose meters, 14 of 18 glucose meters met the minimum accuracy requirements (13). There are single-meter studies in which benefits have been found with individual meter systems, but few studies have compared meters head-to-head. Certain meter system characteristics, such as the use of lancing devices that are less painful (14) and the ability to reapply blood to a strip with an insufficient initial sample, may also be beneficial to people with diabetes (15) and may make BGM less burdensome to perform.

Counterfeit Strips

People with diabetes should be advised against purchasing or reselling preowned or secondhand test strips, as these may give incorrect results. Only unopened and unexpired vials of glucose test strips should be used to ensure BGM accuracy.

Optimizing Blood Glucose Monitoring Device Use

Optimal use of BGM devices requires proper review and interpretation of data by both the person with diabetes and the health care professional to ensure that data are used in an effective and timely manner. In people with type 1 diabetes, there is a correlation between greater BGM frequency and lower A1C (16). Among those who check their blood glucose at least once daily, many report taking no action when results are high or low (17). Some meters now provide advice to the user in real time when monitoring glucose levels (18), whereas others can be used as a part of integrated health platforms (19). People with diabetes should be taught how to use BGM data to adjust food intake, physical activity, or pharmacologic therapy to achieve specific goals. The ongoing need for and frequency of BGM should be reevaluated at each routine visit to ensure its effective use (17,20,21).

People With Diabetes on Intensive Insulin Therapies

BGM is especially important for people with diabetes treated with insulin to monitor for and prevent hypoglycemia and hyperglycemia. Most individuals on intensive insulin therapies (multiple daily injections [MDI] or insulin pump therapy) should be encouraged to assess glucose levels using BGM (and/or CGM) prior to meals and snacks, at bedtime, occasionally postprandially, prior to physical activity, when they suspect hypoglycemia or hyperglycemia, after treating hypoglycemia until they are normoglycemic, and prior to and while performing critical tasks such as driving. For many individuals using BGM, this requires checking up to 6–10 times daily, although individual needs may vary. A database study of almost 27,000 children and adolescents with type 1 diabetes showed that, after adjusting for multiple confounders, increased daily frequency of BGM was significantly associated with lower A1C (−0.2% per additional check per day) and with fewer acute complications (22).

People With Diabetes Using Basal Insulin and/or Oral Agents and Noninsulin Injectables

The evidence is insufficient regarding when to prescribe BGM and how often monitoring is needed for insulin-treated people with diabetes who do not use intensive insulin therapy, such as those

Table 7.1—Comparison of ISO 15197:2013 and FDA blood glucose meter accuracy standards

Setting	FDA (248,254)	ISO 15197:2013 (255)
Home use	95% within 15% for all BG in the usable BG range† 99% within 20% for all BG in the usable BG range†	95% within 15% for BG ≥100 mg/dL 95% within 15 mg/dL for BG <100 mg/dL 99% in A or B region of consensus error grid‡
Hospital use	95% within 12% for BG ≥75 mg/dL 95% within 12 mg/dL for BG <75 mg/dL 98% within 15% for BG ≥75 mg/dL 98% within 15 mg/dL for BG <75 mg/dL	

BG, blood glucose; FDA, U.S. Food and Drug Administration; ISO, International Organization for Standardization. To convert mg/dL to mmol/L, see endmemo.com/medical/unitconvert/Glucose.php. †The range of blood glucose values for which the meter has been proven accurate and will provide readings (other than low, high, or error). ‡Values outside of the "clinically acceptable" A and B regions are considered "outlier" readings and may be dangerous to use for therapeutic decisions (256).

with type 2 diabetes taking basal insulin with or without oral agents and/or noninsulin injectables. However, for those taking basal insulin, assessing fasting glucose with BGM to inform dose adjustments to achieve blood glucose targets results in lower A1C (23,24).

In people with type 2 diabetes not taking insulin, routine glucose monitoring may be of limited additional clinical benefit. By itself, even when combined with education, it has shown limited improvement in outcomes (25–28). However, for some individuals, glucose monitoring can provide insight into the impact of nutrition, physical activity, and medication management on glucose levels. Glucose monitoring may also be useful in assessing hypoglycemia, glucose levels during intercurrent illness, or discrepancies between measured A1C and glucose levels when there is concern an A1C result may not be reliable in specific individuals. It may be useful when coupled with a treatment adjustment program. In a year-long study of insulin-naive people with diabetes with suboptimal initial glycemic outcomes, a group trained in structured BGM (a paper tool was used at least quarterly to collect and interpret seven-point BGM profiles taken on 3 consecutive days) reduced their A1C by 0.3% more than the control group (29). A trial of once-daily BGM that included enhanced feedback from people with diabetes through messaging found no clinically or statistically significant change in A1C at 1 year (28). Meta-analyses have suggested that BGM can reduce A1C by 0.25–0.3% at 6 months (30–32), but the effect was attenuated at 12 months in one analysis (30). Reductions in A1C were greater (−0.3%) in trials where structured BGM data were used to adjust medications, but A1C was not changed significantly without such structured diabetes therapy adjustment (32). A key consideration is that performing BGM alone does not lower blood glucose levels. To be useful, the information must be integrated into clinical and self-management plans.

Glucose Meter Inaccuracy

Although many meters function well under various circumstances, health care professionals and people with diabetes must be aware of factors impairing meter accuracy. A meter reading that seems discordant with the clinical picture needs to be retested or tested in a laboratory. Health care professionals in intensive care unit settings need to be particularly aware of the potential for abnormal meter readings during critical illness, and laboratory-based values should be used if there is any doubt.

Some meters give error messages if meter readings are likely to be false (33).

Oxygen. Currently available glucose monitors utilize an enzymatic reaction linked to an electrochemical reaction, either glucose oxidase or glucose dehydrogenase (34). Glucose oxidase monitors are sensitive to the oxygen available and should only be used with capillary blood in people with normal oxygen saturation. Higher oxygen tensions (i.e., arterial blood or oxygen therapy) may result in false low glucose readings, and low oxygen tensions (i.e., high altitude, hypoxia, or venous blood readings) may lead to false high glucose readings. Glucose dehydrogenase–based monitors are not sensitive to oxygen.

Temperature. Because the reaction is sensitive to temperature, all monitors have an acceptable temperature range (34). Most will show an error if the temperature is unacceptable, but a few will provide a reading and a message indicating that the value may be incorrect. Humidity and altitude may also alter glucose readings.

Interfering Substances. There are a few physiologic and pharmacologic factors that interfere with glucose readings. Most interfere only with glucose oxidase systems (34). They are listed in **Table 7.2**.

Table 7.2—Interfering substances for glucose meter readings

Glucose oxidase monitors
Uric acid
Galactose
Xylose
Acetaminophen
L-DOPA
Ascorbic acid
Glucose dehydrogenase monitors
Icodextrin (used in peritoneal dialysis)

See **Table 7.3** for definitions of types of continuous glucose monitoring devices.

CONTINUOUS GLUCOSE MONITORING DEVICES

Recommendations

7.11 Real-time continuous glucose monitoring **A** or intermittently scanned continuous glucose monitoring **B** should be offered for diabetes management in adults with diabetes on multiple daily injections or continuous subcutaneous insulin infusion who are capable of using the devices safely (either by themselves or with a caregiver). The choice of device should be made based on the individual's circumstances, preferences, and needs.

7.12 Real-time continuous glucose monitoring **A** or intermittently scanned continuous glucose monitoring **C** should be offered for diabetes management in adults with diabetes on basal insulin who are capable of using the devices safely (either by themselves or with a caregiver). The choice of device should be made based on the individual's circumstances, preferences, and needs.

7.13 Real-time continuous glucose monitoring **B** or intermittently scanned continuous glucose monitoring **E** should be offered for diabetes management in youth with type 1 diabetes on multiple daily injections or continuous subcutaneous insulin infusion who are capable of using the devices safely (either by themselves or with a caregiver). The choice of device should be made based on the individual's circumstances, preferences, and needs.

7.14 Real-time continuous glucose monitoring or intermittently scanned continuous glucose monitoring should be offered for diabetes management in youth with type 2 diabetes on multiple daily injections or continuous subcutaneous insulin infusion who are capable of using the devices safely (either by themselves or with a caregiver). The choice of device should be made based on the individual's circumstances, preferences, and needs. **E**

7.15 In people with diabetes on multiple daily injections or continuous subcutaneous insulin infusion, real-time continuous glucose monitoring devices should be used as close to daily as possible for maximal benefit. **A** Intermittently scanned continuous glucose monitoring devices should be scanned frequently, at a minimum once every 8 h. **A** People with diabetes should have uninterrupted access to their supplies to minimize gaps in continuous glucose monitoring. **A**

7.16 When used as an adjunct to pre- and postprandial blood glucose monitoring, continuous glucose monitoring can help to achieve A1C targets in diabetes and pregnancy. **B**

7.17 Periodic use of real-time or intermittently scanned continuous glucose monitoring or use of professional continuous glucose monitoring can be helpful for diabetes management in circumstances where continuous use of continuous glucose monitoring is not appropriate, desired, or available. **C**

7.18 Skin reactions, either due to irritation or allergy, should be assessed and addressed to aid in successful use of devices. **E**

7.19 Continuous glucose monitoring device users should be educated on potential interfering substances and other factors that may affect accuracy. **C**

CGM measures interstitial glucose (which correlates well with plasma glucose, although at times, it can lag if glucose levels are rising or falling rapidly). There are two basic types of CGM devices: those that are owned by the user, unblinded, and intended for frequent/continuous use, including real-time CGM (rtCGM) and intermittently scanned CGM (isCGM), and professional CGM devices that are owned and applied in the clinic, which provide data that are blinded or unblinded for a discrete period of time. The types of sensors currently available are either disposable (rtCGM and isCGM) or implantable (rtCGM). **Table 7.3** provides the definitions for the types of CGM devices. For people with type 1 diabetes using CGM, frequency of sensor use was an important predictor of A1C lowering for all age-groups (35,36). The frequency of scanning with isCGM devices was also correlated with improved outcomes (37–40).

Some real-time systems require calibration by the user, which varies in frequency depending on the device. Additionally, some CGM systems are called "adjunctive," meaning the user should perform BGM for making treatment decisions such as dosing insulin or treating hypoglycemia. Devices that do not have this requirement outside of certain clinical situations (see BLOOD GLUCOSE MONITORING above) are called "nonadjunctive" (41–43).

One specific isCGM device (FreeStyle Libre 2 [no generic form available]) and two specific rtCGM devices (Dexcom G6 [no generic form available] and FreeStyle Libre 3 [no generic form available]) have been designated as integrated CGM (iCGM) devices (44). This is a higher standard set by the FDA so that these devices can be integrated with other digitally connected devices. Presently, although the Medtronic Guardian 3 rtCGM (no generic available) is FDA approved for use with the 670/770G AID systems, Dexcom G6 rtCGM is the only system with iCGM designation and FDA approval for use with AID systems.

Benefits of Continuous Glucose Monitoring

Data From Randomized Controlled Trials

Multiple randomized controlled trials (RCTs) have been performed using rtCGM devices, and the results have largely been positive in terms of reducing A1C levels and/or episodes of hypoglycemia as long as participants regularly wore the devices (35,36,45–67). The initial studies were primarily done in adults and youth with type 1 diabetes on insulin pump therapy and/or MDI (35,36,45–48,51–61). The primary outcome was met and showed benefit in adults of all ages (35,45,46,51,52,54,56,57,68–71) including seniors (53,72,73). Data in children are less consistent; however, rtCGM in young children with type 1 diabetes reduced hypoglycemia; in addition, behavioral support in parents of young children with diabetes using rtCGM showed the benefits of reducing hypoglycemia concerns and diabetes distress (35,60,74). Similarly, A1C reduction was seen in adolescents and young adults with type 1 diabetes using rtCGM (59). RCT data on rtCGM use in individuals with type 2 diabetes on MDI (63), mixed therapies (64,65), and basal insulin (66,75) have consistently shown reductions in A1C but not a reduction in rates of hypoglycemia. The improvements in type 2 diabetes have largely occurred without changes in insulin doses or other diabetes medications. CGM discontinuation in individuals with type 2 diabetes on basal insulin caused partial reversal of A1C reduction and time in range (TIR) improvements, suggesting that continued CGM use achieves the greatest benefits (8).

RCT data for isCGM is more limited. One study was performed in adults with

Table 7.3—Continuous glucose monitoring devices

Type of CGM	Description
rtCGM	CGM systems that measure and display glucose levels continuously
isCGM with and without alarms	CGM systems that measure glucose levels continuously but require scanning for visualization and storage of glucose values
Professional CGM	CGM devices that are placed on the person with diabetes in the health care professional's office (or with remote instruction) and worn for a discrete period of time (generally 7–14 days). Data may be blinded or visible to the person wearing the device. The data are used to assess glycemic patterns and trends. Unlike rtCGM and isCGM devices, these devices are clinic-based and not owned by the person with diabetes.

CGM, continuous glucose monitoring; isCGM, intermittently scanned CGM; rtCGM, real-time CGM.

type 1 diabetes and met its primary outcome of a reduction in rates of hypoglycemia (49). In adults with type 2 diabetes on insulin, two studies were done; one study did not meet its primary end point of A1C reduction (76) but achieved a secondary end point of a reduction in hypoglycemia, and the other study met its primary end point of an improvement in Diabetes Treatment Satisfaction Questionnaire score as well as a secondary end point of A1C reduction (77). In a study of individuals with type 1 or type 2 diabetes taking insulin, the primary outcome of a reduction in severe hypoglycemia was not met (78). One study in youth with type 1 diabetes did not show a reduction in A1C (79); however, the device was well received and was associated with an increased frequency of testing and improved diabetes treatment satisfaction (79). A recent randomized trial of adults with type 1 diabetes showed that the use of iCGM with optional alerts and alarms resulted in reduction of A1C compared with BGM use (80).

Observational and Real-World Studies

isCGM has been widely available in many countries for people with diabetes, and this allows for the collection of large amounts of data across groups of people with diabetes. In adults with diabetes, these data include results from observational studies, retrospective studies, and analyses of registry and population data (81,82). In individuals with type 1 diabetes wearing isCGM devices, most (40,81,83), but not all (84), studies have shown improvement in A1C levels. Reductions in acute diabetes complications, such as diabetic ketoacidosis (DKA), episodes of severe hypoglycemia or diabetes-related coma, and hospitalizations for hypoglycemia and hyperglycemia, have been observed (40,84,85). Some retrospective/observational data have shown an improvement in A1C levels for adults with type 2 diabetes on MDI (86), basal insulin (87), and basal insulin or noninsulin therapies (88). In a retrospective study of adults with type 2 diabetes taking insulin, a reduction in acute diabetes-related events and all-cause hospitalizations was seen (89). Results of self-reported outcomes varied, but where measured, people with diabetes had an increase in treatment satisfaction when comparing isCGM with BGM.

In an observational study in youth with type 1 diabetes, a slight increase in A1C and weight was seen, but the device was associated with a high user satisfaction rate (82).

Retrospective data from rtCGM use in a Veterans Affairs population (90) with type 1 and type 2 diabetes treated with insulin showed that the use of rtCGM significantly lowered A1C and reduced rates of emergency department visits or hospitalizations for hypoglycemia but did not significantly lower overall rates of emergency department visits, hospitalizations, or hyperglycemia.

Real-time Continuous Glucose Monitoring Compared With Intermittently Scanned Continuous Glucose Monitoring

In adults with type 1 diabetes, three RCTs have been done comparing isCGM and rtCGM (91–93). In two of the studies, the primary outcome was a reduction in time spent in hypoglycemia, and rtCGM showed benefit compared with isCGM (91,92). In the other study, the primary outcome was improved TIR, and rtCGM also showed benefit compared with isCGM (93). A retrospective analysis also showed improvement in TIR, comparing rtCGM with isCGM (94).

Data Analysis

The abundance of data provided by CGM offers opportunities to analyze data for people with diabetes more granularly than previously possible, providing additional information to aid in achieving glycemic targets. A variety of metrics have been proposed (95) and are discussed in Section 6, "Glycemic Targets." CGM is essential for creating an ambulatory glucose profile and providing data on TIR, percentage of time spent above and below range, and glycemic variability (96).

Real-time Continuous Glucose Monitoring Device Use in Pregnancy

One well-designed RCT showed a reduction in A1C levels in adult women with type 1 diabetes on MDI or insulin pump therapy who were pregnant and using rtCGM in addition to standard care, including optimization of pre- and postprandial glucose targets (97). This study demonstrated the value of rtCGM in pregnancy complicated by type 1 diabetes by showing a mild improvement in A1C without an increase in hypoglycemia and reductions in large-for-gestational-age births, length of stay, and neonatal hypoglycemia (97). An observational cohort study that evaluated the glycemic variables reported using rtCGM and isCGM found that lower mean glucose, lower standard deviation, and a higher percentage of time in target range were associated with lower risk of large-for-gestational-age births and other adverse neonatal outcomes (98). Use of the rtCGM-reported mean glucose is superior to use of glucose management indicator (GMI) and other calculations to estimate A1C given the changes to A1C that occur in pregnancy (99). Two studies employing intermittent use of rtCGM showed no difference in neonatal outcomes in women with type 1 diabetes (100) or gestational diabetes mellitus (101).

Use of Professional and Intermittent Continuous Glucose Monitoring

Professional CGM devices, which provide retrospective data, either blinded or unblinded, for analysis, can be used to identify patterns of hypoglycemia and hyperglycemia (102,103). Professional CGM can be helpful to evaluate individuals when either rtCGM or isCGM is not available to the individual or they prefer a blinded analysis or a shorter experience with unblinded data. It can be particularly useful to evaluate periods of hypoglycemia in individuals on agents that can cause hypoglycemia in order to make medication dose adjustments. It can also be useful to evaluate individuals for periods of hyperglycemia.

Some data have shown the benefit of intermittent use of CGM (rtCGM or isCGM) in individuals with type 2 diabetes on noninsulin and/or basal insulin therapies (64,104). In these RCTs, people with type 2 diabetes not on intensive insulin therapy used CGM intermittently compared with those randomized to BGM. Both early (64) and late improvements in A1C were found (64,104).

Use of professional or intermittent CGM should always be coupled with analysis and interpretation for people with diabetes, along with education as needed to adjust medication and change lifestyle behaviors (105–107).

Side Effects of Continuous Glucose Monitoring Devices

Contact dermatitis (both irritant and allergic) has been reported with all devices that attach to the skin (108–110). In

Table 7.4—Continuous glucose monitoring devices interfering substances

Medication	Systems affected	Effect
Acetaminophen		
>4 g/day	Dexcom G6	Higher sensor readings than actual glucose
Any dose	Medtronic Guardian	Higher sensor readings than actual glucose
Alcohol	Medtronic Guardian	Sensor readings may be higher than actual glucose
Ascorbic acid (vitamin C), >500 mg/day	FreeStyle Libre	Higher sensor readings than actual glucose
Hydroxyurea	Dexcom G6, Medtronic Guardian	Higher sensor readings than actual glucose
Mannitol	Senseonics Eversense	Sensor bias within therapeutic concentration ranges
Tetracycline	Senseonics Eversense	Sensor bias within therapeutic concentration ranges

some cases, this has been linked to the presence of isobornyl acrylate, a skin sensitizer that can cause an additional spreading allergic reaction (111–113). Patch testing can sometimes identify the cause of contact dermatitis (114). Identifying and eliminating tape allergens is important to ensure the comfortable use of devices and promote self-care (115–118). In some instances, using an implanted sensor can help avoid skin reactions in those sensitive to tape (119,120).

Substances and Factors Affecting Continuous Glucose Monitoring Accuracy

Sensor interference due to several medications/substances is a known potential source of CGM measurement errors (**Table 7.4**). While several of these substances have been reported in the various CGM brands' user manuals, additional interferences have been discovered after the market release of these products. Hydroxyurea, used for myeloproliferative disorders and hematologic conditions, is one of the most recently identified interfering substances that cause a temporary increase in sensor glucose values discrepant from actual glucose values (121–126). Therefore, it is crucial to routinely review the medication list of the person with diabetes to identify possible interfering substances and advise them accordingly on the need to use additional BGM if sensor values are unreliable due to these substances.

INSULIN DELIVERY

Insulin Syringes and Pens

Recommendations

7.20 For people with insulin-requiring diabetes on multiple daily injections, insulin pens are preferred in most cases. Still, insulin syringes may be used for insulin delivery considering individual and caregiver preference, insulin type, dosing therapy, cost, and self-management capabilities. **C**

7.21 Insulin pens or insulin injection aids should be considered for people with dexterity issues or vision impairment to facilitate the accurate dosing and administration of insulin. **C**

7.22 Connected insulin pens can be helpful for diabetes management and may be used in people with diabetes using injectable therapy. **E**

7.23 U.S. Food and Drug Administration–approved insulin dose calculators/decision support systems may be helpful for titrating insulin doses. **C**

Injecting insulin with a syringe or pen (127–143) is the insulin delivery method used by most people with diabetes (134,144), although inhaled insulin is also available. Others use insulin pumps or AID devices (see INSULIN PUMPS AND AUTOMATED INSULIN DELIVERY SYSTEMS). For people with diabetes who use insulin, insulin syringes and pens are both able to deliver insulin safely and effectively for the achievement of glycemic targets. Individual preferences, cost, insulin type, dosing therapy, and self-management capabilities should be considered when choosing among delivery systems. Trials with insulin pens generally show equivalence or small improvements in glycemic outcomes compared with using a vial and syringe. Many individuals with diabetes prefer using a pen due to its simplicity and convenience. It is important to note that while many insulin types are available for purchase as either pens or vials, others may be available in only one form or the other, and there may be significant cost differences between pens and vials (see **Table 9.4** for a list of insulin product costs with dosage forms). Insulin pens may allow people with vision impairment or dexterity issues to dose insulin accurately (145–147), and insulin injection aids are also available to help with these issues. (For a helpful list of injection aids, see consumerguide.diabetes.org/collections/injection-aids). Inhaled insulin can be useful in people who have an aversion to injection.

The most common syringe sizes are 1 mL, 0.5 mL, and 0.3 mL, allowing doses of up to 100 units, 50 units, and 30 units of U-100 insulin, respectively. In a few parts of the world, insulin syringes still have U-80 and U-40 markings for older insulin concentrations and veterinary insulin, and U-500 syringes are available for the use of U-500 insulin. Syringes are generally used once but may be reused by the same individual in resource-limited settings with appropriate storage and cleansing (147).

Insulin pens offer added convenience by combining the vial and syringe into a single device. Insulin pens, allowing push-button injections, come as disposable pens with prefilled cartridges or reusable insulin pens with replaceable insulin cartridges. Pens vary with respect to dosing increment and minimal dose, ranging from half-unit doses to 2-unit dose increments. U-500 pens come in 5-unit dose increments. Some reusable pens include a memory function, which can recall dose amounts and timing. Connected insulin pens are insulin pens with the capacity to record and/or transmit insulin dose data. Insulin pen caps are also available and are placed on existing insulin

pens and assist with calculating insulin doses. Some connected insulin pens and pen caps can be programmed to calculate insulin doses and provide downloadable data reports. These pens and pen caps are useful to people with diabetes for real-time insulin dosing and allow clinicians to retrospectively review the insulin delivery times and in some cases doses and glucose data in order to make informed insulin dose adjustments (148).

Needle thickness (gauge) and length are other considerations. Needle gauges range from 22 to 34, with a higher gauge indicating a thinner needle. A thicker needle can give a dose of insulin more quickly, while a thinner needle may cause less pain. Needle length ranges from 4 to 12.7 mm, with some evidence suggesting shorter needles (4–5 mm) lower the risk of intramuscular injection and possibly the development of lipohypertrophy. When reused, needles may be duller and, thus, injection more painful. Proper insulin injection technique is a requisite for receiving the full dose of insulin with each injection. Concerns with technique and use of the proper technique are outlined in Section 9, "Pharmacologic Approaches to Glycemic Treatment."

Bolus calculators have been developed to aid dosing decisions (149–154). These systems are subject to FDA approval to ensure safety and efficacy in terms of algorithms used and subsequent dosing recommendations. People interested in using these systems should be encouraged to use those that are FDA approved. Health care professional input and education can be helpful for setting the initial dosing calculations with ongoing follow-up for adjustments as needed.

Insulin Pumps and Automated Insulin Delivery Systems

Recommendations

7.24 Automated insulin delivery systems should be offered for diabetes management to youth and adults with type 1 diabetes **A** and other types of insulin-deficient diabetes **E** who are capable of using the device safely (either by themselves or with a caregiver). The choice of device should be made based on the individual's circumstances, preferences, and needs.

7.25 Insulin pump therapy alone with or without sensor-augmented pump low glucose suspend feature and/or automated insulin delivery systems should be offered for diabetes management to youth and adults on multiple daily injections with type 1 diabetes **A** or other types of insulin-deficient diabetes **E** who are capable of using the device safely (either by themselves or with a caregiver) and are not able to use or do not choose an automated insulin delivery system. The choice of device should be made based on the individual's circumstances, preferences, and needs. **A**

7.26 Insulin pump therapy can be offered for diabetes management to youth and adults on multiple daily injections with type 2 diabetes who are capable of using the device safely (either by themselves or with a caregiver). The choice of device should be made based on the individual's circumstances, preferences, and needs. **A**

7.27 Individuals with diabetes who have been using continuous subcutaneous insulin infusion should have continued access across third-party payers. **E**

Insulin Pumps

Insulin pumps have been available in the U.S. for over 40 years. These devices deliver rapid-acting insulin throughout the day to help manage blood glucose levels. Most insulin pumps use tubing to deliver insulin through a cannula, while a few attach directly to the skin without tubing. AID systems, which can adjust insulin delivery rates based on current sensor glucose values, are preferred over nonautomated pumps and MDI in people with type 1 diabetes.

Most studies comparing MDI with insulin pump therapy have been relatively small and of short duration. However, a systematic review and meta-analysis concluded that pump therapy has modest advantages for lowering A1C (−0.30% [95% CI −0.58 to −0.02]) and for reducing severe hypoglycemia rates in children and adults (155). There is no consensus to guide choosing which form of insulin administration is best for a given individual, and research to guide this decision-making process is needed (155). Thus, the choice of MDI or an insulin pump is often based upon the characteristics of the person with diabetes and which method is most likely to benefit them. DiabetesWise (DiabetesWise.org) and the PANTHER Program (pantherprogram.org) have helpful websites to assist health care professionals and people with diabetes in choosing diabetes devices based on their individual needs and the features of the devices. Newer systems, such as sensor-augmented pumps and AID systems, are discussed below.

Adoption of pump therapy in the U.S. shows geographical variations, which may be related to health care professional preference or center characteristics (157,158) and socioeconomic status, as pump therapy is more common in individuals of higher socioeconomic status as reflected by race/ethnicity, private health insurance, family income, and education (157,158). Given the additional barriers to optimal diabetes care observed in disadvantaged groups (159), addressing the differences in access to insulin pumps and other diabetes technology may contribute to fewer health disparities.

Pump therapy can be successfully started at the time of diagnosis (160,161). Practical aspects of pump therapy initiation include assessment of readiness of the person with diabetes and their family, if applicable (although there is no consensus on which factors to consider in adults [162] or children and adolescents with diabetes), selection of pump type and initial pump settings, individual/family education on potential pump complications (e.g., DKA with infusion set failure), transition from MDI, and introduction of advanced pump settings (e.g., temporary basal rates, extended/square/dual wave bolus).

Older individuals with type 1 diabetes benefit from ongoing insulin pump therapy. There are no data to suggest that measurement of C-peptide levels or antibodies predicts success with insulin pump therapy (163,164). Additionally, the frequency of follow-up does not influence outcomes. Access to insulin pump therapy, including AID systems, should be allowed or continued in older adults as it is in younger people.

Complications of the pump can be caused by issues with infusion sets (dislodgement, occlusion), which place individuals at risk for ketosis and DKA and thus must be recognized and managed early (165). Other pump skin issues included lipohypertrophy or, less frequently, lipoatrophy (166,167) and pump site infection (168). Discontinuation of pump therapy is relatively uncommon today; the frequency has decreased over the past few decades, and its causes have changed (168,169). Current reasons for attrition are problems with cost or wearability, dislike for the pump, suboptimal glycemic outcomes, or mood disorders (e.g., anxiety or depression) (170).

Insulin Pumps in Youth

The safety of insulin pumps in youth has been established for over 15 years (171). Studying the effectiveness of insulin pump therapy in lowering A1C has been challenging because of the potential selection bias of observational studies. Participants on insulin pump therapy may have a higher socioeconomic status that may facilitate better glycemic outcomes (172) versus MDI. In addition, the fast pace of development of new insulins and technologies quickly renders comparisons obsolete. However, RCTs comparing insulin pumps and MDI with rapid-acting insulin analogs demonstrate a modest improvement in A1C in participants on insulin pump therapy (173,174). Observational studies, registry data, and meta-analysis have also suggested an improvement in glycemic outcomes in participants on insulin pump therapy (175–177). Although hypoglycemia was a major adverse effect of intensified insulin therapy in the Diabetes Control and Complications Trial (DCCT) (178), data suggest that insulin pumps may reduce the rates of severe hypoglycemia compared with MDI (177,179–181).

There is also evidence that insulin pump therapy may reduce DKA risk (177,182) and diabetes complications, particularly retinopathy and peripheral neuropathy in youth, compared with MDI (162). In addition, treatment satisfaction and quality-of-life measures improved on insulin pump therapy compared with MDI (183,184). Therefore, insulin pumps can be used safely and effectively in youth with type 1 diabetes to assist with achieving targeted glycemic outcomes while reducing the risk of hypoglycemia and DKA, improving quality of life, and preventing long-term complications. Based on shared decision-making by people with diabetes and health care professionals, insulin pumps may be considered in all children and adolescents with type 1 diabetes. In particular, pump therapy may be the preferred mode of insulin delivery for children under 7 years of age (185). Because of a paucity of data in adolescents and youth with type 2 diabetes, there is insufficient evidence to make recommendations.

Common barriers to pump therapy adoption in children and adolescents are concerns regarding the physical interference of the device, discomfort with the idea of having a device on the body, therapeutic effectiveness, and financial burden (175,186).

Sensor-Augmented Pumps

Sensor-augmented pumps that suspend insulin when glucose is low or are predicted to go low within the next 30 min have been approved by the FDA. The Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial of 247 people with type 1 diabetes showed that sensor-augmented insulin pump therapy with a low glucose suspend function significantly reduced nocturnal hypoglycemia over 3 months without increasing A1C levels (55). In a different sensor-augmented pump, predictive low glucose suspend reduced time spent with glucose $<$70 mg/dL from 3.6% at baseline to 2.6% (3.2% with sensor-augmented pump therapy without predictive low glucose suspend) without rebound hyperglycemia during a 6-week randomized crossover trial (187). These devices may offer the opportunity to reduce hypoglycemia for those with a history of nocturnal hypoglycemia. Additional studies have been performed in adults and children, showing the benefits of this technology (188–190).

Automated Insulin Delivery Systems

AID systems increase and decrease insulin delivery based on sensor-derived glucose levels to mimic physiologic insulin delivery. These systems consist of three components: an insulin pump, a continuous glucose monitoring system, and an algorithm that calculates insulin delivery. All AID systems on the market today adjust basal delivery in real time, and some deliver correction doses automatically. While insulin delivery in closed-loop systems eventually may be truly automated, currently used hybrid closed-loop systems require the manual entry of carbohydrates consumed to calculate prandial doses, and adjustments for physical activity must be announced. Multiple studies using various systems with varying algorithms, pumps, and sensors have been performed in adults and children (191–200). Evidence suggests AID systems may reduce A1C levels and improve TIR (201–205). They may also lower the risk of exercise-related hypoglycemia (206) and may have psychosocial benefits (207–210). The use of AID systems depends on the preference of the person with diabetes and the selection of individuals (and/or caregivers) who are capable of safely and effectively using the devices.

Insulin Pumps in People With Type 2 and Other Types of Diabetes

Traditional insulin pumps can be considered for the treatment of people with type 2 diabetes who are on MDI as well as those who have other types of diabetes resulting in insulin deficiency, for instance, those who have had a pancreatectomy and/or individuals with cystic fibrosis (211–215). Similar to data on insulin pump use in people with type 1 diabetes, reductions in A1C levels are not consistently seen in individuals with type 2 diabetes when compared with MDI, although this has been seen in some studies (213,216). Use of insulin pumps in insulin-requiring people with any type of diabetes may improve patient satisfaction and simplify therapy (164,211).

For people with diabetes judged to be clinically insulin deficient who are treated with an intensive insulin therapy, the presence or absence of measurable C-peptide levels does not correlate with response to therapy (164). Alternative pump options in people with type 2 diabetes may include disposable patch-like devices, which provide either a continuous subcutaneous infusion of rapid-acting insulin (basal) with bolus insulin in 2-unit increments at the press of a button or bolus insulin only delivered in 2-unit increments used in conjunction with basal insulin injections (212,214,217,218). Use of an insulin pump as a means of insulin delivery is an individual choice for people with diabetes and should be considered an option in those who are capable of safely using the device.

Do-It-Yourself Closed-Loop Systems

Recommendation

7.28 Individuals with diabetes may be using systems not approved by the U.S. Food and Drug Administration, such as do-it-yourself closed-loop systems and others; health care professionals cannot prescribe these systems but should assist in diabetes management to ensure the safety of people with diabetes. **E**

Some people with type 1 diabetes have been using "do-it-yourself" (DIY) systems that combine an insulin pump and an rtCGM with a controller and an algorithm designed to automate insulin delivery (219–223). These systems are not approved by the FDA, although efforts are underway to obtain regulatory approval for some of them. The information on how to set up and manage these systems is freely available on the internet, and there are internet groups where people inform each other as to how to set up and use them. Although health care professionals cannot prescribe these systems, it is crucial to keep people with diabetes safe if they are using these methods for automated insulin delivery. Part of this entails ensuring people have a backup plan in case of pump failure. Additionally, in most DIY systems, insulin doses are adjusted based on the pump settings for basal rates, carbohydrate ratios, correction doses, and insulin activity. Therefore, these settings can be evaluated and modified based on the individual's insulin requirements.

Digital Health Technology

Recommendation

7.29 Systems that combine technology and online coaching can be beneficial in treating prediabetes and diabetes for some individuals. **B**

Increasingly, people are turning to the internet for advice, coaching, connection, and health care. Diabetes, partly because it is both common and numeric, lends itself to the development of apps and online programs. Recommendations for developing and implementing a digital diabetes clinic have been published (224). The FDA approves and monitors clinically validated, digital, and usually online health technologies intended to treat a medical or psychological condition; these are known as digital therapeutics or "digiceuticals" (fda.gov/medical-devices/digital-health-center-excellence/device-software-functions-including-mobile-medical-applications) (225). Other applications, such as those that assist in displaying or storing data, encourage a healthy lifestyle or provide limited clinical data support. Therefore, it is possible to find apps that have been fully reviewed and approved by the FDA and others designed and promoted by people with relatively little skill or knowledge in the clinical treatment of diabetes. There is insufficient data to provide recommendations for specific apps for diabetes management, education, and support in the absence of RCTs and validations of apps unless they are FDA cleared.

An area of particular importance is that of online privacy and security. Established cloud-based data aggregator programs, such as Tidepool, Glooko, and others, have been developed with appropriate data security features and are compliant with the U.S. Health Insurance Portability and Accountability Act of 1996. These programs can help monitor people with diabetes and provide access to their health care team (226). Consumers should read the policy regarding data privacy and sharing before entering data into an application and learn how they can control the way their data will be used (some programs offer the ability to share more or less information, such as being part of a registry or data repository or not).

Many online programs offer lifestyle counseling to aid with weight loss and increase physical activity (227). Many include a health coach and can create small groups of similar participants on social networks. Some programs aim to treat prediabetes and prevent progression to diabetes, often following the model of the Diabetes Prevention Program (228,229). Others assist in improving diabetes outcomes by remotely monitoring clinical data (for instance, wireless monitoring of glucose levels, weight, or blood pressure) and providing feedback and coaching (230–235). There are text messaging approaches that tie into a variety of different types of lifestyle and treatment programs, which vary in terms of their effectiveness (236,237). There are limited RCT data for many of these interventions, and long-term follow-up is lacking. However, for an individual with diabetes, opting into one of these programs can be helpful in providing support and, for many, is an attractive option.

Inpatient Care

Recommendation

7.30 People with diabetes who are competent to safely use diabetes devices such as insulin pumps and continuous glucose monitoring systems should be supported to continue using them in an inpatient setting or during outpatient procedures, once competency is established and proper supervision is available. **E**

Individuals who are comfortable using their diabetes devices, such as insulin pumps and CGM, should be allowed to use them in an inpatient setting if they are well enough to take care of the devices and have brought the necessary supplies (238–242). People with diabetes who are familiar with treating their own glucose levels can often adjust insulin doses more knowledgeably than inpatient staff who do not personally know the individual or their management style. However, this should occur based on the hospital's policies for diabetes management and use of diabetes technology, and there should be supervision to ensure that the individual is achieving and maintaining glycemic targets during acute illness in a hospitalized setting where factors such as infection, certain medications, immobility, changes in nutrition, and other factors can impact insulin sensitivity and the insulin response.

With the advent of the coronavirus disease 2019 pandemic, the FDA exercised enforcement discretion by allowing CGM device use temporarily in the hospital for patient monitoring (243). This approach has been used to reduce the use of personal protective equipment and more closely monitor patients so that health care personnel do not have to go into a patient room solely to measure a glucose level (244–246). Studies

are underway to assess the effectiveness of this approach, which may ultimately lead to the approved use of CGM for monitoring hospitalized individuals (247–253).

When used in the setting of a clinical trial or when clinical circumstances (such as during a shortage of personal protective equipment) require it, CGM can be used to manage hospitalized individuals in conjunction with BGM. Point-of-care BGM remains the approved method for glucose monitoring in hospitals, especially for dosing insulin and treating hypoglycemia. For more information, see Section 16, "Diabetes Care in the Hospital."

The Future

The pace of development in diabetes technology is extremely rapid. New approaches and tools are available each year. It is hard for research to keep up with these advances because newer versions of the devices and digital solutions are already on the market when a study is completed. The most important component in all of these systems is the person with diabetes. Technology selection must be appropriate for the individual. Simply having a device or application does not change outcomes unless the human being engages with it to create positive health benefits. This underscores the need for the health care team to assist people with diabetes in device and program selection and to support its use through ongoing education and training. Expectations must be tempered by reality—we do not yet have technology that completely eliminates the self-care tasks necessary for managing diabetes, but the tools described in this section can make it easier to manage.

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8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Obesity is a chronic and often progressive disease with numerous medical, physical, and psychosocial complications, including a substantially increased risk for type 2 diabetes (1). There is strong and consistent evidence that obesity management can delay the progression from prediabetes to type 2 diabetes (2–6) and is highly beneficial in treating type 2 diabetes (7–18). In people with type 2 diabetes and overweight or obesity, modest weight loss improves glycemia and reduces the need for glucose-lowering medications (7–9), and larger weight loss substantially reduces A1C and fasting glucose and has been shown to promote sustained diabetes remission through at least 2 years (11,19–23). Several modalities, including intensive behavioral counseling, obesity pharmacotherapy, and bariatric surgery, may aid in achieving and maintaining meaningful weight loss and reducing obesity-associated health risks. Metabolic surgery strongly improves glycemia and often leads to remission of diabetes, improved quality of life, improved cardiovascular outcomes, and reduced mortality. The importance of addressing obesity is further heightened by numerous studies showing that both obesity and diabetes increase the risk for more severe coronavirus disease 2019 (COVID-19) infections (24–27). This section aims to provide evidence-based recommendations for obesity management, including behavioral, pharmacologic, and surgical interventions, in people with type 2 diabetes and in those at risk. This section focuses on obesity management in adults; further discussion on obesity in older individuals and children can be found in Section 13, "Older Adults," and Section 14, "Children and Adolescents," respectively.

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ASSESSMENT

Recommendations

8.1 Use person-centered, nonjudgmental language that fosters collaboration between individuals and health care professionals, including person-first language (e.g., "person with obesity" rather than "obese person"). **E**

8.2 Measure height and weight and calculate BMI at annual visits or more frequently. Assess weight trajectory to inform treatment considerations. **E**

8.3 Based on clinical considerations, such as the presence of comorbid heart failure or significant unexplained weight gain or loss, weight may need to be monitored and evaluated more frequently. **B** If deterioration of medical status is associated with significant weight gain or loss, inpatient evaluation should be considered, especially focused on associations between medication use, food intake, and glycemic status. **E**

8.4 Accommodations should be made to provide privacy during weighing. **E**

8.5 Individuals with diabetes and overweight or obesity may benefit from modest or larger magnitudes of weight loss. Relatively small weight loss (approximately 3–7% of baseline weight) improves glycemia and other intermediate cardiovascular risk factors. **A** Larger, sustained weight losses (>10%) usually confer greater benefits, including disease-modifying effects and possible remission of type 2 diabetes, and may improve long-term cardiovascular outcomes and mortality. **B**

A person-centered communication style that uses inclusive and nonjudgmental language and active listening to elicit individual preferences and beliefs and assesses potential barriers to care should be used to optimize health outcomes and health-related quality of life. Use person-first language (e.g., "person with obesity" rather than "obese person") to avoid defining people by their condition (28–30).

Height and weight should be measured to calculate BMI annually or more frequently when appropriate (20). BMI, calculated as weight in kilograms divided by the square of height in meters (kg/m^2), is calculated automatically by most electronic medical records. Use BMI to document weight status (overweight: BMI 25–29.9 kg/m^2; obesity class I: BMI 30–34.9 kg/m^2; obesity class II: BMI 35–39.9 kg/m^2; obesity class III: BMI ≥40 kg/m^2) but note that misclassification can occur, particularly in very muscular or frail individuals. In some groups, notably Asian and Asian American populations, the BMI cut points to define overweight and obesity are lower than those in other populations due to differences in body composition and cardiometabolic risk (**Table 8.1**) (30,31). Clinical considerations, such as the presence of comorbid heart failure or unexplained weight change, may warrant more frequent weight measurement and evaluation (32,33). If weighing is questioned or refused, the practitioner should be mindful of possible prior stigmatizing experiences and query for concerns, and the value of weight monitoring should be explained as a part of the medical evaluation process that helps to inform treatment decisions (34,35). Accommodations should be made to ensure privacy during weighing, particularly for those individuals who report or exhibit a high level of weight-related distress or dissatisfaction. Scales should be situated in a private area or room. Weight should be measured and reported nonjudgmentally. Care should be taken to regard a person's weight (and weight changes) and BMI as sensitive health information. In addition to weight and BMI, assessment of weight distribution (including propensity for central/visceral adipose deposition) and weight gain pattern and trajectory can further inform risk stratification and treatment options (36).

Health care professionals should advise individuals with overweight or obesity and those with increasing weight trajectories that, in general, higher BMIs increase the risk of diabetes, cardiovascular disease, and all-cause mortality, as well as other adverse health and quality of life outcomes. Health care professionals should assess readiness to engage in behavioral changes for weight loss and jointly determine behavioral and weight loss goals and individualized intervention strategies (37). Strategies may include nutrition changes, physical activity, behavioral counseling, pharmacologic therapy, medical devices, and metabolic surgery (**Table 8.1**). The latter three strategies may be considered for carefully selected individuals as adjuncts to nutrition changes, physical activity, and behavioral counseling.

Among people with type 2 diabetes and overweight or obesity who have inadequate glycemic, blood pressure, and lipid control and/or other obesity-related medical conditions, modest and sustained weight loss improves glycemia, blood pressure, and lipids and may reduce the need for medications (7–9,38). Greater weight loss may produce even greater benefits (21,22).

As little as 3–7% weight loss reduces the risk for diabetes in people at risk and improves glycemia in those with diabetes (2,7,8,39,40). Given the challenge of losing weight and maintaining weight loss, aiming for relatively small and attainable weight loss is often an effective clinical strategy, particularly for individuals who feel overwhelmed by larger weight loss targets. Nevertheless, mounting data from intensive nutrition and behavioral change interventions, pharmacotherapy, and bariatric surgery have shown that more substantial weight loss usually confers still greater benefits on glycemia and possibly disease remission as well as other cardiometabolic and quality-of-life outcomes (6,21–23,41–50).

With the increasing availability of more effective obesity treatments, individuals with diabetes and overweight or obesity should be informed of the potential benefits of both modest and more substantial weight loss and guided in the range of available treatment options, as discussed in the sections below. Shared decision-making should be used when counseling on behavioral changes, intervention choices, and weight management goals.

NUTRITION, PHYSICAL ACTIVITY, AND BEHAVIORAL THERAPY

Recommendations

8.6 Nutrition, physical activity, and behavioral therapy to achieve and maintain ≥5% weight loss are recommended for most people with type 2 diabetes and overweight or obesity. Additional weight loss usually results in further improvements in the management of diabetes and cardiovascular risk. **B**

Table 8.1—Treatment options for overweight and obesity in type 2 diabetes

Treatment	BMI category (kg/m^2)		
	25.0–26.9 (or 23.0–24.9*)	27.0–29.9 (or 25.0–27.4*)	≥30.0 (or ≥27.5*)
Nutrition, physical activity, and behavioral counseling	†	†	†
Pharmacotherapy		†	†
Metabolic surgery			†

*Recommended cut points for Asian American individuals (expert opinion). †Treatment may be indicated for select motivated individuals.

8.7 Such interventions should include a high frequency of counseling (≥16 sessions in 6 months) and focus on nutrition changes, physical activity, and behavioral strategies to achieve a 500–750 kcal/day energy deficit. **A**

8.8 An individual's preferences, motivation, and life circumstances should be considered, along with medical status, when weight loss interventions are recommended. **C**

8.9 Behavioral changes that create an energy deficit, regardless of macronutrient composition, will result in weight loss. Nutrition recommendations should be individualized to the person's preferences and nutritional needs. **A**

8.10 Evaluate systemic, structural, and socioeconomic factors that may impact nutrition patterns and food choices, such as food insecurity and hunger, access to healthful food options, cultural circumstances, and social determinants of health. **C**

8.11 For those who achieve weight loss goals, long-term (≥1 year) weight maintenance programs are recommended when available. Such programs should, at minimum, provide monthly contact and support, recommend ongoing monitoring of body weight (weekly or more frequently) and other self-monitoring strategies, and encourage regular physical activity (200–300 min/week). **A**

8.12 Short-term nutrition intervention using structured, very-low-calorie meals (800–1,000 kcal/day) may be prescribed for carefully selected individuals by trained practitioners in medical settings with close monitoring. Long-term, comprehensive weight maintenance strategies and counseling should be integrated to maintain weight loss. **B**

8.13 There is no clear evidence that nutrition supplements are effective for weight loss. **A**

For a more detailed discussion of lifestyle management approaches and recommendations, see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes." For a detailed discussion of nutrition interventions, please also refer to "Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report" (127).

Look AHEAD Trial

Although the Action for Health in Diabetes (Look AHEAD) trial did not show that the intensive lifestyle intervention reduced cardiovascular events in adults with type 2 diabetes and overweight or obesity (39), it did confirm the feasibility of achieving and maintaining long-term weight loss in people with type 2 diabetes. In the intensive lifestyle intervention group, mean weight loss was 4.7% at 8 years (40). Approximately 50% of intensive lifestyle intervention participants lost and maintained ≥5% of their initial body weight, and 27% lost and maintained ≥10% of their initial body weight at 8 years (40). Participants assigned to the intensive lifestyle group required fewer glucose-, blood pressure–, and lipid-lowering medications than those randomly assigned to standard care. Secondary analyses of the Look AHEAD trial and other large cardiovascular outcome studies document additional weight loss benefits in people with type 2 diabetes, including improved mobility, physical and sexual function, and health-related quality of life (32). Moreover, several subgroups had improved cardiovascular outcomes, including those who achieved >10% weight loss (41) and those with moderately or poorly managed diabetes (A1C >6.8%) at baseline (42).

Behavioral Interventions

Significant weight loss can be attained with lifestyle programs that achieve a 500–750 kcal/day energy deficit, which in most cases is approximately 1,200–1,500 kcal/day for women and 1,500–1,800 kcal/day for men, adjusted for the individual's baseline body weight. Clinical benefits typically begin upon achieving 3–5% weight loss (20,51), and the benefits of weight loss are progressive; more intensive weight loss goals (>5%, >7%, >15%, etc.) may be pursued if needed to achieve further health improvements and/or if the individual is more motivated and more intensive goals can be feasibly and safely attained.

Nutrition interventions may differ by macronutrient goals and food choices as long as they create the necessary energy deficit to promote weight loss (20,52–54). Using meal replacement plans prescribed by trained practitioners, with close monitoring, can be beneficial. Within the intensive lifestyle intervention group of the Look AHEAD trial, for example, the use of a partial meal replacement plan was associated with improvements in nutrition quality and weight loss (51). The nutrition choice should be based on the individual's health status and preferences, including a determination of food availability and other cultural circumstances that could affect nutrition patterns (55).

Intensive behavioral interventions should include ≥16 sessions during the initial 6 months and focus on nutrition changes, physical activity, and behavioral strategies to achieve an ~500–750 kcal/day energy deficit. Interventions should be provided

by trained interventionists in either individual or group sessions (51). Assessing an individual's motivation level, life circumstances, and willingness to implement behavioral changes to achieve weight loss should be considered along with medical status when weight loss interventions are recommended and initiated (37,56).

People with type 2 diabetes and overweight or obesity who have lost weight should be offered long-term (≥1 year) comprehensive weight loss maintenance programs that provide at least monthly contact with trained interventionists and focus on ongoing monitoring of body weight (weekly or more frequently) and/or other self-monitoring strategies such as tracking intake, steps, etc.; continued focus on nutrition and behavioral changes; and participation in high levels of physical activity (200–300 min/week) (57). Some commercial and proprietary weight loss programs have shown promising weight loss results. However, most lack evidence of effectiveness, many do not satisfy guideline recommendations, and some promote unscientific and possibly dangerous practices (58,59).

When provided by trained practitioners in medical settings with ongoing monitoring, short-term (generally up to 3 months) intensive nutrition intervention may be prescribed for carefully selected individuals, such as those requiring weight loss before surgery and those needing greater weight loss and glycemic improvements. When integrated with behavioral support and counseling, structured very-low-calorie meals, typically 800–1,000 kcal/day, utilizing high-protein foods and meal replacement products, may increase the pace and/or magnitude of initial weight loss and glycemic improvements compared with standard behavioral interventions (21,22). As weight regain is common, such interventions should include long-term, comprehensive weight maintenance strategies and counseling to maintain weight loss and behavioral changes (60,61).

Despite widespread marketing and exorbitant claims, there is no clear evidence that nutrition supplements (such as herbs and botanicals, high-dose vitamins and minerals, amino acids, enzymes, antioxidants, etc.) are effective for obesity management or weight loss (62–64). Several large systematic reviews show that most trials evaluating nutrition supplements for weight loss are of low quality and at high risk for bias. High-quality published studies show little or no weight loss benefits. In contrast, vitamin/mineral (e.g., iron, vitamin B12, vitamin D) supplementation may be indicated in cases of documented deficiency, and protein supplements may be indicated as adjuncts to medically supervised weight loss therapies.

Health disparities adversely affect people who have systematically experienced greater obstacles to health based on their race or ethnicity, socioeconomic status, gender, disability, or other factors. Overwhelming research shows that these disparities may significantly affect health outcomes, including increasing the risk for obesity, diabetes, and diabetes-related complications. Health care professionals should evaluate systemic, structural, and socioeconomic factors that may impact food choices, access to healthful foods, and nutrition patterns; behavioral patterns, such as neighborhood safety and availability of safe outdoor spaces for physical activity; environmental exposures; access to health care; social contexts; and, ultimately, diabetes risk and outcomes. For a detailed discussion of social determinants of health, refer to "Social Determinants of Health: A Scientific Review" (65).

PHARMACOTHERAPY

Recommendations

8.14 When choosing glucose-lowering medications for people with type 2 diabetes and overweight or obesity, consider the medication's effect on weight. **B**

8.15 Whenever possible, minimize medications for comorbid conditions that are associated with weight gain. **E**

8.16 Obesity pharmacotherapy is effective as an adjunct to nutrition, physical activity, and behavioral counseling for selected people with type 2 diabetes and BMI ≥27 kg/m^2. Potential benefits and risks must be considered. **A**

8.17 If obesity pharmacotherapy is effective (typically defined as ≥5% weight loss after 3 months' use), further weight loss is likely with continued use. When early response is insufficient (typically <5% weight loss after 3 months' use) or if there are significant safety or tolerability issues, consider discontinuation of the medication and evaluate alternative medications or treatment approaches. **A**

Glucose-Lowering Therapy

A meta-analysis of 227 randomized controlled trials of glucose-lowering treatments in type 2 diabetes found that A1C changes were not associated with baseline BMI, indicating that people with obesity can benefit from the same types of treatments for diabetes as normal-weight individuals (66). As numerous effective medications are available when considering medication plans, health care professionals should consider each medication's effect on weight. Agents associated with varying degrees of weight loss include metformin, α-glucosidase inhibitors, sodium–glucose cotransporter 2 inhibitors, glucagon-like peptide 1 receptor agonists, dual glucagon-like peptide 1/glucose–dependent insulinotropic polypeptide receptor agonist (tirzepatide), and amylin mimetics. Dipeptidyl peptidase 4 inhibitors are weight neutral. In contrast, insulin secretagogues, thiazolidinediones, and insulin are often associated with weight gain (see Section 9, "Pharmacologic Approaches to Glycemic Treatment").

Concomitant Medications

Health care professionals should carefully review the patient's concomitant medications and, whenever possible, minimize or provide alternatives for medications that promote weight gain. Examples of medications associated with weight gain include antipsychotics (e.g., clozapine, olanzapine, risperidone), some antidepressants (e.g., tricyclic antidepressants, some selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors), glucocorticoids, injectable progestins, some anticonvulsants (e.g., gabapentin, pregabalin), and possibly sedating antihistamines and anticholinergics (67).

Approved Obesity Pharmacotherapy Options

The U.S. Food and Drug Administration (FDA) has approved medications for both short-term and long-term weight management as adjuncts to nutrition, physical activity and behavioral therapy. Nearly all

FDA-approved obesity medications have been shown to improve glycemia in people with type 2 diabetes and delay progression to type 2 diabetes in at-risk individuals (23). Phentermine and other older adrenergic agents are indicated for short-term (≤12 weeks) treatment (68). Five medications are FDA approved for long-term use (>12 weeks) in adults with BMI ≥27 kg/m^2 with one or more obesity-associated comorbid conditions (e.g., type 2 diabetes, hypertension, and/or dyslipidemia) who are motivated to lose weight (23). (Refer to Section 14, "Children and Adolescents," for medications approved for adolescents with obesity.) Medications approved by the FDA for the treatment of obesity, summarized in **Table 8.2**, include orlistat, phentermine/topiramate ER, naltrexone/bupropion ER, liraglutide 3 mg, and semaglutide 2.4 mg. (In addition, setmelanotide, a melanocortin 4 receptor agonist, is approved for use in cases of rare genetic mutations resulting in severe hyperphagia and extreme obesity, such as leptin receptor deficiency and proopiomelanocortin deficiency.) In principle, medications help improve adherence to nutrition recommendations, in most cases by modulating appetite or satiety. Health care professionals should be knowledgeable about the product label and balance the potential benefits of successful weight loss against the potential risks of the medication for each individual. These medications are contraindicated in individuals who are pregnant or actively trying to conceive and not recommended for use in women who are nursing. Individuals of reproductive potential should receive counseling regarding the use of reliable methods of contraception. Of note, while weight loss medications are often used in people with type 1 diabetes, clinical trial data in this population are limited.

Assessing Efficacy and Safety

Upon initiating weight loss medication, assess efficacy and safety at least monthly for the first 3 months and at least quarterly thereafter. Modeling from published clinical trials consistently shows that early responders have improved long-term outcomes (69–71). Unless clinical circumstances (such as poor tolerability) or other considerations (such as financial expense or individual preference) suggest otherwise, those who achieve sufficient early weight loss upon starting a chronic weight loss medication (typically defined as >5% weight loss after 3 months' use) should continue the medication. When early use appears ineffective (typically <5% weight loss after 3 months' use), it is unlikely that continued use will improve weight outcomes; as such, it should be recommended to discontinue the medication and consider other treatment options.

MEDICAL DEVICES FOR WEIGHT LOSS

While gastric banding devices have fallen out of favor in recent years, since 2015, several minimally invasive medical devices have been approved by the FDA for short-term weight loss, including implanted gastric balloons, a vagus nerve stimulator, and gastric aspiration therapy (72). Given the current high cost, limited insurance coverage, and paucity of data in people with diabetes, medical devices for weight loss are rarely utilized at this time, and it remains to be seen how they may be used in the future (73).

An oral hydrogel (Plenity) has recently been approved for long-term use in those with BMI >25 kg/m^2 to simulate the space-occupying effect of implantable gastric balloons. Taken with water 30 min before meals, the hydrogel expands to fill a portion of the stomach volume to help decrease food intake during meals. Though average weight loss is relatively small (2–3% greater than placebo), the subgroup of participants with prediabetes or diabetes at baseline had improved weight loss outcomes (8.1% weight loss) compared with the overall treatment (6.4% weight loss) and placebo (4.4% weight loss) groups (74).

METABOLIC SURGERY

Recommendations

8.18 Metabolic surgery should be a recommended option to treat type 2 diabetes in screened surgical candidates with BMI ≥40 kg/m^2 (BMI ≥37.5 kg/m^2 in Asian American individuals) and in adults with BMI 35.0–39.9 kg/m^2 (32.5–37.4 kg/m^2 in Asian American individuals) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods. **A**

8.19 Metabolic surgery may be considered as an option to treat type 2 diabetes in adults with BMI 30.0–34.9 kg/m^2 (27.5–32.4 kg/m^2 in Asian American individuals) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods. **A**

8.20 Metabolic surgery should be performed in high-volume centers with multidisciplinary teams knowledgeable about and experienced in managing obesity, diabetes, and gastrointestinal surgery. **E**

8.21 People being considered for metabolic surgery should be evaluated for comorbid psychological conditions and social and situational circumstances that have the potential to interfere with surgery outcomes. **B**

8.22 People who undergo metabolic surgery should receive long-term medical and behavioral support and routine micronutrient, nutritional, and metabolic status monitoring. **B**

8.23 If postbariatric hypoglycemia is suspected, clinical evaluation should exclude other potential disorders contributing to hypoglycemia, and management includes education, medical nutrition therapy with a dietitian experienced in postbariatric hypoglycemia, and medication treatment, as needed. **A** Continuous glucose monitoring should be considered as an important adjunct to improve safety by alerting individuals to hypoglycemia, especially for those with severe hypoglycemia or hypoglycemia unawareness. **E**

8.24 People who undergo metabolic surgery should routinely be evaluated to assess the need for ongoing mental health services to help with the adjustment to medical and psychosocial changes after surgery. **C**

Surgical procedures for obesity treatment—often referred to interchangeably as bariatric surgery, weight loss surgery, metabolic surgery, or metabolic/bariatric surgery—can promote significant and durable weight loss and improve type 2

Table 8.2—Medications approved by the FDA for the treatment of overweight or obesity in adults

Medication name	Typical adult maintenance dose	Average wholesale price (30-day supply) (128)	National Average Drug Acquisition Cost (30-day supply) (129)	1-Year (52- or 56-week) mean weight loss (% loss from baseline)		Common side effects (130–134)	Possible safety concerns/ considerations (130–134)
				Treatment arms	Weight loss (% loss from baseline)		
Short-term treatment (≤12 weeks)							
Sympathomimetic amine anorectic							
Phentermine (135)	8–37.5 mg q.d.*	$5–$56 (37.5 mg dose)	$2–$3 (37.5 mg dose)	15 mg q.d.† 7.5 mg q.d.† PBO	6.1 5.5 1.2	Dry mouth, insomnia, dizziness, irritability, increased blood pressure, elevated heart rate	• Contraindicated for use in combination with monoamine oxidase inhibitors
Long-term treatment (>12 weeks)							
Lipase inhibitor							
Orlistat (4)	60 mg t.i.d. (OTC) 120 mg t.i.d. (Rx)	$41−$82 $781−$904	NA $722	120 mg t.i.d.‡ PBO	9.6 5.6	Abdominal pain, flatulence, fecal urgency	• Potential malabsorption of fat-soluble vitamins (A, D, E, K) and of certain medications (e.g., cyclosporine, thyroid hormone, anticonvulsants, etc.) • Rare cases of severe liver injury reported • Cholelithiasis • Nephrolithiasis
Sympathomimetic amine anorectic/antiepileptic combination							
Phentermine/ topiramate ER (45)	7.5 mg/46 mg q.d.§	$223 (7.5 mg/46 mg dose)	$179 (7.5 mg/46 mg dose)	15 mg/92 mg q.d.‖ 7.5 mg/46 mg q.d.‖ PBO	9.8 7.8 1.2	Constipation, paresthesia, insomnia, nasopharyngitis, xerostomia, increased blood pressure	• Contraindicated for use in combination with monoamine oxidase inhibitors • Birth defects • Cognitive impairment • Acute angle-closure glaucoma
Opioid antagonist/antidepressant combination							
Naltrexone/ bupropion ER (16)	16 mg/180 mg b.i.d.	$750	$599	16 mg/180 mg b.i.d. PBO	5.0 1.8	Constipation, nausea, headache, xerostomia, insomnia, elevated heart rate and blood pressure	• Contraindicated in people with unmanaged hypertension and/or seizure disorders • Contraindicated for use with chronic opioid therapy • Acute angle-closure glaucoma **Black box warning:** • Risk of suicidal behavior/ideation in people younger than 24 years old who have depression

Continued on p. S134

Table 8.2—Continued

Medication name	Typical adult maintenance dose	Average wholesale price (30-day supply) (128)	National Average Drug Acquisition Cost (30-day supply) (129)	1-Year (52- or 56-week) mean weight loss (% loss from baseline)		Common side effects (130–134)	Possible safety concerns/ considerations (130–134)
				Treatment arms	Weight loss (% loss from baseline)		
Glucagon-like peptide 1 receptor agonist							
Liraglutide (17)**	3 mg q.d.	$1,619	$1,295	3.0 mg q.d. 1.8 mg q.d. PBO	6.0 4.7 2.0	Gastrointestinal side effects (nausea, vomiting, diarrhea, esophageal reflux), injection site reactions, elevated heart rate, hypoglycemia	• Pancreatitis has been reported in clinical trials, but causality has not been established. Discontinue if pancreatitis is suspected. • Use caution in people with kidney disease when initiating or increasing dose due to potential risk of acute kidney injury. • May cause cholelithiasis and gallstone-related complications. **Black box warning:** • Risk of thyroid C-cell tumors in rodents; human relevance not determined
Semaglutide (46,47)	2.4 mg once weekly	$1,619	$1,295	2.4 mg weekly PBO	9.6 3.4	Gastrointestinal side effects (nausea, vomiting, diarrhea, esophageal reflux), injection site reactions, elevated heart rate, hypoglycemia	• Pancreatitis has been reported in clinical trials, but causality has not been established. Discontinue if pancreatitis is suspected. • May cause cholelithiasis and gallstone-related complications. **Black box warning:** • Risk of thyroid C-cell tumors in rodents; human relevance not determined

All medications are contraindicated in individuals who are or may become pregnant. Individuals of reproductive potential must be counseled regarding the use of reliable methods of contraception. Select safety and side effect information is provided; for a comprehensive discussion of safety considerations, please refer to the prescribing information for each agent. b.i.d., twice daily; ER, extended release; OTC, over the counter; NA, data not available; PBO, placebo; q.d., daily; Rx, prescription; t.i.d., three times daily. *Use lowest effective dose; maximum appropriate dose is 37.5 mg. †Duration of treatment was 28 weeks in a general adult population with obesity. ‡Enrolled participants had normal (79%) or impaired (21%) glucose tolerance. §Maximum dose, depending on response, is 15 mg/92 mg q.d. ||Approximately 68% of enrolled participants had type 2 diabetes or impaired glucose tolerance. **Agent has demonstrated cardiovascular safety in a dedicated cardiovascular outcome trial (47).

diabetes. Given the magnitude and rapidity of improvement of hyperglycemia and glucose homeostasis, these procedures have been suggested as treatments for type 2 diabetes even in the absence of severe obesity and will be referred to here as "metabolic surgery."

A substantial body of evidence, including data from numerous large cohort studies and randomized controlled (nonblinded) clinical trials, demonstrates that metabolic surgery achieves superior glycemic control and reduction of cardiovascular risk in people with type 2 diabetes and obesity compared with nonsurgical intervention (18). In addition to improving glycemia, metabolic surgery reduces the incidence of microvascular disease (75), improves quality of life (43,76,77), decreases cancer risk, and improves cardiovascular disease risk factors and long-term cardiovascular events (78–89). Cohort studies that match surgical and nonsurgical subjects strongly suggest that metabolic surgery reduces all-cause mortality (90,91).

The overwhelming majority of procedures in the U.S. are vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass (RYGB). Both procedures result in an anatomically smaller stomach pouch and often robust changes in enteroendocrine hormones. In VSG, ~80% of the stomach is removed, leaving behind a long, thin sleeve-shaped pouch. RYGB creates a much smaller stomach pouch (roughly the size of a walnut), which is then attached to the distal small intestine, thereby bypassing the duodenum and jejunum (**Fig. 8.1**).

Several organizations recommend lowering the BMI criteria for metabolic surgery to 30 kg/m^2 (27.5 kg/m^2 for Asian American individuals) for people with type 2 diabetes who have not achieved sufficient weight loss and improved comorbidities (including hyperglycemia) with reasonable nonsurgical treatments. Studies have documented diabetes remission after 1–5 years in 30–63% of patients with RYGB (18,93).

Most notably, the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial, which randomized 150 participants with unmanaged diabetes to receive either metabolic surgery or medical treatment, found that 29% of those treated with RYGB and 23% treated with VSG achieved A1C of 6.0% or lower after 5 years (43). Available data suggest an erosion of diabetes remission over time (44); at least 35–50% of patients who initially achieve remission of diabetes eventually experience recurrence. Still, the median disease-free period among such individuals following RYGB is 8.3 years (94,95), and the majority of those who undergo surgery maintain substantial improvement of glycemia from baseline for at least 5–15 years (43,76,79,80,95–98).

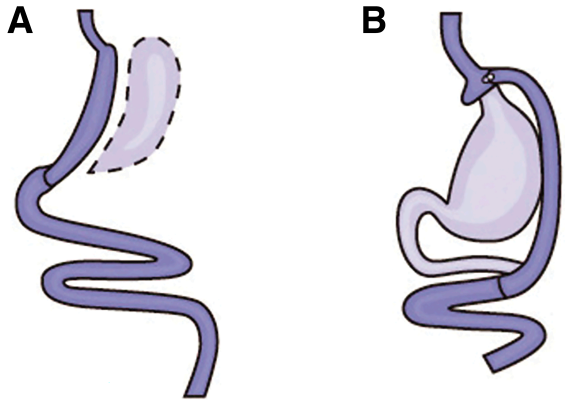

Figure 8.1—*A*: Vertical sleeve gastrectomy. *B*: Roux-en-Y gastric bypass surgery. Images reprinted from National Institute of Diabetes and Digestive and Kidney Diseases (92).

Exceedingly few presurgical predictors of success have been identified, but younger age, shorter duration of diabetes (e.g., <8 years) (70), and lesser severity of diabetes (better glycemic control, nonuse of insulin) are associated with higher rates of diabetes remission (43,79,97,99). Greater baseline visceral fat area may also predict improved postoperative outcomes, especially among Asian American people with type 2 diabetes (100).

Although surgery has been shown to improve the metabolic profiles of people with type 1 diabetes, larger and longer-term studies are needed to determine the role of metabolic surgery in such individuals (101).

Whereas metabolic surgery has greater initial costs than nonsurgical obesity treatments, retrospective analyses and modeling studies suggest that surgery may be cost-effective or even cost-saving for individuals with type 2 diabetes. However, these results largely depend on assumptions about the long-term effectiveness and safety of the procedures (102,103).

Potential Risks and Complications

The safety of metabolic surgery has improved significantly with continued refinement of minimally invasive (laparoscopic) approaches, enhanced training and credentialing, and involvement of multidisciplinary teams. Perioperative mortality rates are typically 0.1–0.5%, similar to those of common abdominal procedures such as cholecystectomy or hysterectomy (104–108). Major complications occur in 2–6% of those undergoing metabolic surgery, which compares favorably with the rates for other commonly performed elective operations (108). Postsurgical recovery times and morbidity have also dramatically declined. Minor complications and need for operative reintervention occur in up to 15% (104–113). Empirical data suggest that the proficiency of the operating surgeon and surgical team is an important factor in determining mortality, complications, reoperations, and readmissions (114). Accordingly, metabolic surgery should be performed in high-volume centers with multidisciplinary teams experienced in managing diabetes, obesity, and gastrointestinal surgery.

Beyond the perioperative period, longer-term risks include vitamin and mineral deficiencies, anemia, osteoporosis, dumping syndrome, and severe hypoglycemia (115). Nutritional and micronutrient deficiencies and related complications occur with a variable frequency depending on the type of procedure and require routine monitoring of micronutrient and nutritional status and lifelong vitamin/nutritional supplementation (115). Dumping syndrome usually occurs shortly (10–30 min) after a meal and may present with diarrhea, nausea, vomiting, palpitations, and fatigue; hypoglycemia is usually not present at the time of symptoms but, in some cases, may develop several hours later.

Postbariatric hypoglycemia (PBH) can occur with RYGB, VSG, and other gastrointestinal procedures and may severely impact quality of life (116–118). PBH is driven in part by altered gastric emptying of ingested nutrients, leading to rapid intestinal glucose absorption and excessive postprandial secretion of glucagon-like peptide 1 and other gastrointestinal peptides. As a result, overstimulation of insulin release and a sharp drop in plasma glucose occur, most commonly 1–3 h after a high-carbohydrate meal. Symptoms range from sweating, tremor, tachycardia, and increased hunger to impaired cognition, loss of consciousness, and seizures. In contrast to dumping syndrome, which often occurs soon after surgery and improves over time, PBH typically presents >1 year post-surgery. Diagnosis is primarily made by a thorough history, detailed records of food intake, physical activity, and symptom patterns, and exclusion of other potential causes (e.g., malnutrition, side effects of medications or supplements, dumping syndrome, and insulinoma). Initial management includes education to facilitate reduced intake of rapidly digested carbohydrates while ensuring adequate intake of protein and healthy fats, and vitamin/nutrient supplements. When available, patients should be offered medical nutrition therapy with a dietitian experienced in PBH and the use of continuous glucose monitoring (ideally real-time continuous glucose monitoring, which can detect dropping glucose levels before severe hypoglycemia occurs), especially for those with hypoglycemia unawareness. Medication treatment, if needed, is primarily aimed at slowing carbohydrate absorption (e.g., acarbose) or reducing glucagon-like peptide 1 and insulin secretion (e.g., diazoxide, octreotide) (119).

People who undergo metabolic surgery may also be at increased risk for substance abuse, worsening or new-onset depression and/or anxiety disorders, and suicidal ideation (115,120–125). Candidates for metabolic surgery should be assessed by a mental health professional with expertise in obesity management prior to consideration for surgery (126). Surgery should be postponed in individuals with alcohol or substance use disorders, severe depression, suicidal ideation, or other significant mental health conditions until these conditions have been sufficiently addressed. Individuals with preoperative or new-onset psychopathology should be assessed regularly following surgery to optimize mental health and postsurgical outcomes.

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9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 1 DIABETES

Recommendations

9.1 Most individuals with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. **A**

9.2 Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. **A**

9.3 Individuals with type 1 diabetes should receive education on how to match mealtime insulin doses to carbohydrate intake, fat and protein content, and anticipated physical activity. **B**

Insulin Therapy

Because the hallmark of type 1 diabetes is absent or near-absent β-cell function, insulin treatment is essential for individuals with type 1 diabetes. In addition to hyperglycemia, insulinopenia can contribute to other metabolic disturbances like hypertriglyceridemia and ketoacidosis as well as tissue catabolism that can be life threatening. Severe metabolic decompensation can be, and was, mostly prevented with once- or twice-daily injections for the six or seven decades after the discovery of insulin. However, over the past three decades, evidence has accumulated supporting more intensive insulin replacement, using multiple daily injections of insulin or continuous subcutaneous administration through an insulin pump, as providing the best combination of effectiveness and safety for people with type 1 diabetes. The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy with multiple daily injections or continuous subcutaneous insulin infusion (CSII) reduced A1C and was associated with improved long-term outcomes (1–3).

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The study was carried out with short-acting (regular) and intermediate-acting (NPH) human insulins. In this landmark trial, lower A1C with intensive control (7%) led to ~50% reductions in microvascular complications over 6 years of treatment. However, intensive therapy was associated with a higher rate of severe hypoglycemia than conventional treatment (62 compared with 19 episodes per 100 patient-years of therapy). Follow-up of subjects from the DCCT more than 10 years after the active treatment component of the study demonstrated fewer macrovascular as well as fewer microvascular complications in the group that received intensive treatment (2,4).

Insulin replacement regimens typically consist of basal insulin, mealtime insulin, and correction insulin (5). Basal insulin includes NPH insulin, long-acting insulin analogs, and continuous delivery of rapid-acting insulin via an insulin pump. Basal insulin analogs have longer duration of action with flatter, more constant plasma concentrations and activity profiles than NPH insulin; rapid-acting analogs (RAA) have a quicker onset and peak and shorter duration of action than regular human insulin. In people with type 1 diabetes, treatment with analog insulins is associated with less hypoglycemia and weight gain as well as lower A1C compared with human insulins (6–8). More recently, two injectable insulin formulations with enhanced rapid-action profiles have been introduced. Inhaled human insulin has a rapid peak and shortened duration of action compared with RAA and may cause less hypoglycemia and weight gain (9) (see also subsection ALTERNATIVE INSULIN ROUTES in PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES), and faster-acting insulin aspart and insulin lispro-aabc may reduce prandial excursions better than RAA (10–12). In addition, longer-acting basal analogs (U-300 glargine or degludec) may confer a lower hypoglycemia risk compared with U-100 glargine in individuals with type 1 diabetes (13,14). Despite the advantages of insulin analogs in individuals with type 1 diabetes, for some individuals the expense and/or intensity of treatment required for their use is prohibitive. There are multiple approaches to insulin treatment, and the central precept in the management of type 1 diabetes is that some form of insulin be given in a planned regimen tailored to the individual to keep them safe and out of diabetic ketoacidosis and to avoid significant hypoglycemia, with every effort made to reach the individual's glycemic targets.

Most studies comparing multiple daily injections with CSII have been relatively small and of short duration. However, a systematic review and meta-analysis concluded that CSII via pump therapy has modest advantages for lowering A1C (−0.30% [95% CI −0.58 to −0.02]) and for reducing severe hypoglycemia rates in children and adults (15). However, there is no consensus to guide the choice of injection or pump therapy in a given individual, and research to guide this decision-making is needed (16). The arrival of continuous glucose monitors (CGM) to clinical practice has proven beneficial in people using insulin therapy. Its use is now considered standard of care for most people with type 1 diabetes (5) (see Section 7, "Diabetes Technology"). Reduction of nocturnal hypoglycemia in individuals with type 1 diabetes using insulin pumps with CGM is improved by automatic suspension of insulin delivery at a preset glucose level (16–18). When choosing among insulin delivery systems, individual preferences, cost, insulin type and dosing regimen, and self-management capabilities should be considered (see Section 7, "Diabetes Technology").

The U.S. Food and Drug Administration (FDA) has now approved multiple hybrid closed-loop pump systems (also called automated insulin delivery [AID] systems). The safety and efficacy of hybrid closed-loop systems has been supported in the literature in adolescents and adults with type 1 diabetes (19,20), and evidence suggests that a closed-loop system is superior to sensor-augmented pump therapy for glycemic control and reduction of hypoglycemia over 3 months of comparison in children and adults with type 1 diabetes (21). In the International Diabetes Closed Loop (iDCL) trial, a 6-month trial in people with type 1 diabetes at least 14 years of age, the use of a closed-loop system was associated with a greater percentage of time spent in the target glycemic range, reduced mean glucose and A1C levels, and a lower percentage of time spent in hypoglycemia compared with use of a sensor-augmented pump (22).

Intensive insulin management using a version of CSII and continuous glucose monitoring should be considered in most individuals with type 1 diabetes. AID systems may be considered in individuals with type 1 diabetes who are capable of using the device safely (either by themselves or with a caregiver) in order to improve time in range and reduce A1C and hypoglycemia (22). See Section 7, "Diabetes Technology," for a full discussion of insulin delivery devices.

In general, individuals with type 1 diabetes require 50% of their daily insulin as basal and 50% as prandial, but this is dependent on a number of factors, including whether the individual consumes lower or higher carbohydrate meals. Total daily insulin requirements can be estimated based on weight, with typical doses ranging from 0.4 to 1.0 units/kg/day. Higher amounts are required during puberty, pregnancy, and medical illness. The *American Diabetes Association/JDRF Type 1 Diabetes Sourcebook* notes 0.5 units/kg/day as a typical starting dose in individuals with type 1 diabetes who are metabolically stable, with half administered as prandial insulin given to control blood glucose after meals and the other half as basal insulin to control glycemia in the periods between meal absorption (23); this guideline provides detailed information on intensification of therapy to meet individualized needs. In addition, the American Diabetes Association (ADA) position statement "Type 1 Diabetes Management Through the Life Span" provides a thorough overview of type 1 diabetes treatment (24).

Typical multidose regimens for individuals with type 1 diabetes combine premeal use of shorter-acting insulins with a longer-acting formulation. The long-acting basal dose is titrated to regulate overnight and fasting glucose. Postprandial glucose excursions are best controlled by a well-timed injection of prandial insulin. The optimal time to administer prandial insulin varies, based on the pharmacokinetics of the formulation (regular, RAA, inhaled), the premeal blood glucose level, and carbohydrate consumption. Recommendations for prandial insulin dose administration should therefore be individualized. Physiologic insulin secretion varies with glycemia, meal size, meal composition, and tissue demands for glucose. To approach this variability in people using insulin treatment, strategies have evolved to adjust prandial doses based on predicted needs. Thus, education on how to

adjust prandial insulin to account for carbohydrate intake, premeal glucose levels, and anticipated activity can be effective and should be offered to most individuals (25,26). For individuals in whom carbohydrate counting is effective, estimates of the fat and protein content of meals can be incorporated into their prandial dosing for added benefit (27) (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes").

The 2021 ADA/European Association for the Study of Diabetes (EASD) consensus report on the management of type 1 diabetes in adults summarizes different insulin regimens and glucose monitoring strategies in individuals with type 1 diabetes (**Fig. 9.1** and **Table 9.1**) (5).

Insulin Injection Technique

Ensuring that individuals and/or caregivers understand correct insulin injection technique is important to optimize glucose control and insulin use safety. Thus, it is important that insulin be delivered into the proper tissue in the correct way. Recommendations have been published elsewhere outlining best practices for insulin injection (28). Proper insulin injection technique includes injecting into appropriate body areas, injection site rotation, appropriate care of injection sites to avoid infection or other complications, and avoidance of intramuscular (IM) insulin delivery.

Exogenously delivered insulin should be injected into subcutaneous tissue, not intramuscularly. Recommended sites for insulin injection include the abdomen, thigh, buttock, and upper arm. Insulin absorption from IM sites differs from that in subcutaneous sites and is also influenced by the activity of the muscle. Inadvertent IM injection can lead to unpredictable insulin absorption and variable effects on glucose and is associated with frequent and unexplained hypoglycemia. Risk for IM insulin delivery is increased in younger, leaner individuals when injecting into the limbs rather than truncal sites (abdomen and buttocks) and when using longer needles. Recent evidence supports the use of short needles (e.g., 4-mm pen needles) as effective and well tolerated when compared with longer needles, including a study performed in adults with obesity (29).

Injection site rotation is additionally necessary to avoid lipohypertrophy, an accumulation of subcutaneous fat in response to the adipogenic actions of insulin at a site of multiple injections. Lipohypertrophy appears as soft, smooth raised areas several centimeters in breadth and can contribute to erratic insulin absorption, increased glycemic variability, and unexplained hypoglycemic episodes. People treated with insulin and/or caregivers should receive education about proper injection site rotation and how to recognize and avoid areas of lipohypertrophy. As noted in **Table 4.1**, examination of insulin injection sites for the presence of lipohypertrophy, as well as assessment of injection device use and injection technique, are key components of a comprehensive diabetes medical evaluation and treatment plan. Proper insulin injection technique may lead to more effective use of this therapy and, as such, holds the potential for improved clinical outcomes.

Noninsulin Treatments for Type 1 Diabetes

Injectable and oral glucose-lowering drugs have been studied for their efficacy as adjuncts to insulin treatment of type 1 diabetes. Pramlintide is based on the naturally occurring β-cell peptide amylin and is approved for use in adults with type 1 diabetes. Clinical trials have demonstrated a modest reduction in A1C (0.3–0.4%) and modest weight loss (~1 kg) with pramlintide (30–33). Similarly, results have been reported for several agents currently approved only for the treatment of type 2 diabetes. The addition of metformin in adults with type 1 diabetes caused small reductions in body weight and lipid levels but did not improve A1C (34,35). The largest clinical trials of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in type 1 diabetes have been conducted with liraglutide 1.8 mg daily, showing modest A1C reductions (~0.4%), decreases in weight (~5 kg), and reductions in insulin doses (36,37). Similarly, sodium–glucose cotransporter 2 (SGLT2) inhibitors have been studied in clinical trials in people with type 1 diabetes, showing improvements in A1C, reduced body weight, and improved blood pressure (38–40); however, SGLT2 inhibitor use in type 1 diabetes is associated with an increased rate of diabetic ketoacidosis. The risks and benefits of adjunctive agents continue to be evaluated, with consensus statements providing guidance on patient selection and precautions (41).

SURGICAL TREATMENT FOR TYPE 1 DIABETES

Pancreas and Islet Transplantation

Successful pancreas and islet transplantation can normalize glucose levels and mitigate microvascular complications of type 1 diabetes. However, people receiving these treatments require lifelong immunosuppression to prevent graft rejection and/or recurrence of autoimmune islet destruction. Given the potential adverse effects of immunosuppressive therapy, pancreas transplantation should be reserved for people with type 1 diabetes undergoing simultaneous renal transplantation, following renal transplantation, or for those with recurrent ketoacidosis or severe hypoglycemia despite intensive glycemic management (42).

The 2021 ADA/EASD consensus report on the management of type 1 diabetes in adults offers a simplified overview of indications for β-cell replacement therapy in people with type 1 diabetes (**Fig. 9.2**) (5).

PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES

Recommendations

9.4a Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. **A**

9.4b In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk (**Fig. 9.3** and **Table 9.2**). **A**

9.4c Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy (**Fig. 9.3** and **Table 9.2**). **A**

9.4d Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering

Representative relative attributes of insulin delivery approaches in people with type 1 diabetes[1]

Injected insulin regimens	Flexibility	Lower risk of hypoglycemia	Higher costs
MDI with LAA + RAA or URAA	+++	+++	+++
Less-preferred, alternative injected insulin regimens			
MDI with NPH + RAA or URAA	++	++	++
MDI with NPH + short-acting (regular) insulin	++	+	+
Two daily injections with NPH + short-acting (regular) insulin or premixed	+	+	+

Continuous insulin infusion regimens	Flexibility	Lower risk of hypoglycemia	Higher costs
Hybrid closed-loop technology	+++++	+++++	++++++
Insulin pump with threshold/ predictive low-glucose suspend	++++	++++	+++++
Insulin pump therapy without automation	+++	+++	++++

Figure 9.1—Choices of insulin regimens in people with type 1 diabetes. Continuous glucose monitoring improves outcomes with injected or infused insulin and is superior to blood glucose monitoring. Inhaled insulin may be used in place of injectable prandial insulin in the U.S. [1]The number of plus signs (+) is an estimate of relative association of the regimen with increased flexibility, lower risk of hypoglycemia, and higher costs between the considered regimens. LAA, long-acting insulin analog; MDI, multiple daily injections; RAA, rapid-acting insulin analog; URAA, ultra-rapid-acting insulin analog. Reprinted from Holt et al. (5).

treatment regimen should consider approaches that support weight management goals (**Fig. 9.3** and **Table 9.2**). **A**

9.5 Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. **A**

9.6 Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. **A**

9.7 The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. **E**

9.8 A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences (**Fig. 9.3** and **Table 9.2**). **E**

9.9 Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit (**Fig. 9.3**, **Table 9.2**, **Table 10.3*B***, and **Table 10.3*C***) is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors (**Fig. 9.3**) (see Section 10, "Cardiovascular Disease and Risk Management," for details on cardiovascular risk reduction recommendations). **A**

9.10 In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. **A**

9.11 If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. **A**

9.12 Recommendation for treatment intensification for individuals not meeting treatment goals should not be delayed. **A**

9.13 Medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate specific factors that impact choice of treatment (**Fig. 4.1** and **Table 9.2**). **E**

9.14 Clinicians should be aware of the potential for overbasalization with insulin therapy. Clinical signals that may prompt evaluation of overbasalization include basal dose more than ~0.5 units/kg/day, high bedtime–morning or postpreprandial glucose differential, hypoglycemia (aware or unaware), and high glycemic variability. Indication of overbasalization should prompt reevaluation to further individualize therapy. **E**

The ADA/EASD consensus report "Management of Hyperglycemia in Type 2 Diabetes, 2022" (43–45) recommends a holistic, multifactorial person-centered approach accounting for the lifelong nature of type 2 diabetes. Person-specific factors that affect choice of treatment include individualized glycemic and weight goals, impact on weight, hypoglycemia and cardiorenal protection (see Section 10, "Cardiovascular Disease and Risk Management," and Section 11 "Chronic Kidney Disease and Risk Management"), underlying physiologic factors, side effect profiles of medications, complexity of regimen, regimen choice to optimize medication use and reduce treatment discontinuation, and access, cost, and availability of medication. Lifestyle

Table 9.1—Examples of subcutaneous insulin regimens

Regimen	Timing and distribution	Advantages	Disadvantages	Adjusting doses
Regimens that more closely mimic normal insulin secretion				
Insulin pump therapy (hybrid closed-loop, low-glucose suspend, CGM-augmented open-loop, BGM-augmented open-loop)	Basal delivery of URAA or RAA; generally 40–60% of TDD. Mealtime and correction: URAA or RAA by bolus based on ICR and/or ISF and target glucose, with pre-meal insulin ∼15 min before eating.	Can adjust basal rates for varying insulin sensitivity by time of day, for exercise and for sick days. Flexibility in meal timing and content. Pump can deliver insulin in increments of fractions of units. Potential for integration with CGM for low-glucose suspend or hybrid closed-loop. TIR % highest and TBR % lowest with: hybrid closed-loop > low-glucose suspend > CGM-augmented open-loop > BGM-augmented open-loop.	Most expensive regimen. Must continuously wear one or more devices. Risk of rapid development of ketosis or DKA with interruption of insulin delivery. Potential reactions to adhesives and site infections. Most technically complex approach (harder for people with lower numeracy or literacy skills).	Mealtime insulin: if carbohydrate counting is accurate, change ICR if glucose after meal consistently out of target. Correction insulin: adjust ISF and/or target glucose if correction does not consistently bring glucose into range. Basal rates: adjust based on overnight, fasting or daytime glucose outside of activity of URAA/RAA bolus.
MDI: LAA + flexible doses of URAA or RAA at meals	LAA once daily (insulin detemir or insulin glargine may require twice-daily dosing); generally 50% of TDD. Mealtime and correction: URAA or RAA based on ICR and/or ISF and target glucose.	Can use pens for all components. Flexibility in meal timing and content. Insulin analogs cause less hypoglycemia than human insulins.	At least four daily injections. Most costly insulins. Smallest increment of insulin is 1 unit (0.5 unit with some pens). LAAs may not cover strong dawn phenomenon (rise in glucose in early morning hours) as well as pump therapy.	Mealtime insulin: if carbohydrate counting is accurate, change ICR if glucose after meal consistently out of target. Correction insulin: adjust ISF and/or target glucose if correction does not consistently bring glucose into range. LAA: based on overnight or fasting glucose or daytime glucose outside of activity time course, or URAA or RAA injections.
MDI regimens with less flexibility				
Four injections daily with fixed doses of N and RAA	Pre-breakfast: RAA ∼20% of TDD. Pre-lunch: RAA ∼10% of TDD. Pre-dinner: RAA ∼10% of TDD. Bedtime: N ∼50% of TDD.	May be feasible if unable to carbohydrate count. All meals have RAA coverage. N is less expensive than LAAs.	Shorter duration RAA may lead to basal deficit during day; may need twice-daily N. Greater risk of nocturnal hypoglycemia with N. Requires relatively consistent mealtimes and carbohydrate intake.	Pre-breakfast RAA: based on BGM after breakfast or before lunch. Pre-lunch RAA: based on BGM after lunch or before dinner. Pre-dinner RAA: based on BGM after dinner or at bedtime. Evening N: based on fasting or overnight BGM.

Continued on p. S145

Table 9.1—Continued

Regimen	Timing and distribution	Advantages	Disadvantages	Adjusting doses
Four injections daily with fixed doses of N and R	Pre-breakfast: R ∼20% of TDD. Pre-lunch: R ∼10% of TDD. Pre-dinner: R ∼10% of TDD. Bedtime: N ∼50% of TDD.	May be feasible if unable to carbohydrate count. R can be dosed based on ICR and correction. All meals have R coverage. Least expensive insulins.	Greater risk of nocturnal hypoglycemia with N. Greater risk of delayed post-meal hypoglycemia with R. Requires relatively consistent mealtimes and carbohydrate intake. R must be injected at least 30 min before meal for better effect.	Pre-breakfast R: based on BGM after breakfast or before lunch. Pre-lunch R: based on BGM after lunch or before dinner. Pre-dinner R: based on BGM after dinner or at bedtime. Evening N: based on fasting or overnight BGM.
Regimens with fewer daily injections				
Three injections daily: N+R or N+RAA	Pre-breakfast: ∼40% N + ∼15% R or RAA. Pre-dinner: ∼15% R or RAA. Bedtime: 30% N.	Morning insulins can be mixed in one syringe. May be appropriate for those who cannot take injection in middle of day. Morning N covers lunch to some extent. Same advantages of RAAs over R. Least (N+R) or less expensive insulins than MDI with analogs.	Greater risk of nocturnal hypoglycemia with N than LAAs. Greater risk of delayed post-meal hypoglycemia with R than RAAs. Requires relatively consistent mealtimes and carbohydrate intake. Coverage of post-lunch glucose often suboptimal. R must be injected at least 30 min before meal for better effect.	Morning N: based on pre-dinner BGM. Morning R: based on pre-lunch BGM. Morning RAA: based on post-breakfast or pre-lunch BGM. Pre-dinner R: based on bedtime BGM. Pre-dinner RAA: based on post-dinner or bedtime BGM. Evening N: based on fasting BGM.
Twice-daily "split-mixed": N+R or N+RAA	Pre-breakfast: ∼40% N + ∼15% R or RAA. Pre-dinner: ∼30% N + ∼15% R or RAA.	Least number of injections for people with strong preference for this. Insulins can be mixed in one syringe. Least (N+R) or less (N+RAA) expensive insulins vs analogs. Eliminates need for doses during the day.	Risk of hypoglycemia in afternoon or middle of night from N. Fixed mealtimes and meal content. Coverage of post-lunch glucose often suboptimal. Difficult to reach targets for blood glucose without hypoglycemia.	Morning N: based on pre-dinner BGM. Morning R: based on pre-lunch BGM. Morning RAA: based on post-breakfast or pre-lunch BGM. Evening R: based on bedtime BGM. Evening RAA: based on post-dinner or bedtime BGM. Evening N: based on fasting BGM.

BGM, blood glucose monitoring; CGM, continuous glucose monitoring; ICR, insulin-to-carbohydrate ratio; ISF, insulin sensitivity factor; LAA, long-acting analog; MDI, multiple daily injections; N, NPH insulin; R, short-acting (regular) insulin; RAA, rapid-acting analog; TDD, total daily insulin dose; URAA, ultra-rapid-acting analog. Reprinted from Holt et al. (5).

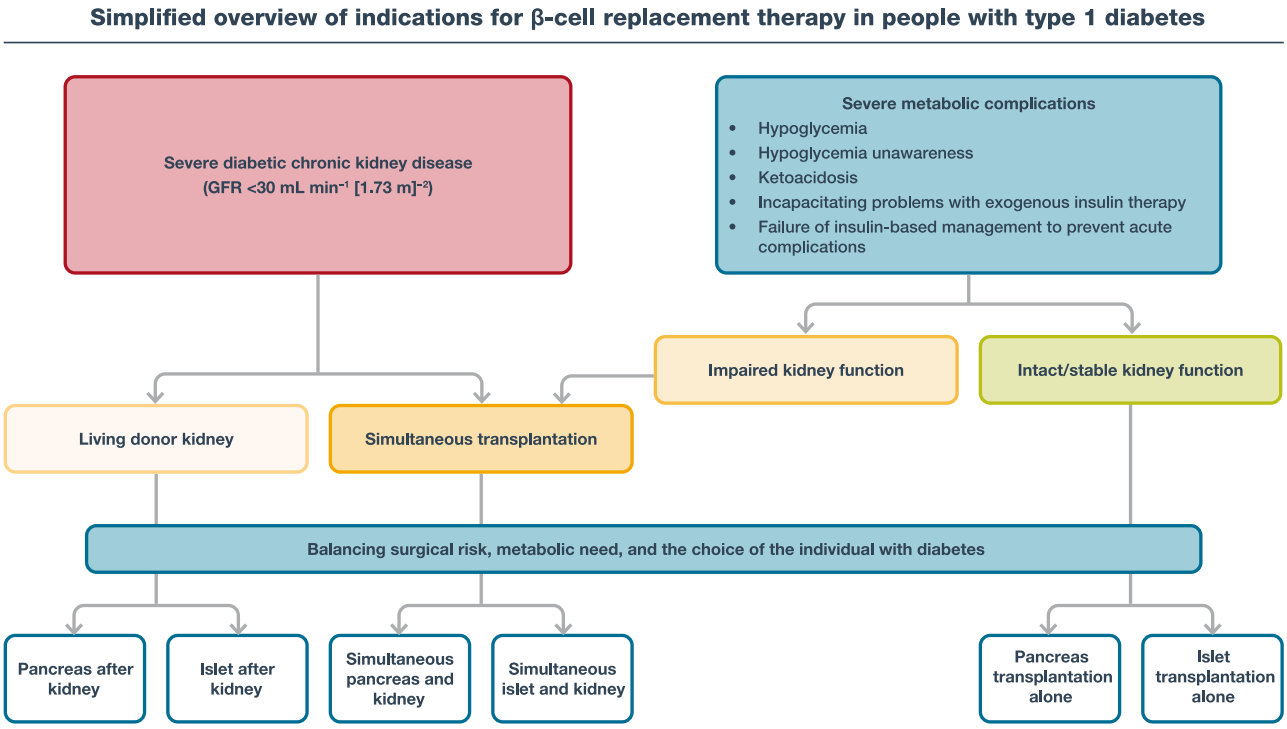


Figure 9.2—Simplified overview of indications for β-cell replacement therapy in people with type 1 diabetes. The two main forms of β-cell replacement therapy are whole-pancreas transplantation or islet cell transplantation. β-Cell replacement therapy can be combined with kidney transplantation if the individual has end-stage renal disease, which may be performed simultaneously or after kidney transplantation. All decisions about transplantation must balance the surgical risk, metabolic need, and the choice of the individual with diabetes. GFR, glomerular filtration rate. Reprinted from Holt et al. (5).

modifications and health behaviors that improve health (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes") should be emphasized along with any pharmacologic therapy. Section 13, "Older Adults," and Section 14, "Children and Adolescents," have recommendations specific for older adults and for children and adolescents with type 2 diabetes, respectively. Section 10, "Cardiovascular Disease and Risk Management," and Section 11, "Chronic Kidney Disease and Risk Management," have recommendations for the use of glucose-lowering drugs in the management of cardiovascular and renal disease, respectively.

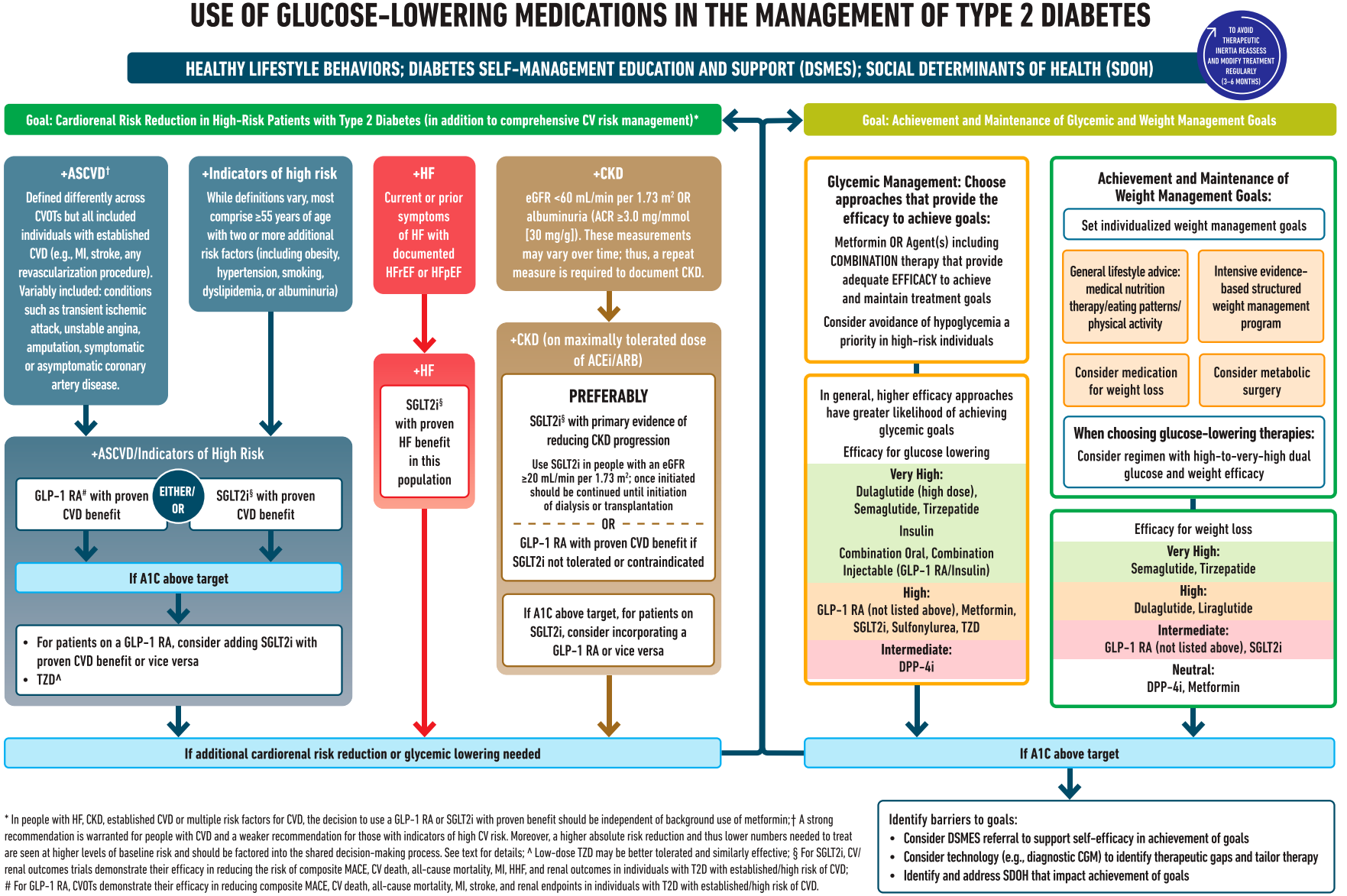
Choice of Glucose-Lowering Therapy

Healthy lifestyle behaviors, diabetes self-management, education, and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. Pharmacotherapy should be started at the time type 2 diabetes is diagnosed unless there are contraindications. Pharmacologic approaches that provide the efficacy to achieve treatment goals should be considered, such as metformin or other agents, including combination therapy, that provide adequate efficacy to achieve and maintain treatment goals (45). In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and/or chronic kidney disease (CKD), the treatment regimen should include agents that reduce cardiorenal risk (see **Fig. 9.3**, **Table 9.2**, Section 10, "Cardiovascular Disease and Risk Management," and Section 11, "Chronic Kidney Disease and Risk Management"). Pharmacologic approaches that provide the efficacy to achieve treatment goals should be considered, specified as metformin or agent(s), including combination therapy, that provide adequate efficacy to achieve and maintain treatment goals (**Fig. 9.3** and **Table 9.2**). In general, higher-efficacy approaches have greater likelihood of achieving glycemic goals, with the following considered to have very high efficacy for glucose lowering: the GLP-1 RAs dulaglutide (high dose) and semaglutide, the gastric inhibitory peptide (GIP) and GLP-1 RA tirzepatide, insulin, combination oral therapy, and combination injectable therapy. Weight management is an impactful component of glucose-lowering management in type 2 diabetes (45,46). The glucose-lowering treatment regimen should consider approaches that support weight management goals, with very high efficacy for weight loss seen with semaglutide and tirzepatide (**Fig. 9.3** and **Table 9.2**) (45).

Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death (47). Metformin is available in an immediate-release form for twice-daily dosing or as an extended-release form that can be given once daily. Compared with sulfonylureas, metformin as first-line therapy has beneficial effects on A1C, weight, and cardiovascular mortality (48).

The principal side effects of metformin are gastrointestinal intolerance due to bloating, abdominal discomfort, and diarrhea; these can be mitigated by gradual dose titration. The drug is cleared by renal filtration, and very high circulating levels (e.g., as a result of overdose or acute renal failure) have been associated with lactic acidosis. However, the occurrence of this complication is now known to be very rare, and metformin may be

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin;† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

Figure 9.3—Use of glucose-lowering medications in the management of type 2 diabetes. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TZD, thiazolidinedione. Adapted from Davies et al. (45).

Table 9.2—Medications for lowering glucose, summary of characteristics

	Efficacy[1]	Hypoglycemia	Weight change[2]	CV effects		Renal effects		Oral/SQ	Cost	Clinical considerations
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*			
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	• Contraindicated with eGFR <30 mL/min per 1.73 m^2	Oral	Low	• GI side effects common; to mitigate GI side effects, consider slow dose titration, extended release formulations, and administration with food • Potential for vitamin B12 deficiency; monitor at regular intervals
SGLT2 inhibitors	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	• See labels for renal dose considerations of individual agents • Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR	Oral	High	• DKA risk, rare in T2DM: discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentation (including euglycemic DKA); discontinue before scheduled surgery (e.g., 3–4 days), during critical illness, or during prolonged fasting to mitigate potential risk • Increased risk of genital mycotic infections • Necrotizing fasciitis of the perineum (Fournier gangrene), rare reports: institute prompt treatment if suspected • Attention to volume status, blood pressure; adjust other volume-contracting agents as applicable
GLP-1 RAs	High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ) Neutral: exenatide once weekly, lixisenatide	Neutral	Benefit for renal endpoints in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ)	• See labels for renal dose considerations of individual agents • No dose adjustment for dulaglutide, liraglutide, semaglutide • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ; oral (semaglutide)	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined (liraglutide, dulaglutide, exenatide extended release, semaglutide) • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected
GIP and GLP-1 RA	Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	• See label for renal dose considerations • No dose adjustment • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Neutral (potential risk, saxagliptin)	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	Oral	High	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Joint pain • Bullous pemphigoid (postmarketing): discontinue if suspected
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	Oral	Low	• Congestive HF (pioglitazone, rosiglitazone) • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Weight gain: consider lower doses to mitigate weight gain and edema
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Neutral	• Glyburide: generally not recommended in chronic kidney disease • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	Oral	Low	• FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide); glimepiride shown to be CV safe (see text) • Use with caution in persons at risk for hypoglycemia
Insulin **Human**	High to very high	Yes	Gain	Neutral	Neutral	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	SQ; inhaled	Low (SQ)	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Analogs								SQ	High	

CV, cardiovascular; CVOT, cardiovascular outcomes trial; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; GIP, gastric inhibitory polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; NASH, nonalcoholic steatohepatitis; MACE, major adverse cardiovascular events; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes mellitus. *For agent-specific dosing recommendations, please refer to manufacturers' prescribing information. [1]Tsapas et al. (62). [2]Tsapas et al. (114). Reprinted from Davies et al. (45).

safely used in people with reduced estimated glomerular filtration rates (eGFR); the FDA has revised the label for metformin to reflect its safety in people with eGFR ≥30 mL/min/1.73 m^2 (49). A randomized trial confirmed previous observations that metformin use is associated with vitamin B12 deficiency and worsening of symptoms of neuropathy (50). This is compatible with a report from the Diabetes Prevention Program Outcomes Study (DPPOS) suggesting periodic testing of vitamin B12 (51) (see Section 3, "Prevention or Delay of Type 2 Diabetes and Associated Comorbidities").

When A1C is ≥1.5% (12.5 mmol/mol) above the glycemic target (see Section 6, "Glycemic Targets," for appropriate targets), many individuals will require dual-combination therapy or a more potent glucose-lowering agent to achieve and maintain their target A1C level (45,52) (**Fig. 9.3** and **Table 9.2**). Insulin has the advantage of being effective where other agents are not and should be considered as part of any combination regimen when hyperglycemia is severe, especially if catabolic features (weight loss, hypertriglyceridemia, ketosis) are present. It is common practice to initiate insulin therapy for people who present with blood glucose levels ≥300 mg/dL (16.7 mmol/L) or A1C >10% (86 mmol/mol) or if the individual has symptoms of hyperglycemia (i.e., polyuria or polydipsia) or evidence of catabolism (weight loss) (**Fig. 9.4**). As glucose toxicity resolves, simplifying the regimen and/or changing to noninsulin agents is often possible. However, there is evidence that people with uncontrolled hyperglycemia associated with type 2 diabetes can also be effectively treated with a sulfonylurea (53).

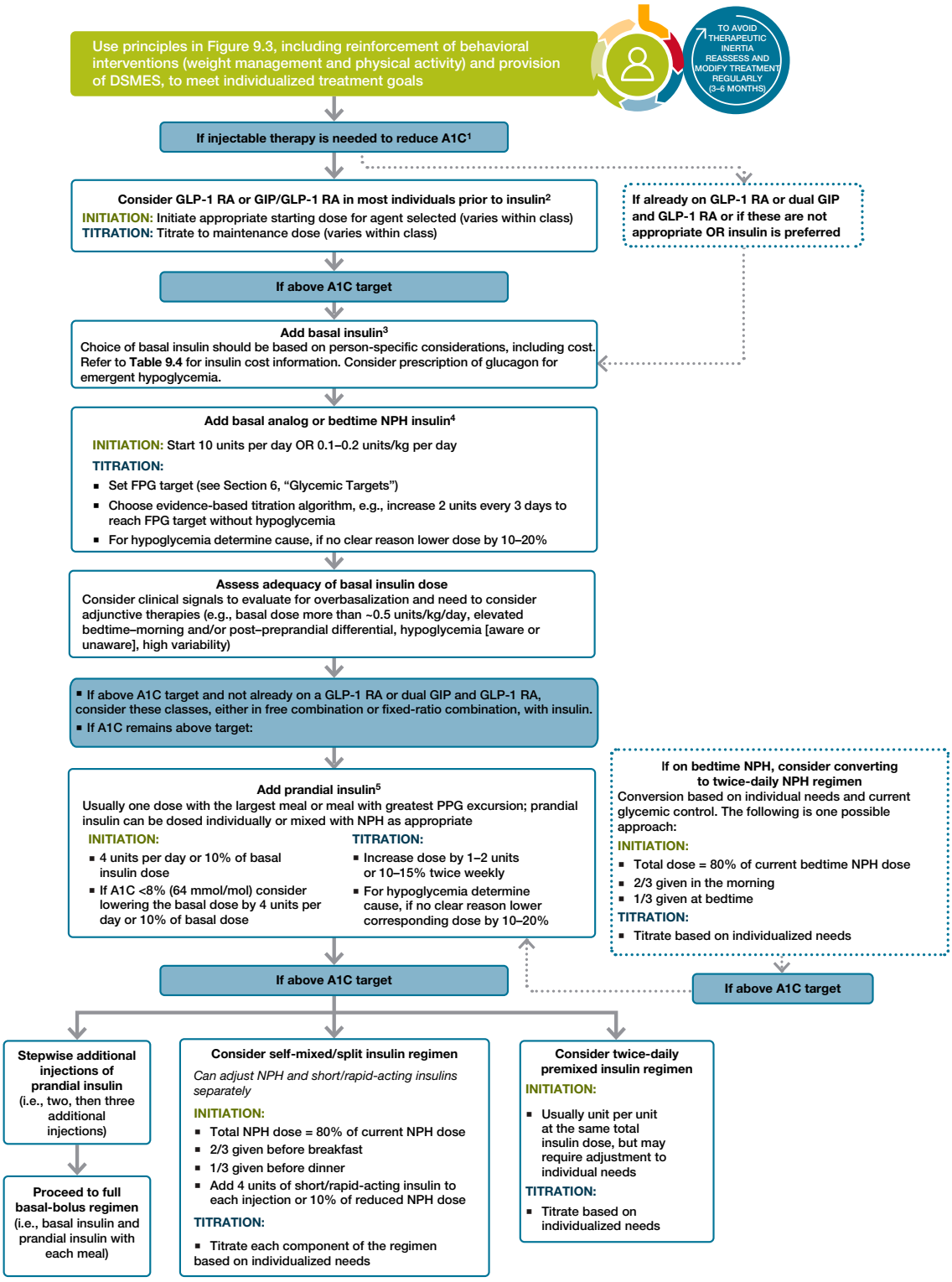
Combination Therapy

Because type 2 diabetes is a progressive disease in many individuals, maintenance of glycemic targets often requires combination therapy. Traditional recommendations have been to use stepwise addition of medications to metformin to maintain A1C at target. The advantage of this is to provide a clear assessment of the positive and negative effects of new drugs and reduce potential side effects and expense (54). However, there are data to support initial combination therapy for more rapid attainment of glycemic goals (55,56) and later combination therapy for longer durability of glycemic effect (57). The VERIFY (Vildagliptin Efficacy in combination with metfoRmln For earlY treatment of type 2 diabetes) trial demonstrated that initial combination therapy is superior to sequential addition of medications for extending primary and secondary failure (58). In the VERIFY trial, participants receiving the initial combination of metformin and the dipeptidyl peptidase 4 (DPP-4) inhibitor vildagliptin had a slower decline of glycemic control compared with metformin alone and with vildagliptin added sequentially to metformin. These results have not been generalized to oral agents other than vildagliptin, but they suggest that more intensive early treatment has some benefits and should be considered through a shared decision-making process, as appropriate. Initial combination therapy should be considered in people presenting with A1C levels 1.5–2.0% above target. Finally, incorporation of high-glycemic-efficacy therapies or therapies for cardiovascular/renal risk reduction (e.g., GLP-1 RAs, SGLT2 inhibitors) may allow for weaning of the current regimen, particularly of agents that may increase the risk of hypoglycemia. Thus, treatment intensification may not necessarily follow a pure sequential addition of therapy but instead reflect a tailoring of the regimen in alignment with person-centered treatment goals (**Fig. 9.3**).

Recommendations for treatment intensification for people not meeting treatment goals should not be delayed. Shared decision-making is important in discussions regarding treatment intensification. The choice of medication added to initial therapy is based on the clinical characteristics of the individual and their preferences. Important clinical characteristics include the presence of established ASCVD or indicators of high ASCVD risk, HF, CKD, obesity, nonalcoholic fatty liver disease or nonalcoholic steatohepatitis, and risk for specific adverse drug effects, as well as safety, tolerability, and cost. Results from comparative effectiveness meta-analyses suggest that each new class of noninsulin agents added to initial therapy with metformin generally lowers A1C approximately 0.7–1.0% (59,60) (**Fig. 9.3** and **Table 9.2**).

For people with type 2 diabetes and established ASCVD or indicators of high ASCVD risk, HF, or CKD, an SGLT2 inhibitor and/or GLP-1 RA with demonstrated CVD benefit (see **Table 9.2**, **Table 10.3*B***, **Table 10.3*C***, and Section 10, "Cardiovascular Disease and Risk Management") is recommended as part of the glucose-lowering regimen independent of A1C, independent of metformin use and in consideration of person-specific factors (**Fig. 9.3**). For people without established ASCVD, indicators of high ASCVD risk, HF, or CKD, medication choice is guided by efficacy in support of individualized glycemic and weight management goals, avoidance of side effects (particularly hypoglycemia and weight gain), cost/access, and individual preferences (61). A systematic review and network meta-analysis suggests greatest reductions in A1C level with insulin regimens and specific GLP-1 RAs added to metformin-based background therapy (62). In all cases, treatment regimens need to be continuously reviewed for efficacy, side effects, and burden (**Table 9.2**). In some instances, the individual will require medication reduction or discontinuation. Common reasons for this include ineffectiveness, intolerable side effects, expense, or a change in glycemic goals (e.g., in response to development of comorbidities or changes in treatment goals). Section 13, "Older Adults," has a full discussion of treatment considerations in older adults, in whom changes of glycemic goals and de-escalation of therapy are common.

The need for the greater potency of injectable medications is common, particularly in people with a longer duration of diabetes. The addition of basal insulin, either human NPH or one of the long-acting insulin analogs, to oral agent regimens is a well-established approach that is effective for many individuals. In addition, evidence supports the utility of GLP-1 RAs in people not at glycemic goal. While most GLP-1 RAs are injectable, an oral formulation of semaglutide is commercially available (63). In trials comparing the addition of an injectable GLP-1 RA or insulin in people needing further glucose lowering, glycemic efficacy of injectable GLP-1 RA was similar or greater than that of basal insulin (64–70). GLP-1 RAs in these trials had a lower risk of hypoglycemia and beneficial effects on body weight compared with insulin, albeit with greater gastrointestinal side effects. Thus, trial results support GLP-1 RAs as the preferred option for individuals requiring the potency of an injectable therapy for glucose control (**Fig. 9.4**). In individuals



1. Consider insulin as the first injectable if evidence of ongoing catabolism, symptoms of hyperglycemia are present, when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (300 mg/dL [16.7 mmol/L]) are very high, or a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RA, consider individual preference, A1C lowering, weight-lowering effect, or fequency of injection. If CVD is present, consider GLP-1 RA with proven CVD benefit. Oral or injectable GLP-1 RA are appropriate.
3. For people on GLP-1 RA and basal insulin combination, consider use of a fixed-ratio combination product (IDegLira or iGlarLixi).
4. Consider switching from evening NPH to a basal analog if the individual develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with an A.M. dose of a long-acting basal insulin.
5. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin regimen to decrease the number of injections required.

Figure 9.4—Intensifying to injectable therapies in type 2 diabetes. DSMES, diabetes self-management education and support; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide 1 receptor agonist; max, maximum; PPG, postprandial glucose. Adapted from Davies et al. (43).

who are intensified to insulin therapy, combination therapy with a GLP-1 RA has been shown to have greater efficacy and durability of glycemic treatment effect, as well as weight and hypoglycemia benefit, than treatment intensification with insulin alone (45). However, cost and tolerability issues are important considerations in GLP-1 RA use.

Costs for diabetes medications have increased dramatically over the past two decades, and an increasing proportion is now passed on to patients and their families (71). **Table 9.3** provides cost information for currently approved noninsulin therapies. Of note, prices listed are average wholesale prices (AWP) (72) and National Average Drug Acquisition Costs (NADAC) (73), separate measures to allow for a comparison of drug prices, but do not account for discounts, rebates, or other price adjustments often involved in prescription sales that affect the actual cost incurred by the patient. Medication costs can be a major source of stress for people with diabetes and contribute to worse medication-taking behavior (74); cost-reducing strategies may improve medication-taking behavior in some cases (75).

Cardiovascular Outcomes Trials

There are now multiple large randomized controlled trials reporting statistically significant reductions in cardiovascular events in adults with type 2 diabetes treated with an SGLT2 inhibitor or GLP-1 RA; see Section 10, "Cardiovascular Disease and Risk Management" for details. Participants enrolled in many of the cardiovascular outcomes trials had A1C ≥6.5%, with more than 70% taking metformin at baseline, with analyses indicating benefit with or without metformin (45). Thus, a practical extension of these results to clinical practice is to use these medications preferentially in people with type 2 diabetes and established ASCVD or indicators of high ASCVD risk. For these individuals, incorporating one of the SGLT2 inhibitors and/or GLP-1 RAs that have been demonstrated to have cardiovascular disease benefit is recommended (see **Fig. 9.3**, **Table 9.2**, and Section 10, "Cardiovascular Disease and Risk Management"). Emerging data suggest that use of both classes of drugs will provide additional cardiovascular and kidney outcomes benefit; thus, combination therapy with an SGLT2 inhibitor and a GLP-1 RA may be considered to provide the complementary outcomes benefits associated with these classes of medication (76). In cardiovascular outcomes trials, empagliflozin, canagliflozin, dapagliflozin, liraglutide, semaglutide, and dulaglutide all had beneficial effects on indices of CKD, while dedicated renal outcomes studies have demonstrated benefit of specific SGLT2 inhibitors. See Section 11, "Chronic Kidney Disease and Risk Management," for discussion of how CKD may impact treatment choices. Additional large randomized trials of other agents in these classes are ongoing.

Insulin Therapy

Many adults with type 2 diabetes eventually require and benefit from insulin therapy (**Fig. 9.4**). See the section INSULIN INJECTION TECHNIQUE, above, for guidance on how to administer insulin safely and effectively. The progressive nature of type 2 diabetes should be regularly and objectively explained to patients, and clinicians should avoid using insulin as a threat or describing it as a sign of personal failure or punishment. Rather, the utility and importance of insulin to maintain glycemic control once progression of the disease overcomes the effect of other agents should be emphasized. Educating and involving patients in insulin management is beneficial. For example, instruction of individuals with type 2 diabetes initiating insulin in self-titration of insulin doses based on glucose monitoring improves glycemic control (77). Comprehensive education regarding blood glucose monitoring, nutrition, and the avoidance and appropriate treatment of hypoglycemia are critically important in any individual using insulin.

Basal Insulin

Basal insulin alone is the most convenient initial insulin treatment and can be added to metformin and other noninsulin injectables. Starting doses can be estimated based on body weight (0.1–0.2 units/kg/day) and the degree of hyperglycemia, with individualized titration over days to weeks as needed. The principal action of basal insulin is to restrain hepatic glucose production and limit hyperglycemia overnight and between meals (78,79). Control of fasting glucose can be achieved with human NPH insulin or a long-acting insulin analog. In clinical trials, long-acting basal analogs (U-100 glargine or detemir) have been demonstrated to reduce the risk of symptomatic and nocturnal hypoglycemia compared with NPH insulin (80–85), although these advantages are modest and may not persist (86). Longer-acting basal analogs (U-300 glargine or degludec) may convey a lower hypoglycemia risk compared with U-100 glargine when used in combination with oral agents (87–93). Clinicians should be aware of the potential for overbasalization with insulin therapy. Clinical signals that may prompt evaluation of overbasalization include basal dose greater than ∼0.5 units/kg, high bedtime–morning or postprepandial glucose differential (e.g., bedtime–morning glucose differential ≥50 mg/dL), hypoglycemia (aware or unaware), and high variability. Indication of overbasalization should prompt reevaluation to further individualize therapy (94).

The cost of insulin has been rising steadily over the past two decades, at a pace severalfold that of other medical expenditures (95). This expense contributes significant burden to patients as insulin has become a growing "out-of-pocket" cost for people with diabetes, and direct patient costs contribute to decrease in medication-taking behavior (95). Therefore, consideration of cost is an important component of effective management. For many individuals with type 2 diabetes (e.g., individuals with relaxed A1C goals, low rates of hypoglycemia, and prominent insulin resistance, as well as those with cost concerns), human insulin (NPH and regular) may be the appropriate choice of therapy, and clinicians should be familiar with its use (96). Human regular insulin, NPH, and 70/30 NPH/regular products can be purchased for considerably less than the AWP and NADAC prices listed in **Table 9.4** at select pharmacies. Additionally, approval of follow-on biologics for insulin glargine, the first interchangeable insulin glargine product, and generic versions of analog insulins may expand cost-effective options.

Prandial Insulin

Many individuals with type 2 diabetes require doses of insulin before meals, in addition to basal insulin, to reach glycemic targets. If the individual is not already being treated with a GLP-1 RA, a GLP-1 RA (either in free combination or fixed-ratio combination) should be considered prior to prandial insulin to further

Table 9.3—Median monthly (30-day) AWP and NADAC of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.

Class	Compound(s)	Dosage strength/ product (if applicable)	Median AWP (min, max)†	Median NADAC (min, max)†	Maximum approved daily dose*
Biguanides	• Metformin	850 mg (IR)	$106 ($5, $189)	$2	2,550 mg
		1,000 mg (IR)	$87 ($3, $144)	$2	2,000 mg
		1,000 mg (ER)	$242 ($242, $7,214)	$32 ($32, $160)	2,000 mg
Sulfonylureas (2nd generation)	• Glimepiride	4 mg	$74 ($71, $198)	$3	8 mg
	• Glipizide	10 mg (IR)	$70 ($67, $91)	$6	40 mg
		10 mg (XL/ER)	$48 ($46, $48)	$11	20 mg
	• Glyburide	6 mg (micronized)	$52 ($48, $71)	$12	12 mg
		5 mg	$79 ($63, $93)	$9	20 mg
Thiazolidinedione	• Pioglitazone	45 mg	$345 ($7, $349)	$4	45 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	$106 ($104, $106)	$29	300 mg
	• Miglitol	100 mg	$241 ($241, $346)	NA	300 mg
Meglitinides	• Nateglinide	120 mg	$155	$27	360 mg
	• Repaglinide	2 mg	$878 ($58, $897)	$31	16 mg
DPP-4 inhibitors	• Alogliptin	25 mg	$234	$154	25 mg
	• Saxagliptin	5 mg	$565	$452	5 mg
	• Linagliptin	5 mg	$606	$485	5 mg
	• Sitagliptin	100 mg	$626	$500	100 mg
SGLT2 inhibitors	• Ertugliflozin	15 mg	$390	$312	15 mg
	• Dapagliflozin	10 mg	$659	$527	10 mg
	• Canagliflozin	300 mg	$684	$548	300 mg
	• Empagliflozin	25 mg	$685	$547	25 mg
GLP-1 RAs	• Exenatide (extended release)	2 mg powder for suspension or pen	$936	$726	2 mg**
	• Exenatide	10 μg pen	$961	$770	20 μg
	• Dulaglutide	4.5 mg mL pen	$1,064	$852	4.5 mg**
	• Semaglutide	1 mg pen	$1,070	$858	2 mg**
		14 mg (tablet)	$1,070	$858	14 mg
	• Liraglutide	1.8 mg pen	$1,278	$1,022	1.8 mg
	• Lixisenatide	20 μg pen	$814	NA	20 μg
GLP-1/GIP dual agonist	• Tirzepatide	15 mg pen	$1,169	$935	15 mg**
Bile acid sequestrant	• Colesevelam	625 mg tabs	$711 ($674, $712)	$83	3.75 g
		3.75 g suspension	$674 ($673, $675)	$177	3.75 g
Dopamine-2 agonist	• Bromocriptine	0.8 mg	$1,118	$899	4.8 mg
Amylin mimetic	• Pramlintide	120 μg pen	$2,783	NA	120 μg/injection††

AWP, average wholesale price; DPP-4, dipeptidyl peptidase 4; ER and XL, extended release; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; IR, immediate release; max, maximum; min, minimum; NA, data not available; NADAC, National Average Drug Acquisition Cost; SGLT2, sodium-glucose cotransporter 2. †Calculated for 30-day supply (AWP [72] or NADAC [73] unit price × number of doses required to provide maximum approved daily dose × 30 days); median AWP or NADAC listed alone when only one product and/or price. *Utilized to calculate median AWP and NADAC (min, max); generic prices used, if available commercially. **Administered once weekly. ††AWP and NADAC calculated based on 120 μg three times daily.

address prandial control and to minimize the risks of hypoglycemia and weight gain associated with insulin therapy (45). For individuals who advance to prandial insulin, a prandial insulin dose of 4 units or 10% of the amount of basal insulin at the largest meal or the meal with the greatest postprandial excursion is a safe estimate for initiating therapy. The prandial insulin regimen can then be intensified based on individual needs (**Fig. 9.4**). Individuals with type 2 diabetes are generally more insulin resistant than those with type 1 diabetes, require higher daily doses (~1 unit/kg), and have lower rates of hypoglycemia (97). Titration can be based on home glucose monitoring or A1C. With significant additions to the prandial insulin dose, particularly with the evening meal, consideration should be given to decreasing basal insulin. Meta-analyses of trials comparing rapid-acting insulin analogs with human regular insulin in type 2 diabetes have not reported important differences in A1C or hypoglycemia (98,99).

Concentrated Insulins

Several concentrated insulin preparations are currently available. U-500 regular insulin is, by definition, five times more concentrated than U-100 regular insulin. U-500 regular insulin has distinct pharmacokinetics with delayed onset and longer duration of action, has characteristics more like an intermediate-acting (NPH) insulin, and can be used as two or three daily injections (100). U-300 glargine and U-200 degludec are three and two times as concentrated as their U-100

Table 9.4—Median cost of insulin products in the U.S. calculated as AWP (72) and NADAC (73) per 1,000 units of specified dosage form/product

Insulins	Compounds	Dosage form/product	Median AWP (min, max)*	Median NADAC*
Rapid-acting	• Lispro follow-on product	U-100 vial	$118 ($118, $157)	$94
		U-100 prefilled pen	$151	$121
	• Lispro	U-100 vial	$99†	$79†
		U-100 cartridge	$408	$326
		U-100 prefilled pen	$127†	$102†
		U-200 prefilled pen	$424	$339
	• Lispro-aabc	U-100 vial	$330	$261
		U-100 prefilled pen	$424	$339
		U-200 prefilled pen	$424	NA
	• Glulisine	U-100 vial	$341	$272
		U-100 prefilled pen	$439	$351
	• Aspart	U-100 vial	$174†	$140†
		U-100 cartridge	$215†	$172†
		U-100 prefilled pen	$224†	$180†
	• Aspart (“faster acting product”)	U-100 vial	$347	$277
		U-100 cartridge	$430	$344
		U-100 prefilled pen	$447	$357
	• Inhaled insulin	Inhalation cartridges	$1,418	NA
Short-acting	• Human regular	U-100 vial	$165††	$132††
		U-100 prefilled pen	$208	$166
Intermediate-acting	• Human NPH	U-100 vial	$165††	$132††
		U-100 prefilled pen	$208	$168
Concentrated human regular insulin	• U-500 human regular insulin	U-500 vial	$178	$142
		U-500 prefilled pen	$230	$184
Long-acting	• Glargine follow-on products	U-100 prefilled pen	$261 ($118, $323)	$209 ($209, $258)
		U-100 vial	$118 ($118, $323)	$95
	• Glargine	U-100 vial; U-100 prefilled pen	$136†	$109†
		U-300 prefilled pen	$346	$277
	• Detemir	U-100 vial; U-100 prefilled pen	$370	$296
	• Degludec	U-100 vial; U-100 prefilled pen; U-200 prefilled pen	$407	$326
Premixed insulin products	• NPH/regular 70/30	U-100 vial	$165††	$133††
		U-100 prefilled pen	$208	$167
	• Lispro 50/50	U-100 vial	$342	$274
		U-100 prefilled pen	$424	$339
	• Lispro 75/25	U-100 vial	$342	$273
		U-100 prefilled pen	$127†	$103†
	• Aspart 70/30	U-100 vial	$180†	$146†
		U-100 prefilled pen	$224†	$178†
Premixed insulin/GLP-1 RA products	• Glargine/Lixisenatide	100/33 μg prefilled pen	$646	$517
	• Degludec/Liraglutide	100/3.6 μg prefilled pen	$944	$760

AWP, average wholesale price; GLP-1 RA, glucagon-like peptide 1 receptor agonist; NA, data not available; NADAC, National Average Drug Acquisition Cost. *AWP or NADAC calculated as in **Table 9.3**. †Generic prices used when available. ††AWP and NADAC data presented do not include vials of regular human insulin and NPH available at Walmart for approximately $25/vial; median listed alone when only one product and/or price.

formulations, respectively, and allow higher doses of basal insulin administration per volume used. U-300 glargine has a longer duration of action than U-100 glargine but modestly lower efficacy per unit administered (101,102). The FDA has also approved a concentrated formulation of rapid-acting insulin lispro, U-200 (200 units/mL), and insulin lispro-aabc (U-200). These concentrated preparations may be more convenient and comfortable for individuals to inject and may improve treatment plan engagement in those with insulin resistance who require large doses of insulin. While U-500 regular insulin is available in both prefilled pens and vials, other concentrated insulins are available only in prefilled pens to minimize the risk of dosing errors.

Alternative Insulin Routes

Insulins with different routes of administration (inhaled, bolus-only insulin delivery patch pump) are also available (45). Inhaled insulin is available as a rapid-acting insulin; studies in individuals with type 1 diabetes suggest rapid pharmacokinetics (8). Studies comparing inhaled insulin with injectable insulin have demonstrated its faster onset and shorter duration compared with rapid-acting insulin lispro as well as clinically meaningful A1C reductions and weight reductions compared with insulin aspart over 24 weeks (103–105). Use of inhaled insulin may result in a decline in lung function (reduced forced expiratory volume in 1 s [FEV_1]). Inhaled insulin is contraindicated in individuals with chronic lung disease, such as asthma and chronic obstructive pulmonary disease, and is not

recommended in individuals who smoke or who recently stopped smoking. All individuals require spirometry (FEV_1) testing to identify potential lung disease prior to and after starting inhaled insulin therapy.

Combination Injectable Therapy

If basal insulin has been titrated to an acceptable fasting blood glucose level (or if the dose is >0.5 units/kg/day with indications of need for other therapy) and A1C remains above target, consider advancing to combination injectable therapy (**Fig. 9.4**). This approach can use a GLP-1 RA or dual GIP and GLP-1 RA added to basal insulin or multiple doses of insulin. The combination of basal insulin and GLP-1 RA has potent glucose-lowering actions and less weight gain and hypoglycemia compared with intensified insulin regimens (106–111). The DUAL VIII (Durability of Insulin Degludec Plus Liraglutide Versus Insulin Glargine U100 as Initial Injectable Therapy in Type 2 Diabetes) randomized controlled trial demonstrated greater durability of glycemic treatment effect with the combination GLP-1 RA–insulin therapy compared with addition of basal insulin alone (57). In select individuals, complex insulin regimens can also be simplified with combination GLP-1 RA–insulin therapy in type 2 diabetes (112). Two different once-daily, fixed dual combination products containing basal insulin plus a GLP-1 RA are available: insulin glargine plus lixisenatide (iGlarLixi) and insulin degludec plus liraglutide (IDegLira).

Intensification of insulin treatment can be done by adding doses of prandial insulin to basal insulin. Starting with a single prandial dose with the largest meal of the day is simple and effective, and it can be advanced to a regimen with multiple prandial doses if necessary (113). Alternatively, in an individual on basal insulin in whom additional prandial coverage is desired, the regimen can be converted to two doses of a premixed insulin. Each approach has advantages and disadvantages. For example, basal-prandial regimens offer greater flexibility for individuals who eat on irregular schedules. On the other hand, two doses of premixed insulin is a simple, convenient means of spreading insulin across the day. Moreover, human insulins, separately, self-mixed, or as premixed NPH/regular (70/30) formulations, are less costly alternatives to insulin analogs. **Figure 9.4** outlines these options as well as recommendations for further intensification, if needed, to achieve glycemic goals. When initiating combination injectable therapy, metformin therapy should be maintained, while sulfonylureas and DPP-4 inhibitors are typically weaned or discontinued. In individuals with suboptimal blood glucose control, especially those requiring large insulin doses, adjunctive use of a thiazolidinedione or an SGLT2 inhibitor may help to improve control and reduce the amount of insulin needed, though potential side effects should be considered. Once a basal-bolus insulin regimen is initiated, dose titration is important, with adjustments made in both mealtime and basal insulins based on the blood glucose levels and an understanding of the pharmacodynamic profile of each formulation (also known as pattern control or pattern management). As people with type 2 diabetes get older, it may become necessary to simplify complex insulin regimens because of a decline in self-management ability (see Section 13, "Older Adults").

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10. Cardiovascular Disease and Risk Management: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For prevention and management of diabetes complications in children and adolescents, please refer to Section 14, "Children and Adolescents."

Atherosclerotic cardiovascular disease (ASCVD)—defined as coronary heart disease (CHD), cerebrovascular disease, or peripheral arterial disease presumed to be of atherosclerotic origin—is the leading cause of morbidity and mortality for individuals with diabetes and results in an estimated $37.3 billion in cardiovascular-related spending per year associated with diabetes (1). Common conditions coexisting with type 2 diabetes (e.g., hypertension and dyslipidemia) are clear risk factors for ASCVD, and diabetes itself confers independent risk. Numerous studies have shown the efficacy of controlling individual cardiovascular risk factors in preventing or slowing ASCVD in people with diabetes. Furthermore, large benefits are seen when multiple cardiovascular risk factors are addressed simultaneously. Under the current paradigm of aggressive risk factor modification in people with diabetes, there is evidence that measures of 10-year CHD risk among U.S. adults with diabetes have improved significantly over the past decade (2) and that ASCVD morbidity and mortality have decreased (3,4).

Heart failure is another major cause of morbidity and mortality from cardiovascular disease. Recent studies have found that rates of incident heart failure hospitalization (adjusted for age and sex) were twofold higher in people with diabetes compared with those without (5,6). People with diabetes may have heart failure with preserved ejection fraction (HFpEF) or with reduced ejection fraction (HFrEF). Hypertension is often a precursor of heart failure of either type, and ASCVD can coexist with either type (7), whereas prior myocardial infarction (MI) is often a major factor in HFrEF. Rates of heart failure hospitalization have been improved in recent trials including people with type 2 diabetes, most of whom also had ASCVD, with sodium–glucose cotransporter 2 (SGLT2) inhibitors (8–11).

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A recent meta-analysis indicated that SGLT2 inhibitors reduce the risk of heart failure hospitalization, cardiovascular mortality, and all-cause mortality in people with (secondary prevention) and without (primary prevention) cardiovascular disease (12).

For prevention and management of both ASCVD and heart failure, cardiovascular risk factors should be systematically assessed at least annually in all people with diabetes. These risk factors include duration of diabetes, obesity/overweight, hypertension, dyslipidemia, smoking, a family history of premature coronary disease, chronic kidney disease (CKD), and the presence of albuminuria. Modifiable abnormal risk factors should be treated as described in these guidelines. Notably, the majority of evidence supporting interventions to reduce cardiovascular risk in diabetes comes from trials of people with type 2 diabetes. No randomized trials have been specifically designed to assess the impact of cardiovascular risk reduction strategies in people with type 1 diabetes. Therefore, the recommendations for cardiovascular risk factor modification for people with type 1 diabetes are extrapolated from data obtained in people with type 2 diabetes and are similar to those for people with type 2 diabetes.

As depicted in **Fig. 10.1**, a comprehensive approach to the reduction in risk of diabetes-related complications is recommended. Therapy that includes multiple, concurrent evidence-based approaches to care will provide complementary reduction in the risks of microvascular, kidney, neurologic, and cardiovascular complications. Management of glycemia, blood pressure, and lipids and the incorporation of specific therapies with cardiovascular and kidney outcomes benefit (as individually appropriate) are considered fundamental elements of global risk reduction in diabetes.

THE RISK CALCULATOR

The American College of Cardiology/American Heart Association ASCVD risk calculator (Risk Estimator Plus) is generally a useful tool to estimate 10-year risk of a first ASCVD event (available online at tools.acc.org/ASCVD-Risk-Estimator-Plus). The calculator includes diabetes as a risk factor, since diabetes itself confers increased risk for ASCVD, although it should be acknowledged that these risk calculators do not account for the duration of diabetes or the presence of diabetes complications, such as albuminuria. Although some variability in calibration exists in various subgroups, including by sex, race, and diabetes, the overall risk prediction does not differ in those with or without diabetes (13–16), validating the use of risk calculators in people with diabetes. The 10-year risk of a first ASCVD event should be assessed to better stratify ASCVD risk and help guide therapy, as described below.

Recently, risk scores and other cardiovascular biomarkers have been developed for risk stratification of secondary prevention patients (i.e., those who are already high risk because they have ASCVD) but are not yet in widespread use (17,18). With newer, more expensive lipid-lowering therapies now available, use of these risk assessments may help target these new therapies to "higher risk" ASCVD patients in the future.

HYPERTENSION/BLOOD PRESSURE CONTROL

Hypertension is defined as a systolic blood pressure ≥130 mmHg or a diastolic blood pressure ≥80 mmHg (19). This is in agreement with the definition of hypertension by the American College of Cardiology and American Heart Association (19). Hypertension is common among people with either type 1 or type 2 diabetes. Hypertension is a major risk factor for both ASCVD and microvascular complications. Moreover, numerous studies have shown that antihypertensive therapy reduces ASCVD events, heart failure, and microvascular complications. Please refer to the American Diabetes Association position statement "Diabetes and Hypertension" for a detailed review of the epidemiology, diagnosis, and treatment of hypertension (20) and recent updated hypertension guideline recommendations (19,21,22).

Screening and Diagnosis

Recommendations

10.1 Blood pressure should be measured at every routine clinical visit. When possible, individuals found to have elevated blood pressure (systolic blood pressure 120–129 mmHg and diastolic <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements

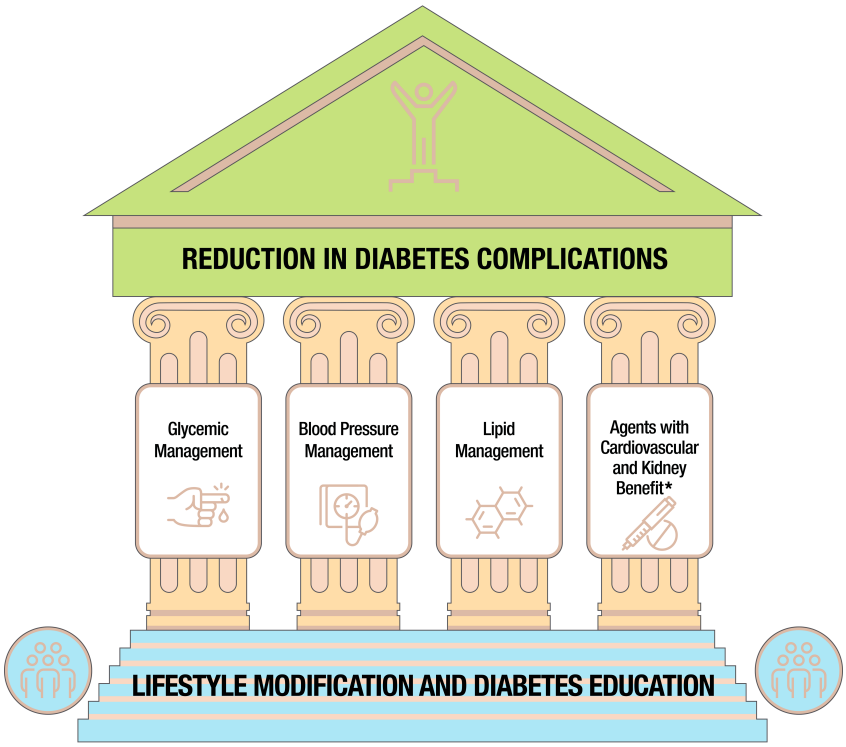

Figure 10.1—Multifactorial approach to reduction in risk of diabetes complications. *Risk reduction interventions to be applied as individually appropriate.

on a separate day, to diagnose hypertension. **A** Hypertension is defined as a systolic blood pressure ≥130 mmHg or a diastolic blood pressure ≥80 mmHg based on an average of ≥2 measurements obtained on ≥2 occasions. **A** Individuals with blood pressure ≥180/110 mmHg and cardiovascular disease could be diagnosed with hypertension at a single visit. **E**

10.2 All people with hypertension and diabetes should monitor their blood pressure at home. **A**

Blood pressure should be measured at every routine clinical visit by a trained individual and should follow the guidelines established for the general population: measurement in the seated position, with feet on the floor and arm supported at heart level, after 5 min of rest. Cuff size should be appropriate for the upper-arm circumference. Elevated values should preferably be confirmed on a separate day; however, in individuals with cardiovascular disease and blood pressure ≥180/110 mmHg, it is reasonable to diagnose hypertension at a single visit (21). Postural changes in blood pressure and pulse may be evidence of autonomic neuropathy and therefore require adjustment of blood pressure targets. Orthostatic blood pressure measurements should be checked on initial visit and as indicated.

Home blood pressure self-monitoring and 24-h ambulatory blood pressure monitoring may provide evidence of white coat hypertension, masked hypertension, or other discrepancies between office and "true" blood pressure (23,24). In addition to confirming or refuting a diagnosis of hypertension, home blood pressure assessment may be useful to monitor antihypertensive treatment. Studies of individuals without diabetes found that home measurements may better correlate with ASCVD risk than office measurements (23,24). Moreover, home blood pressure monitoring may improve patient medication taking and thus help reduce cardiovascular risk (25).

Treatment Goals

Recommendations

10.3 For people with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences. **B**

10.4 People with diabetes and hypertension qualify for antihypertensive drug therapy when the blood pressure is persistently elevated ≥130/80 mmHg. The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. **B**

10.5 In pregnant individuals with diabetes and chronic hypertension, a blood pressure threshold of 140/90 mmHg for initiation or titration of therapy is associated with better pregnancy outcomes than reserving treatment for severe hypertension, with no increase in risk of small-for-gestational age birth weight. **A** There are limited data on the optimal lower limit, but therapy should be lessened for blood pressure <90/60 mmHg. **E** A blood pressure target of 110–135/85 mmHg is suggested in the interest of reducing the risk for accelerated maternal hypertension. **A**

Randomized clinical trials have demonstrated unequivocally that treatment of hypertension reduces cardiovascular events as well as microvascular complications (26–32). There has been controversy on the recommendation of a specific blood pressure goal in people with diabetes. The committee recognizes that there has been no randomized controlled trial to specifically demonstrate a decreased incidence of cardiovascular events in people with diabetes by targeting a blood pressure <130/80 mmHg. The recommendation to support a blood pressure goal of <130/80 mmHg in people with diabetes is consistent with guidelines from the American College of Cardiology and American Heart Association (20), the International Society of Hypertension (21), and the European Society of Cardiology (22). The committee's recommendation for the blood pressure target of <130/80 mmHg derives primarily from the collective evidence of the following randomized controlled trials. The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that treatment to a target systolic blood pressure of <120 mmHg decreases cardiovascular event rates by 25% in high-risk patients, although people with diabetes were excluded from this trial (33). The recently completed Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial included nearly 20% of people with diabetes and noted decreased cardiovascular events with treatment of hypertension to a blood pressure target of <130 mmHg (34). While the ACCORD (Action to Control Cardiovascular Risk in Diabetes) blood pressure trial (ACCORD BP) did not confirm that targeting a systolic blood pressure of <120 mmHg in people with diabetes results in decreased cardiovascular event rates, the prespecified secondary outcome of stroke was reduced by 41% with intensive treatment (35). The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial revealed that treatment with perindopril/indapamide to an achieved systolic blood pressure of ∼135 mmHg significantly decreased cardiovascular event rates compared with a placebo treatment with an achieved blood pressure of 140 mmHg (36). Therefore, it is recommended that people with diabetes who have hypertension should be treated to blood pressure targets of <130/80 mmHg. Notably, there is an absence of high-quality data available to guide blood pressure targets in people with type 1 diabetes, but a similar blood pressure target of <130/80 mmHg is recommended in people with type 1 diabetes. As discussed below, treatment should be individualized and treatment should not be targeted to <120/80 mmHg, as a mean achieved blood pressure of <120/80 mmHg is associated with adverse events.

Randomized Controlled Trials of Intensive Versus Standard Blood Pressure Control

SPRINT provides the strongest evidence to support lower blood pressure goals in patients at increased cardiovascular risk, although this trial excluded people with diabetes (33). The trial enrolled 9,361 patients with a systolic blood pressure of

≥130 mmHg and increased cardiovascular risk and treated to a systolic blood pressure target of <120 mmHg (intensive treatment) versus a target of <140 mmHg (standard treatment). The primary composite outcome of myocardial infarction (MI), coronary syndromes, stroke, heart failure, or death from cardiovascular causes was reduced by 25% in the intensive treatment group. The achieved systolic blood pressures in the trial were 121 mmHg and 136 mmHg in the intensive versus standard treatment group, respectively. Adverse outcomes, including hypotension, syncope, electrolyte abnormality, and acute kidney injury were more common in the intensive treatment arm; risk of adverse outcomes needs to be weighed against the cardiovascular benefit of more intensive blood pressure lowering.

ACCORD BP provides the strongest direct assessment of the benefits and risks of intensive blood pressure control in people with type 2 diabetes (35). In the study, a total of 4,733 with type 2 diabetes were assigned to intensive therapy (targeting a systolic blood pressure <120 mmHg) or standard therapy (targeting a systolic blood pressure <140 mmHg). The mean achieved systolic blood pressures were 119 mmHg and 133 mmHg in the intensive versus standard group, respectively. The primary composite outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular causes was not significantly reduced in the intensive treatment group. The prespecified secondary outcome of stroke was significantly reduced by 41% in the intensive treatment group. Adverse events attributed to blood pressure treatment, including hypotension, syncope, bradycardia, hyperkalemia, and elevations in serum creatinine occurred more frequently in the intensive treatment arm than in the standard therapy arm (**Table 10.1**).

Of note, the ACCORD BP and SPRINT trials targeted a similar systolic blood pressure <120 mmHg, but in contrast to SPRINT, the primary composite cardiovascular end point was nonsignificantly reduced in ACCORD BP. The results have been interpreted to be generally consistent between both trials, but ACCORD BP was viewed as underpowered due to the composite primary end point being less sensitive to blood pressure regulation (33).

The more recent STEP trial assigned 8,511 patients aged 60–80 years with hypertension to a systolic blood pressure target of 110 to <130 mmHg (intensive treatment) or a target of 130 to <150 mmHg (34). In this trial, the primary composite outcome of stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes was reduced by 26% in the intensive treatment group. In this trial, 18.9% of patients in the intensive treatment arm and 19.4% in the standard treatment arm had a diagnosis of type 2 diabetes. Hypotension occurred more frequently in the intensive treatment group (3.4%) compared with the standard treatment group (2.6%), without significant differences in other adverse events, including dizziness, syncope, or fractures.

In ADVANCE, 11,140 people with type 2 diabetes were randomized to receive either treatment with fixed combination perindopril/indapamide or matching placebo (36). The primary end point, a composite of cardiovascular death, nonfatal stroke infarction, or worsening renal or diabetic eye disease, was reduced by 9% in the combination treatment. The achieved systolic blood pressure was ~135 mmHg in the treatment group and 140 mmHg in the placebo group.

The Hypertension Optimal Treatment (HOT) trial enrolled 18,790 patients and targeted diastolic blood pressure <90 mmHg, <85 mmHg, or <80 mmHg (37). The cardiovascular event rates, defined as fatal or nonfatal MI, fatal and nonfatal strokes, and all other cardiovascular events, were not significantly different between diastolic blood pressure targets (≤90 mmHg, ≤85 mmHg, and ≤80 mmHg), although the lowest incidence of cardiovascular events occurred with an achieved diastolic blood pressure of 82 mmHg. However, in people with diabetes, there was a significant 51% reduction in the treatment group with a target diastolic blood pressure of <80 mmHg compared with a target diastolic blood pressure of <90 mmHg.

Meta-analyses of Trials

To clarify optimal blood pressure targets in people with diabetes, multiple meta-analyses have been performed. One of the largest meta-analyses included 73,913 people with diabetes. Compared with a less tight blood pressure control, allocation to a tighter blood pressure control significantly reduced the risk of stroke by 31% but did not reduce the risk of MI (38). Another meta-analysis of 19 trials including 44,989 patients showed that a mean blood pressure of 133/76 mmHg is associated with a 14% risk reduction for major cardiovascular events compared with a mean blood pressure of 140/81 mmHg (32). This benefit was greatest in people with diabetes. An analysis of trials including people with type 2 diabetes and impaired glucose tolerance with achieved systolic blood pressures of <135 mmHg in the intensive blood pressure treatment group and <140 mmHg in the standard treatment group revealed a 10% reduction in all-cause mortality and a 17% reduction in stroke (30). More intensive reduction to <130 mmHg was associated with a further reduction in stroke but not other cardiovascular events.

Several meta-analyses stratified clinical trials by mean baseline blood pressure or mean blood pressure attained in the intervention (or intensive treatment) arm. Based on these analyses, antihypertensive treatment appears to be most beneficial when mean baseline blood pressure is ≥140/90 mmHg (19,26,27,29–31). Among trials with lower baseline or attained blood pressure, antihypertensive treatment reduced the risk of stroke, retinopathy, and albuminuria, but effects on other ASCVD outcomes and heart failure were not evident.

Individualization of Treatment Targets

Patients and clinicians should engage in a shared decision-making process to determine individual blood pressure targets (19). This approach acknowledges that the benefits and risks of intensive blood pressure targets are uncertain and may vary across patients and is consistent with a patient-focused approach to care that values patient priorities and health care professional judgment (39). Secondary analyses of ACCORD BP and SPRINT suggest that clinical factors can help determine individuals more likely to benefit and less likely to be harmed by intensive blood pressure control (40,41).

Absolute benefit from blood pressure reduction correlated with absolute baseline cardiovascular risk in SPRINT and in earlier clinical trials conducted at higher baseline blood pressure levels (13,41). Extrapolation of these studies suggests that people with diabetes may also be more likely to benefit from intensive blood

Table 10.1—Randomized controlled trials of intensive versus standard hypertension treatment strategies

Clinical trial	Population	Intensive	Standard	Outcomes
ACCORD BP (35)	4,733 participants with T2D aged 40–79 years with prior evidence of CVD or multiple cardiovascular risk factors	SBP target: <120 mmHg Achieved (mean) SBP/DBP: 119.3/64.4 mmHg	SBP target: 130–140 mmHg Achieved (mean) SBP/DBP: 135/70.5 mmHg	• No benefit in primary end point: composite of nonfatal MI, nonfatal stroke, and CVD death • Stroke risk reduced 41% with intensive control, not sustained through follow-up beyond the period of active treatment • Adverse events more common in intensive group, particularly elevated serum creatinine and electrolyte abnormalities
ADVANCE (36)	11,140 participants with T2D aged ≥55 years with prior evidence of CVD or multiple cardiovascular risk factors	Intervention: a single-pill, fixed-dose combination of perindopril and indapamide Achieved (mean) SBP/DBP: 136/73 mmHg	Control: placebo Achieved (mean) SBP/DBP: 141.6/75.2 mmHg	• Intervention reduced risk of primary composite end point of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%) • 6-year observational follow-up found reduction in risk of death in intervention group attenuated but still significant (242)
HOT (37)	18,790 participants, including 1,501 with diabetes	DBP target: ≤80 mmHg Achieved (mean): 81.1 mmHg, ≤80 group; 85.2 mmHg, ≤90 group	DBP target: ≤90 mmHg	• In the overall trial, there was no cardiovascular benefit with more intensive targets • In the subpopulation with diabetes, an intensive DBP target was associated with a significantly reduced risk (51%) of CVD events
SPRINT (43)	9,361 participants without diabetes	SBP target: <120 mmHg Achieved (mean): 121.4 mmHg	SBP target: <140 mmHg Achieved (mean): 136.2 mmHg	• Intensive SBP target lowered risk of the primary composite outcome 25% (MI, ACS, stroke, heart failure, and death due to CVD) • Intensive target reduced risk of death 27% • Intensive therapy increased risks of electrolyte abnormalities and AKI
STEP (34)	8,511 participants aged 60–80 years, including 1,627 with diabetes	SBP target: <130 mmHg Achieved (mean): 127.5 mmHg	SBP target: <150 mmHg Achieved (mean): 135.3 mmHg	• Intensive SBP target lowered risk of the primary composite outcome 26% (stroke, ACS [acute MI and hospitalization for unstable angina], acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes) • Intensive target reduced risk of cardiovascular death 28% • Intensive therapy increased risks of hypotension

ACCORD BP, Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial; ACS, acute coronary syndrome; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; AKI, acute kidney injury; CVD, cardiovascular disease; DBP, diastolic blood pressure; HOT, Hypertension Optimal Treatment trial; MI, myocardial infarction; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial; STEP, Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients; T2D, type 2 diabetes.

pressure control when they have high absolute cardiovascular risk. This approach is consistent with guidelines from the American College of Cardiology and American Heart Association, which also advocate a blood pressure target of <130/80 mmHg for all people, with or without diabetes (20).

Potential adverse effects of antihypertensive therapy (e.g., hypotension, syncope, falls, acute kidney injury, and electrolyte abnormalities) should also be taken into account (33,35,42,43). Individuals with older age, CKD, and frailty have been shown to be at higher risk of adverse effects of intensive blood pressure control (43). In addition, individuals with orthostatic hypotension, substantial comorbidity, functional limitations, or polypharmacy may be at high risk of adverse effects, and some patients may prefer higher blood pressure targets to enhance quality of life. However, in ACCORD BP, it was found that intensive

blood pressure lowering decreased the risk of cardiovascular events irrespective of baseline diastolic blood pressure in patients who also received standard glycemic control (44). Therefore, the presence of low diastolic blood pressure is not necessarily a contraindication to more intensive blood pressure management in the context of otherwise standard care.

Pregnancy and Antihypertensive Medications

There are few randomized controlled trials of antihypertensive therapy in pregnant individuals with diabetes. A 2014 Cochrane systematic review of antihypertensive therapy for mild to moderate chronic hypertension that included 49 trials and over 4,700 women did not find any conclusive evidence for or against blood pressure treatment to reduce the risk of preeclampsia for the mother or effects on perinatal outcomes such as preterm birth, small-for-gestational-age infants, or fetal death (45). The Control of Hypertension in Pregnancy Study (CHIPS) (46) enrolled mostly women with chronic hypertension. In CHIPS, targeting a diastolic blood pressure of 85 mmHg during pregnancy was associated with reduced likelihood of developing accelerated maternal hypertension and no demonstrable adverse outcome for infants compared with targeting a higher diastolic blood pressure. The mean systolic blood pressure achieved in the more intensively treated group was 133.1 ± 0.5 mmHg, and the mean diastolic blood pressure achieved in that group was 85.3 ± 0.3 mmHg. A similar approach is supported by the International Society for the Study of Hypertension in Pregnancy, which specifically recommends use of antihypertensive therapy to maintain systolic blood pressure between 110 and 140 mmHg and diastolic blood pressure between 80 and 85 mmHg (47).

The more recent Chronic Hypertension and Pregnancy (CHAP) trial assigned pregnant individuals with mild chronic hypertension to antihypertensive medications to target a blood pressure goal of <140/90 mmHg (active treatment group) or to control treatment, in which antihypertensive therapy was withheld unless severe hypertension (systolic pressure ≥160 mmHg or diastolic pressure ≥105 mmHg) developed (control group) (48). The primary outcome, a composite of preeclampsia with severe features, medically indicated preterm birth at <35 weeks of gestation, placental abruption, or fetal/neonatal death, occurred in 30.2% of female participants in the active treatment group vs. 37.0% in the control group ($P < 0.001$). The mean systolic blood pressure between randomization and delivery was 129.5 mmHg in the active treatment group and 132.6 mmHg in the control group.

Current evidence supports controlling blood pressure to 110–135/85 mmHg to reduce the risk of accelerated maternal hypertension but also to minimize impairment of fetal growth. During pregnancy, treatment with ACE inhibitors, angiotensin receptor blockers (ARBs), and spironolactone are contraindicated as they may cause fetal damage. Special consideration should be taken for individuals of childbearing potential, and people intending to become pregnant should switch from an ACE inhibitor/ARB or spironolactone to an alternative antihypertensive medication approved during pregnancy. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, and long-acting nifedipine, while hydralzine may be considered in the acute management of hypertension in pregnancy or severe preeclampsia (49). Diuretics are not recommended for blood pressure control in pregnancy but may be used during late-stage pregnancy if needed for volume control (49,50). The American College of Obstetricians and Gynecologists also recommends that postpartum individuals with gestational hypertension, preeclampsia, and superimposed preeclampsia have their blood pressures observed for 72 h in the hospital and for 7–10 days postpartum. Long-term follow-up is recommended for these individuals as they have increased lifetime cardiovascular risk (51). See Section 15, "Management of Diabetes in Pregnancy," for additional information.

Treatment Strategies

Lifestyle Intervention

Recommendation

10.6 For people with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity. **A**

Lifestyle management is an important component of hypertension treatment because it lowers blood pressure, enhances the effectiveness of some antihypertensive medications, promotes other aspects of metabolic and vascular health, and generally leads to few adverse effects. Lifestyle therapy consists of reducing excess body weight through caloric restriction (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes"), at least 150 min of moderate-intensity aerobic activity per week (see Section 3, "Prevention or Delay of Type 2 Diabetes and Associated Comorbidities"), restricting sodium intake (<2,300 mg/day), increasing consumption of fruits and vegetables (8–10 servings per day) and low-fat dairy products (2–3 servings per day), avoiding excessive alcohol consumption (no more than 2 servings per day in men and no more than 1 serving per day in women) (52), and increasing activity levels (53) (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes").

These lifestyle interventions are reasonable for individuals with diabetes and mildly elevated blood pressure (systolic >120 mmHg or diastolic >80 mmHg) and should be initiated along with pharmacologic therapy when hypertension is diagnosed (**Fig. 10.2**) (53). A lifestyle therapy plan should be developed in collaboration with the patient and discussed as part of diabetes management. Use of internet or mobile-based digital platforms to reinforce healthy behaviors may be considered as a component of care, as these interventions have been found to enhance the efficacy of medical therapy for hypertension (54,55).

Pharmacologic Interventions

Recommendations

10.7 Individuals with confirmed office-based blood pressure ≥130/80 mmHg qualify for initiation and titration of pharmacologic therapy to achieve

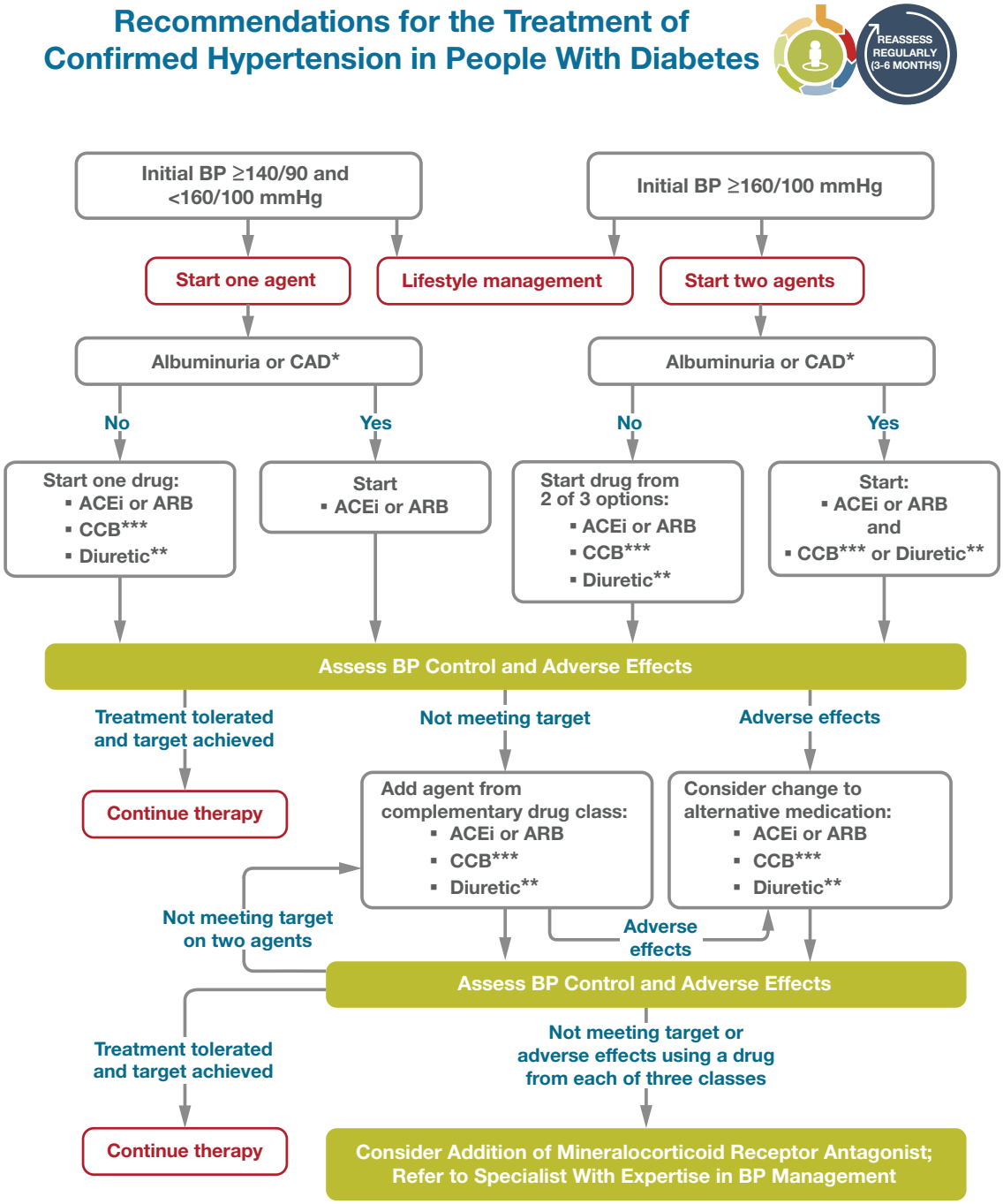

Figure 10.2—Recommendations for the treatment of confirmed hypertension in people with diabetes. *An ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) is suggested to treat hypertension for people with coronary artery disease (CAD) or urine albumin-to-creatinine ratio 30–299 mg/g creatinine and strongly recommended for individuals with urine albumin-to-creatinine ratio ≥300 mg/g creatinine. **Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred. ***Dihydropyridine calcium channel blocker (CCB). BP, blood pressure. Adapted from de Boer et al. (20).

10.8 the recommended blood pressure goal of <130/80 mmHg. **A** Individuals with confirmed office-based blood pressure ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single-pill combination of drugs demonstrated to reduce cardiovascular events in people with diabetes. **A**

10.9 Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in people with diabetes. **A** ACE inhibitors or angiotensin receptor blockers are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. **A**

10.10 Multiple-drug therapy is generally required to achieve blood

pressure targets. However, combinations of ACE inhibitors and angiotensin receptor blockers and combinations of ACE inhibitors or angiotensin receptor blockers with direct renin inhibitors should not be used. **A**

10.11 An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in people with diabetes and urinary albumin-to-creatinine ratio ≥300 mg/g creatinine **A** or 30–299 mg/g creatinine. **B** If one class is not tolerated, the other should be substituted. **B**

10.12 For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually. **B**

Initial Number of Antihypertensive Medications. Initial treatment for people with diabetes depends on the severity of hypertension (**Fig. 10.2**). Those with blood pressure between 130/80 mmHg and 160/100 mmHg may begin with a single drug. For patients with blood pressure ≥160/100 mmHg, initial pharmacologic treatment with two antihypertensive medications is recommended in order to more effectively achieve adequate blood pressure control (56–58). Single-pill antihypertensive combinations may improve medication taking in some patients (59).

Classes of Antihypertensive Medications. Initial treatment for hypertension should include any of the drug classes demonstrated to reduce cardiovascular events in people with diabetes: ACE inhibitors (60,61), ARBs (60,61), thiazide-like diuretics (62), or dihydropyridine calcium channel blockers (63). In people with diabetes and established coronary artery disease, ACE inhibitors or ARBs are recommended first-line therapy for hypertension (64–66). For patients with albuminuria (urine albumin-to-creatinine ratio [UACR] ≥30 mg/g), initial treatment should include an ACE inhibitor or ARB to reduce the risk of progressive kidney disease (20) (**Fig. 10.2**). In patients receiving ACE inhibitor or ARB therapy, continuation of those medications as kidney function declines to estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 may provide cardiovascular benefit without significantly increasing the risk of end-stage kidney disease (67). In the absence of albuminuria, risk of progressive kidney disease is low, and ACE inhibitors and ARBs have not been found to afford superior cardioprotection when compared with thiazide-like diuretics or dihydropyridine calcium channel blockers (68). β-Blockers are indicated in the setting of prior MI, active angina, or HfrEF but have not been shown to reduce mortality as blood pressure-lowering agents in the absence of these conditions (28,69,70).

Multiple-Drug Therapy. Multiple-drug therapy is often required to achieve blood pressure targets (**Fig. 10.2**), particularly in the setting of diabetic kidney disease. However, the use of both ACE inhibitors and ARBs in combination, or the combination of an ACE inhibitor or ARB and a direct renin inhibitor, is contraindicated given the lack of added ASCVD benefit and increased rate of adverse events—namely, hyperkalemia, syncope, and acute kidney injury (AKI) (71–73). Titration of and/or addition of further blood pressure medications should be made in a timely fashion to overcome therapeutic inertia in achieving blood pressure targets.

Bedtime Dosing. Although prior analyses of randomized clinical trials found a benefit to evening versus morning dosing of antihypertensive medications (74,75), these results have not been reproduced in subsequent trials. Therefore, preferential use of antihypertensives at bedtime is not recommended (76).

Hyperkalemia and Acute Kidney Injury. Treatment with ACE inhibitors or ARBs can cause AKI and hyperkalemia, while diuretics can cause AKI and either hypokalemia or hyperkalemia (depending on mechanism of action) (77,78). Detection and management of these abnormalities is important because AKI and hyperkalemia each increase the risks of cardiovascular events and death (79). Therefore, serum creatinine and potassium should be monitored during treatment with an ACE inhibitor, ARB, or diuretic, particularly among patients with reduced glomerular filtration who are at increased risk of hyperkalemia and AKI (77,78,80).

Resistant Hypertension

Recommendation

10.13 Individuals with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. **A**

Resistant hypertension is defined as blood pressure ≥140/90 mmHg despite a therapeutic strategy that includes appropriate lifestyle management plus a diuretic and two other antihypertensive drugs with complementary mechanisms of action at adequate doses. Prior to diagnosing resistant hypertension, a number of other conditions should be excluded, including missed doses of antihypertensive medications, white coat hypertension, and secondary hypertension. In general, barriers to medication taking (such as cost and side effects) should be identified and addressed (**Fig. 10.2**). Mineralocorticoid receptor antagonists, including spironolactone and eplerenone, are effective for management of resistant hypertension in people with type 2 diabetes when added to existing treatment with an ACE inhibitor or ARB, thiazide-like diuretic, or dihydropyridine calcium channel blocker (81). In addition, mineralocorticoid receptor antagonists reduce albuminuria in people with diabetic nephropathy (82–84). However, adding a mineralocorticoid receptor antagonist to a regimen including an ACE inhibitor or ARB may increase the risk for hyperkalemia, emphasizing the importance of regular monitoring for serum creatinine and potassium in these patients, and long-term outcome studies are needed to better evaluate the role of mineralocorticoid receptor antagonists in blood pressure management.

LIPID MANAGEMENT

Lifestyle Intervention

Recommendations

10.14 Lifestyle modification focusing on weight loss (if indicated);

application of a Mediterranean or Dietary Approaches to Stop Hypertension (DASH) eating pattern; reduction of saturated fat and *trans* fat; increase of dietary n-3 fatty acids, viscous fiber, and plant stanols/sterols intake; and increased physical activity should be recommended to improve the lipid profile and reduce the risk of developing atherosclerotic cardiovascular disease in people with diabetes. A

10.15 Intensify lifestyle therapy and optimize glycemic control for patients with elevated triglyceride levels (≥150 mg/dL [1.7 mmol/L]) and/or low HDL cholesterol (<40 mg/dL [1.0 mmol/L] for men, <50 mg/dL [1.3 mmol/L] for women). C

Lifestyle intervention, including weight loss in people with overweight or obesity (when appropriate) (85), increased physical activity, and medical nutrition therapy, allows some patients to reduce ASCVD risk factors. Nutrition intervention should be tailored according to each patient's age, pharmacologic treatment, lipid levels, and medical conditions.

Recommendations should focus on application of a Mediterranean (83) or Dietary Approaches to Stop Hypertension (DASH) eating pattern, reducing saturated and *trans* fat intake and increasing plant stanols/sterols, n-3 fatty acids, and viscous fiber (such as in oats, legumes, and citrus) intake (86,87). Glycemic control may also beneficially modify plasma lipid levels, particularly in patients with very high triglycerides and poor glycemic control. See Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for additional nutrition information.

Ongoing Therapy and Monitoring With Lipid Panel

Recommendations

10.16 In adults not taking statins or other lipid-lowering therapy, it is reasonable to obtain a lipid profile at the time of diabetes diagnosis, at an initial medical evaluation, and every 5 years thereafter if under the age of 40 years, or more frequently if indicated. E

10.17 Obtain a lipid profile at initiation of statins or other lipid-lowering therapy, 4–12 weeks after initiation or a change in dose, and annually thereafter as it may help to monitor the response to therapy and inform medication taking. E

In adults with diabetes, it is reasonable to obtain a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) at the time of diagnosis, at the initial medical evaluation, and at least every 5 years thereafter in patients <40 years of age. In younger people with longer duration of disease (such as those with youth-onset type 1 diabetes), more frequent lipid profiles may be reasonable. A lipid panel should also be obtained immediately before initiating statin therapy. Once a patient is taking a statin, LDL cholesterol levels should be assessed 4–12 weeks after initiation of statin therapy, after any change in dose, and on an individual basis (e.g., to monitor for medication taking and efficacy). If LDL cholesterol levels are not responding in spite of medication taking, clinical judgment is recommended to determine the need for and timing of lipid panels. In individual patients, the highly variable LDL cholesterol–lowering response seen with statins is poorly understood (88). Clinicians should attempt to find a dose or alternative statin that is tolerable if side effects occur. There is evidence for benefit from even extremely low, less than daily statin doses (89).

STATIN TREATMENT

Primary Prevention

Recommendations

10.18 For people with diabetes aged 40–75 years without atherosclerotic cardiovascular disease, use moderate-intensity statin therapy in addition to lifestyle therapy. A

10.19 For people with diabetes aged 20–39 years with additional atherosclerotic cardiovascular disease risk factors, it may be reasonable to initiate statin therapy in addition to lifestyle therapy. C

10.20 For people with diabetes aged 40–75 at higher cardiovascular risk, including those with one or more atherosclerotic cardiovascular disease risk factors, it is recommended to use high-intensity statin therapy to reduce LDL cholesterol by ≥50% of baseline and to target an LDL cholesterol goal of <70 mg/dL. B

10.21 For people with diabetes aged 40–75 years at higher cardiovascular risk, especially those with multiple atherosclerotic cardiovascular disease risk factors and an LDL cholesterol ≥70 mg/dL, it may be reasonable to add ezetimibe or a PCSK9 inhibitor to maximum tolerated statin therapy. C

10.22 In adults with diabetes aged >75 years already on statin therapy, it is reasonable to continue statin treatment. B

10.23 In adults with diabetes aged >75 years, it may be reasonable to initiate moderate-intensity statin therapy after discussion of potential benefits and risks. C

10.24 Statin therapy is contraindicated in pregnancy. B

Secondary Prevention

Recommendations

10.25 For people of all ages with diabetes and atherosclerotic cardiovascular disease, high-intensity statin therapy should be added to lifestyle therapy. A

10.26 For people with diabetes and atherosclerotic cardiovascular disease, treatment with high-intensity statin therapy is recommended to target an LDL cholesterol reduction of ≥50% from baseline and an LDL cholesterol goal of <55 mg/dL. Addition of ezetimibe or a PCSK9 inhibitor with proven benefit in this population is recommended if this goal is not achieved on maximum tolerated statin therapy. B

10.27 For individuals who do not tolerate the intended intensity, the maximum tolerated statin dose should be used. E

Table 10.2—High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30–49%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 1–4 mg

*Once-daily dosing. XL, extended release.

Initiating Statin Therapy Based on Risk

People with type 2 diabetes have an increased prevalence of lipid abnormalities, contributing to their high risk of ASCVD. Multiple clinical trials have demonstrated the beneficial effects of statin therapy on ASCVD outcomes in subjects with and without CHD (90,91). Subgroup analyses of people with diabetes in larger trials (92–96) and trials in people with diabetes (97,98) showed significant primary and secondary prevention of ASCVD events and CHD death in people with diabetes. Meta-analyses, including data from over 18,000 people with diabetes from 14 randomized trials of statin therapy (mean follow-up 4.3 years), demonstrate a 9% proportional reduction in all-cause mortality and 13% reduction in vascular mortality for each 1 mmol/L (39 mg/dL) reduction in LDL cholesterol (99). The cardiovascular benefit in this large meta-analysis did not depend on baseline LDL cholesterol levels and was linearly related to the LDL cholesterol reduction without a low threshold beyond which there was no benefit observed (99).

Accordingly, statins are the drugs of choice for LDL cholesterol lowering and cardioprotection. **Table 10.2** shows the two statin dosing intensities that are recommended for use in clinical practice: high-intensity statin therapy will achieve approximately a ≥50% reduction in LDL cholesterol, and moderate-intensity statin regimens achieve 30–49% reductions in LDL cholesterol. Low-dose statin therapy is generally not recommended in people with diabetes but is sometimes the only dose of statin that a patient can tolerate. For patients who do not tolerate the intended intensity of statin, the maximum tolerated statin dose should be used.

As in those without diabetes, absolute reductions in ASCVD outcomes (CHD death and nonfatal MI) are greatest in people with high baseline ASCVD risk (known ASCVD and/or very high LDL cholesterol levels), but the overall benefits of statin therapy in people with diabetes at moderate or even low risk for ASCVD are convincing (100,101). The relative benefit of lipid-lowering therapy has been uniform across most subgroups tested (91,99), including subgroups that varied with respect to age and other risk factors.

Primary Prevention (People Without ASCVD)

For primary prevention, moderate-dose statin therapy is recommended for those aged ≥40 years (93,100,101), although high-intensity therapy should be considered in the context of additional ASCVD risk factors. The evidence is strong for people with diabetes aged 40–75 years, an age-group well represented in statin trials showing benefit. Since cardiovascular risk is enhanced in people with diabetes, as noted above, patients who also have multiple other coronary risk factors have increased risk, equivalent to that of those with ASCVD. Therefore, current guidelines recommend that in people with diabetes who are at higher cardiovascular risk, especially those with one or more ASCVD risk factors, high-intensity statin therapy should be prescribed to reduce LDL cholesterol by ≥50% from baseline and to target an LDL cholesterol of <70 mg/dL (102–104). Since in clinical practice it is frequently difficult to ascertain the baseline LDL cholesterol level prior to statin therapy initiation, in those individuals, a focus on an LDL cholesterol target level of <70 mg/dL rather than the percent reduction in LDL cholesterol is recommended. In those individuals, it may also be reasonable to add ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy to maximum tolerated statin therapy if needed to reduce LDL cholesterol levels by ≥50% and to achieve the recommended LDL cholesterol target of <70 mg/dL (14). The evidence is lower for patients aged >75 years; relatively few older people with diabetes have been enrolled in primary prevention trials. However, heterogeneity by age has not been seen in the relative benefit of lipid-lowering therapy in trials that included older participants (91,98,99), and because older age confers higher risk, the absolute benefits are actually greater (91,105). Moderate-intensity statin therapy is recommended in people with diabetes who are ≥75 years of age. However, the risk-benefit profile should be routinely evaluated in this population, with downward titration of dose performed as needed. See Section 13, "Older Adults," for more details on clinical considerations for this population.

Age <40 Years and/or Type 1 Diabetes. Very little clinical trial evidence exists for people with type 2 diabetes under the age of 40 years or for people with type diabetes of any age. For pediatric recommendations, see Section 14, "Children and Adolescents." In the Heart Protection Study (lower age limit 40 years), the subgroup of ~600 people with type 1 diabetes had a proportionately similar, although not statistically significant, reduction in risk to that in people with type 2 diabetes (93). Even though the data are not definitive, similar statin treatment approaches should be considered for people with type 1 or type 2 diabetes, particularly in the presence of other cardiovascular risk factors. Patients <40 years of age have lower risk of developing a cardiovascular event over a 10-year horizon; however, their lifetime risk of developing cardiovascular disease and suffering an MI, stroke, or cardiovascular death is high. For people who are <40 years of age and/or have type 1 diabetes with other ASCVD risk factors, it is recommended that the patient and health care professional discuss the relative benefits and risks and consider the use of moderate-intensity statin therapy. Please refer to "Type 1 Diabetes Mellitus and Cardiovascular Disease: A Scientific Statement From the American Heart Association and American Diabetes Association" (106) for additional discussion.

Secondary Prevention (People With ASCVD)

Because cardiovascular event rates are increased in people with diabetes and

established ASCVD, intensive therapy is indicated and has been shown to be of benefit in multiple large meta-analyses and randomized cardiovascular outcomes trials (91,99,105,107,108). High-intensity statin therapy is recommended for all people with diabetes and ASCVD to target an LDL cholesterol reduction of ≥50% from baseline and an LDL cholesterol goal of <55 mg/dL. Based on the evidence discussed below, addition of ezetimibe or a PCSK9 inhibitor is recommended if this goal is not achieved on maximum tolerated statin therapy. These recommendations are based on the observation that high-intensity versus moderate-intensity statin therapy reduces cardiovascular event rates in high-risk individuals with established cardiovascular disease in randomized trials (95,107). In addition, the Cholesterol Treatment Trialists' Collaboration involving 26 statin trials, of which 5 compared high-intensity versus moderate-intensity statins (99), showed a 21% reduction in major cardiovascular events in people with diabetes for every 39 mg/dL of LDL cholesterol lowering, irrespective of baseline LDL cholesterol or patient characteristics (99). However, the best evidence to support lower LDL cholesterol targets in people with diabetes and established cardiovascular disease derives from multiple large randomized trials investigating the benefits of adding nonstatin agents to statin therapy. As discussed in detail below, these include combination treatment with statins and ezetimibe (105,109) or PCSK9 inhibitors (108,110–112). Each trial found a significant benefit in the reduction of ASCVD events that was directly related to the degree of further LDL cholesterol lowering. These large trials included a significant number of participants with diabetes and prespecified analyses on cardiovascular outcomes in people with and without diabetes (109,111,112). The decision to add a nonstatin agent should be made following a clinician-patient discussion about the net benefit, safety, and cost of combination therapy.

Combination Therapy for LDL Cholesterol Lowering

Statins and Ezetimibe

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a randomized controlled trial in 18,144 patients comparing the addition of ezetimibe to simvastatin therapy versus simvastatin alone (105). Individuals were ≥50 years of age, had experienced a recent acute coronary syndrome (ACS) and were treated for an average of 6 years. Overall, the addition of ezetimibe led to a 6.4% relative benefit and a 2% absolute reduction in major adverse cardiovascular events (atherosclerotic cardiovascular events), with the degree of benefit being directly proportional to the change in LDL cholesterol, which was 70 mg/dL in the statin group on average and 54 mg/dL in the combination group (105). In those with diabetes (27% of participants), the combination of moderate-intensity simvastatin (40 mg) and ezetimibe (10 mg) showed a significant reduction of major adverse cardiovascular events with an absolute risk reduction of 5% (40% vs. 45% cumulative incidence at 7 years) and a relative risk reduction of 14% (hazard ratio [HR] 0.86 [95% CI 0.78–0.94]) over moderate-intensity simvastatin (40 mg) alone (109).

Statins and PCSK9 Inhibitors

Placebo-controlled trials evaluating the addition of the PCSK9 inhibitors evolocumab and alirocumab to maximum tolerated doses of statin therapy in participants who were at high risk for ASCVD demonstrated an average reduction in LDL cholesterol ranging from 36 to 59%. These agents have been approved as adjunctive therapy for individuals with ASCVD or familial hypercholesterolemia who are receiving maximum tolerated statin therapy but require additional lowering of LDL cholesterol (113,114). No cardiovascular outcome trials have been performed to assess whether PCSK9 inhibitor therapy reduces ASCVD event rates in individuals without established cardiovascular disease (primary prevention).

The effects of PCSK9 inhibition on ASCVD outcomes was investigated in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, which enrolled 27,564 individuals with prior ASCVD and an additional high-risk feature who were receiving their maximum tolerated statin therapy (two-thirds were on high-intensity statin) but who still had LDL cholesterol ≥70 mg/dL or non-HDL cholesterol ≥100 mg/dL (108). Patients were randomized to receive subcutaneous injections of evolocumab (either 140 mg every 2 weeks or 420 mg every month based on patient preference) versus placebo. Evolocumab reduced LDL cholesterol by 59% from a median of 92 to 30 mg/dL in the treatment arm.

During the median follow-up of 2.2 years, the composite outcome of cardiovascular death, MI, stroke, hospitalization for angina, or revascularization occurred in 11.3% vs. 9.8% of the placebo and evolocumab groups, respectively, representing a 15% relative risk reduction ($P < 0.001$). The combined end point of cardiovascular death, MI, or stroke was reduced by 20%, from 7.4 to 5.9% ($P < 0.001$). Evolocumab therapy also significantly reduced all strokes (1.5% vs. 1.9%; HR 0.79 [95% CI 0.66–0.95]; $P = 0.01$) and ischemic stroke (1.2% vs. 1.6%; HR 0.75 [95% CI 0.62–0.92]; $P = 0.005$) in the total population, with findings being consistent in individuals with or without a history of ischemic stroke at baseline (115). Importantly, similar benefits were seen in a prespecified subgroup of people with diabetes, comprising 11,031 patients (40% of the trial) (112).

In the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), 18,924 patients (28.8% of whom had diabetes) with recent acute coronary syndrome were randomized to the PCSK9 inhibitor alirocumab or placebo every 2 weeks in addition to maximum tolerated statin therapy, with alirocumab dosing titrated between 75 and 150 mg to achieve LDL cholesterol levels between 25 and 50 mg/dL (110). Over a median follow-up of 2.8 years, a composite primary end point (comprising death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospital admission) occurred in 903 patients (9.5%) in the alirocumab group and in 1,052 patients (11.1%) in the placebo group (HR 0.85 [95% CI 0.78–0.93]; $P < 0.001$). Combination therapy with alirocumab plus statin therapy resulted in a greater absolute reduction in the incidence of the primary end point in people with diabetes (2.3% [95% CI 0.4–4.2]) than in those with prediabetes (1.2% [0.0–2.4]) or normoglycemia (1.2% [–0.3 to 2.7]) (111).

In addition to monoclonal antibodies targeting PCSK9, the siRNA inclisiran has been developed and has recently become available in the U.S. In the Inclisiran for

Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol (ORION-10) and Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated Low-density Lipoprotein Cholesterol (ORION-11) trials (116), individuals with established cardiovascular disease or ASCVD risk equivalent were randomized to receive inclisiran or placebo. Inclisiran allows less frequent administration compared with monoclonal antibodies and was administered on day 1, on day 90, and every 6 months in these trials. In the ORION-10 trial, 47.5% of patients in the inclisiran group and 42.4% in the placebo group had diabetes; in the ORION-11 trial, 36.5% of patients in the inclisiran group and 33.7% in the placebo group had diabetes. The coprimary end point of placebo-corrected percentage change in LDL cholesterol level from baseline to day 510 was 52.3% in the ORION-10 trial and 49.9% in the ORION-11 trial. In an exploratory analysis, the prespecified cardiovascular end point, defined as a cardiovascular basket of nonadjudicated terms, including those classified within cardiac death, and any signs or symptoms of cardiac arrest, nonfatal MI, or stroke, occurred in 7.4% of the inclisiran group and 10.2% of the placebo group in the ORION-10 trial and in 7.8% of the inclisiran group and 10.3% of the placebo group in the ORION-11 trial. A cardiovascular outcome trial using inclisiran in people with established cardiovascular disease is currently ongoing (117).

Statins and Bempedoic Acid

Bempedoic acid is a novel LDL cholesterol–lowering agent that is indicated as an adjunct to diet and maximum tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established ASCVD who require additional lowering of LDL cholesterol. A pooled analysis suggests that bempedoic acid therapy lowers LDL cholesterol levels by about 23% compared with placebo (118). At this time, there are no completed trials demonstrating a cardiovascular outcomes benefit to use of this medication; however, this agent may be considered for patients who cannot use or tolerate other evidence-based LDL cholesterol-lowering approaches, or for whom those other therapies are inadequately effective (119).

Treatment of Other Lipoprotein Fractions or Targets

Recommendations

10.28 For individuals with fasting triglyceride levels ≥500 mg/dL, evaluate for secondary causes of hypertriglyceridemia and consider medical therapy to reduce the risk of pancreatitis. **C**

10.29 In adults with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175–499 mg/dL), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that raise triglycerides. **C**

10.30 In individuals with atherosclerotic cardiovascular disease or other cardiovascular risk factors on a statin with controlled LDL cholesterol but elevated triglycerides (135–499 mg/dL), the addition of icosapent ethyl can be considered to reduce cardiovascular risk. **A**

Hypertriglyceridemia should be addressed with dietary and lifestyle changes including weight loss and abstinence from alcohol (120). Severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL and especially >1,000 mg/dL) may warrant pharmacologic therapy (fibric acid derivatives and/or fish oil) and reduction in dietary fat to reduce the risk of acute pancreatitis. Moderate- or high-intensity statin therapy should also be used as indicated to reduce risk of cardiovascular events (see statin treatment). In people with moderate hypertriglyceridemia, lifestyle interventions, treatment of secondary factors, and avoidance of medications that might raise triglycerides are recommended.

The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) enrolled 8,179 adults receiving statin therapy with moderately elevated triglycerides (135–499 mg/dL, median baseline of 216 mg/dL) who had either established cardiovascular disease (secondary prevention cohort) or diabetes plus at least one other cardiovascular risk factor (primary prevention cohort) (121). Patients were randomized to icosapent ethyl 4 g/day (2 g twice daily with food) versus placebo. The trial met its primary end point, demonstrating a 25% relative risk reduction ($P < 0.001$) for the primary end point composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina. This reduction in risk was seen in people with or without diabetes at baseline. The composite of cardiovascular death, nonfatal MI, or nonfatal stroke was reduced by 26% ($P < 0.001$). Additional ischemic end points were significantly lower in the icosapent ethyl group than in the placebo group, including cardiovascular death, which was reduced by 20% ($P = 0.03$). The proportions of patients experiencing adverse events and serious adverse events were similar between the active and placebo treatment groups. It should be noted that data are lacking with other n-3 fatty acids, and results of the REDUCE-IT trial should not be extrapolated to other products (121). As an example, the addition of 4 g per day of a carboxylic acid formulation of the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (n-3 carboxylic acid) to statin therapy in patients with atherogenic dyslipidemia and high cardiovascular risk, 70% of whom had diabetes, did not reduce the risk of major adverse cardiovascular events compared with the inert comparator of corn oil (122).

Low levels of HDL cholesterol, often associated with elevated triglyceride levels, are the most prevalent pattern of dyslipidemia in people with type 2 diabetes. However, the evidence for the use of drugs that target these lipid fractions is substantially less robust than that for statin therapy (123). In a large trial in people with diabetes, fenofibrate failed to reduce overall cardiovascular outcomes (124).

Other Combination Therapy

Recommendations

10.31 Statin plus fibrate combination therapy has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended. **A**

10.32 Statin plus niacin combination therapy has not been shown

to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. A

Statin and Fibrate Combination Therapy

Combination therapy (statin and fibrate) is associated with an increased risk for abnormal transaminase levels, myositis, and rhabdomyolysis. The risk of rhabdomyolysis is more common with higher doses of statins and renal insufficiency and appears to be higher when statins are combined with gemfibrozil (compared with fenofibrate) (125).

In the ACCORD study, in people with type 2 diabetes who were at high risk for ASCVD, the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal MI, or nonfatal stroke compared with simvastatin alone. Prespecified subgroup analyses suggested heterogeneity in treatment effects with possible benefit for men with both a triglyceride level ≥204 mg/dL (2.3 mmol/L) and an HDL cholesterol level ≤34 mg/dL (0.9 mmol/L) (126).

Statin and Niacin Combination Therapy

The Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial randomized over 3,000 people (about one-third with diabetes) with established ASCVD, LDL cholesterol levels <180 mg/dL [4.7 mmol/L], low HDL cholesterol levels (men <40 mg/dL [1.0 mmol/L] and women <50 mg/dL [1.3 mmol/L]), and triglyceride levels of 150–400 mg/dL (1.7–4.5 mmol/L) to statin therapy plus extended-release niacin or placebo. The trial was halted early due to lack of efficacy on the primary ASCVD outcome (first event of the composite of death from CHD, nonfatal MI, ischemic stroke, hospitalization for an ACS, or symptom-driven coronary or cerebral revascularization) and a possible increase in ischemic stroke in those on combination therapy (127).

The much larger Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial also failed to show a benefit of adding niacin to background statin therapy (128). A total of 25,673 individuals with prior vascular disease were randomized to receive 2 g of extended-release niacin and 40 mg of laropiprant (an antagonist of the prostaglandin D2 receptor DP1 that has been shown to improve participation in niacin therapy) versus a matching placebo daily and followed for a median follow-up period of 3.9 years. There was no significant difference in the rate of coronary death, MI, stroke, or coronary revascularization with the addition of niacin–laropiprant versus placebo (13.2% vs. 13.7%; rate ratio 0.96; $P = 0.29$). Niacin–laropiprant was associated with an increased incidence of new-onset diabetes (absolute excess, 1.3 percentage points; $P < 0.001$) and disturbances in diabetes management among those with diabetes. In addition, there was an increase in serious adverse events associated with the gastrointestinal system, musculoskeletal system, skin, and, unexpectedly, infection and bleeding.

Therefore, combination therapy with a statin and niacin is not recommended given the lack of efficacy on major ASCVD outcomes and increased side effects.

Diabetes Risk With Statin Use

Several studies have reported a modestly increased risk of incident diabetes with statin use (129,130), which may be limited to those with diabetes risk factors. An analysis of one of the initial studies suggested that although statin use was associated with diabetes risk, the cardiovascular event rate reduction with statins far outweighed the risk of incident diabetes even for patients at highest risk for diabetes (131). The absolute risk increase was small (over 5 years of follow-up, 1.2% of participants on placebo developed diabetes and 1.5% on rosuvastatin developed diabetes) (131). A meta-analysis of 13 randomized statin trials with 91,140 participants showed an odds ratio of 1.09 for a new diagnosis of diabetes, so that (on average) treatment of 255 patients with statins for 4 years resulted in one additional case of diabetes while simultaneously preventing 5.4 vascular events among those 255 patients (130).

Lipid-Lowering Agents and Cognitive Function

Although concerns regarding a potential adverse impact of lipid-lowering agents on cognitive function have been raised, several lines of evidence point against this association, as detailed in a 2018 European Atherosclerosis Society Consensus Panel statement (132). First, there are three large randomized trials of statin versus placebo where specific cognitive tests were performed, and no differences were seen between statin and placebo (133–136). In addition, no change in cognitive function has been reported in studies with the addition of ezetimibe (105) or PCSK9 inhibitors (108,137) to statin therapy, including among patients treated to very low LDL cholesterol levels. In addition, the most recent systematic review of the U.S. Food and Drug Administration's (FDA's) postmarketing surveillance databases, randomized controlled trials, and cohort, case-control, and cross-sectional studies evaluating cognition in patients receiving statins found that published data do not reveal an adverse effect of statins on cognition (138). Therefore, a concern that statins or other lipid-lowering agents might cause cognitive dysfunction or dementia is not currently supported by evidence and should not deter their use in individuals with diabetes at high risk for ASCVD (138).

ANTIPLATELET AGENTS

Recommendations

10.33 Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of atherosclerotic cardiovascular disease. A

10.34 For individuals with atherosclerotic cardiovascular disease and documented aspirin allergy, clopidogrel (75 mg/day) should be used. B

10.35 Dual antiplatelet therapy (with low-dose aspirin and a P2Y12 inhibitor) is reasonable for a year after an acute coronary syndrome and may have benefits beyond this period. A

10.36 Long-term treatment with dual antiplatelet therapy should be considered for individuals with prior coronary intervention, high ischemic risk, and low bleeding risk to prevent major adverse cardiovascular events. A

10.37 Combination therapy with aspirin plus low-dose rivaroxaban

should be considered for individuals with stable coronary and/or peripheral artery disease and low bleeding risk to prevent major adverse limb and cardiovascular events. **A**

10.38 Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a comprehensive discussion with the patient on the benefits versus the comparable increased risk of bleeding. **A**

Risk Reduction

Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk patients with previous MI or stroke (secondary prevention) and is strongly recommended. In primary prevention, however, among patients with no previous cardiovascular events, its net benefit is more controversial (129,140).

Previous randomized controlled trials of aspirin specifically in people with diabetes failed to consistently show a significant reduction in overall ASCVD end points, raising questions about the efficacy of aspirin for primary prevention in people with diabetes, although some sex differences were suggested (141–143).

The Antithrombotic Trialists' Collaboration published an individual patient–level meta-analysis (139) of the six large trials of aspirin for primary prevention in the general population. These trials collectively enrolled over 95,000 participants, including almost 4,000 with diabetes. Overall, they found that aspirin reduced the risk of serious vascular events by 12% (relative risk 0.88 [95% CI 0.82–0.94]). The largest reduction was for nonfatal MI, with little effect on CHD death (relative risk 0.95 [95% CI 0.78–1.15]) or total stroke.

Most recently, the ASCEND (A Study of Cardiovascular Events iN Diabetes) trial randomized 15,480 people with diabetes but no evident cardiovascular disease to aspirin 100 mg daily or placebo (144). The primary efficacy end point was vascular death, MI, or stroke or transient ischemic attack. The primary safety outcome was major bleeding (i.e., intracranial hemorrhage, sight-threatening bleeding in the eye, gastrointestinal bleeding, or other serious bleeding). During a mean follow-up of 7.4 years, there was a significant 12% reduction in the primary efficacy end point (8.5% vs. 9.6%; $P = 0.01$). In contrast, major bleeding was significantly increased from 3.2 to 4.1% in the aspirin group (rate ratio 1.29; $P = 0.003$), with most of the excess being gastrointestinal bleeding and other extracranial bleeding. There were no significant differences by sex, weight, or duration of diabetes or other baseline factors including ASCVD risk score.

Two other large, randomized trials of aspirin for primary prevention, in people without diabetes (ARRIVE [Aspirin to Reduce Risk of Initial Vascular Events]) (145) and in the elderly (ASPREE [Aspirin in Reducing Events in the Elderly]) (146), which included 11% with diabetes, found no benefit of aspirin on the primary efficacy end point and an increased risk of bleeding. In ARRIVE, with 12,546 patients over a period of 60 months follow-up, the primary end point occurred in 4.29% vs. 4.48% of patients in the aspirin versus placebo groups (HR 0.96 [95% CI 0.81–1.13]; $P = 0.60$). Gastrointestinal bleeding events (characterized as mild) occurred in 0.97% of patients in the aspirin group vs. 0.46% in the placebo group (HR 2.11 [95% CI 1.36–3.28]; $P = 0.0007$). In ASPREE, including 19,114 individuals, for cardiovascular disease (fatal CHD, MI, stroke, or hospitalization for heart failure) after a median of 4.7 years of follow-up, the rates per 1,000 person-years were 10.7 vs. 11.3 events in aspirin vs. placebo groups (HR 0.95 [95% CI 0.83–1.08]). The rate of major hemorrhage per 1,000 person-years was 8.6 events vs. 6.2 events, respectively (HR 1.38 [95% CI 1.18–1.62]; $P < 0.001$).

Thus, aspirin appears to have a modest effect on ischemic vascular events, with the absolute decrease in events depending on the underlying ASCVD risk. The main adverse effect is an increased risk of gastrointestinal bleeding. The excess risk may be as high as 5 per 1,000 per year in real-world settings. However, for adults with ASCVD risk >1% per year, the number of ASCVD events prevented will be similar to the number of episodes of bleeding induced, although these complications do not have equal effects on long-term health (147).

Recommendations for using aspirin as primary prevention include both men and women aged ≥50 years with diabetes and at least one additional major risk factor (family history of premature ASCVD, hypertension, dyslipidemia, smoking, or CKD/albuminuria) who are not at increased risk of bleeding (e.g., older age, anemia, renal disease) (148–151). Noninvasive imaging techniques such as coronary calcium scoring may potentially help further tailor aspirin therapy, particularly in those at low risk (152,153). For people >70 years of age (with or without diabetes), the balance appears to have greater risk than benefit (144,146). Thus, for primary prevention, the use of aspirin needs to be carefully considered and may generally not be recommended. Aspirin may be considered in the context of high cardiovascular risk with low bleeding risk, but generally not in older adults. Aspirin therapy for primary prevention may be considered in the context of shared decision-making, which carefully weighs the cardiovascular benefits with the fairly comparable increase in risk of bleeding.

For people with documented ASCVD, use of aspirin for secondary prevention has far greater benefit than risk; for this indication, aspirin is still recommended (139).

Aspirin Use in People <50 Years of Age

Aspirin is not recommended for those at low risk of ASCVD (such as men and women aged <50 years with diabetes with no other major ASCVD risk factors) as the low benefit is likely to be outweighed by the risks of bleeding. Clinical judgment should be used for those at intermediate risk (younger patients with one or more risk factors or older patients with no risk factors) until further research is available. Patients' willingness to undergo long-term aspirin therapy should also be considered (154). Aspirin use in patients aged <21 years is generally contraindicated due to the associated risk of Reye syndrome.

Aspirin Dosing

Average daily dosages used in most clinical trials involving people with diabetes ranged from 50 mg to 650 mg but were mostly in the range of 100–325 mg/day. There is little evidence to support any specific dose but using the lowest possible dose may help to reduce side effects (155). In the ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness) trial of individuals with established cardiovascular disease, 38% of whom had

diabetes, there were no significant differences in cardiovascular events or major bleeding between patients assigned to 81 mg and those assigned to 325 mg of aspirin daily (156). In the U.S., the most common low-dose tablet is 81 mg. Although platelets from people with diabetes have altered function, it is unclear what, if any, effect that finding has on the required dose of aspirin for cardioprotective effects in people with diabetes. Many alternate pathways for platelet activation exist that are independent of thromboxane A_2 and thus are not sensitive to the effects of aspirin (157). "Aspirin resistance" has been described in people with diabetes when measured by a variety of ex vivo and in vitro methods (platelet aggregometry, measurement of thromboxane B_2) (158), but other studies suggest no impairment in aspirin response among people with diabetes (159). A trial suggested that more frequent dosing regimens of aspirin may reduce platelet reactivity in individuals with diabetes (160); however, these observations alone are insufficient to empirically recommend that higher doses of aspirin be used in this group at this time. Another meta-analysis raised the hypothesis that low-dose aspirin efficacy is reduced in those weighing >70 kg (161); however, the ASCEND trial found benefit of low-dose aspirin in those in this weight range, which would thus not validate this suggested hypothesis (144). It appears that 75–162 mg/day is optimal.

Indications for P2Y12 Receptor Antagonist Use

A P2Y12 receptor antagonist in combination with aspirin is reasonable for at least 1 year in patients following an ACS and may have benefits beyond this period. Evidence supports use of either ticagrelor or clopidogrel if no percutaneous coronary intervention was performed and clopidogrel, ticagrelor, or prasugrel if a percutaneous coronary intervention was performed (162). In people with diabetes and prior MI (1–3 years before), adding ticagrelor to aspirin significantly reduces the risk of recurrent ischemic events including cardiovascular and CHD death (163). Similarly, the addition of ticagrelor to aspirin reduced the risk of ischemic cardiovascular events compared with aspirin alone in people with diabetes and stable coronary artery disease (164,165). However, a higher incidence of major bleeding, including intracranial hemorrhage, was noted with dual antiplatelet therapy. The net clinical benefit (ischemic benefit vs. bleeding risk) was improved with ticagrelor therapy in the large prespecified subgroup of patients with history of percutaneous coronary intervention, while no net benefit was seen in patients without prior percutaneous coronary intervention (165). However, early aspirin discontinuation compared with continued dual antiplatelet therapy after coronary stenting may reduce the risk of bleeding without a corresponding increase in the risks of mortality and ischemic events, as shown in a prespecified analysis of people with diabetes enrolled in the TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) trial and a recent meta-analysis (166,167).

Combination Antiplatelet and Anticoagulation Therapy

Combination therapy with aspirin plus low dose rivaroxaban may be considered for people with stable coronary and/or peripheral artery disease to prevent major adverse limb and cardiovascular complications. In the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial of 27,395 individuals with established coronary artery disease and/or peripheral artery disease, aspirin plus rivaroxaban 2.5 mg twice daily was superior to aspirin plus placebo in the reduction of cardiovascular ischemic events including major adverse limb events. The absolute benefits of combination therapy appeared larger in people with diabetes, who comprised 10,341 of the trial participants (168,169). A similar treatment strategy was evaluated in the Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease (VOYAGER PAD) trial (170), in which 6,564 individuals with peripheral artery disease who had undergone revascularization were randomly assigned to receive rivaroxaban 2.5 mg twice daily plus aspirin or placebo plus aspirin. Rivaroxaban treatment in this group of patients was also associated with a significantly lower incidence of ischemic cardiovascular events, including major adverse limb events. However, an increased risk of major bleeding was noted with rivaroxaban added to aspirin treatment in both COMPASS and VOYAGER PAD.

The risks and benefits of dual antiplatelet or antiplatelet plus anticoagulant treatment strategies should be thoroughly discussed with eligible patients, and shared decision-making should be used to determine an individually appropriate treatment approach. This field of cardiovascular risk reduction is evolving rapidly, as are the definitions of optimal care for patients with differing types and circumstances of cardiovascular complications.

CARDIOVASCULAR DISEASE

Screening

Recommendations

10.39 In asymptomatic individuals, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. **A**

10.40 Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). **E**

Treatment

Recommendations

10.41 Among people with type 2 diabetes who have established atherosclerotic cardiovascular disease or established kidney disease, a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit (**Table 10.3*B*** and **Table 10.3*C***) is recommended as part of the comprehensive cardiovascular risk reduction and/or glucose-lowering regimens. **A**

Table 10.3A—Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: DPP-4 inhibitors

	SAVOR-TIMI 53 (224) (*n* = 16,492)	EXAMINE (235) (*n* = 5,380)	TECOS (226) (*n* = 14,671)	CARMELINA (193,236) (*n* = 6,979)	CAROLINA (193,237) (*n* = 6,042)
Intervention	Saxagliptin/placebo	Alogliptin/placebo	Sitagliptin/placebo	Linagliptin/placebo	Linagliptin/ glimepiride
Main inclusion criteria	Type 2 diabetes and history of or multiple risk factors for CVD	Type 2 diabetes and ACS within 15–90 days before randomization	Type 2 diabetes and preexisting CVD	Type 2 diabetes and high CV and renal risk	Type 2 diabetes and high CV risk
A1C inclusion criteria (%)	≥6.5	6.5–11.0	6.5–8.0	6.5–10.0	6.5–8.5
Age (years)†	65.1	61.0	65.4	65.8	64.0
Race (% White)	75.2	72.7	67.9	80.2	73.0
Sex (% male)	66.9	67.9	70.7	62.9	60.0
Diabetes duration (years)†	10.3	7.1	11.6	14.7	6.2
Median follow-up (years)	2.1	1.5	3.0	2.2	6.3
Statin use (%)	78	91	80	71.8	64.1
Metformin use (%)	70	66	82	54.8	82.5
Prior CVD/CHF (%)	78/13	100/28	74/18	57/26.8	34.5/4.5
Mean baseline A1C (%)	8.0	8.0	7.2	7.9	7.2
Mean difference in A1C between groups at end of treatment (%)	−0.3‡	−0.3‡	−0.3‡	−0.36‡	0
Year started/ reported	2010/2013	2009/2013	2008/2015	2013/2018	2010/2019
Primary outcome§	3-point MACE 1.00 (0.89–1.12)	3-point MACE 0.96 (95% UL ≤1.16)	4-point MACE 0.98 (0.89–1.08)	3-point MACE 1.02 (0.89–1.17)	3-point MACE 0.98 (0.84–1.14)
Key secondary outcome§	Expanded MACE 1.02 (0.94–1.11)	4-point MACE 0.95 (95% UL ≤1.14)	3-point MACE 0.99 (0.89–1.10)	Kidney composite (ESRD, sustained ≥40% decrease in eGFR, or renal death) 1.04 (0.89–1.22)	4-point MACE 0.99 (0.86–1.14)
Cardiovascular death§	1.03 (0.87–1.22)	0.85 (0.66–1.10)	1.03 (0.89–1.19)	0.96 (0.81–1.14)	1.00 (0.81–1.24)
MI§	0.95 (0.80–1.12)	1.08 (0.88–1.33)	0.95 (0.81–1.11)	1.12 (0.90–1.40)	1.03 (0.82–1.29)
Stroke§	1.11 (0.88–1.39)	0.91 (0.55–1.50)	0.97 (0.79–1.19)	0.91 (0.67–1.23)	0.86 (0.66–1.12)
HF hospitalization§	1.27 (1.07–1.51)	1.19 (0.90–1.58)	1.00 (0.83–1.20)	0.90 (0.74–1.08)	1.21 (0.92–1.59)
Unstable angina hospitalization§	1.19 (0.89–1.60)	0.90 (0.60–1.37)	0.90 (0.70–1.16)	0.87 (0.57–1.31)	1.07 (0.74–1.54)
All-cause mortality§	1.11 (0.96–1.27)	0.88 (0.71–1.09)	1.01 (0.90–1.14)	0.98 (0.84–1.13)	0.91 (0.78–1.06)
Worsening nephropathy§‖	1.08 (0.88–1.32)	—	—	Kidney composite (see above)	—

—, not assessed/reported; ACS, acute coronary syndrome; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GLP-1, glucagon-like peptide 1; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; UL, upper limit. Data from this table was adapted from Cefalu et al. (238) in the January 2018 issue of *Diabetes Care*. †Age was reported as means in all trials except EXAMINE, which reported medians; diabetes duration was reported as means in all trials except SAVOR-TIMI 53 and EXAMINE, which reported medians. ‡Significant difference in A1C between groups ($P < 0.05$). §Outcomes reported as hazard ratio (95% CI). ‖Worsening nephropathy is defined as a doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dL (530 mmol/L) in SAVOR-TIMI 53. Worsening nephropathy was a prespecified exploratory adjudicated outcome in SAVOR-TIMI 53.

Table 10.3*B*—Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: GLP-1 receptor agonists

	ELIXA (208) (*n* = 6,068)	LEADER (203) (*n* = 9,340)	SUSTAIN-6 (204)* (*n* = 3,297)	EXSCEL (209) (*n* = 14,752)	REWIND (207) (*n* = 9,901)	PIONEER-6 (205) (*n* = 3,183)
Intervention	Lixisenatide/placebo	Liraglutide/placebo	Semaglutide s.c. injection/placebo	Exenatide QW/ placebo	Dulaglutide/ placebo	Semaglutide oral/ placebo
Main inclusion criteria	Type 2 diabetes and history of ACS (<180 days)	Type 2 diabetes and preexisting CVD, CKD, or HF at ≥50 years of age or CV risk at ≥60 years of age	Type 2 diabetes and preexisting CVD, HF, or CKD at ≥50 years of age or CV risk at ≥60 years of age	Type 2 diabetes with or without preexisting CVD	Type 2 diabetes and prior ASCVD event or risk factors for ASCVD	Type 2 diabetes and high CV risk (age of ≥50 years with established CVD or CKD, or age of ≥60 years with CV risk factors only)
A1C inclusion criteria (%)	5.5–11.0	≥7.0	≥7.0	6.5–10.0	≤9.5	None
Age (years)†	60.3	64.3	64.6	62	66.2	66
Race (% White)	75.2	77.5	83.0	75.8	75.7	72.3
Sex (% male)	69.3	64.3	60.7	62	53.7	68.4
Diabetes duration (years)†	9.3	12.8	13.9	12	10.5	14.9
Median follow-up (years)	2.1	3.8	2.1	3.2	5.4	1.3
Statin use (%)	93	72	73	74	66	85.2 (all lipid-lowering)
Metformin use (%)	66	76	73	77	81	77.4
Prior CVD/CHF (%)	100/22	81/18	60/24	73.1/16.2	32/9	84.7/12.2
Mean baseline A1C (%)	7.7	8.7	8.7	8.0	7.4	8.2
Mean difference in A1C between groups at end of treatment (%)	−0.3‡^	−0.4‡	−0.7 or −1.0^	−0.53‡^	−0.61‡	−0.7
Year started/reported	2010/2015	2010/2016	2013/2016	2010/2017	2011/2019	2017/2019
Primary outcome§	4-point MACE 1.02 (0.89–1.17)	3-point MACE 0.87 (0.78–0.97)	3-point MACE 0.74 (0.58–0.95)	3-point MACE 0.91 (0.83–1.00)	3-point MACE 0.88 (0.79–0.99)	3-point MACE 0.79 (0.57–1.11)

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Table 10.3B—Continued

	ELIXA (208) (*n* = 6,068)	LEADER (203) (*n* = 9,340)	SUSTAIN-6 (204)* (*n* = 3,297)	EXSCEL (209) (*n* = 14,752)	REWIND (207) (*n* = 9,901)	PIONEER-6 (205) (*n* = 3,183)
Key secondary outcomes§	Expanded MACE 1.02 (0.90–1.11)	Expanded MACE 0.88 (0.81–0.96)	Expanded MACE 0.74 (0.62–0.89)	Individual components of MACE (see below)	Composite microvascular outcome (eye or renal outcome) 0.87 (0.79–0.95)	Expanded MACE or HF hospitalization 0.82 (0.61–1.10)
Cardiovascular death§	0.98 (0.78–1.22)	0.78 (0.66–0.93)	0.98 (0.65–1.48)	0.88 (0.76–1.02)	0.91 (0.78–1.06)	0.49 (0.27–0.92)
MI§	1.03 (0.87–1.22)	0.86 (0.73–1.00)	0.74 (0.51–1.08)	0.97 (0.85–1.10)	0.96 (0.79–1.15)	1.18 (0.73–1.90)
Stroke§	1.12 (0.79–1.58)	0.86 (0.71–1.06)	0.61 (0.38–0.99)	0.85 (0.70–1.03)	0.76 (0.61–0.95)	0.74 (0.35–1.57)
HF hospitalization§	0.96 (0.75–1.23)	0.87 (0.73–1.05)	1.11 (0.77–1.61)	0.94 (0.78–1.13)	0.93 (0.77–1.12)	0.86 (0.48–1.55)
Unstable angina hospitalization§	1.11 (0.47–2.62)	0.98 (0.76–1.26)	0.82 (0.47–1.44)	1.05 (0.94–1.18)	1.14 (0.84–1.54)	1.56 (0.60–4.01)
All-cause mortality§	0.94 (0.78–1.13)	0.85 (0.74–0.97)	1.05 (0.74–1.50)	0.86 (0.77–0.97)	0.90 (0.80–1.01)	0.51 (0.31–0.84)
Worsening nephropathy§‖	—	0.78 (0.67–0.92)	0.64 (0.46–0.88)	—	0.85 (0.77–0.93)	—

—, not assessed/reported; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; GLP-1, glucagon-like peptide 1; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction. Data from this table was adapted from Cefalu et al. (238) in the January 2018 issue of *Diabetes Care*. *Powered to rule out a hazard ratio of 1.8; superiority hypothesis not prespecified. †Age was reported as means in all trials; diabetes duration was reported as means in all trials except EXSCEL, which reported medians. ‡Significant difference in A1C between groups ($P < 0.05$). ^AIC change of 0.66% with 0.5 mg and 1.05% with 1 mg dose of semaglutide. §Outcomes reported as hazard ratio (95% CI). ‖Worsening nephropathy is defined as the new onset of urine albumin-to-creatinine ratio >300 mg/g creatinine or a doubling of the serum creatinine level and an estimated glomerular filtration rate of <45 mL/min/1.73 m^2, the need for continuous renal replacement therapy, or death from renal disease in LEADER and SUSTAIN-6 and as new macroalbuminuria, a sustained decline in estimated glomerular filtration rate of 30% or more from baseline, or chronic renal replacement therapy in REWIND. Worsening nephropathy was a prespecified exploratory adjudicated outcome in LEADER, SUSTAIN-6, and REWIND.

10.41a In people with type 2 diabetes and established atherosclerotic cardiovascular disease, multiple atherosclerotic cardiovascular disease risk factors, or diabetic kidney disease, a sodium–glucose cotransporter 2 inhibitor with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events and/or heart failure hospitalization. **A**

10.41b In people with type 2 diabetes and established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease, a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events. **A**

10.41c In people with type 2 diabetes and established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease, combined therapy with a sodium–glucose cotransporter 2 inhibitor with demonstrated cardiovascular benefit and a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular benefit may be considered for additive reduction in the risk of adverse cardiovascular and kidney events. **A**

10.42a In people with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction, a sodium–glucose cotransporter 2 inhibitor with proven benefit in this patient population is recommended to reduce risk of worsening heart failure and cardiovascular death. **A**

10.42b In people with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction, a sodium–glucose cotransporter 2 inhibitor with proven benefit in this patient population is recommended to improve

symptoms, physical limitations, and quality of life. **A**

10.43 For people with type 2 diabetes and chronic kidney disease with albuminuria treated with maximum tolerated doses of ACE inhibitor or angiotensin receptor blocker, addition of finerenone is recommended to improve cardiovascular outcomes and reduce the risk of chronic kidney disease progression. **A**

10.44 In people with known atherosclerotic cardiovascular disease, particularly coronary artery disease, ACE inhibitor or angiotensin receptor blocker therapy is recommended to reduce the risk of cardiovascular events. **A**

10.45 In people with prior myocardial infarction, β-blockers should be continued for 3 years after the event. **B**

10.46 Treatment of individuals with heart failure with reduced ejection fraction should include a β-blocker with proven cardiovascular outcomes benefit, unless otherwise contraindicated. **A**

10.47 In people with type 2 diabetes with stable heart failure, metformin may be continued for glucose lowering if estimated glomerular filtration rate remains >30 mL/min/1.73 m^2 but should be avoided in unstable or hospitalized individuals with heart failure. **B**

Cardiac Testing

Candidates for advanced or invasive cardiac testing include those with *1*) typical or atypical cardiac symptoms and *2*) an abnormal resting electrocardiogram (ECG). Exercise ECG testing without or with echocardiography may be used as the initial test. In adults with diabetes ≥40 years of age, measurement of coronary artery calcium is also reasonable for cardiovascular risk assessment. Pharmacologic stress echocardiography or nuclear imaging should be considered in individuals with diabetes in whom resting ECG abnormalities preclude exercise stress testing (e.g., left bundle branch block or ST-T abnormalities). In addition, individuals who require stress testing and are unable to exercise should undergo pharmacologic stress echocardiography or nuclear imaging.

Screening Asymptomatic Patients

The screening of asymptomatic patients with high ASCVD risk is not recommended (171), in part because these high-risk patients should already be receiving intensive medical therapy—an approach that provides benefit similar to invasive revascularization (172,173). There is also some evidence that silent ischemia may reverse over time, adding to the controversy concerning aggressive screening strategies (174). In prospective studies, coronary artery calcium has been established as an independent predictor of future ASCVD events in people with diabetes and is consistently superior to both the UK Prospective Diabetes Study (UKPDS) risk engine and the Framingham Risk Score in predicting risk in this population (175–177). However, a randomized observational trial demonstrated no clinical benefit to routine screening of asymptomatic people with type 2 diabetes and normal ECGs (178). Despite abnormal myocardial perfusion imaging in more than one in five patients, cardiac outcomes were essentially equal (and very low) in screened versus unscreened patients. Accordingly, indiscriminate screening is not considered cost-effective. Studies have found that a risk factor-based approach to the initial diagnostic evaluation and subsequent follow-up for coronary artery disease fails to identify which people with type 2 diabetes will have silent ischemia on screening tests (179,180).

Any benefit of newer noninvasive coronary artery disease screening methods, such as computed tomography calcium scoring and computed tomography angiography, to identify patient subgroups for different treatment strategies remains unproven in asymptomatic people with diabetes, though research is ongoing. Since asymptomatic people with diabetes with higher coronary disease burden have more future cardiac events (175,181,182), these additional imaging tests may provide reasoning for treatment intensification and/or guide informed patient decision-making and willingness for medication initiation and participation.

While coronary artery screening methods, such as calcium scoring, may improve cardiovascular risk assessment in people with type 2 diabetes (183), their routine use leads to radiation exposure and may result in unnecessary invasive testing such as coronary angiography and revascularization procedures. The ultimate balance of benefit, cost, and risks of such an approach in asymptomatic patients remains controversial, particularly in the modern setting of aggressive ASCVD risk factor control.

Lifestyle and Pharmacologic Interventions

Intensive lifestyle intervention focusing on weight loss through decreased caloric intake and increased physical activity as performed in the Action for Health in Diabetes (Look AHEAD) trial may be considered for improving glucose control, fitness, and some ASCVD risk factors (184). Patients at increased ASCVD risk should receive statin, ACE inhibitor, or ARB therapy if the patient has hypertension, and possibly aspirin, unless there are contraindications to a particular drug class. Clear benefit exists for ACE inhibitor or ARB therapy in people with diabetic kidney disease or hypertension, and these agents are recommended for hypertension management in people with known ASCVD (particularly coronary artery disease) (65,66,185). People with type 2 diabetes and CKD should be considered for treatment with finerenone to reduce cardiovascular outcomes and the risk of CKD progression (186–189). β-Blockers should be used in individuals with active angina or HFrEF and for 3 years after MI in those with preserved left ventricular function (190,191).

Glucose-Lowering Therapies and Cardiovascular Outcomes

In 2008, the FDA issued a guidance for industry to perform cardiovascular outcomes trials for all new medications for the treatment for type 2 diabetes amid concerns of increased cardiovascular risk (192). Previously approved diabetes medications were not subject to the guidance. Recently published cardiovascular outcomes trials have provided additional data on cardiovascular and renal outcomes in people with type 2 diabetes with cardiovascular disease or at high risk for cardiovascular disease (**Table 10.3*A***, **Table 10.3*B***, and **Table 10.3*C***). An expanded review of the effects of glucose-lowering and other therapies

in people with CKD is included in Section 11, "Chronic Kidney Disease and Risk Management."

Cardiovascular outcomes trials of dipeptidyl peptidase 4 (DPP-4) inhibitors have all, so far, not shown cardiovascular benefits relative to placebo. In addition, the CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Type 2 Diabetes) study demonstrated noninferiority between a DPP-4 inhibitor, linagliptin, and a sulfonylurea, glimepiride, on cardiovascular outcomes despite lower rates of hypoglycemia in the linagliptin treatment group (193). However, results from other new agents have provided a mix of results.

SGLT2 Inhibitor Trials

The BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was a randomized, double-blind trial that assessed the effect of empagliflozin, an SGLT2 inhibitor, versus placebo on cardiovascular outcomes in 7,020 people with type 2 diabetes and existing cardiovascular disease. Study participants had a mean age of 63 years, 57% had diabetes for more than 10 years, and 99% had established cardiovascular disease. EMPA-REG OUTCOME showed that over a median follow-up of 3.1 years, treatment reduced the composite outcome of MI, stroke, and cardiovascular death by 14% (absolute rate 10.5% vs. 12.1% in the placebo group, HR in the empagliflozin group 0.86 [95% CI 0.74–0.99]; $P = 0.04$ for superiority) and cardiovascular death by 38% (absolute rate 3.7% vs. 5.9%, HR 0.62 [95% CI 0.49–0.77]; $P < 0.001$) (8).

Two large outcomes trials of the SGLT2 inhibitor canagliflozin have been conducted that separately assessed *1*) the cardiovascular effects of treatment in patients at high risk for major adverse cardiovascular events (9) and *2*) the impact of canagliflozin therapy on cardiorenal outcomes in people with diabetes-related CKD (194). First, the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program integrated data from two trials. The CANVAS trial that started in 2009 was partially unblinded prior to completion because of the need to file interim cardiovascular outcomes data for regulatory approval of the drug (195). Thereafter, the post approval CANVAS-Renal (CANVAS-R) trial was started in 2014. Combining both trials, 10,142 participants with type 2 diabetes were randomized to canagliflozin or placebo and were followed for an average 3.6 years. The mean age of patients was 63 years, and 66% had a history of cardiovascular disease. The combined analysis of the two trials found that canagliflozin significantly reduced the composite outcome of cardiovascular death, MI, or stroke versus placebo (occurring in 26.9 vs. 31.5 participants per 1,000 patient-years; HR 0.86 [95% CI 0.75–0.97]). The specific estimates for canagliflozin versus placebo on the primary composite cardiovascular outcome were HR 0.88 (95% CI 0.75–1.03) for the CANVAS trial and 0.82 (0.66–1.01) for CANVAS-R, with no heterogeneity found between trials. Of note, there was an increased risk of lower-limb amputation with canagliflozin (6.3 vs. 3.4 participants per 1,000 patient-years; HR 1.97 [95% CI 1.41–2.75]) (9). Second, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial randomized 4,401 people with type 2 diabetes and chronic diabetes-related kidney disease (UACR $>$300 mg/g and eGFR 30 to $<$90 mL/min/1.73 m^2) to canagliflozin 100 mg daily or placebo (194). The primary outcome was a composite of end-stage kidney disease, doubling of serum creatinine, or death from renal or cardiovascular causes. The trial was stopped early due to conclusive evidence of efficacy identified during a prespecified interim analysis with no unexpected safety signals. The risk of the primary composite outcome was 30% lower with canagliflozin treatment when compared with placebo (HR 0.70 [95% CI 0.59–0.82]). Moreover, it reduced the prespecified end point of end-stage kidney disease alone by 32% (HR 0.68 [95% CI 0.54–0.86]). Canagliflozin was additionally found to have a lower risk of the composite of cardiovascular death, MI, or stroke (HR 0.80 [95% CI 0.67–0.95]), as well as lower risk of hospitalizations for heart failure (HR 0.61 [95% CI 0.47–0.80]) and of the composite of cardiovascular death or hospitalization for heart failure (HR 0.69 [95% CI 0.57–0.83]). In terms of safety, no significant increase in lower-limb amputations, fractures, acute kidney injury, or hyperkalemia was noted for canagliflozin relative to placebo in CREDENCE. An increased risk for diabetic ketoacidosis was noted, however, with 2.2 and 0.2 events per 1,000 patient-years noted in the canagliflozin and placebo groups, respectively (HR 10.80 [95% CI 1.39–83.65]) (194).

The Dapagliflozin Effect on Cardiovascular Events-Thrombosis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial was another randomized, double-blind trial that assessed the effects of dapagliflozin versus placebo on cardiovascular and renal outcomes in 17,160 people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD (196). Study participants had a mean age of 64 years, with ~40% of study participants having established ASCVD at baseline—a characteristic of this trial that differs from other large cardiovascular trials where a majority of participants had established cardiovascular disease. DECLARE-TIMI 58 met the prespecified criteria for noninferiority to placebo with respect to major adverse cardiovascular events but did not show a lower rate of major adverse cardiovascular events when compared with placebo (8.8% in the dapagliflozin group and 9.4% in the placebo group; HR 0.93 [95% CI 0.84–1.03]; $P = 0.17$). A lower rate of cardiovascular death or hospitalization for heart failure was noted (4.9% vs. 5.8%; HR 0.83 [95% CI 0.73–0.95]; $P = 0.005$), which reflected a lower rate of hospitalization for heart failure (HR 0.73 [95% CI 0.61–0.88]). No difference was seen in cardiovascular death between groups.

In the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial (197), 4,304 individuals with CKD (UACR 200–5,000 mg/g and eGFR 25–75 mL/min/1.73 m^2), with or without diabetes, were randomized to dapagliflozin 10 mg daily or placebo. The primary outcome was a composite of sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes. Over a median follow-up period of 2.4 years, a primary outcome event occurred in 9.2% of participants in the dapagliflozin group and 14.5% of those in the placebo group. The risk of the primary composite outcome was significantly lower with dapagliflozin therapy compared with placebo (HR 0.61 [95% CI 0.51–0.72]), as were the risks for a renal composite outcome of sustained decline in eGFR of at least 50%, endstage kidney disease, or death from renal causes (HR 0.56 [95% CI 0.45–0.68]), and a composite of cardiovascular death

Table 10.3C—Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: SGLT2 inhibitors

	EMPA-REG OUTCOME (8) (*n* = 7,020)	CANVAS Program (9) (*n* = 10,142)	DECLARE-TIMI 58 (196) (*n* = 17,160)	CREDENCE (194) (*n* = 4,401)	DAPA-CKD (197,239) (*n* = 4,304; 2,906 with diabetes)	VERTIS CV (201,240) (*n* = 8,246)	DAPA-HF (11) (*n* = 4,744; 1,983 with diabetes)	EMPEROR-Reduced (200) (*n* = 3,730; 1,856 with diabetes)	EMPEROR-Preserved (189,241) (*n* = 5,988; 2,938 with diabetes)	DELIVER (199) (*n* = 6,263; 2,807 with diabetes)
Intervention	Empagliflozin/placebo	Canagliflozin/placebo	Dapagliflozin/placebo	Canagliflozin/placebo	Dapagliflozin/placebo	Ertugliflozin/placebo	Dapagliflozin/placebo	Empagliflozin/placebo*	Empagliflozin/placebo	Dapagliflozin/placebo
Main inclusion criteria	Type 2 diabetes and preexisting CVD	Type 2 diabetes and preexisting CVD at ≥30 years of age or ≥2 CV risk factors at ≥50 years of age	Type 2 diabetes and established ASCVD or multiple risk factors for ASCVD	Type 2 diabetes and albuminuric kidney disease	Albuminuric kidney disease, with or without diabetes	Type 2 diabetes and ASCVD	NYHA class II, III, or IV heart failure and an ejection fraction ≤40%, with or without diabetes	NYHA class II, III, or IV heart failure and an ejection fraction ≤40%, with or without diabetes	NYHA class II, III, or IV heart failure and an ejection fraction >40%	NYHA class II, III, or IV heart failure and an ejection fraction >40% with or without diabetes
A1C inclusion criteria (%)	7.0–10.0	7.0–10.5	≥6.5	6.5–12	—	7.0–10.5	—	—	—	—
Age (years)†	63.1	63.3	64.0	63	61.8	64.4	66	67.2, 66.5	71.8, 71.9	71.7
Race (% White)	72.4	78.3	79.6	66.6	53.2	87.8	70.3	71.1, 69.8	76.3, 75.4	71.2
Sex (% male)	71.5	64.2	62.6	66.1	66.9	70	76.6	76.5, 75.6	55.4, 55.3	56.1
Diabetes duration (years)†	57% >10	13.5	11.0	15.8		12.9				
Median follow-up (years)	3.1	3.6	4.2	2.6	2.4	3.5	1.5	1.3	2.2	2.3
Statin use (%)	77	75	75 (statin or ezetimibe use)	69	64.9	—	—	—	68.1, 68.8	—
Metformin use (%)	74	77	82	57.8	29		51.2% (of people with diabetes)	—	—	—
Prior CVD/CHF (%)	99/10	65.6/14.4	40/10	50.4/14.8	37.4/10.9	99.9/23.1	100% with CHF	100% with CHF	100% with CHF	100% with CHF
Mean baseline A1C (%)	8.1	8.2	8.3	8.3	7.1% (7.8% in those with diabetes)	8.2	—	—	—	6.6
Mean difference in A1C between groups at end of treatment (%)	−0.3^	−0.58‡	−0.43‡	−0.31	—	−0.48 to −0.5	—	—	—	—
Year started/reported	2010/2015	2009/2017	2013/2018	2017/2019	2017/2020	2013/2020	2017/2019	2017/2020	2017/2020	2018/2022

Continued on p. S179

Table 10.3C—Continued

	EMPA-REG OUTCOME (8) (*n* = 7,020)	CANVAS Program (9) (*n* = 10,142)	DECLARE-TIMI 58 (196) (*n* = 17,160)	CREDENCE (194) (*n* = 4,401)	DAPA-CKD (197,239) (*n* = 4,304; 2,906 with diabetes)	VERTIS CV (201,240) (*n* = 8,246)	DAPA-HF (11) (*n* = 4,744; 1,983 with diabetes)	EMPEROR-Reduced (200) (*n* = 3,730; 1,856 with diabetes)	EMPEROR-Preserved (189,241) (*n* = 5,988; 2,938 with diabetes)	DELIVER (199) (*n* = 6,263; 2,807 with diabetes)
Primary outcome§	3-point MACE 0.86 (0.74–0.99)	3-point MACE 0.86 (0.75–0.97)	3-point MACE 0.93 (0.84–1.03) CV death or HF hospitalization 0.83 (0.73–0.95)	ESRD, doubling of creatinine, or death from renal or CV cause 0.70 (0.59–0.82)	≥50% decline in eGFR, ESKD, or death from renal or CV cause 0.61 (0.51–0.72)	3-point MACE 0.97 (0.85–1.11)	Worsening heart failure or death from CV causes 0.74 (0.65–0.85) Results did not differ by diabetes status	CV death or HF hospitalization 0.75 (0.65–0.86)	CV death or HF hospitalization 0.79 (0.69–0.90)	Worsening HF or CV death 0.82 (0.73–0.92)
Key secondary outcome§	4-point MACE 0.89 (0.78–1.01)	All-cause and CV mortality (see below)	Death from any cause 0.93 (0.82–1.04) Renal composite (≥40% decrease in eGFR rate to <60 mL/min/1.73 m^2, new ESRD, or death from renal or CV causes 0.76 (0.67–0.87)	CV death or HF hospitalization 0.69 (0.57–0.83) 3-point MACE 0.80 (0.67–0.95)	≥50% decline in eGFR, ESKD, or death from renal cause 0.56 (0.45–0.68) CV death or HF hospitalization 0.71 (0.55–0.92) Death from any cause 0.69 (0.53–0.88)	CV death or HF hospitalization 0.88 (0.75–1.03) CV death 0.92 (0.77–1.11) Renal death, renal replacement therapy, or doubling of creatinine 0.81 (0.63–1.04)	CV death or HF hospitalization 0.75 (0.65–0.85)	Total HF hospitalizations 0.70 (0.58–0.85) Mean slope of change in eGFR 1.73 (1.10–2.37)	All HF hospitalizations (first and recurrent) 0.73 (0.61–0.88) Rate of decline in eGFR (−1.25 vs. −2.62 mL/min/1.73 m^2; $P < 0.001$)	Total number worsening HF and CV deaths 0.77 (0.67–0.89) Change in KCCQ TSS at month 8 1.11 (1.03–1.21) Mean change in KCCQ TSS 2.4 (1.5–3.4) All-cause mortality 0.94 (0.83–1.07)
Cardiovascular death§	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.98 (0.82–1.17)	0.78 (0.61–1.00)	0.81 (0.58–1.12)	0.92 (0.77–1.11)	0.82 (0.69–0.98)	0.92 (0.75–1.12)	0.91 (0.76–1.09)	0.88 (0.74–1.05)
MI§	0.87 (0.70–1.09)	0.89 (0.73–1.09)	0.89 (0.77–1.01)	—	—	1.04 (0.86–1.26)	—	—	—	—
Stroke§	1.18 (0.89–1.56)	87 (0.69–1.09)	1.01 (0.84–1.21)	—	—	1.06 (0.82–1.37)	—	—	—	—
HF hospitalization§	0.65 (0.50–0.85)	67 (0.52–0.87)	0.73 (0.61–0.88)	0.61 (0.47–0.80)	—	0.70 (0.54–0.90)	0.70 (0.59–0.83)	0.69 (0.59–0.81)	0.73 (0.61–0.88)	0.77 (0.67–0.89)
Unstable angina hospitalization§	0.99 (0.74–1.34)	—	—	—	—	—	—	—	—	—
All-cause mortality§	0.68 (0.57–0.82)	87 (0.74–1.01)	0.93 (0.82–1.04)	0.83 (0.68–1.02)	0.69 (0.53–0.88)	0.93 (0.80–1.08)	0.83 (0.71–0.97)	0.92 (0.77–1.10)	1.00 (0.87–1.15)	0.94 (0.83–1.07)
Worsening nephropathy§‖	0.61 (0.53–0.70)	0.60 (0.47–0.77)	0.53 (0.43–0.66)	(See primary outcome)	(See primary outcome)	(See secondary outcomes)	0.71 (0.44–1.16)	Composite renal outcome 0.50 (0.32–0.77)	Composite renal outcome** 0.95 (0.73–1.24)	—

—, not assessed/reported; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; KCCQ TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; MACE, major adverse cardiovascular event; MI, myocardial infarction; SGLT2, sodium–glucose cotransporter 2; NYFIA, New York Fleart Association. Data from this table was adapted from Cefalu et al. (238) in the January 2018 issue of *Diabetes Care*. *Baseline characteristics for EMPEROR-Reduced displayed as empagliflozin, placebo. †Age was reported as means in all trials; diabetes duration was reported as means in all trials except EMPA-REG OUTCOME, which reported as percentage of population with diabetes duration >10 years, and DECLARE-TIMI 58, which reported median. ‡Significant difference in A1C between groups ($P < 0.05$). ^AIC change of 0.30 in EMPA-REG OUTCOME is based on pooled results for both doses (i.e., 0.24% for 10 mg and 0.36% for 25 mg of empagliflozin). §Outcomes reported as hazard ratio (95% CI). ||Definitions of worsening nephropathy differed between trials. **Composite outcome in EMPEROR-Preserved: time to first occurrence of chronic dialysis, renal transplantation; sustained reduction of ≥40% in eGFR, sustained eGFR <15 mL/min/1.73 m^2 for individuals with baseline eGFR ≥30 mL/min/1.73 m^2.

or hospitalization for heart failure (HR 0.71 [95% CI 0.55–0.92]). The effects of dapagliflozin therapy were similar in individuals with and without type 2 diabetes.

Results of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced), Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved), Effects of Dapagliflozin on Biomarkers, Symptoms and Functional Status in Patients With PRESERVED Ejection Fraction Heart Failure (PRESERVED-HF), and Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER), which assessed the effects of dapagliflozin and empagliflozin in individuals with established heart failure (11,189,198,199,200), are described below in GLUCOSE-LOWERING THERAPIES AND HEART FAILURE.

The Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV) (201) was a randomized, double-blind trial that established the effects of ertugliflozin versus placebo on cardiovascular outcomes in 8,246 people with type 2 diabetes and established ASCVD. Participants were assigned to the addition of 5 mg or 15 mg of ertugliflozin or to placebo once daily to background standard care. Study participants had a mean age of 64.4 years and a mean duration of diabetes of 13 years at baseline and were followed for a median of 3.0 years. VERTIS CV met the prespecified criteria for noninferiority of ertugliflozin to placebo with respect to the primary outcome of major adverse cardiovascular events (11.9% in the pooled ertugliflozin group and 11.9% in the placebo group; HR 0.97 [95% CI 0.85–1.11]; $P < 0.001$). Ertugliflozin was not superior to placebo for the key secondary outcomes of death from cardiovascular causes or hospitalization for heart failure; death from cardiovascular causes; or the composite of death from renal causes, renal replacement therapy, or doubling of the serum creatinine level. The HR for a secondary outcome of hospitalization for heart failure (ertugliflozin vs. placebo) was 0.70 [95% CI 0.54–0.90], consistent with findings from other SGLT2 inhibitor cardiovascular outcomes trials.

Sotagliflozin, an SGLT1 and SGLT2 inhibitor not currently approved by the FDA in the U.S., lowers glucose via delayed glucose absorption in the gut in addition to increasing urinary glucose excretion and has been evaluated in the Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial (202). A total of 10,584 people with type 2 diabetes, CKD, and additional cardiovascular risk were enrolled in SCORED and randomized to sotagliflozin 200 mg once daily (uptitrated to 400 mg once daily if tolerated) or placebo. SCORED ended early due to a lack of funding; thus, changes to the prespecified primary end points were made prior to unblinding to accommodate a lower than anticipated number of end point events. The primary end point of the trial was the total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure. After a median of 16 months of follow-up, the rate of primary end point events was reduced with sotagliflozin (5.6 events per 100 patient-years in the sotagliflozin group and 7.5 events per 100 patient-years in the placebo group [HR 0.74 (95% CI 0.63–0.88); $P < 0.001$]). Sotagliflozin also reduced the risk of the secondary end point of total number of hospitalizations for heart failure and urgent visits for heart failure (3.5% in the sotagliflozin group and 5.1% in the placebo group; HR 0.67 [95% CI 0.55–0.82]; $P < 0.001$) but not the secondary end point of deaths from cardiovascular causes. No significant between-group differences were found for the outcome of all-cause mortality or for a composite renal outcome comprising the first occurrence of long-term dialysis, renal transplantation, or a sustained reduction in eGFR. In general, the adverse effects of sotagliflozin were similar to those seen with use of SGLT2 inhibitors, but they also included an increased rate of diarrhea potentially related to the inhibition of SGLT1.

GLP-1 Receptor Agonist Trials

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was a randomized, double-blind trial that assessed the effect of liraglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, versus placebo on cardiovascular outcomes in 9,340 people with type 2 diabetes at high risk for cardiovascular disease or with cardiovascular disease (203). Study participants had a mean age of 64 years and a mean duration of diabetes of nearly 13 years. Over 80% of study participants had established cardiovascular disease. After a median follow-up of 3.8 years, LEADER showed that the primary composite outcome (MI, stroke, or cardiovascular death) occurred in fewer participants in the treatment group (13.0%) when compared with the placebo group (14.9%) (HR 0.87 [95% CI 0.78–0.97]; $P < 0.001$ for noninferiority; $P = 0.01$ for superiority). Deaths from cardiovascular causes were significantly reduced in the liraglutide group (4.7%) compared with the placebo group (6.0%) (HR 0.78 [95% CI 0.66–0.93]; $P = 0.007$) (203).

Results from a moderate-sized trial of another GLP-1 receptor agonist, semaglutide, were consistent with the LEADER trial (204). Semaglutide is a once-weekly GLP-1 receptor agonist approved by the FDA for the treatment of type 2 diabetes. The Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) was the initial randomized trial powered to test noninferiority of semaglutide for the purpose of regulatory approval (204). In this study, 3,297 people with type 2 diabetes were randomized to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 2 years. The primary outcome (the first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke) occurred in 108 patients (6.6%) in the semaglutide group vs. 146 patients (8.9%) in the placebo group (HR 0.74 [95% CI 0.58–0.95]; $P < 0.001$). More patients discontinued treatment in the semaglutide group because of adverse events, mainly gastrointestinal. The cardiovascular effects of the oral formulation of semaglutide compared with placebo have been assessed in Peptide Innovation for Early Diabetes Treatment (PIONEER) 6, a preapproval trial designed to rule out an unacceptable increase in cardiovascular risk (205). In this trial of 3,183 people with type 2 diabetes and high cardiovascular risk followed for a median of 15.9 months, oral semaglutide was noninferior to placebo for the primary composite outcome of cardiovascular death, nonfatal MI, or nonfatal stroke (HR 0.79 [95% CI 0.57–1.11]; $P < 0.001$

for noninferiority) (205). The cardiovascular effects of this formulation of semaglutide will be further tested in a large, longer-term outcomes trial.

The Harmony Outcomes trial randomized 9,463 people with type 2 diabetes and cardiovascular disease to once-weekly subcutaneous albiglutide or matching placebo, in addition to their standard care (206). Over a median duration of 1.6 years, the GLP-1 receptor agonist reduced the risk of cardiovascular death, MI, or stroke to an incidence rate of 4.6 events per 100 person-years in the albiglutide group vs. 5.9 events in the placebo group (HR ratio 0.78, $P = 0.0006$ for superiority) (206). This agent is not currently available for clinical use.

The Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) trial was a randomized, double-blind, placebo-controlled trial that assessed the effect of the once-weekly GLP-1 receptor agonist dulaglutide versus placebo on major adverse cardiovascular events in ~9,990 people with type 2 diabetes at risk for cardiovascular events or with a history of cardiovascular disease (207). Study participants had a mean age of 66 years and a mean duration of diabetes of ~10 years. Approximately 32% of participants had history of atherosclerotic cardiovascular events at baseline. After a median follow-up of 5.4 years, the primary composite outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular causes occurred in 12.0% and 13.4% of participants in the dulaglutide and placebo treatment groups, respectively (HR 0.88 [95% CI 0.79–0.99]; $P = 0.026$). These findings equated to incidence rates of 2.4 and 2.7 events per 100 person-years, respectively. The results were consistent across the subgroups of patients with and without history of CV events. Allcause mortality did not differ between groups ($P = 0.067$).

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial studied the once-daily GLP-1 receptor agonist lixisenatide on cardiovascular outcomes in people with type 2 diabetes who had had a recent acute coronary event (208). A total of 6,068 people with type 2 diabetes with a recent hospitalization for MI or unstable angina within the previous 180 days were randomized to receive lixisenatide or placebo in addition to standard care and were followed for a median of ~2.1 years. The primary outcome of cardiovascular death, MI, stroke, or hospitalization for unstable angina occurred in 406 patients (13.4%) in the lixisenatide group vs. 399 (13.2%) in the placebo group (HR 1.2 [95% CI 0.89–1.17]), which demonstrated the noninferiority of lixisenatide to placebo ($P < 0.001$) but did not show superiority ($P = 0.81$).

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial also reported results with the once-weekly GLP-1 receptor agonist extended-release exenatide and found that major adverse cardiovascular events were numerically lower with use of extended-release exenatide compared with placebo, although this difference was not statistically significant (209). A total of 14,752 people with type 2 diabetes (of whom 10,782 [73.1%] had previous cardiovascular disease) were randomized to receive extended-release exenatide 2 mg or placebo and followed for a median of 3.2 years. The primary end point of cardiovascular death, MI, or stroke occurred in 839 patients (11.4%; 3.7 events per 100 person-years) in the exenatide group and in 905 patients (12.2%; 4.0 events per 100 person-years) in the placebo group (HR 0.91 [95% CI 0.83–1.00]; $P < 0.001$ for noninferiority), but exenatide was not superior to placebo with respect to the primary end point ($P = 0.06$ for superiority). However, all-cause mortality was lower in the exenatide group (HR 0.86 [95% CI 0.77–0.97]). The incidence of acute pancreatitis, pancreatic cancer, medullary thyroid carcinoma, and serious adverse events did not differ significantly between the two groups.

In summary, there are now numerous large randomized controlled trials reporting statistically significant reductions in cardiovascular events for three of the FDA-approved SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin, with lesser benefits seen with ertugliflozin) and four FDA-approved GLP-1 receptor agonists (liraglutide, albiglutide [although that agent was removed from the market for business reasons], semaglutide [lower risk of cardiovascular events in a moderate-sized clinical trial but one not powered as a cardiovascular outcomes trial], and dulaglutide). Meta-analyses of the trials reported to date suggest that GLP-1 receptor agonists and SGLT2 inhibitors reduce risk of atherosclerotic major adverse cardiovascular events to a comparable degree in people with type 2 diabetes and established ASCVD (210,211). SGLT2 inhibitors also reduce risk of heart failure hospitalization and progression of kidney disease in people with established ASCVD, multiple risk factors for ASCVD, or albuminuric kidney disease (212,213). In people with type 2 diabetes and established ASCVD, multiple ASCVD risk factors, or diabetic kidney disease, an SGLT2 inhibitor with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events and/or heart failure hospitalization. In people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD, a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events. For many patients, use of either an SGLT2 inhibitor or a GLP-1 receptor agonist to reduce cardiovascular risk is appropriate. Emerging data suggest that use of both classes of drugs will provide an additive cardiovascular and kidney outcomes benefit; thus, combination therapy with an SGLT2 inhibitor and a GLP-1 receptor agonist may be considered to provide the complementary outcomes benefits associated with these classes of medication. Evidence to support such an approach includes findings from AMPLITUDE-O (Effect of Efpeglenatide on Cardiovascular Outcomes), an outcomes trial of people with type 2 diabetes and either cardiovascular or kidney disease plus at least one other risk factor randomized to the investigational GLP-1 receptor agonist efpeglenatide or placebo (214). Randomization was stratified by current or potential use of SGLT2 inhibitor therapy, a class ultimately used by >15% of the trial participants. Over a median follow-up of 1.8 years, efpeglenatide therapy reduced the risk of incident major adverse cardiovascular events by 27% and of a composite renal outcome event by 32%. Importantly, the effects of efpeglenatide did not vary by use of SGLT2 inhibitors, suggesting that the beneficial effects of the GLP-1 receptor agonist were independent of those provided by SGLT2 inhibitor therapy (215). Efpeglenatide is currently not approved by the FDA for use in the U.S.

Glucose-Lowering Therapies and Heart Failure

As many as 50% of people with type 2 diabetes may develop heart failure (216). These conditions, which are each

associated with increased morbidity and mortality, commonly coincide, and independently contribute to adverse outcomes (217). Strategies to mitigate these risks are needed, and the heart failure-related risks and benefits of glucose-lowering medications should be considered carefully when determining a regimen of care for people with diabetes and either established heart failure or high risk for the development of heart failure.

Data on the effects of glucose-lowering agents on heart failure outcomes have demonstrated that thiazolidinediones have a strong and consistent relationship with increased risk of heart failure (218–220). Therefore, thiazolidinedione use should be avoided in people with symptomatic heart failure. Restrictions to use of metformin in people with medically treated heart failure were removed by the FDA in 2006 (221). Observational studies of people with type 2 diabetes and heart failure suggest that metformin users have better outcomes than individuals treated with other antihyperglycemic agents (222); however, no randomized trial of metformin therapy has been conducted in people with heart failure. Metformin may be used for the management of hyperglycemia in people with stable heart failure as long as kidney function remains within the recommended range for use (223).

Recent studies examining the relationship between DPP-4 inhibitors and heart failure have had mixed results. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) study showed that patients treated with the DPP-4 inhibitor saxagliptin were more likely to be hospitalized for heart failure than those given placebo (3.5% vs. 2.8%, respectively) (224). However, three other cardiovascular outcomes trials—Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) (225), Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) (226), and the Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) (193)—did not find a significant increase in risk of heart failure hospitalization with DPP-4 inhibitor use compared with placebo. No increased risk of heart failure hospitalization has been identified in the cardiovascular outcomes trials of the GLP-1 receptor agonists lixisenatide, liraglutide, semaglutide, exenatide once-weekly, albiglutide, or dulaglutide compared with placebo (**Table 10.3*B***) (203,204,207–209).

Reduced incidence of heart failure has been observed with the use of SGLT2 inhibitors (8,194,196). In EMPA-REG OUTCOME, the addition of empagliflozin to standard care led to a significant 35% reduction in hospitalization for heart failure compared with placebo (8). Although the majority of patients in the study did not have heart failure at baseline, this benefit was consistent in patients with and without a history of heart failure (10). Similarly, in CANVAS and DECLARE-TIMI 58, there were 33% and 27% reductions in hospitalization for heart failure, respectively, with SGLT2 inhibitor use versus placebo (9,196). Additional data from the CREDENCE trial with canagliflozin showed a 39% reduction in hospitalization for heart failure, and 31% reduction in the composite of cardiovascular death or hospitalization for heart failure, in a diabetic kidney disease population with albuminuria (UACR >300 to 5,000 mg/g) (194). These combined findings from four large outcomes trials of three different SGLT2 inhibitors are highly consistent and clearly indicate robust benefits of SGLT2 inhibitors in the prevention of heart failure hospitalizations. The EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, and CREDENCE trials suggested, but did not prove, that SGLT2 inhibitors would be beneficial in the treatment of people with established heart failure. More recently, the placebo-controlled DAPA-HF trial evaluated the effects of dapagliflozin on the primary outcome of a composite of worsening heart failure or cardiovascular death in patients with New York Heart Association (NYHA) class II, III, or IV heart failure and an ejection fraction of 40% or less. Of the 4,744 trial participants, 45% had a history of type 2 diabetes. Over a median of 18.2 months, the group assigned to dapagliflozin treatment had a lower risk of the primary outcome (HR 0.74 [95% CI 0.65–0.85]), lower risk of first worsening heart failure event (HR 0.70 [95% CI 0.59–0.83]), and lower risk of cardiovascular death (HR 0.82 [95% CI 0.69–0.98]) compared with placebo. The effect of dapagliflozin on the primary outcome was consistent regardless of the presence or absence of type 2 diabetes (11).

EMPEROR-Reduced assessed the effects of empagliflozin 10 mg once daily versus placebo on a primary composite outcome of cardiovascular death or hospitalization for worsening heart failure in a population of 3,730 patients with NYHA class II, III, or IV heart failure and an ejection fraction of 40% or less (200). At baseline, 49.8% of participants had a history of diabetes. Over a median follow-up of 16 months, those in the empagliflozin-treated group had a reduced risk of the primary outcome (HR 0.75 [95% CI 0.65–0.86]; $P < 0.001$) and fewer total hospitalizations for heart failure (HR 0.70 [95% CI 0.58–0.85]; $P < 0.001$). The effect of empagliflozin on the primary outcome was consistent irrespective of diabetes diagnosis at baseline. The risk of a prespecified renal composite outcome (chronic dialysis, renal transplantation, or a sustained reduction in eGFR) was lower in the empagliflozin group than in the placebo group (1.6% in the empagliflozin group vs. 3.1% in the placebo group; HR 0.50 [95% CI 0.32–0.77]).

EMPEROR-Preserved, a randomized double-blinded placebo-controlled trial of 5,988 adults with NYHA functional class I–IV chronic HFpEF (left ventricular ejection fraction >40%), evaluated the efficacy of empagliflozin 10 mg daily versus placebo on top of standard of care on the primary outcome of composite cardiovascular death or hospitalization for heart failure (189). Approximately 50% of subjects had type 2 diabetes at baseline. Over a median of 26.2 months, there was a 21% reduction (HR 0.79 [95% CI 0.69–0.90]; $P < 0.001$) of the primary outcome. The effects of empagliflozin were consistent in people with or without diabetes (189).

In the DELIVER trial, 6,263 individuals with heart failure and an ejection fraction >40% were randomized to receive either dapagliflozin or placebo (199). The primary outcome of a composite of worsening heart failure, defined as hospitalization or urgent visit for heart failure, or cardiovascular death was reduced by 18% in patients treated with dapagliflozin compared with placebo (HR 0.82 [95% CI 0.73–0.92]; $P < 0.001$). Approximately 44% of patients randomized to either dapagliflozin or placebo had type 2 diabetes, and results were consistent regardless of the presence of type 2 diabetes.

A large recent meta-analysis (227) including data from EMPEROR-Reduced, EMPEROR-Preserved, DAPA-HF, DELIVER, and Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes

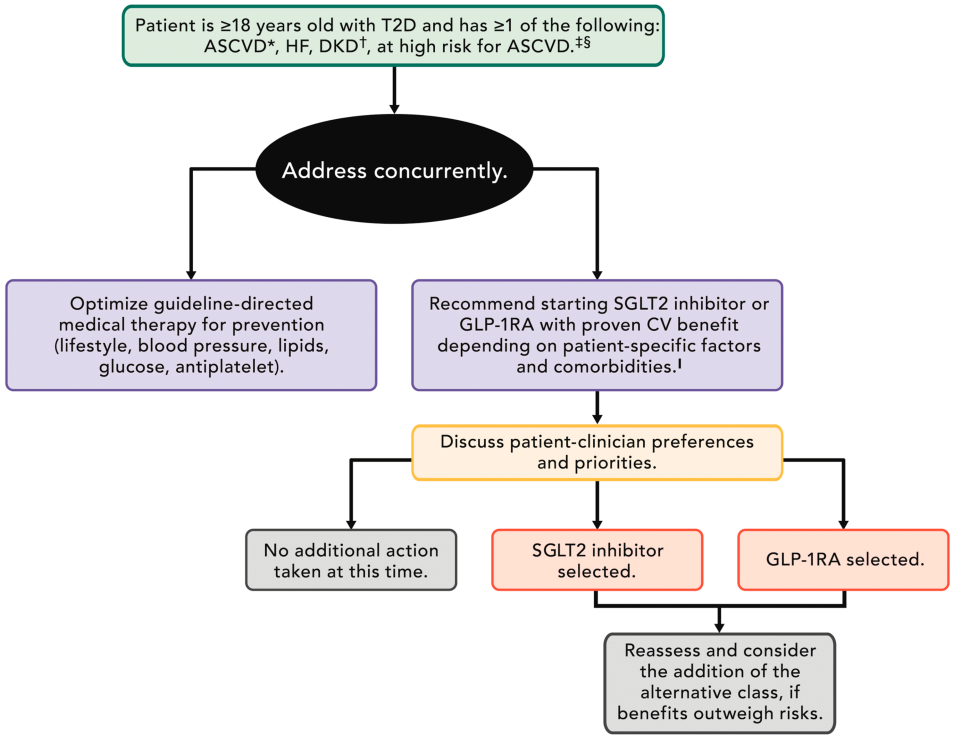
Post Worsening Heart Failure (SOLOIST-WHF) included 21,947 patients and demonstrated reduced risk for the composite of cardiovascular death or hospitalization for heart failure, cardiovascular death, first hospitalization for heart failure, and all-cause mortality. The findings on the studied end points were consistent in both trials of heart failure with mildly reduced or preserved ejection fraction and in all five trials combined. Collectively, these studies indicate that SGLT2 inhibitors reduce the risk for heart failure hospitalization and cardiovascular death in a wide range of people with heart failure.

Additional data are accumulating regarding the effects of SGLT inhibition in people hospitalized for acute decompensated heart failure and in people with heart failure and HFpEF. As an example, the investigational SGLT1 and SGLT2 inhibitor sotagliflozin has also been studied in the SOLOIST-WHF trial (228). In SOLOIST-WHF, 1,222 people with type 2 diabetes who were recently hospitalized for worsening heart failure were randomized to sotagliflozin 200 mg once daily (with uptitration to 400 mg once daily if tolerated) or placebo either before or within 3 days after hospital discharge. Patients were eligible if hospitalized for signs and symptoms of heart failure (including elevated natriuretic peptide levels) requiring treatment with intravenous diuretic therapy. Exclusion criteria included end-stage heart failure or recent acute coronary syndrome or intervention, or an eGFR $<$30 mL/min/1.73 m^2). Patients were required to be clinically stable prior to randomization, defined as no use of supplemental oxygen, a systolic blood pressure $\geq$100 mmHg, and no need for intravenous inotropic or vasodilator therapy other than nitrates. Similar to SCORED, SOLOIST-WHF ended early due to a lack of funding, resulting in a change to the prespecified primary end point prior to unblinding to accommodate a lower than anticipated number of end point events. At a median follow-up of 9 months, the rate of primary end point events (the total number of cardiovascular deaths and hospitalizations and urgent visits for heart failure) was lower in the sotagliflozin group than in the placebo group (51.0 vs. 76.3; HR 0.67 [95% CI 0.52–0.85]; $P < 0.001$). No significant between-group differences were found in the rates of cardiovascular death or all-cause mortality. Both diarrhea (6.1% vs. 3.4%) and severe hypoglycemia (1.5% vs. 0.3%) were more common with sotagliflozin than with placebo. The trial was originally also intended to evaluate the effects of SGLT inhibition in people with HFpEF, and ultimately no evidence of heterogeneity of treatment effect by ejection fraction was noted. However, the relatively small percentage of such patients enrolled (only 21% of participants had ejection fraction $>$50%) and the early termination of the trial limited the ability to determine the effects of sotagliflozin in HFpEF specifically.

In addition to the hospitalization and mortality benefit in people with heart failure, several recent analyses have addressed whether SGLT2 inhibitor treatment improves clinical stability and functional status in individuals with heart failure. In 3,730 patients with NYHA class II–IV heart failure with an ejection fraction of $\leq$40%, treatment with empagliflozin reduced the combined risk of death, hospitalization for heart failure, or an emergent/urgent heart failure visit requiring intravenous treatment and reduced the total number of hospitalizations for heart failure requiring intensive care, a vasopressor or positive inotropic drug, or mechanical or surgical intervention (229). In addition, patients treated with empagliflozin were more likely to experience an improvement in NYHA functional class (229). In people hospitalized for acute de novo or decompensated chronic heart failure, initiation of empagliflozin treatment during hospitalization reduced the primary outcome of a composite of death from any cause, number of heart failure events and time to first heart failure event, or a 5-point or greater difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score (230). Furthermore, PRESERVED-HF, a multicenter study (26 sites in the U.S.) showed that dapagliflozin treatment leads to significant improvement in both symptoms and physical limitation, as well as objective measures of exercise function in people with chronic HFpEF, regardless of diabetes status (198). Finally, canagliflozin improved heart failure symptoms assessed using the Kansas City Cardiomyopathy Questionnaire Total Symptom Score, irrespective of left ventricular ejection fraction or the presence of diabetes (231). Therefore, in people with type 2 diabetes and established HFpEF or HFrEF, an SGLT2 inhibitor with proven benefit in this patient population is recommended to reduce the risk of worsening heart failure and cardiovascular death. In addition, an SGLT2 inhibitor is recommended in this patient population to improve symptoms, physical limitations, and quality of life. The benefits seen in this patient population likely represent a class effect, and they appear unrelated to glucose lowering given comparable outcomes in people with heart failure with and without diabetes.

Finerenone in People With Type 2 Diabetes and Chronic Kidney Disease

As discussed in detail in Section 11, "Chronic Kidney Disease and Risk Management," people with diabetes are at an increased risk for CKD, which increases cardiovascular risk (232). Finerenone, a selective nonsteroidal mineralocorticoid antagonist, has been shown in the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial to improve CKD outcomes in people with type 2 diabetes with stage 3 or 4 CKD and severe albuminuria (233). In the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial, 7,437 patients with UACR 30–300 mg/g and eGFR 25–90 mL/min/1.73 m^2 or UACR 300–5,000 and eGFR $\geq$60 mL/min/1.73 m^2 on maximum dose of renin-angiotensin system blockade were randomized to receive finerenone or placebo (186). The HR of the primary outcome of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization from heart failure was reduced by 13% in patients treated with finerenone. A prespecified subgroup analysis from FIGARO-DKD further revealed that in patients without symptomatic HFrEF, finerenone reduces the risk for new-onset heart failure and improves heart failure outcomes in people with type 2 diabetes and CKD (187). Finally, in the pooled analysis of 13,026 people with type 2 diabetes and CKD from both FIDELIO-DKD and FIGARO-DKD, the HRs for the composite of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure as well as a composite of kidney failure, a sustained $\geq$57% decrease in eGFR from baseline over $\geq$4 weeks, or renal death were 0.86 and 0.77, respectively (188). These collective studies indicate that finerenone improves cardiovascular and renal outcomes in people with type 2 diabetes. Therefore, in people with type 2 diabetes and CKD with albuminuria treated with maximum tolerated doses of ACE



*ASCVD is defined as a history of an acute coronary syndrome or MI, stable or unstable angina, coronary heart disease with or without revascularization, other arterial revascularization, stroke, or peripheral artery disease assumed to be atherosclerotic in origin.

†DKD is a clinical diagnosis marked by reduced eGFR, the presence of albuminuria, or both.

‡ Consider an SGLT2 inhibitor when your patient has established ASCVD, HF, DKD or is at high risk for ASCVD. Consider a GLP-1RA when your patient has established ASCVD or is at high risk for ASCVD.

§ Patients at high risk for ASCVD include those with end organ damage such as left ventricular hypertrophy or retinopathy or with multiple CV risk factors (e.g., age, hypertension, smoking, dyslipidemia, obesity).

ǁ Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; MI = myocardial infarction; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes

Figure 10.3—Approach to risk reduction with SGLT2 inhibitor or GLP-1 receptor agonist therapy in conjunction with other traditional, guideline-based preventive medical therapies for blood pressure, lipids, and glycemia and antiplatelet therapy. Reprinted with permission from Das et al. (234).

inhibitor or ARB, addition of finernone should be considered to improve cardiovascular outcomes and reduce the risk of CKD progression.

Clinical Approach

As has been carefully outlined in **Fig. 9.3** in the preceding Section 9, "Pharmacologic Approaches to Glycemic Treatment," people with type 2 diabetes with or at high risk for ASCVD, heart failure, or CKD should be treated with a cardioprotective SGLT2 inhibitor and/or GLP-1 receptor agonist as part of the comprehensive approach to cardiovascular and kidney risk reduction. Importantly, these agents should be included in the regimen of care irrespective of the need for additional glucose lowering, and irrespective of metformin use. Such an approach has also been described in the American Diabetes Association–endorsed American College of Cardiology "2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes" (234). **Figure 10.3**, reproduced from that decision pathway, outlines the approach to risk reduction with SGLT2 inhibitor or GLP-1 receptor agonist therapy in conjunction with other traditional, guideline-based preventive medical therapies for blood pressure, lipids, and glycemia and antiplatelet therapy.

Adoption of these agents should be reasonably straightforward in people with established cardiovascular or kidney disease who are later diagnosed with diabetes, as the cardioprotective agents can be used from the outset of diabetes management. On the other hand, incorporation of SGLT2 inhibitor or GLP-1 receptor agonist therapy in the care of individuals with more long-standing diabetes may be more challenging, particularly if patients are using an already complex glucose-lowering regimen. In such patients, SGLT2 inhibitor or GLP-1 receptor agonist therapy may need to replace some or all of their existing medications to minimize risks of hypoglycemia and adverse side effects, and potentially to minimize medication costs. Close collaboration between primary and specialty care professionals can help to facilitate these transitions in clinical care and, in turn, improve outcomes for highrisk people with type 2 diabetes.

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11. Chronic Kidney Disease and Risk Management: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For prevention and management of diabetes complications in children and adolescents, please refer to Section 14, "Children and Adolescents."

CHRONIC KIDNEY DISEASE

Screening

Recommendations

11.1a At least annually, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be assessed in people with type 1 diabetes with duration of ≥5 years and in all people with type 2 diabetes regardless of treatment. **B**

11.1b In people with established diabetic kidney disease, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be monitored 1–4 times per year depending on the stage of the disease (**Fig. 11.1**). **B**

Treatment

Recommendations

11.2 Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease. **A**

11.3 Optimize blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of chronic kidney disease. **A**

11.4a In nonpregnant people with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with moderately increased albuminuria (urinary albumin-to-creatinine ratio 30–299 mg/g creatinine) **B** and is strongly recommended for those

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CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m^2) Description and range	G1	Normal to high	≥90	1 if CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Figure 11.1—Risk of chronic kidney disease (CKD) progression, frequency of visits, and referral to a nephrologist according to glomerular filtration rate (GFR) and albuminuria. The GFR and albuminuria grid depicts the risk of progression, morbidity, and mortality by color, from best to worst (green, yellow, orange, red, dark red). The numbers in the boxes are a guide to the frequency of visits (number of times per year). Green can reflect CKD with normal estimated GFR and albumin-to-creatinine ratio only in the presence of other markers of kidney damage, such as imaging showing polycystic kidney disease or kidney biopsy abnormalities, with follow-up measurements annually; yellow requires caution and measurements at least once per year; orange requires measurements twice per year; red requires measurements three times per year; and dark red requires measurements four times per year. These are general parameters only, based on expert opinion, and underlying comorbid conditions and disease state, as well as the likelihood of impacting a change in management for any individual patient, must be taken into account. "Refer" indicates that nephrology services are recommended. *Referring clinicians may wish to discuss with their nephrology service, depending on local arrangements regarding treating or referring. Reprinted with permission from Vassalotti et al. (121).

with severely increased albuminuria (urinary albumin-to-creatinine ratio ≥300 mg/g creatinine) and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. **A**

11.4b Periodically monitor serum creatinine and potassium levels for the development of increased creatinine and hyperkalemia when ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists are used, or hypokalemia when diuretics are used. **B**

11.4c An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of chronic kidney disease in people with diabetes who have normal blood pressure, normal urinary albumin-to-creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. **A**

11.4d Do not discontinue renin-angiotensin system blockade for increases in serum creatinine (≤30%) in the absence of volume depletion. **A**

11.5a For people with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine. **A**

11.5b For people with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine. **B**

11.5c In people with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥20 mL/min/1.73 m^2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration

rate is ≥25 mL/min/1.73 m^2) additionally for cardiovascular risk reduction. **A**

11.5d In people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events. **A**

11.6 In people with chronic kidney disease who have ≥300 mg/g urinary albumin, a reduction of 30% or greater in mg/g urinary albumin is recommended to slow chronic kidney disease progression. **B**

11.7 For people with non–dialysis-dependent stage 3 or higher chronic kidney disease, dietary protein intake should be aimed to a target level of 0.8 g/kg body weight per day. **A** For patients on dialysis, higher levels of dietary protein intake should be considered since protein energy wasting is a major problem in some individuals on dialysis. **B**

11.8 Patients should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing estimated glomerular filtration rate and if the estimated glomerular filtration rate is <30 mL/min/1.73 m^2. **A**

11.9 Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease. **A**

EPIDEMIOLOGY OF DIABETES AND CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is diagnosed by the persistent elevation of urinary albumin excretion (albuminuria), low estimated glomerular filtration rate (eGFR), or other manifestations of kidney damage (1,2). In this section, the focus is on CKD attributed to diabetes (diabetic kidney disease) in adults, which occurs in 20–40% of people with diabetes (1,3–5). Diabetic kidney disease typically develops after a diabetes duration of 10 years in type 1 diabetes (the most common presentation is 5–15 years after the diagnosis of type 1 diabetes) but may be present at diagnosis of type 2 diabetes. CKD can progress to end-stage renal disease (ESRD) requiring dialysis or kidney transplantation and is the leading cause of ESRD in the U.S. (6). In addition, among people with type 1 or type 2 diabetes, the presence of CKD markedly increases cardiovascular risk and health care costs (7). For details on the management of diabetic kidney disease in children, please see section 14, "Children and Adolescents."

ASSESSMENT OF ALBUMINURIA AND ESTIMATED GLOMERULAR FILTRATION RATE

Screening for albuminuria can be most easily performed by urinary albumin-to-creatinine ratio (UACR) in a random spot urine collection (1,2). Timed or 24-h collections are more burdensome and add little to prediction or accuracy. Measurement of a spot urine sample for albumin alone (whether by immunoassay or by using a sensitive dipstick test specific for albuminuria) without simultaneously measuring urine creatinine is less expensive but susceptible to false-negative and false-positive determinations as a result of variation in urine concentration due to hydration (8). Thus, to be useful for patient screening, semiquantitative or qualitative (dipstick) screening tests should be >85% positive in those with moderately increased albuminuria (≥30 mg/g) and confirmed by albumin-to-creatinine values in an accredited laboratory (9,10). Hence, it is better to simply collect a spot urine sample for albumin-to-creatinine ratio because it will ultimately need to be done.

Normal albuminuria is defined as <30 mg/g creatinine, moderately elevated albuminuria is defined as ≥30–300 mg/g creatinine, and severely elevated albuminuria is defined as ≥300 mg/g creatinine. However, UACR is a continuous measurement, and differences within the normal and abnormal ranges are associated with renal and cardiovascular outcomes (7,11,12). Furthermore, because of high biological variability of >20% between measurements in urinary albumin excretion, two of three specimens of UACR collected within a 3- to 6-month period should be abnormal before considering a patient to have moderately or severely elevated albuminuria (1,2,13,14). Exercise within 24 h, infection, fever, congestive heart failure, marked hyperglycemia, menstruation, and marked hypertension may elevate UACR independently of kidney damage (15).

Traditionally, eGFR is calculated from serum creatinine using a validated formula (16). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is preferred (2). eGFR is routinely reported by laboratories along with serum creatinine, and eGFR calculators are available online at nkdep.nih.gov. An eGFR persistently <60 mL/min/1.73 m^2 in concert with a urinary albumin value of >30 mg/g creatinine is considered abnormal, though optimal thresholds for clinical diagnosis are debated in older adults over age 70 years (2,17). Historically, a correction factor for muscle mass was included in a modified equation for African American people; however, race is a social and not a biologic construct, making it problematic to apply race to clinical algorithms, and the need to advance health equity and social justice is clear. Thus, it was decided that the equation should be altered such that it applies to all (16). Hence, a committee was convened, resulting in the recommendation for immediate implementation of the CKD-EPI creatinine equation refit without the race variable in all laboratories in the U.S. Additionally, increased use of cystatin C (another marker of eGFR) is suggested in combination with the serum creatinine because combining filtration markers (creatinine and cystatin C) is more accurate and would support better clinical decisions than either marker alone.

DIAGNOSIS OF DIABETIC KIDNEY DISEASE

Diabetic kidney disease is usually a clinical diagnosis made based on the presence of albuminuria and/or reduced eGFR in the absence of signs or symptoms of other primary causes of kidney damage. The typical presentation of diabetic kidney disease is considered to include a long-standing duration of diabetes, retinopathy, albuminuria without gross hematuria, and gradually progressive loss of eGFR. However, signs of

diabetic kidney disease may be present at diagnosis or without retinopathy in type 2 diabetes. Reduced eGFR without albuminuria has been frequently reported in type 1 and type 2 diabetes and is becoming more common over time as the prevalence of diabetes increases in the U.S. (3,4,18,19).

An active urinary sediment (containing red or white blood cells or cellular casts), rapidly increasing albuminuria or total proteinuria, the presence of nephrotic syndrome, rapidly decreasing eGFR, or the absence of retinopathy (in type 1 diabetes) suggests alternative or additional causes of kidney disease. For patients with these features, referral to a nephrologist for further diagnosis, including the possibility of kidney biopsy, should be considered. It is rare for people with type 1 diabetes to develop kidney disease without retinopathy. In type 2 diabetes, retinopathy is only moderately sensitive and specific for CKD caused by diabetes, as confirmed by kidney biopsy (20).

STAGING OF CHRONIC KIDNEY DISEASE

Stage 1 and stage 2 CKD are defined by evidence of high albuminuria with eGFR $\geq$60 mL/min/1.73 m^2, and stages 3–5 CKD are defined by progressively lower ranges of eGFR (21) (**Fig. 11.1**). At any eGFR, the degree of albuminuria is associated with risk of cardiovascular disease (CVD), CKD progression, and mortality (7). Therefore, Kidney Disease: Improving Global Outcomes (KDIGO) recommends a more comprehensive CKD staging that incorporates albuminuria at all stages of eGFR; this system is more closely associated with risk but is also more complex and does not translate directly to treatment decisions (2). Thus, based on the current classification system, both eGFR and albuminuria must be quantified to guide treatment decisions. This is also important because eGFR levels are essential for modifications of drug dosages or restrictions of use (**Fig. 11.1**) (22,23). The degree of albuminuria should influence the choice of antihypertensive medications (see Section 10, "Cardiovascular Disease and Risk Management") or glucose-lowering medications (see below). Observed history of eGFR loss (which is also associated with risk of CKD progression and other adverse health outcomes) and cause of kidney damage (including possible causes other than diabetes) may also affect these decisions (24).

ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is diagnosed by a 50% or greater sustained increase in serum creatinine over a short period of time, which is also reflected as a rapid decrease in eGFR (25,26). People with diabetes are at higher risk of AKI than those without diabetes (27). Other risk factors for AKI include preexisting CKD, the use of medications that cause kidney injury (e.g., nonsteroidal anti-inflammatory drugs), and the use of medications that alter renal blood flow and intrarenal hemodynamics. In particular, many antihypertensive medications (e.g., diuretics, ACE inhibitors, and angiotensin receptor blockers [ARBs]) can reduce intravascular volume, renal blood flow, and/or glomerular filtration. There was concern that sodium–glucose cotransporter 2 (SGLT2) inhibitors may promote AKI through volume depletion, particularly when combined with diuretics or other medications that reduce glomerular filtration; however, this has not been found to be true in randomized clinical outcome trials of advanced kidney disease (28) or high CVD risk with normal kidney function (29–31). It is also noteworthy that the nonsteroidal mineralocorticoid receptor antagonists (MRAs) do not increase the risk of AKI when used to slow kidney disease progression (32). Timely identification and treatment of AKI is important because AKI is associated with increased risks of progressive CKD and other poor health outcomes (33).

Elevations in serum creatinine (up to 30% from baseline) with renin-angiotensin system (RAS) blockers (such as ACE inhibitors and ARBs) must not be confused with AKI (34). An analysis of the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial demonstrates that participants randomized to intensive blood pressure lowering with up to a 30% increase in serum creatinine did not have any increase in mortality or progressive kidney disease (35–38). Moreover, a measure of markers for AKI showed no significant increase of any markers with increased creatinine (37). Accordingly, ACE inhibitors and ARBs should not be discontinued for increases in serum creatinine ($<$30%) in the absence of volume depletion.

Lastly, it should be noted that ACE inhibitors and ARBs are commonly not dosed at maximum tolerated doses because of fear that serum creatinine will rise. As noted above, this is an error. Note that in all clinical trials demonstrating efficacy of ACE inhibitors and ARBs in slowing kidney disease progression, the maximum tolerated doses were used—not very low doses that do not provide benefit. Moreover, there are now studies demonstrating outcome benefits on both mortality and slowed CKD progression in people with diabetes who have an eGFR $<$30 mL/min/1.73 m^2 (38). Additionally, when increases in serum creatinine reach 30% without associated hyperkalemia, RAS blockade should be continued (36,39).

SURVEILLANCE

Both albuminuria and eGFR should be monitored annually to enable timely diagnosis of CKD, monitor progression of CKD, detect superimposed kidney diseases including AKI, assess risk of CKD complications, dose drugs appropriately, and determine whether nephrology referral is needed. Among people with existing kidney disease, albuminuria and eGFR may change due to progression of CKD, development of a separate superimposed cause of kidney disease, AKI, or other effects of medications, as noted above. Serum potassium should also be monitored in patients treated with diuretics because these medications can cause hypokalemia, which is associated with cardiovascular risk and mortality (40–42). Patients with eGFR $<$60 mL/min/1.73 m^2 receiving ACE inhibitors, ARBs, or MRAs should have serum potassium measured periodically. Additionally, people with this lower range of eGFR should have their medication dosing verified, their exposure to nephrotoxins (e.g., nonsteroidal anti-inflammatory drugs and iodinated contrast) should be minimized, and they should be evaluated for potential CKD complications (**Table 11.1**).

There is a clear need for annual quantitative assessment of urinary albumin excretion. This is especially true after a diagnosis of albuminuria, institution of ACE inhibitors or ARB therapy to maximum tolerated doses, and achievement of blood pressure targets. Early changes in

Table 11.1—Selected complications of chronic kidney disease

Complication	Physical and laboratory evaluation
Blood pressure >130/80 mmHg	Blood pressure, weight
Volume overload	History, physical examination, weight
Electrolyte abnormalities	Serum electrolytes
Metabolic acidosis	Serum electrolytes
Anemia	Hemoglobin; iron testing if indicated
Metabolic bone disease	Serum calcium, phosphate, PTH, vitamin 25(OH)D

Complications of chronic kidney disease (CKD) generally become prevalent when estimated glomerular filtration rate falls below 60 mL/min/1.73 m^2 (stage 3 CKD or greater) and become more common and severe as CKD progresses. Evaluation of elevated blood pressure and volume overload should occur at every clinical contact possible; laboratory evaluations are generally indicated every 6–12 months for stage 3 CKD, every 3–5 months for stage 4 CKD, and every 1–3 months for stage 5 CKD, or as indicated to evaluate symptoms or changes in therapy. PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.

kidney function may be detected by increases in albuminuria before changes in eGFR (43), and this also significantly affects cardiovascular risk. Moreover, an initial reduction of >30% from baseline, subsequently maintained over at least 2 years, is considered a valid surrogate for renal benefit by the Division of Cardiology and Nephrology of the U.S. Food and Drug Administration (FDA) (10). Continued surveillance can assess both response to therapy and disease progression and may aid in assessing participation in ACE inhibitor or ARB therapy. In addition, in clinical trials of ACE inhibitors or ARB therapy in type 2 diabetes, reducing albuminuria to levels <300 mg/g creatinine or by >30% from baseline has been associated with improved renal and cardiovascular outcomes, leading some to suggest that medications should be titrated to maximize reduction in UACR. Data from post hoc analyses demonstrate less benefit on cardiorenal outcomes at half doses of RAS blockade (44). In type 1 diabetes, remission of albuminuria may occur spontaneously, and cohort studies evaluating associations of change in albuminuria with clinical outcomes have reported inconsistent results (45,46).

The prevalence of CKD complications correlates with eGFR (42). When eGFR is <60 mL/min/1.73 m^2, screening for complications of CKD is indicated (**Table 11.1**). Early vaccination against hepatitis B virus is indicated in individuals likely to progress to ESRD (see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities," for further information on immunization).

Prevention

The only proven primary prevention interventions for CKD are blood glucose and blood pressure control. There is no evidence that renin-angiotensin-aldosterone system (RAAS) inhibitors or any other interventions prevent the development of diabetic kidney disease. Thus, the American Diabetes Association does not recommend routine use of these medications solely for the purpose of prevention of the development of diabetic kidney disease.

INTERVENTIONS

Nutrition

For people with non-dialysis-dependent CKD, dietary protein intake should be ~0.8 g/kg body weight per day (the recommended daily allowance) (1). Compared with higher levels of dietary protein intake, this level slowed GFR decline with evidence of a greater effect over time. Higher levels of dietary protein intake (>20% of daily calories from protein or >1.3 g/kg/day) have been associated with increased albuminuria, more rapid kidney function loss, and CVD mortality and therefore should be avoided. Reducing the amount of dietary protein below the recommended daily allowance of 0.8 g/kg/day is not recommended because it does not alter blood glucose levels, cardiovascular risk measures, or the course of GFR decline (47).

Restriction of dietary sodium (to <2,300 mg/day) may be useful to control blood pressure and reduce cardiovascular risk (48,49), and individualization of dietary potassium may be necessary to control serum potassium concentrations (27,40–42). These interventions may be most important for individuals with reduced eGFR, for whom urinary excretion of sodium and potassium may be impaired. For patients on dialysis, higher levels of dietary protein intake should be considered since malnutrition is a major problem for some patients on dialysis (50). Recommendations for dietary sodium and potassium intake should be individualized based on comorbid conditions, medication use, blood pressure, and laboratory data.

Glycemic Targets

Intensive lowering of blood glucose with the goal of achieving near-normoglycemia has been shown in large randomized studies to delay the onset and progression of albuminuria and reduce eGFR in people with type 1 diabetes (51,52) and type 2 diabetes (1,53–58). Insulin alone was used to lower blood glucose in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study of type 1 diabetes, while a variety of agents were used in clinical trials of type 2 diabetes, supporting the conclusion that lowering blood glucose itself helps prevent CKD and its progression. The effects of glucose-lowering therapies on CKD have helped define A1C targets (see **Table 6.2**).

The presence of CKD affects the risks and benefits of intensive lowering of blood glucose and a number of specific glucose-lowering medications. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial of type 2 diabetes, adverse effects of intensive management of blood glucose levels (hypoglycemia and mortality) were increased among people with kidney disease at baseline (59,60). Moreover, there is a lag time of at least 2 years in type 2 diabetes to over 10 years in type 1 diabetes for the effects of intensive glucose control to manifest as improved eGFR outcomes (56,60,61). Therefore, in some people with prevalent CKD and substantial comorbidity, target A1C levels may be less intensive (1,62).

Blood Pressure and Use of RAAS Inhibitors

RAAS inhibition remains a mainstay of management for people with diabetic kidney disease with albuminuria and for the treatment of hypertension in people with diabetes (with or without diabetic kidney disease). Indeed, all the trials that evaluated the benefits of SGLT2 inhibition or nonsteroidal mineralocorticoid receptor antagonist effects were done in individuals who were being treated with an ACE inhibitor or ARB, in some trials up to maximum tolerated doses.

Hypertension is a strong risk factor for the development and progression of CKD (63). Antihypertensive therapy reduces the risk of albuminuria (64–67), and among people with type 1 or 2 diabetes with established CKD (eGFR $<$60 mL/min/1.73 m^2 and UACR $\geq$300 mg/g creatinine), ACE inhibitor or ARB therapy reduces the risk of progression to ESRD (68–70,74–80). Moreover, antihypertensive therapy reduces the risk of cardiovascular events (64).

A blood pressure level $<$130/80 mmHg is recommended to reduce CVD mortality and slow CKD progression among all people with diabetes. Lower blood pressure targets (e.g., $<$130/80 mmHg) should be considered for patients based on individual anticipated benefits and risks. People with CKD are at increased risk of CKD progression (particularly those with albuminuria) and CVD; therefore, lower blood pressure targets may be suitable in some cases, especially in individuals with severely elevated albuminuria ($\geq$300 mg/g creatinine).

ACE inhibitors or ARBs are the preferred first-line agents for blood pressure treatment among people with diabetes, hypertension, eGFR $<$60 mL/min/1.73 m^2, and UACR $\geq$300 mg/g creatinine because of their proven benefits for prevention of CKD progression (68,69,74). ACE inhibitors and ARBs are considered to have similar benefits (75,76) and risks. In the setting of lower levels of albuminuria (30–299 mg/g creatinine), ACE inhibitor or ARB therapy at maximum tolerated doses in trials has reduced progression to more advanced albuminuria ($\geq$300 mg/g creatinine), slowed CKD progression, and reduced cardiovascular events but has not reduced progression to ESRD (74,77). While ACE inhibitors or ARBs are often prescribed for moderately increased albuminuria without hypertension, outcome trials have not been performed in this setting to determine whether they improve renal outcomes. Moreover, two long-term, double-blind studies demonstrated no renoprotective effect of either ACE inhibitors or ARBs in type 1 and type 2 diabetes among those who were normotensive with or without high albuminuria (formerly microalbuminuria) (78,79).

Absent kidney disease, ACE inhibitors or ARBs are useful to manage blood pressure but have not proven superior to alternative classes of antihypertensive therapy, including thiazide-like diuretics and dihydropyridine calcium channel blockers (80). In a trial of people with type 2 diabetes and normal urinary albumin excretion, an ARB reduced or suppressed the development of albuminuria but increased the rate of cardiovascular events (81). In a trial of people with type 1 diabetes exhibiting neither albuminuria nor hypertension, ACE inhibitors or ARBs did not prevent the development of diabetic glomerulopathy assessed by kidney biopsy (78). This was further supported by a similar trial in people with type 2 diabetes (79).

Two clinical trials studied the combinations of ACE inhibitors and ARBs and found no benefits on CVD or CKD, and the drug combination had higher adverse event rates (hyperkalemia and/or AKI) (82,83). Therefore, the combined use of ACE inhibitors and ARBs should be avoided.

Direct Renal Effects of Glucose-Lowering Medications

Some glucose-lowering medications also have effects on the kidney that are direct, i.e., not mediated through glycemia. For example, SGLT2 inhibitors reduce renal tubular glucose reabsorption, weight, systemic blood pressure, intraglomerular pressure, and albuminuria and slow GFR loss through mechanisms that appear independent of glycemia (30,84–87). Moreover, recent data support the notion that SGLT2 inhibitors reduce oxidative stress in the kidney by $>$50% and blunt increases in angiotensinogen as well as reduce NLRP3 inflammasome activity (88–90). Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) also have direct effects on the kidney and have been reported to improve renal outcomes compared with placebo (91–95). Renal effects should be considered when selecting antihyperglycemia agents (see Section 9, "Pharmacologic Approaches to Glycemic Treatment").

Selection of Glucose-Lowering Medications for People With Chronic Kidney Disease

For people with type 2 diabetes and established CKD, special considerations for the selection of glucose-lowering medications include limitations to available medications when eGFR is diminished and a desire to mitigate risks of CKD progression, CVD, and hypoglycemia (96,97). Drug dosing may require modification with eGFR $<$60 mL/min/1.73 m^2 (1).

The FDA revised its guidance for the use of metformin in CKD in 2016 (98), recommending use of eGFR instead of serum creatinine to guide treatment and expanding the pool of people with kidney disease for whom metformin treatment should be considered. The revised FDA guidance states that *1*) metformin is contraindicated in patients with an eGFR $<$30 mL/min/1.73 m^2, *2*) eGFR should be monitored while taking metformin, *3*) the benefits and risks of continuing treatment should be reassessed when eGFR falls to $<$45 mL/min/1.73 m^2 (99,100), *4*) metformin should not be initiated for patients with an eGFR $<$45 mL/min/1.73 m^2, and *5*) metformin should be temporarily discontinued at the time of or before iodinated contrast imaging procedures in patients with eGFR 30–60 mL/min/1.73 m^2.

A number of recent studies have shown cardiovascular protection from SGLT2 inhibitors and GLP-1 RAs as well as renal protection from SGLT2 inhibitors and possibly from GLP-1 RAs. Selection of which glucose-lowering medications to use should be based on the usual criteria of an individual patient's risks (cardiovascular and renal in addition to glucose control) as well as convenience and cost.

SGLT2 inhibitors are recommended for people with stage 3 CKD or higher and type 2 diabetes, as they slow CKD progression and reduce heart failure risk independent of glucose management (101). GLP-1 RAs are suggested for cardiovascular risk reduction if such risk is a predominant problem, as they reduce risks of CVD events and hypoglycemia and appear to possibly slow CKD progression (102–105).

A number of large cardiovascular outcomes trials in people with type 2 diabetes at high risk for CVD or with existing CVD examined kidney effects as secondary outcomes. These trials include EMPA-REG OUTCOME [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients], CANVAS (Canagliflozin Cardiovascular Assessment Study), LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), and SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) (71,86,91,94,102). Specifically, compared with placebo, empagliflozin reduced the risk of incident or worsening nephropathy (a composite of progression to UACR >300 mg/g creatinine, doubling of serum creatinine, ESRD, or death from ESRD) by 39% and the risk of doubling of serum creatinine accompanied by eGFR ≤45 mL/min/1.73 m^2 by 44%; canagliflozin reduced the risk of progression of albuminuria by 27% and the risk of reduction in eGFR, ESRD, or death from ESRD by 40%; liraglutide reduced the risk of new or worsening nephropathy (a composite of persistent macroalbuminuria, doubling of serum creatinine, ESRD, or death from ESRD) by 22%; and semaglutide reduced the risk of new or worsening nephropathy (a composite of persistent UACR >300 mg/g creatinine, doubling of serum creatinine, or ESRD) by 36% (each $P < 0.01$). These analyses were limited by evaluation of study populations not selected primarily for CKD and examination of renal effects as secondary outcomes.

Some large clinical trials of SGLT2 inhibitors have focused on people with advanced CKD, and assessment of primary renal outcomes is either completed or ongoing. Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), a placebo-controlled trial of canagliflozin among 4,401 adults with type 2 diabetes, UACR ≥300–5,000 mg/g creatinine, and eGFR range 30–90 mL/min/1.73 m^2 (mean eGFR 56 mL/min/1.73 m^2 with a mean albuminuria level of >900 mg/day), had a primary composite end point of ESRD, doubling of serum creatinine, or renal or cardiovascular death (28,72). It was stopped early due to positive efficacy and showed a 32% risk reduction for development of ESRD over control (28). Additionally, the development of the primary end point, which included chronic dialysis for ≥30 days, kidney transplantation or eGFR <15 mL/min/1.73 m^2 sustained for ≥30 days by central laboratory assessment, doubling from the baseline serum creatinine average sustained for ≥30 days by central laboratory assessment, or renal death or cardiovascular death, was reduced by 30%. This benefit was on background ACE inhibitor or ARB therapy in >99% of the patients (28). Moreover, in this advanced CKD group, there were clear benefits on cardiovascular outcomes demonstrating a 31% reduction in cardiovascular death or heart failure hospitalization and a 20% reduction in cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (28,73,105).

A second trial in advanced diabetic kidney disease was the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) study (106). This trial examined a cohort similar to that in CREDENCE except 67.5% of the participants had type 2 diabetes and CKD (the other one-third had CKD without type 2 diabetes), and the end points were slightly different. The primary outcome was time to the first occurrence of any of the components of the composite, including ≥50% sustained decline in eGFR or reaching ESRD or cardiovascular death, or renal death. Secondary outcome measures included time to the first occurrence of any of the components of the composite kidney outcome (≥50% sustained decline in eGFR or reaching ESRD or renal death), time to the first occurrence of either of the components of the cardiovascular composite (cardiovascular death or hospitalization for heart failure), and time to death from any cause. The trial had 4,304 participants with a mean eGFR at baseline of 43.1 ± 12.4 mL/min/1.73 m^2 (range 25–75 mL/min/1.73 m^2) and a median UACR of 949 mg/g (range 200–5,000 mg/g). There was a significant benefit by dapagliflozin for the primary end point (hazard ratio [HR] 0.61 [95% CI 0.51–0.72]; $P < 0.001$) (106).

The HR for the kidney composite of a sustained decline in eGFR of ≥50%, ESRD, or death from renal causes was 0.56 (95% CI 0.45–0.68; $P < 0.001$). The HR for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI 0.55–0.92; $P = 0.009$). Finally, all-cause mortality was decreased in the dapagliflozin group compared with the placebo group ($P < 0.004$).

In addition to renal effects, while SGLT2 inhibitors demonstrated reduced risk of heart failure hospitalizations, some also demonstrated cardiovascular risk reduction. GLP-1 RAs clearly demonstrated cardiovascular benefits. Namely, in the EMPA-REG OUTCOME, CANVAS, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58), LEADER, and SUSTAIN-6 trials, empagliflozin, canagliflozin, dapagliflozin, liraglutide, and semaglutide, respectively, each reduced cardiovascular events, evaluated as primary outcomes, compared with placebo (see Section 10, "Cardiovascular Disease and Risk Management," for further discussion). While the glucose-lowering effects of SGLT2 inhibitors are blunted with eGFR <45 mL/min/1.73 m^2, the renal and cardiovascular benefits were still seen at eGFR levels of 25 mL/min/1.73 m^2 with no significant change in glucose (28,30, 51,62,71,94,106,107). Most participants with CKD in these trials also had diagnosed atherosclerotic cardiovascular disease (ASCVD) at baseline, although ∼28% of CANVAS participants with CKD did not have diagnosed ASCVD (31).

Based on evidence from the CREDENCE and DAPA-CKD trials, as well as secondary analyses of cardiovascular outcomes trials with SGLT2 inhibitors, cardio-vascular and renal events are reduced with SGLT2 inhibitor use in patients with an eGFR of 20 mL/min/1.73 m^2, independent of glucose-lowering effects (73,105).

While there is clear cardiovascular risk reduction associated with GLP-1 RA use in people with type 2 diabetes and CKD, the proof of benefit on renal outcomes will come with the results of the ongoing FLOW (A Research Study to See How Semaglutide Works Compared with Placebo in People With Type 2 Diabetes and Chronic Kidney Disease) trial with injectable semaglutide (108). As noted above, published data address a limited group of people with CKD, mostly with coexisting ASCVD. Renal events, however, have been examined as both primary and secondary outcomes in large published trials. Adverse event profiles of these agents also must be considered. Please refer to **Table 9.2** for drug-specific factors, including adverse

event information, for these agents. Additional clinical trials focusing on CKD and cardiovascular outcomes in people with CKD are ongoing and will be reported in the next few years.

For people with type 2 diabetes and CKD, the selection of specific agents may depend on comorbidity and CKD stage. SGLT2 inhibitors may be more useful for individuals at high risk of CKD progression (i.e., with albuminuria or a history of documented eGFR loss) (**Fig. 9.3**) due to an apparent large beneficial effect on CKD incidence. However, for people with type 2 diabetes and diabetic kidney disease, use of an SGLT2 inhibitor in individuals with eGFR ≥20 mL/min/1.73 m^2 and UACR ≥200 mg/g creatinine is recommended to reduce CKD progression and cardiovascular events. This is a change in eGFR from previous recommendations that suggested an eGFR level >25 mL/min/1.73 m^2. The reason for the lower limit of eGFR is as follows. The major clinical trials for SGLT2 inhibitors that showed benefit for people with diabetic kidney disease are CREDENCE and DAPA-CKD (28,105). CREDENCE enrollment criteria included an eGFR >30 mL/min/1.73 m^2 and UACR >300 mg/g (28,105). DAPA-CKD enrolled individuals with eGFR >25 mL/min/1.73 m^2 and UACR >200 mg/g. Subgroup analyses from DAPA-CKD (109) and analyses from the EMPEROR heart failure trials suggest that SGLT2 inhibitors are safe and effective at eGFR levels of >20 mL/min/1.73 m^2. The Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved) enrolled 5,998 participants (110), and the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) enrolled 3,730 participants (111); enrollment criteria included eGFR >60 mL/min/1.73 m^2, but efficacy was seen at eGFR >20 mL/min/1.73 m^2 in people with heart failure. Hence, the new recommendation is to use SGLT2 inhibitors in individuals with eGFR as low as 20 mL/min/1.73 m^2. In addition, the DECLARE-TIMI 58 trial suggested effectiveness in participants with normal urinary albumin levels (112). In sum, for people with type 2 diabetes and diabetic kidney disease, use of an SGLT2 inhibitor is recommended to reduce CKD progression and cardiovascular events in people with an eGFR ≥20 mL/min/1.73 m^2.

Of note, GLP-1 RAs may also be used at low eGFR for cardiovascular protection but may require dose adjustment (113).

Renal and Cardiovascular Outcomes of Mineralocorticoid Receptor Antagonists in Chronic Kidney Disease

MRAs historically have not been well studied in diabetic kidney disease because of the risk of hyperkalemia (114,115). However, data that do exist suggest sustained benefit on albuminuria reduction. There are two different classes of MRAs, steroidal and nonsteroidal, with one group not extrapolatable to the other (116). Late in 2020, the results of the first of two trials, the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial, which examined the renal effects of finerenone, demonstrated a significant reduction in diabetic kidney disease progression and cardiovascular events in people with advanced diabetic kidney disease (32,117). This trial had a primary end point of time to first occurrence of the composite end point of onset of kidney failure, a sustained decrease of eGFR >40% from baseline over at least 4 weeks, or renal death. A prespecified secondary outcome was time to first occurrence of the composite end point cardiovascular death or nonfatal cardiovascular events (myocardial infarction, stroke, or hospitalization for heart failure). Other secondary outcomes included all-cause mortality, time to all-cause hospitalizations, and change in UACR from baseline to month 4, and time to first occurrence of the following composite end point: onset of kidney failure, a sustained decrease in eGFR of ≥57% from baseline over at least 4 weeks, or renal death.

The double-blind, placebo-controlled trial randomized 5,734 people with CKD and type 2 diabetes to receive finerenone, a novel nonsteroidal MRA, or placebo. Eligible participants had a UACR of 30 to <300 mg/g, an eGFR of 25 to <60 mL/min/1.73 m^2, and diabetic retinopathy, or a UACR of 300–5,000 mg/g and an eGFR of 25 to <75 mL/min/1.73 m^2. The mean age of participants was 65.6 years, and 30% were female. The mean eGFR was 44.3 mL/min/1.73 m^2, and the mean albuminuria was 852 mg/g (interquartile range 446–1,634 mg/g). The primary end point was reduced with finerenone compared with placebo (HR 0.82 [95% CI 0.73–0.93]; P = 0.001), as was the key secondary composite of cardiovascular outcome (HR 0.86 [95% CI 0.75–0.99]; P = 0.03). Hyperkalemia resulted in 2.3% discontinuation in the study group compared with 0.9% in the placebo group. However, the study was completed, and there were no deaths related to hyperkalemia. Of note, 4.5% of the total group were being treated with SGLT2 inhibitors.

The Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial assessed the safety and efficacy of finerenone in reducing cardiovascular events among people with type 2 diabetes and CKD with elevated UACR (30 to <300 mg/g creatinine) and eGFR 25–90 mL/min/1.73 m^2 (118). The study randomized eligible subjects to either finerenone (n = 3,686) or placebo (n = 3,666). Participants with an eGFR of 25–60 mL/min/1.73 m^2 at the screening visit received an initial dose at baseline of 10 mg once daily, and if eGFR at screening was ≥60 mL/min/1.73 m^2, the initial dose was 20 mg once daily. An increase in the dose from 10 to 20 mg once daily was encouraged after 1 month, provided the serum potassium level was ≤4.8 mmol/L and eGFR was stable. The mean age of participants was 64.1 years (31% were female), and the median follow-up duration was 3.4 years. The median A1C was 7.7%, the mean systolic blood pressure was 136 mmHg, and the mean GFR was 67.8 mL/min/1.73 m^2. People with heart failure with a reduced ejection fraction and uncontrolled hypertension were excluded.

The primary composite outcome was cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure. The finerenone group showed a 13% reduction in the primary end point compared with the placebo group (12.4% vs. 14.2%; HR 0.87 [95% CI 0.76–0.98]; P = 0.03). This benefit was primarily driven by a reduction in heart failure hospitalizations: 3.2% vs. 4.4% in the placebo group (HR 0.71 [95% CI 0.56–0.90]).

Of the secondary outcomes, the most noteworthy was a 36% reduction in end-stage kidney disease: 0.9% vs. 1.3% in

the placebo group (HR 0.64 [95% CI 0.41–0.995]). There was a higher incidence of hyperkalemia in the finerenone group, 10.8% vs. 5.3%, although only 1.2% of the 3,686 individuals on finerenone stopped the study due to hyperkalemia (0.6% vs. 0.4% of the placebo group).

The FIDELITY prespecified pooled efficacy and safety analysis incorporated individuals from both the FIGARO-DKD and FIDELIO-DKD trials ($N = 13,171$) to allow for evaluation across the spectrum of severity of CKD, since the populations were different (with a slight overlap) and the study designs were similar (119). The analysis showed a 14% reduction in composite cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure for finerenone vs. placebo (12.7% vs. 14.4%; HR 0.86 [95% CI 0.78–0.95]; $P = 0.0018$).

It also demonstrated a 23% reduction in the composite kidney outcome, consisting of sustained ≥57% decrease in eGFR from baseline over ≥4 weeks, or renal death, for finerenone vs. placebo (5.5% vs. 7.1%; HR 0.77 [95% CI 0.67–0.88]; $P = 0.0002$).

The pooled FIDELITY trial analysis confirms and strengthens the positive cardiovascular and renal outcomes with finerenone across the spectrum of CKD, irrespective of baseline ASCVD history (with the exclusion of those with heart failure with reduced ejection fraction).

REFERRAL TO A NEPHROLOGIST

Health care professionals should consider referral to a nephrologist if the patient has continuously rising UACR levels and/or continuously declining eGFR, if there is uncertainty about the etiology of kidney disease, for difficult management issues (anemia, secondary hyperparathyroidism, significant increases in albuminuria in spite of good blood pressure management, metabolic bone disease, resistant hypertension, or electrolyte disturbances), or when there is advanced kidney disease (eGFR <30 mL/min/1.73 m^2) requiring discussion of renal replacement therapy for ESRD (2). The threshold for referral may vary depending on the frequency with which a health care professional encounters people with diabetes and kidney disease. Consultation with a nephrologist when stage 4 CKD develops (eGFR <30 mL/min/1.73 m^2) has been found to reduce cost, improve quality of care, and delay dialysis (120). However, other specialists and health care professionals should also educate their patients about the progressive nature of CKD, the kidney preservation benefits of proactive treatment of blood pressure and blood glucose, and the potential need for renal replacement therapy.

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12. Retinopathy, Neuropathy, and Foot Care: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For prevention and management of diabetes complications in children and adolescents, please refer to Section 14, "Children and Adolescents."

DIABETIC RETINOPATHY

Recommendations

12.1 Optimize glycemic control to reduce the risk or slow the progression of diabetic retinopathy. **A**

12.2 Optimize blood pressure and serum lipid control to reduce the risk or slow the progression of diabetic retinopathy. **A**

Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2 diabetes, with prevalence strongly related to both the duration of diabetes and the level of glycemic control (1). Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years in developed countries. Glaucoma, cataracts, and other eye disorders occur earlier and more frequently in people with diabetes.

In addition to diabetes duration, factors that increase the risk of, or are associated with, retinopathy include chronic hyperglycemia (2,3), nephropathy (4), hypertension (5), and dyslipidemia (6). Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to prevent and/or delay the onset and progression of diabetic retinopathy, reduce the need for future ocular surgical procedures, and potentially improve patient-reported visual function (2,7–10). A meta-analysis of data from cardiovascular outcomes studies showed no association between glucagon-like peptide 1 receptor agonist (GLP-1 RA) treatment and retinopathy per se, except through the association between retinopathy and average A1C reduction at the 3-month and 1-year follow-up. Long-term impact of improved glycemic control on retinopathy was not studied

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in these trials. Retinopathy status should be assessed when intensifying glucose-lowering therapies such as those using GLP-1 RAs, since rapid reductions in A1C can be associated with initial worsening of retinopathy (11).

Screening

Recommendations

12.3 Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. **B**

12.4 People with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis. **B**

12.5 If there is no evidence of retinopathy for one or more annual eye exams and glycemia is well controlled, then screening every 1–2 years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations should be repeated at least annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations will be required more frequently. **B**

12.6 Programs that use retinal photography (with remote reading or use of a validated assessment tool) to improve access to diabetic retinopathy screening can be appropriate screening strategies for diabetic retinopathy. Such programs need to provide pathways for timely referral for a comprehensive eye examination when indicated. **B**

12.7 Individuals of childbearing potential with preexisting type 1 or type 2 diabetes who are planning pregnancy or who are pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. **B**

12.8 Individuals with preexisting type 1 or type 2 diabetes should receive an eye exam before pregnancy and in the first trimester and should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy. **B**

The preventive effects of therapy and the fact that individuals with proliferative diabetic retinopathy (PDR) or macular edema may be asymptomatic provide strong support for screening to detect diabetic retinopathy. Prompt diagnosis allows triage of patients and timely intervention that may prevent vision loss in individuals who are asymptomatic despite advanced diabetic eye disease.

Diabetic retinopathy screening should be performed using validated approaches and methodologies. Youth with type 1 or type 2 diabetes are also at risk for complications and need to be screened for diabetic retinopathy (12) (see Section 14, "Children and Adolescents"). If diabetic retinopathy is evident on screening, prompt referral to an ophthalmologist is recommended. Subsequent examinations for individuals with type 1 or type 2 diabetes are generally repeated annually for individuals with minimal to no retinopathy. Exams every 1–2 years may be cost-effective after one or more normal eye exams. In a population with well-controlled type 2 diabetes, there was little risk of development of significant retinopathy within a 3-year interval after a normal examination (13), and less frequent intervals have been found in simulated modeling to be potentially effective in screening for diabetic retinopathy in individuals without diabetic retinopathy (14). However, it is important to adjust screening intervals based on the presence of specific risk factors for retinopathy onset and worsening retinopathy. More frequent examinations by the ophthalmologist will be required if retinopathy is progressing or risk factors such as uncontrolled hyperglycemia, advanced baseline retinopathy, or diabetic macular edema are present.

Retinal photography with remote reading by experts has great potential to provide screening services in areas where qualified eye care professionals are not readily available (15–17). High-quality fundus photographs can detect most clinically significant diabetic retinopathy. Interpretation of the images should be performed by a trained eye care professional. Retinal photography may also enhance efficiency and reduce costs when the expertise of ophthalmologists can be used for more complex examinations and for therapy (15,18,19). In-person exams are still necessary when the retinal photos are of unacceptable quality and for follow-up if abnormalities are detected. Retinal photos are not a substitute for dilated comprehensive eye exams, which should be performed at least initially and at yearly intervals thereafter or more frequently as recommended by an eye care professional. Artificial intelligence systems that detect more than mild diabetic retinopathy and diabetic macular edema, authorized for use by the U.S. Food and Drug Administration (FDA), represent an alternative to traditional screening approaches (20). However, the benefits and optimal utilization of this type of screening have yet to be fully determined. Results of all screening eye examinations should be documented and transmitted to the referring health care professional.

Type 1 Diabetes

Because retinopathy is estimated to take at least 5 years to develop after the onset of hyperglycemia, people with type 1 diabetes should have an initial dilated and comprehensive eye examination within 5 years after the diagnosis of diabetes (21).

Type 2 Diabetes

People with type 2 diabetes who may have had years of undiagnosed diabetes and have a significant risk of prevalent diabetic retinopathy at the time of diagnosis should have an initial dilated and comprehensive eye examination at the time of diagnosis.

Pregnancy

Individuals who develop gestational diabetes mellitus do not require eye examinations during pregnancy since they do not appear to be at increased risk of developing diabetic retinopathy during pregnancy (22). However, individuals of childbearing potential with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the baseline prevalence and risk of development and/or progression of diabetic retinopathy. In a systematic review and meta-analysis of 18 observational studies of pregnant individuals with preexisting

type 1 or type 2 diabetes, the prevalence of any diabetic retinopathy and PDR in early pregnancy was 52.3% and 6.1%, respectively. The pooled progression rate per 100 pregnancies for new diabetic retinopathy development was 15.0 (95% CI 9.9–20.8), worsened nonproliferative diabetic retinopathy was 31.0 (95% CI 23.2–39.2), pooled sight-threatening progression rate from nonproliferative diabetic retinopathy to PDR was 6.3 (95% CI 3.3–10.0), and worsened PDR was 37.0 (95% CI 21.2–54.0), demonstrating that close follow-up should be maintained during pregnancy to prevent vision loss (23). In addition, rapid implementation of intensive glycemic management in the setting of retinopathy is associated with early worsening of retinopathy (24).

A systematic review and meta-analysis and a controlled prospective study demonstrate that pregnancy in individuals with type 1 diabetes may aggravate retinopathy and threaten vision, especially when glycemic control is poor or retinopathy severity is advanced at the time of conception (23,24). Laser photocoagulation surgery can minimize the risk of vision loss during pregnancy for individuals with high-risk PDR or center-involved diabetic macular edema (24). Anti–vascular endothelial growth factor (anti-VEGF) medications should not be used in pregnant individuals with diabetes because of theoretical risks to the vasculature of the developing fetus.

Treatment

Recommendations

12.9 Promptly refer individuals with any level of diabetic macular edema, moderate or worse nonproliferative diabetic retinopathy (a precursor of proliferative diabetic retinopathy), or any proliferative diabetic retinopathy to an ophthalmologist who is knowledgeable and experienced in the management of diabetic retinopathy. **A**

12.10 Panretinal laser photocoagulation therapy is indicated to reduce the risk of vision loss in individuals with high-risk proliferative diabetic retinopathy and, in some cases, severe nonproliferative diabetic retinopathy. **A**

12.11 Intravitreous injections of anti–vascular endothelial growth factor are a reasonable alternative to traditional panretinal laser photocoagulation for some individuals with proliferative diabetic retinopathy and also reduce the risk of vision loss in these individuals. **A**

12.12 Intravitreous injections of anti–vascular endothelial growth factor are indicated as first-line treatment for most eyes with diabetic macular edema that involves the foveal center and impairs vision acuity. **A**

12.13 Macular focal/grid photocoagulation and intravitreal injections of corticosteroid are reasonable treatments in eyes with persistent diabetic macular edema despite previous anti–vascular endothelial growth factor therapy or eyes that are not candidates for this first-line approach. **A**

12.14 The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage. **A**

Two of the main motivations for screening for diabetic retinopathy are to prevent loss of vision and to intervene with treatment when vision loss can be prevented or reversed.

Photocoagulation Surgery

Two large trials, the Diabetic Retinopathy Study (DRS) in individuals with PDR and the Early Treatment Diabetic Retinopathy Study (ETDRS) in individuals with macular edema, provide the strongest support for the therapeutic benefits of photocoagulation surgery. The DRS (25) showed in 1978 that panretinal photocoagulation surgery reduced the risk of severe vision loss from PDR from 15.9% in untreated eyes to 6.4% in treated eyes with the greatest benefit ratio in those with more advanced baseline disease (disc neovascularization or vitreous hemorrhage). In 1985, the ETDRS also verified the benefits of panretinal photocoagulation for high-risk PDR and in older-onset individuals with severe nonproliferative diabetic retinopathy or less-than-high-risk PDR. Panretinal laser photocoagulation is still commonly used to manage complications of diabetic retinopathy that involve retinal neovascularization and its complications. A more gentle, macular focal/grid laser photocoagulation technique was shown in the ETDRS to be effective in treating eyes with clinically significant macular edema from diabetes (26), but this is now largely considered to be second-line treatment for diabetic macular edema.

Anti–Vascular Endothelial Growth Factor Treatment

Data from the DRCR Retina Network (formerly the Diabetic Retinopathy Clinical Research Network) and others demonstrate that intravitreal injections of anti-VEGF agents are effective at regressing proliferative disease and lead to noninferior or superior visual acuity outcomes compared with panretinal laser over 2 years of follow-up (27,28). In addition, it was observed that individuals treated with ranibizumab tended to have less peripheral visual field loss, fewer vitrectomy surgeries for secondary complications from their proliferative disease, and a lower risk of developing diabetic macular edema. However, a potential drawback in using anti-VEGF therapy to manage proliferative disease is that patients were required to have a greater number of visits and received a greater number of treatments than is typically required for management with panretinal laser, which may not be optimal for some individuals. The FDA has approved aflibercept and ranibizumab for the treatment of eyes with diabetic retinopathy. Other emerging therapies for retinopathy that may use sustained intravitreal delivery of pharmacologic agents are currently under investigation. Anti-VEGF treatment of eyes with nonproliferative diabetic retinopathy has been demonstrated to reduce subsequent development of retinal neovascularization and diabetic macular edema but has not been shown to improve visual outcomes over 2 years of therapy and therefore is not routinely recommended for this indication (29).

While the ETDRS (26) established the benefit of focal laser photocoagulation surgery in eyes with clinically significant macular edema (defined as retinal edema

located at or threatening the macular center), current data from well-designed clinical trials demonstrate that intravitreal anti-VEGF agents provide a more effective treatment plan for center-involved diabetic macular edema than monotherapy with laser (30,31). Most patients require near-monthly administration of intravitreal therapy with anti-VEGF agents during the first 12 months of treatment, with fewer injections needed in subsequent years to maintain remission from central-involved diabetic macular edema. There are currently three anti-VEGF agents commonly used to treat eyes with central-involved diabetic macular edema—bevacizumab, ranibizumab, and aflibercept (1)—and a comparative effectiveness study demonstrated that aflibercept provides vision outcomes superior to those of bevacizumab when eyes have moderate visual impairment (vision of 20/50 or worse) from diabetic macular edema (32). For eyes that have good vision (20/25 or better) despite diabetic macular edema, close monitoring with initiation of anti-VEGF therapy if vision worsens provides similar 2-year vision outcomes compared with immediate initiation of anti-VEGF therapy (33).

Eyes that have persistent diabetic macular edema despite anti-VEGF treatment may benefit from macular laser photocoagulation or intravitreal therapy with corticosteroids. Both of these therapies are also reasonable first-line approaches for individuals who are not candidates for anti-VEGF treatment due to systemic considerations such as pregnancy.

Adjunctive Therapy

Lowering blood pressure has been shown to decrease retinopathy progression, although tight targets (systolic blood pressure <120 mmHg) do not impart additional benefit (8). In individuals with dyslipidemia, retinopathy progression may be slowed by the addition of fenofibrate, particularly with very mild nonproliferative diabetic retinopathy at baseline (34,35).

NEUROPATHY

Screening

Recommendations

12.15 All people with diabetes should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter. **B**

12.16 Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation (small-fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function). All people with diabetes should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation. **B**

12.17 Symptoms and signs of autonomic neuropathy should be assessed in people with diabetes starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter and with evidence of other microvascular complications, particularly kidney disease and diabetic peripheral neuropathy. Screening can include asking about orthostatic dizziness, syncope, or dry cracked skin in the extremities. Signs of autonomic neuropathy include orthostatic hypotension, a resting tachycardia, or evidence of peripheral dryness or cracking of skin. **E**

Diabetic neuropathies are a heterogeneous group of disorders with diverse clinical manifestations. The early recognition and appropriate management of neuropathy in people with diabetes is important. Points to be aware of include the following:

1. Diabetic neuropathy is a diagnosis of exclusion. Nondiabetic neuropathies may be present in people with diabetes and may be treatable.
2. Up to 50% of diabetic peripheral neuropathy may be asymptomatic. If not recognized and if preventive foot care is not implemented, people with diabetes are at risk for injuries as well as diabetic foot ulcers and amputations.
3. Recognition and treatment of autonomic neuropathy may improve symptoms, reduce sequelae, and improve quality of life.

Specific treatment to reverse the underlying nerve damage is currently not available. Glycemic control can effectively prevent diabetic peripheral neuropathy (DPN) and cardiac autonomic neuropathy (CAN) in type 1 diabetes (36,37) and may modestly slow their progression in type 2 diabetes (38), but it does not reverse neuronal loss. Treatments of other modifiable risk factors (including lipids and blood pressure) can aid in prevention of DPN progression in type 2 diabetes and may reduce disease progression in type 1 diabetes (39–41). Therapeutic strategies (pharmacologic and nonpharmacologic) for the relief of painful DPN and symptoms of autonomic neuropathy can potentially reduce pain (42) and improve quality of life.

Diagnosis

Diabetic Peripheral Neuropathy

Individuals with a type 1 diabetes duration ≥5 years and all individuals with type 2 diabetes should be assessed annually for DPN using the medical history and simple clinical tests (42). Symptoms vary according to the class of sensory fibers involved. The most common early symptoms are induced by the involvement of small fibers and include pain and dysesthesia (unpleasant sensations of burning and tingling). The involvement of large fibers may cause numbness and loss of protective sensation (LOPS). LOPS indicates the presence of distal sensorimotor polyneuropathy and is a risk factor for diabetic foot ulceration. The following clinical tests may be used to assess small- and large-fiber function and protective sensation:

1. Small-fiber function: pinprick and temperature sensation.
2. Large-fiber function: lower-extremity reflexes, vibration perception, and 10-g monofilament.
3. Protective sensation: 10-g monofilament.

These tests not only screen for the presence of dysfunction but also predict future risk of complications. Electrophysiological testing or referral to a neurologist is rarely needed, except in situations

where the clinical features are atypical or the diagnosis is unclear.

In all people with diabetes and DPN, causes of neuropathy other than diabetes should be considered, including toxins (e.g., alcohol), neurotoxic medications (e.g., chemotherapy), vitamin B12 deficiency, hypothyroidism, renal disease, malignancies (e.g., multiple myeloma, bronchogenic carcinoma), infections (e.g., HIV), chronic inflammatory demyelinating neuropathy, inherited neuropathies, and vasculitis (43). See the American Diabetes Association position statement "Diabetic Neuropathy" for more details (42).

Diabetic Autonomic Neuropathy

Individuals who have had type 1 diabetes for ≥5 years and all individuals with type 2 diabetes should be assessed annually for autonomic neuropathy (42). The symptoms and signs of autonomic neuropathy should be elicited carefully during the history and physical examination. Major clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction with either increased or decreased sweating. Screening for symptoms of autonomic neuropathy includes asking about symptoms of orthostatic intolerance (dizziness, lightheadedness, or weakness with standing), syncope, exercise intolerance, constipation, diarrhea, urinary retention, urinary incontinence, or changes in sweat function. Further testing can be considered if symptoms are present and will depend on the end organ involved but might include cardiovascular autonomic testing, sweat testing, urodynamic studies, gastric emptying, or endoscopy/colonoscopy. Impaired counterregulatory responses to hypoglycemia in type 1 and type 2 diabetes can lead to hypoglycemia unawareness but are not directly linked to autonomic neuropathy.

Cardiovascular Autonomic Neuropathy. CAN is associated with mortality independently of other cardiovascular risk factors (44,45). In its early stages, CAN may be completely asymptomatic and detected only by decreased heart rate variability with deep breathing. Advanced disease may be associated with resting tachycardia (>100 bpm) and orthostatic hypotension (a fall in systolic or diastolic blood pressure by >20 mmHg or >10 mmHg, respectively, upon standing without an appropriate increase in heart rate). CAN treatment is generally focused on alleviating symptoms.

Gastrointestinal Neuropathies. Gastrointestinal neuropathies may involve any portion of the gastrointestinal tract, with manifestations including esophageal dysmotility, gastroparesis, constipation, diarrhea, and fecal incontinence. Gastroparesis should be suspected in individuals with erratic glycemic control or with upper gastrointestinal symptoms without another identified cause. Exclusion of reversible/iatrogenic causes such as medications or organic causes of gastric outlet obstruction or peptic ulcer disease (with esophagogastroduodenoscopy or a barium study of the stomach) is needed before considering a diagnosis of or specialized testing for gastroparesis. The diagnostic gold standard for gastroparesis is the measurement of gastric emptying with scintigraphy of digestible solids at 15-min intervals for 4 h after food intake. The use of ^{13}C octanoic acid breath test is an approved alternative.

Genitourinary Disturbances. Diabetic autonomic neuropathy may also cause genitourinary disturbances, including sexual dysfunction and bladder dysfunction. In men, diabetic autonomic neuropathy may cause erectile dysfunction and/or retrograde ejaculation (42). Female sexual dysfunction occurs more frequently in those with diabetes and presents as decreased sexual desire, increased pain during intercourse, decreased sexual arousal, and inadequate lubrication (46). Lower urinary tract symptoms manifest as urinary incontinence and bladder dysfunction (nocturia, frequent urination, urination urgency, and weak urinary stream). Evaluation of bladder function should be performed for individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder.

Treatment

Recommendations

12.18 Optimize glucose control to prevent or delay the development of neuropathy in people with type 1 diabetes **A** and to slow the progression of neuropathy in people with type 2 diabetes. **C** Optimize blood pressure and serum lipid control to reduce the risk or slow the progression of diabetic neuropathy. **B**

12.19 Assess and treat pain related to diabetic peripheral neuropathy **B** and symptoms of autonomic neuropathy to improve quality of life. **E**

12.20 Gabapentinoids, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and sodium channel blockers are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. **A** Refer to neurologist or pain specialist when pain control is not achieved within the scope of practice of the treating physician. **E**

Glycemic Control

Near-normal glycemic control, implemented early in the course of diabetes, has been shown to effectively delay or prevent the development of DPN and CAN in people with type 1 diabetes (47–50). Although the evidence for the benefit of near-normal glycemic control is not as strong that for type 2 diabetes, some studies have demonstrated a modest slowing of progression without reversal of neuronal loss (38,51). Specific glucose-lowering strategies may have different effects. In a post hoc analysis, participants, particularly men, in the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial treated with insulin sensitizers had a lower incidence of distal symmetric polyneuropathy over 4 years than those treated with insulin/sulfonylurea (52). Additionally, recent evidence from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed clear benefit of intensive glucose and blood pressure control on the prevention of CAN in type 2 diabetes (53).

Lipid Control

Dyslipidemia is a key factor in the development of neuropathy in people with type 2 diabetes and may contribute to neuropathy risk in people with type 1 diabetes (54,55). Although the evidence for a relationship between lipids

and neuropathy development has become increasingly clear in type 2 diabetes, the optimal therapeutic intervention has not been identified. Positive effects of physical activity, weight loss, and bariatric surgery have been reported in individuals with DPN, but use of conventional lipid-lowering pharmacotherapy (such as statins or fenofibrates) does not appear to be effective in treating or preventing DPN development (56).

Blood Pressure Control

There are multiple reasons for blood pressure control in people with diabetes, but neuropathy progression (especially in type 2 diabetes) has now been added to this list. Although data from many studies have supported the role of hypertension in risk of neuropathy development, a recent meta-analysis of data from 14 countries in the International Prevalence and Treatment of Diabetes and Depression (INTERPRET-DD) study revealed hypertension as an independent risk of DPN development with an odds ratio of 1.58 (57). In the ACCORD trial, intensive blood pressure intervention decreased CAN risk by 25% (53).

Neuropathic Pain

Neuropathic pain can be severe and can impact quality of life, limit mobility, and contribute to depression and social dysfunction (58). No compelling evidence exists in support of glycemic control or lifestyle management as therapies for neuropathic pain in diabetes or prediabetes, which leaves only pharmaceutical interventions (59). A recent guideline by the American Academy of Neurology recommends that the initial treatment of pain should also focus on the concurrent treatment of both sleep and mood disorders because of increased frequency of these problems in individuals with DPN (60).

A number of pharmacologic therapies exist for treatment of pain in diabetes. The American Academy of Neurology update suggested that gabapentinoids, serotonin-norepinephrine reuptake inhibitors (SNRIs), sodium channel blockers, tricyclic antidepressants (TCAs), and SNRI/opioid dual-mechanism agents could all be considered in the treatment of pain in DPN (60). These American Academy of Neurology recommendations offer a supplement to a recent American Diabetes Association pain monograph, although some areas of disagreement exist, particularly around SNRI/opioid dual-mechanism agents (61). A recent head-to-head trial suggested therapeutic equivalency for TCAs, SNRIs, and gabapentinoids in the treatment of pain in DPN (62). The trial also supported the role of combination therapy over monotherapy for the treatment of pain in DPN.

Gabapentinoids. Gabapentinoids include several calcium channel α2-δ subunit ligands. Eight high-quality studies and seven medium-quality studies support the role of pregabalin in treatment of pain in DPN. One high-quality study and many small studies support the role of gabapentin in the treatment of pain in DPN. Two medium-quality studies suggest that mirogabalin has a small effect on pain in DPN (60). Adverse effects may be more severe in older individuals (63) and may be attenuated by lower starting doses and more gradual titration.

SNRIs. SNRIs include duloxetine, venlafaxine, and desvenlafaxine, all selective SNRIs. Two high-quality studies and five medium-quality studies support the role of duloxetine in the treatment of pain in DPN. A high-quality study supports the role of venlafaxine in the treatment of pain in DPN. Only one medium-quality study supports a possible role for desvenlafaxine for treatment of pain in DPN (60). Adverse events may be more severe in older people but may be attenuated with lower doses and slower titration of duloxetine.

Tapentadol and Tramadol. Tapentadol and tramadol are centrally acting opioid analgesics that exert their analgesic effects through both μ-opioid receptor agonism and norepinephrine and serotonin reuptake inhibition. SNRI/opioid agents are probably effective in the treatment of pain in DPN. However, the use of any opioids for management of chronic neuropathic pain carries the risk of addiction and should be avoided.

Tricyclic Antidepressants. Tricyclic antidepressants have been studied for treatment of pain, and most of the relevant data was acquired from trials of amitriptyline and include two high-quality studies and two medium-quality studies supporting the treatment of pain in DPN (60,62). Anticholinergic side effects may be dose limiting and restrict use in individuals $\geq$65 years of age.

Sodium Channel Blockers. Sodium channel blockers include lamotrigine, lacosamide, oxcarbazepine, and valproic acid. Five medium-quality studies support the role of sodium channel blockers in treating pain in DPN (60).

Capsaicin. Capsaicin has received FDA approval for treatment of pain in DPN using an 8% patch, with one high-quality study reported. One medium-quality study of 0.075% capsaicin cream has been reported. In patients with contraindications to oral pharmacotherapy or who prefer topical treatments, the use of topical capsaicin can be considered.

Carbamazepine and α-Lipoic Acid. Carbamazepine and α-lipoic acid, although not approved for the treatment of painful DPN, may be effective and considered for the treatment of painful DPN (41,54,56).

Orthostatic Hypotension

Treating orthostatic hypotension is challenging. The therapeutic goal is to minimize postural symptoms rather than to restore normotension. Most patients require both nonpharmacologic measures (e.g., ensuring adequate salt intake, avoiding medications that aggravate hypotension, or using compressive garments over the legs and abdomen) and pharmacologic measures. Physical activity and exercise should be encouraged to avoid deconditioning, which is known to exacerbate orthostatic intolerance, and volume repletion with fluids and salt is critical. There have been clinical studies that assessed the impact of an approach incorporating the aforementioned nonpharmacologic measures. Additionally, supine blood pressure tends to be much higher in these individuals, often requiring treatment of blood pressure at bedtime with shorter-acting drugs that also affect baroreceptor activity such as guanfacine or clonidine, shorter-acting calcium blockers (e.g., isradipine), or shorter-acting β-blockers such as atenolol or metoprolol tartrate. Alternatives can include enalapril if an individual is unable to tolerate preferred agents (64–66). Midodrine and droxidopa are approved by the FDA for the treatment of orthostatic hypotension.

Gastroparesis

Treatment for diabetic gastroparesis may be very challenging. A low-fiber, low-fat eating plan provided in small frequent meals with a greater proportion of liquid calories may be useful (67–69). In addition, foods with small particle size may improve key symptoms (70). Withdrawing drugs with adverse effects on

gastrointestinal motility, including opioids, anticholinergics, tricyclic antidepressants, GLP-1 RAs, and pramlintide, may also improve intestinal motility (67,71). However, the risk of removal of GLP-1 RAs should be balanced against their potential benefits. In cases of severe gastroparesis, pharmacologic interventions are needed. Only metoclopramide, a prokinetic agent, is approved by the FDA for the treatment of gastroparesis. However, the level of evidence regarding the benefits of metoclopramide for the management of gastroparesis is weak, and given the risk for serious adverse effects (extrapyramidal signs such as acute dystonic reactions, drug-induced parkinsonism, akathisia, and tardive dyskinesia), its use in the treatment of gastroparesis beyond 12 weeks is no longer recommended by the FDA. It should be reserved for severe cases that are unresponsive to other therapies (71). Other treatment options include domperidone (available outside the U.S.) and erythromycin, which is only effective for short-term use due to tachyphylaxis (72,73). Gastric electrical stimulation using a surgically implantable device has received approval from the FDA, although its efficacy is variable and use is limited to individuals with severe symptoms that are refractory to other treatments (74).

Erectile Dysfunction

In addition to treatment of hypogonadism if present, treatments for erectile dysfunction may include phosphodiesterase type 5 inhibitors, intracorporeal or intraurethral prostaglandins, vacuum devices, or penile prostheses. As with DPN treatments, these interventions do not change the underlying pathology and natural history of the disease process but may improve a person's quality of life.

FOOT CARE

Recommendations

12.21 Perform a comprehensive foot evaluation at least annually to identify risk factors for ulcers and amputations. **A**

12.22 The examination should include inspection of the skin, assessment of foot deformities, neurological assessment (10-g monofilament testing with at least one other assessment: pinprick, temperature, vibration), and vascular assessment, including pulses in the legs and feet. **B**

12.23 Individuals with evidence of sensory loss or prior ulceration or amputation should have their feet inspected at every visit. **A**

12.24 Obtain a prior history of ulceration, amputation, Charcot foot, angioplasty or vascular surgery, cigarette smoking, retinopathy, and renal disease and assess current symptoms of neuropathy (pain, burning, numbness) and vascular disease (leg fatigue, claudication). **B**

12.25 Initial screening for peripheral arterial disease should include assessment of lower-extremity pulses, capillary refill time, rubor on dependency, pallor on elevation, and venous filling time. Individuals with a history of leg fatigue, claudication, and rest pain relieved with dependency or decreased or absent pedal pulses should be referred for ankle–brachial index and for further vascular assessment as appropriate. **B**

12.26 A multidisciplinary approach is recommended for individuals with foot ulcers and high-risk feet (e.g., those on dialysis, those with Charcot foot, those with a history of prior ulcers or amputation, and those with peripheral arterial disease). **B**

12.27 Refer individuals who smoke and have a history of prior lower-extremity complications, loss of protective sensation, structural abnormalities, or peripheral arterial disease to foot care specialists for ongoing preventive care and lifelong surveillance. **B**

12.28 Provide general preventive foot self-care education to all people with diabetes, including those with loss of protective sensation, on appropriate ways to examine their feet (palpation or visual inspection with an unbreakable mirror) for daily surveillance of early foot problems. **B**

12.29 The use of specialized therapeutic footwear is recommended for people with diabetes at high risk for ulceration, including those with loss of protective sensation, foot deformities, ulcers, callous formation, poor peripheral circulation, or history of amputation. **B**

12.30 For chronic diabetic foot ulcers that have failed to heal with optimal standard care alone, adjunctive treatment with randomized controlled trial–proven advanced agents should be considered. Considerations might include negative-pressure wound therapy, placental membranes, bioengineered skin substitutes, several acellular matrices, autologous fibrin and leukocyte platelet patches, and topical oxygen therapy. **A**

Foot ulcerations and amputations are common complications associated with diabetes. These may be the consequences of several factors, including peripheral neuropathy, peripheral arterial disease (PAD), and foot deformities. They represent major causes of morbidity and mortality in people with diabetes. Early recognition of at-risk feet, preulcerative lesions, and prompt treatment of ulcerations and other lower-extremity complications can delay or prevent adverse outcomes.

Early recognition requires an understanding of those factors that put people with diabetes at increased risk for ulcerations and amputations. Factors that are associated with the at-risk foot include the following:

- Poor glycemic control
- Peripheral neuropathy/LOPS
- PAD
- Foot deformities (bunions, hammertoes, Charcot joint, etc.)
- Preulcerative corns or calluses
- Prior ulceration
- Prior amputation
- Smoking
- Retinopathy
- Nephropathy (particularly individuals on dialysis or posttransplant)

Identifying the at-risk foot begins with a detailed history documenting diabetes control, smoking history, exercise tolerance, history of claudication or rest pain, and prior ulcerations or amputations. A thorough examination of the feet should be performed annually in all people with diabetes and more frequently in at-risk individuals (75). The examination should include assessment of skin integrity, assessment for LOPS using the 10-g monofilament along with at least one other neurological assessment tool, pulse examination of the dorsalis pedis and posterior tibial arteries, and assessment for foot deformities such as bunions, hammertoes, and prominent metatarsals, which increase plantar foot pressures and increase risk for ulcerations. At-risk individuals should be assessed at each visit and should be referred to foot care specialists for ongoing preventive care and surveillance. The physical examination can stratify patients into different categories and determine the frequency of these visits (76) (**Table 12.1**).

Evaluation for Loss of Protective Sensation

The presence of peripheral sensory neuropathy is the single most common component cause for foot ulceration. In a multicenter trial, peripheral neuropathy was found to be a component cause in 78% of people with diabetes with ulcerations and that the triad of peripheral sensory neuropathy, minor trauma, and foot deformity was present in >63% of participants (77). All people with diabetes should undergo a comprehensive foot examination at least annually, or more frequently for those in higher-risk categories (75,76).

LOPS is vital to risk assessment. One of the most useful tests to determine LOPS is the 10-g monofilament test. Studies have shown that clinical examination and the 10-g monofilament test are the two most sensitive tests in identifying the foot at risk for ulceration (78). The monofilament test should be performed with at least one other neurologic assessment tool (e.g., pinprick, temperature perception, ankle reflexes, or vibratory perception with a 128-Hz tuning fork or similar device). Absent monofilament sensation and one other abnormal test confirms the presence of LOPS. Further neurological testing, such as nerve conduction, electromyography, nerve biopsy, or intraepidermal nerve fiber density biopsies, are rarely indicated for the diagnosis of peripheral sensory neuropathy (42).

Evaluation for Peripheral Arterial Disease

Initial screening for PAD should include a history of leg fatigue, claudication, and rest pain relieved with dependency. Physical examination for PAD should include assessment of lower-extremity pulses, capillary refill time, rubor on dependency, pallor on elevation, and venous filling time (75,79). Any patient exhibiting signs and symptoms of PAD should be referred for noninvasive arterial studies in the form of Doppler ultrasound with pulse volume recordings. While ankle–brachial indices will be calculated, they should be interpreted carefully, as they are known to be inaccurate in people with diabetes due to noncompressible vessels. Toe systolic blood pressure tends to be more accurate. Toe systolic blood pressures <30 mmHg are suggestive of PAD and an inability to heal foot ulcerations (80). Individuals with abnormal pulse volume recording tracings and toe pressures <30 mmHg with foot ulcers should be referred for immediate vascular evaluation. Due to the high prevalence of PAD in people with diabetes, it has been recommended by the Society for Vascular Surgery and the American Podiatric Medical Association in their 2016 guidelines that all people with diabetes >50 years of age should undergo screening via noninvasive arterial studies (79,81). If normal, these should be repeated every 5 years (79).

Patient Education

All people with diabetes (and their families), particularly those with the aforementioned high-risk conditions, should receive general foot care education, including appropriate management strategies (82–84). This education should be provided to all newly diagnosed people with diabetes as part of an annual comprehensive examination and to individuals with high-risk conditions at every visit. Recent studies have shown that while education improves knowledge of diabetic foot problems and self-care of the foot, it does not improve behaviors associated with active participation in their overall diabetes care and to achieve personal health goals (85). Evidence also suggests that while patient and family education are important, the knowledge is quickly forgotten and needs to be reinforced regularly (86).

Table 12.1—International Working Group on the Diabetic Foot risk stratification system and corresponding foot screening frequency

Category	Ulcer risk	Characteristics	Examination frequency*
0	Very low	No LOPS and No PAD	Annually
1	Low	LOPS or PAD	Every 6–12 months
2	Moderate	LOPS + PAD, or LOPS + foot deformity, or PAD + foot deformity	Every 3–6 months
3	High	LOPS or PAD and one or more of the following: • History of foot ulcer • Amputation (minor or major) • End-stage renal disease	Every 1–3 months

Adapted with permission from Schaper et al. (76). LOPS, loss of protective sensation; PAD, peripheral artery disease. *Examination frequency suggestions are based on expert opinion and patient-centered requirements.

Individuals considered at risk should understand the implications of foot deformities, LOPS, and PAD; the proper care of the foot, including nail and skin care; and the importance of foot inspections on a daily basis. Individuals with LOPS should be educated on appropriate ways to examine their feet (palpation or visual inspection with an unbreakable mirror) for daily surveillance of early foot problems. Patients should also be educated on the importance of referrals to foot care specialists. A recent study showed that people with diabetes and foot disease lacked awareness of their risk status and why they were being referred to a multidisciplinary team of foot care specialists. Further, they exhibited a variable degree of interest in learning further about foot complications (87).

Patients' understanding of these issues and their physical ability to conduct proper foot surveillance and care should be assessed. Those with visual difficulties, physical constraints preventing movement, or cognitive problems that impair their ability to assess the condition of the foot and to institute appropriate responses will need other people, such as family members, to assist with their care.

The selection of appropriate footwear and footwear behaviors at home should also be discussed (e.g., no walking barefoot, avoiding open-toed shoes). Therapeutic footwear with custom-made orthotic devices have been shown to reduce peak plantar pressures (84). Most studies use reduction in peak plantar pressures as an outcome as opposed to ulcer prevention. Certain design features of the orthoses, such as rocker soles and metatarsal accommodations, can reduce peak plantar pressures more significantly than insoles alone. A systematic review, however, showed there was no significant reduction in ulcer incidence after 18 months compared with standard insoles and extra-depth shoes. Further, it was also noted that evidence to prevent first ulcerations was nonexistent (88).

Treatment

Treatment recommendations for people with diabetes will be determined by their risk category. No-risk or low-risk individuals can often be managed with education and self-care. People in the moderate- to high-risk category should be referred to foot care specialists for further evaluation and regular surveillance as outlined in **Table 12.1**. This includes individuals with LOPS, PAD, and/or structural foot deformities, such as Charcot foot, bunions, or hammertoes. Individuals with any open ulceration or unexplained swelling, erythema, or increased skin temperature should be referred urgently to a foot care specialist or multidisciplinary team.

Initial treatment recommendations should include daily foot inspection, use of moisturizers for dry, scaly skin, and avoidance of self-care of ingrown nails and calluses. Well-fitted athletic or walking shoes with customized pressure-relieving orthoses should be part of initial recommendations for people with increased plantar pressures (as demonstrated by plantar calluses). Individuals with deformities such as bunions or hammertoes may require specialized footwear such as extra-depth shoes. Those with even more significant deformities, as in Charcot joint disease, may require custom-made footwear.

Special consideration should be given to individuals with neuropathy who present with a warm, swollen, red foot with or without a history of trauma and without an open ulceration. These individuals require a thorough workup for possible Charcot neuroarthropathy (89). Early diagnosis and treatment of this condition is of paramount importance in preventing deformities and instability that can lead to ulceration and amputation. These individuals require total non–weight-bearing and urgent referral to a foot care specialist for further management. Foot and ankle X-rays should be performed in all individuals presenting with the above clinical findings.

There have been a number of developments in the treatment of ulcerations over the years (90). These include negative-pressure therapy, growth factors, bioengineered tissue, acellular matrix tissue, stem cell therapy, hyperbaric oxygen therapy, and, most recently, topical oxygen therapy (91–93). While there is literature to support many modalities currently used to treat diabetic foot wounds, robust randomized controlled trials (RCTs) are often lacking. However, it is agreed that the initial treatment and evaluation of ulcerations include the following five basic principles of ulcer treatment:

- Offloading of plantar ulcerations
- Debridement of necrotic, nonviable tissue
- Revascularization of ischemic wounds when necessary
- Management of infection: soft tissue or bone
- Use of physiologic, topical dressings

However, despite following the above principles, some ulcerations will become chronic and fail to heal. In those situations, advanced wound therapy can play a role. When to employ advanced wound therapy has been the subject of much discussion, as the therapy is often quite expensive. It has been determined that if a wound fails to show a reduction of 50% or more after 4 weeks of appropriate wound management (i.e., the five basic principles above), consideration should be given to the use of advanced wound therapy (94). Treatment of these chronic wounds is best managed in a multidisciplinary setting.

Evidence to support advanced wound therapy is challenging to produce and to assess. Randomization of trial participants is difficult, as there are many variables that can affect wound healing. In addition, many RCTs exclude certain cohorts of people, e.g., individuals with chronic renal disease or those on dialysis. Finally, blinding of participants and clinicians is not always possible. Meta-analyses and systematic reviews of observational studies are used to determine the clinical effectiveness of these modalities. Such studies can augment formal RCTs by including a greater variety of participants in various clinical settings who are typically excluded from the more rigidly structured clinical trials.

Advanced wound therapy can be categorized into nine broad categories (90) (**Table 12.2**). Topical growth factors, acellular matrix tissues, and bioengineered cellular therapies are commonly employed in offices and wound care centers to expedite healing of chronic, more superficial ulcerations. Numerous clinical reports and retrospective studies have demonstrated the clinical effectiveness of each of these modalities. Over the years, there has been increased evidence to support the use of these modalities.

Table 12.2—Categories of advanced wound therapies

Negative-pressure wound therapy
Standard electrically powered
Mechanically powered
Oxygen therapies
Hyperbaric oxygen therapy
Topical oxygen therapy
Oxygen-releasing sprays, dressings
Biophysical
Electrical stimulation, diathermy
Pulsed electromagnetic fields, pulsed radiofrequency energy
Low-frequency noncontact ultrasound
Extracorporeal shock wave therapy
Growth factors
Becaplermin: platelet-derived growth factor
Fibroblast growth factor
Epidermal growth factor
Autologous blood products
Platelet-rich plasma
Leukocyte, platelet, fibrin multilayered patches
Whole blood clot
Acellular matrix tissues
Xenograft dermis
Bovine dermis
Xenograft acellular matrices
Small intestine submucosa
Porcine urinary bladder matrix
Ovine forestomach
Equine pericardium
Bovine collagen
Bilayered dermal regeneration matrix
Human dermis products
Human pericardium
Placental tissues
Amniotic tissues/amniotic fluid
Umbilical cord
Bioengineered allogeneic cellular therapies
Bilayered skin equivalent (human keratinocytes and fibroblasts)
Dermal replacement therapy (human fibroblasts)
Stem cell therapies
Autogenous: bone marrow–derived stem cells
Allogeneic: amniotic matrix with mesenchymal stem cells
Miscellaneous active dressings
Hyaluronic acid, honey dressings, etc.
Sucrose octasulfate dressing

Adapted with permission from Frykberg and Banks (90).

Nonetheless, use of those products or agents with robust RCTs or systematic reviews should generally be preferred over those without level 1 evidence (**Table 12.2**).

Negative-pressure wound therapy was first introduced in the early to mid-1990s. It has become especially useful in wound preparation for skin grafts and flaps and assists in the closure of deep, large wounds (95,96). A variety of types exist in the marketplace and range from electrically powered to mechanically powered in different sizes depending upon the specific wound requirements.

Electrical stimulation, pulsed radiofrequency energy, and extracorporeal shockwave therapy are biophysical modalities that are believed to upregulate growth factors or cytokines to stimulate wound healing, while low-frequency noncontact ultrasound is used to debride wounds. However, most of the studies advocating the use of these modalities have been retrospective observational or poor-quality RCTs.

Hyperbaric oxygen therapy is the delivery of oxygen through a chamber, either individual or multiperson, with the intention of increasing tissue oxygenation to increase tissue perfusion and neovascularization, combat resistant bacteria, and stimulate wound healing. While there had been great interest in this modality being able to expedite healing of chronic diabetic foot ulcers (DFUs), there has only been one positive RCT published in the last decade that reported increased healing rates at 9 and 12 months compared with control subjects (97). More recent studies with significant design deficiencies and participant dropouts have failed to provide corroborating evidence that hyperbaric oxygen therapy should be widely used for managing nonhealing DFUs (98,99). While there may be some benefit in prevention of amputation in selected chronic neuroischemic ulcers, recent studies have shown no benefit in healing DFUs in the absence of ischemia and/or infection (93,100).

Topical oxygen therapy has been studied rather vigorously in recent years, with several high-quality RCTs and at least five systematic reviews and meta-analyses all supporting its efficacy in healing chronic DFUs at 12 weeks (19,20,30–34,91,92,101–105). Three types of topical oxygen devices are available, including continuous-delivery, low-constant-pressure, and cyclical-pressure modalities. Importantly, topical oxygen therapy devices provide for home-based therapy rather than the need for daily visits to specialized centers. Very high participation with very few reported adverse events combined with improved healing rates makes this therapy another attractive option for advanced wound care.

If DFUs fail to heal despite appropriate wound care, adjunctive advanced therapies should be instituted and are best managed in a multidisciplinary manner. Once healed, all individuals should be enrolled in a formal comprehensive prevention program focused on reducing the incidence of recurrent ulcerations and subsequent amputations (75,106,107).

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13. Older Adults: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Recommendations

13.1 Consider the assessment of medical, psychological, functional (self-management abilities), and social domains in older adults to provide a framework to determine targets and therapeutic approaches for diabetes management. **B**

13.2 Screen for geriatric syndromes (i.e., polypharmacy, cognitive impairment, depression, urinary incontinence, falls, persistent pain, and frailty) in older adults, as they may affect diabetes self-management and diminish quality of life. **B**

Diabetes is a highly prevalent health condition in the aging population. Over one-quarter of people over the age of 65 years have diabetes, and one-half of older adults have prediabetes (1,2), and the number of older adults living with these conditions is expected to increase rapidly in the coming decades. Diabetes in older adults is also a highly heterogeneous condition. While type 2 diabetes predominates in the older population as much as in the younger population, improvements in insulin delivery, technology, and care over the last few decades have led to increasing numbers of people with childhood and adult-onset type 1 diabetes surviving and thriving into their later decades. Diabetes management in older adults requires regular assessment of medical, psychological, functional, and social domains. When assessing older adults with diabetes, it is important to accurately categorize the type of diabetes as well as other factors, including diabetes duration, the presence of complications, and treatment-related concerns, such as fear of hypoglycemia. Screening for diabetes complications in older adults should be individualized and periodically revisited, as the results of screening tests may impact targets and therapeutic approaches (3–5). Older adults with diabetes have higher rates of premature death, functional disability, accelerated muscle loss, and coexisting illnesses, such as hypertension, coronary heart disease, and stroke, than those

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without diabetes. At the same time, older adults with diabetes are also at greater risk than other older adults for several common geriatric syndromes, such as polypharmacy, cognitive impairment, depression, urinary incontinence, injurious falls, persistent pain, and frailty (1). These conditions may impact older adults' diabetes self-management abilities and quality of life if left unaddressed (2,6,7). See Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities," for the full range of issues to consider when caring for older adults with diabetes.

The comprehensive assessment described above may provide a framework to determine targets and therapeutic approaches (8–10), including whether referral for diabetes self-management education is appropriate (when complicating factors arise or when transitions in care occur) or whether the current plan is too complex for the individual's self-management ability or the caregivers providing care (11). Particular attention should be paid to complications that can develop over short periods of time and/or would significantly impair functional status, such as visual and lower-extremity complications. Please refer to the American Diabetes Association (ADA) consensus report "Diabetes in Older Adults" for details (3).

NEUROCOGNITIVE FUNCTION

Recommendation

13.3 Screening for early detection of mild cognitive impairment or dementia should be performed for adults 65 years of age or older at the initial visit, annually, and as appropriate. **B**

Older adults with diabetes are at higher risk of cognitive decline and institutionalization (12,13). The presentation of cognitive impairment ranges from subtle executive dysfunction to memory loss and overt dementia. People with diabetes have higher incidences of all-cause dementia, Alzheimer disease, and vascular dementia than people with normal glucose tolerance (14). The effects of hypoglycemia, hyperglycemia, and hyperinsulinemia on the brain are areas of intense research. Poor glycemic control is associated with a decline in cognitive function (15,16), and longer duration of diabetes is associated with worsening cognitive function. There are ongoing studies evaluating whether preventing or delaying diabetes onset may help to maintain cognitive function in older adults. However, studies examining the effects of intensive glycemic and blood pressure control to achieve specific targets have not demonstrated a reduction in brain function decline (17,18).

Clinical trials of specific interventions—including cholinesterase inhibitors and glutamatergic antagonists—have not shown positive therapeutic benefit in maintaining or significantly improving cognitive function or in preventing cognitive decline (19). Pilot studies in individuals with mild cognitive impairment evaluating the potential benefits of intranasal insulin therapy and metformin therapy provide insights for future clinical trials and mechanistic studies (20–23).

Despite the paucity of therapies to prevent or remedy cognitive decline, identifying cognitive impairment early has important implications for diabetes care. The presence of cognitive impairment can make it challenging for clinicians to help their patients reach individualized glycemic, blood pressure, and lipid targets. Cognitive dysfunction makes it difficult for individuals to perform complex self-care tasks (24), such as monitoring glucose and adjusting insulin doses. It also hinders their ability to appropriately maintain the timing of meals and content of the diet. When clinicians are providing care for people with cognitive dysfunction, it is critical to simplify care plans and to facilitate and engage the appropriate support structure to assist individuals in all aspects of care.

Older adults with diabetes should be carefully screened and monitored for cognitive impairment (2). Several simple assessment tools are available to screen for cognitive impairment (24,25), such as the Mini-Mental State Examination (26), Mini-Cog (27), and the Montreal Cognitive Assessment (28), which may help to identify individuals requiring neuropsychological evaluation, particularly those in whom dementia is suspected (i.e., experiencing memory loss and decline in their basic and instrumental activities of daily living). Annual screening is indicated for adults 65 years of age or older for early detection of mild cognitive impairment or dementia (4,29). Screening for cognitive impairment should additionally be considered when an individual presents with a significant decline in clinical status due to increased problems with self-care activities, such as errors in calculating insulin dose, difficulty counting carbohydrates, skipped meals, skipped insulin doses, and difficulty recognizing, preventing, or treating hypoglycemia. People who screen positive for cognitive impairment should receive diagnostic assessment as appropriate, including referral to a behavioral health professional for formal cognitive/neuropsychological evaluation (30).

HYPOGLYCEMIA

Recommendations

13.4 Because older adults with diabetes have a greater risk of hypoglycemia than younger adults, episodes of hypoglycemia should be ascertained and addressed at routine visits. **B**

13.5 For older adults with type 1 diabetes, continuous glucose monitoring is recommended to reduce hypoglycemia. **A**

13.6 For older adults with type 2 diabetes on multiple daily doses of insulin, continuous glucose monitoring should be considered to improve glycemic outcomes and decrease glucose variability. **B**

13.7 For older adults with type 1 diabetes, consider the use of automated insulin delivery systems **B** and other advanced insulin delivery devices such as connected pens **E** to reduce risk of hypoglycemia, based on individual ability.

Older adults are at higher risk of hypoglycemia for many reasons, including insulin deficiency necessitating insulin therapy and progressive renal insufficiency (31). As described above, older adults have higher rates of unidentified cognitive impairment and dementia, leading to difficulties in adhering to complex self-care activities (e.g., glucose monitoring, insulin dose adjustment). Cognitive decline has been associated with increased risk of hypoglycemia,

and conversely, severe hypoglycemia has been linked to increased risk of dementia (32,33). Therefore, as discussed in Recommendation 13.3, it is important to routinely screen older adults for cognitive impairment and dementia and discuss findings with the patients and their caregivers.

People with diabetes and their caregivers should be routinely queried about hypoglycemia (e.g., selected questions from the Diabetes Care Profile) (34) and hypoglycemia unawareness (35). Older adults can also be stratified for future risk for hypoglycemia with validated risk calculators (e.g., Kaiser Hypoglycemia Model) (36). An important step to mitigate hypoglycemia risk is to determine whether the person with diabetes is skipping meals or inadvertently repeating doses of their medications. Glycemic targets and pharmacologic treatments may need to be adjusted to minimize the occurrence of hypoglycemic events (2). This recommendation is supported by results from multiple randomized controlled trials, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study and the Veterans Affairs Diabetes Trial (VADT), which showed that intensive treatment protocols targeting A1C <6.0% with complex drug regimens significantly increased the risk for hypoglycemia requiring assistance compared with standard treatment (37,38). However, these intensive treatment plans included extensive use of insulin and minimal use of glucagon-like peptide 1 (GLP-1) receptor agonists, and they preceded the availability of sodium–glucose cotransporter 2 (SGLT2) inhibitors.

For older people with type 1 diabetes, continuous glucose monitoring (CGM) is a useful approach to predicting and reducing the risk of hypoglycemia (39). In the Wireless Innovation in Seniors with Diabetes Mellitus (WISDM) trial, adults over 60 years of age with type 1 diabetes were randomized to CGM or standard blood glucose monitoring. Over 6 months, use of CGM resulted in a small but statistically significant reduction in time spent with hypoglycemia (glucose level <70 mg/dL) compared with standard blood glucose monitoring (adjusted treatment difference −1.9% [−27 min/day]; 95% CI −2.8% to −1.1% [−40 to −16 min/day]; $P < 0.001$) (40,41). Among secondary outcomes, glycemic variability was reduced with CGM, as reflected by an 8% (95% CI 6.0–11.5) increase in time spent in range between 70 and 180 mg/dL. A 6-month extension of the trial demonstrated that these benefits were sustained for up to a year (42). These and other short-term trials are supported by observational data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study indicating that among older adults (mean age 58 years) with long-standing type 1 diabetes, routine CGM and insulin pump use was associated with fewer hypoglycemic events and hyperglycemic excursions and lower A1C levels (43). While the current evidence base for older adults is primarily in type 1 diabetes, the evidence demonstrating the clinical benefits of CGM for people with type 2 diabetes using insulin is growing (44) (see Section 7, "Diabetes Technology"). The DIAMOND (Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes) study demonstrated that in adults ≥60 years of age with either type 1 or type 2 diabetes using multiple daily injections, CGM use was associated with improved A1C and reduced glycemic variability (45). Another population for which CGM may play an increasing role is older adults with physical or cognitive limitations who require monitoring of blood glucose by a surrogate.

The availability of accurate CGM devices that can communicate with insulin pumps through Bluetooth has enabled the development of advanced insulin delivery algorithms for pumps. These algorithms fall into two categories: predictive low-glucose suspend algorithms that automatically shut off insulin delivery if a hypoglycemic event is imminent and hybrid closed-loop algorithms that automatically adjust insulin infusion rates based on feedback from a CGM to keep glucose levels in a target range. Advanced insulin delivery devices have been shown to improve glycemic outcomes in both children and adults with type 1 diabetes. Most trials of these devices have included a broad range of people with type 1 diabetes but relatively few older adults. Recently, two small randomized controlled trials in older adults have been published. The Older Adult Closed Loop (ORACL) trial in 30 older adults (mean age 67 years) with type 1 diabetes found that a hybrid closed-loop insulin delivery strategy was associated with significant improvements in time in range compared with sensor-augmented pump therapy (46). Moreover, they found small but significant decreases in hypoglycemia with the hybrid closed-loop strategy. Boughton et al. (47) reported results of an open-label, crossover design clinical trial in 37 older adults (≥60 years) in which 16 weeks of treatment with a hybrid closed-loop advanced insulin delivery system was compared with sensor-augmented pump therapy. They found that hybrid closed-loop insulin delivery improved the proportion of time glucose was in range largely due to decreases in hyperglycemia. In contrast to the ORACL study, no significant differences in hypoglycemia were observed. Both studies enrolled older individuals whose blood glucose was relatively well managed (mean A1C ∼7.4%), and both used a crossover design comparing hybrid closed-loop insulin delivery to sensor-augmented pump therapy. These trials provide the first evidence that older individuals with long-standing type 1 diabetes can successfully use advanced insulin delivery technologies to improve glycemic outcomes, as has been seen in younger populations. Use of such technologies should be periodically reassessed, as the burden may outweigh the benefits in those with declining cognitive or functional status.

TREATMENT GOALS

Recommendations

13.8 Older adults who are otherwise healthy with few coexisting chronic illnesses and intact cognitive function and functional status should have lower glycemic goals (such as A1C <7.0–7.5% [53–58 mmol/mol]), while those with multiple coexisting chronic illnesses, cognitive impairment, or functional dependence should have less-stringent glycemic goals (such as A1C <8.0% [64 mmol/mol]). **C**

13.9 Glycemic goals for some older adults might reasonably be relaxed as part of individualized care, but hyperglycemia leading to symptoms or risk of acute hyperglycemia complications should be avoided in all people with diabetes. **C**

13.10 Screening for diabetes complications should be individualized in older adults. Particular attention should be paid to complications that would lead to functional impairment. **C**

13.11 Treatment of hypertension to individualized target levels is indicated in most older adults. **C**

13.12 Treatment of other cardiovascular risk factors should be individualized in older adults considering the time frame of benefit. Lipid-lowering therapy and aspirin therapy may benefit those with life expectancies at least equal to the time frame of primary prevention or secondary intervention trials. **E**

The care of older adults with diabetes is complicated by their clinical, cognitive, and functional heterogeneity. Some older individuals may have developed diabetes years earlier and have significant complications, others are newly diagnosed and may have had years of undiagnosed diabetes with resultant complications, and still, other older adults may have truly recent-onset disease with few or no complications (48). Some older adults with diabetes have other underlying chronic conditions, substantial diabetes-related comorbidity, limited cognitive or physical functioning, or frailty (49,50). Other older individuals with diabetes have little comorbidity and are active. Life expectancies are highly variable but are often longer than clinicians realize. Multiple prognostic tools for life expectancy for older adults are available (51), including tools specifically designed for older adults with diabetes (52). Older patients also vary in their preferences for the intensity and mode of glucose control (53). Health care professionals caring for older adults with diabetes must take this heterogeneity into consideration when setting and prioritizing treatment goals (9,10) (**Table 13.1**). In addition, older adults with diabetes should be assessed for disease treatment and self-management knowledge, health literacy, and mathematical literacy (numeracy) at the onset of treatment. See **Fig. 6.2** for patient/disease-related factors to consider when determining individualized glycemic targets.

A1C may have limitations in those who have medical conditions that impact red blood cell turnover (see Section 2, "Classification and Diagnosis of Diabetes," for additional details on the limitations of A1C) (54). Many conditions associated with increased red blood cell turnover, such as hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, are commonly seen in older adults and can falsely increase or decrease A1C. In these instances, plasma blood glucose fingerstick and sensor glucose readings should be used for goal setting (**Table 13.1**).

Older Adults With Good Functional Status and Without Complications

There are few long-term studies in older adults demonstrating the benefits of intensive glycemic, blood pressure, and lipid control. Older adults who can be expected to live long enough to realize the benefits of long-term intensive diabetes management, who have good cognitive and physical function, and who choose to do so via shared decision-making may be treated using therapeutic interventions and goals similar to those for younger adults with diabetes (**Table 13.1**).

As for all people with diabetes, diabetes self-management education and ongoing diabetes self-management support are vital components of diabetes care for older adults and their caregivers. Self-management knowledge and skills should be reassessed when treatment plan changes are made or an individual's functional abilities diminish. In addition, declining or impaired ability to perform diabetes self-care behaviors may be an indication that an older person with diabetes needs a referral for cognitive and physical functional assessment, using age-normalized evaluation tools, as well as help establishing a support structure for diabetes care (3,30).

Patients With Complications and Reduced Functionality

For people with advanced diabetes complications, life-limiting comorbid illnesses, or substantial cognitive or functional impairments, it is reasonable to set less-intensive glycemic goals (**Table 13.1**). Factors to consider in individualizing glycemic goals are outlined in **Fig. 6.2**. Based on concepts of competing mortality and time to benefit, people with advanced diabetes complications are less likely to benefit from reducing the risk of microvascular complications (55). In addition, they are more likely to suffer serious adverse effects of therapeutics, such as hypoglycemia (56). However, those with poorly managed diabetes may be subject to acute complications of diabetes, including dehydration, poor wound healing, and hyperglycemic hyperosmolar coma. Glycemic goals should, at a minimum, avoid these consequences.

While **Table 13.1** provides overall guidance for identifying complex and very complex patients, there is not yet global consensus on geriatric patient classification. Ongoing empiric research on the classification of older adults with diabetes based on comorbid illness has repeatedly found three major classes of patients: a healthy, a geriatric, and a cardiovascular class (9,57). The geriatric class has the highest prevalence of obesity, hypertension, arthritis, and incontinence, and the cardiovascular class has the highest prevalence of myocardial infarctions, heart failure, and stroke. Compared with the healthy class, the cardiovascular class has the highest risk of frailty and subsequent mortality. Additional research is needed to develop a reproducible classification scheme to distinguish the natural history of disease as well as differential response to glucose control and specific glucose-lowering agents (58).

Vulnerable Patients at the End of Life

For people with diabetes receiving palliative care and end-of-life care, the focus should be to avoid hypoglycemia and symptomatic hyperglycemia while reducing the burdens of glycemic management. Thus, as organ failure develops, several agents will have to be deintensified or discontinued. For a dying person, most agents for type 2 diabetes may be removed (59). There is, however, no consensus for the management of type 1 diabetes in this scenario (60). See the section END-OF-LIFE CARE below for additional information.

Beyond Glycemic Management

Although minimizing hyperglycemia may be important in older individuals with diabetes, greater reductions in

Table 13.1—Framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes

Patient characteristics/ health status	Rationale	Reasonable A1C goal‡	Fasting or preprandial glucose	Bedtime glucose	Blood pressure	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.0–7.5% (53–58 mmol/mol)	80–130 mg/dL (4.4–7.2 mmol/L)	80–180 mg/dL (4.4–10.0 mmol/L)	<130/80 mmHg	Statin, unless contraindicated or not tolerated
Complex/intermediate (multiple coexisting chronic illnesses* or two or more instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0% (64 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L)	<130/80 mmHg	Statin, unless contraindicated or not tolerated
Very complex/poor health (LTC or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or two or more ADL impairments)	Limited remaining life expectancy makes benefit uncertain	Avoid reliance on A1C; glucose control decisions should be based on avoiding hypoglycemia and symptomatic hyperglycemia	100–180 mg/dL (5.6–10.0 mmol/L)	110–200 mg/dL (6.1–11.1 mmol/L)	<140/90 mmHg	Consider likelihood of benefit with statin

This table represents a consensus framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes. The patient characteristic categories are general concepts. Not every patient will clearly fall into a particular category. Consideration of patient and caregiver preferences is an important aspect of treatment individualization. Additionally, a patient's health status and preferences may change over time. ADL, activities of daily living; LTC, long-term care. ‡A lower A1C goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden. *Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. "Multiple" means at least three, but many patients may have five or more (66). **The presence of a single end-stage chronic illness, such as stage 3–4 heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy. Adapted from Kirkman et al. (3).

morbidity and mortality are likely to result from a clinical focus on comprehensive cardiovascular risk factor modification. There is strong evidence from clinical trials of the value of treating hypertension in older adults (61,62), with treatment of hypertension to individualized target levels indicated in most. There is less evidence for lipid-lowering therapy and aspirin therapy, although the benefits of these interventions for primary and secondary prevention are likely to apply to older adults whose life expectancies equal or exceed the time frames of the clinical trials (63). In the case of statins, the follow-up time of clinical trials ranged from 2 to 6 years. While the time frame of trials can be used to inform treatment decisions, a more specific concept is the time to benefit for a therapy. For statins, a meta-analysis of the previously mentioned trials showed that the time to benefit is 2.5 years (64).

LIFESTYLE MANAGEMENT

Recommendations

13.13 Optimal nutrition and protein intake is recommended for older adults; regular exercise, including aerobic activity, weight-bearing exercise, and/or resistance training, should be encouraged in all older adults who can safely engage in such activities. **B**

13.14 For older adults with type 2 diabetes, overweight/obesity, and capacity to safely exercise, an intensive lifestyle intervention focused on dietary changes, physical activity, and modest weight loss (e.g., 5–7%) should be considered for its benefits on quality of life, mobility and physical functioning, and cardiometabolic risk factor control. **A**

Lifestyle management in older adults should be tailored to frailty status. Diabetes in the aging population is associated with reduced muscle strength, poor muscle quality, and accelerated loss of muscle mass, which may result in sarcopenia and/or osteopenia (65,66). Diabetes is also recognized as an independent risk factor for frailty. Frailty is characterized by decline in physical performance and an increased risk of poor health outcomes due to physiologic vulnerability and functional or psychosocial stressors. Inadequate nutritional intake, particularly inadequate protein intake, can increase the risk of sarcopenia and frailty in older adults. Management of frailty in diabetes includes optimal nutrition with adequate protein intake combined with an exercise program that includes aerobic, weight-bearing, and resistance training. The benefits of a structured exercise program (as in the Lifestyle Interventions and Independence for Elders [LIFE] study) in frail

older adults include reducing sedentary time, preventing mobility disability, and reducing frailty (67,68). The goal of these programs is not weight loss but enhanced functional status.

For nonfrail older adults with type 2 diabetes and overweight or obesity, an intensive lifestyle intervention designed to reduce weight is beneficial across multiple outcomes. The Look AHEAD (Action for Health in Diabetes) trial is described in Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes." Look AHEAD specifically excluded individuals with a low functional status. It enrolled people between 45 and 74 years of age and required that they be able to perform a maximal exercise test (69,70). While the Look AHEAD trial did not achieve its primary outcome of reducing cardiovascular events, the intensive lifestyle intervention had multiple clinical benefits that are important to the quality of life of older adults. Benefits included weight loss, improved physical fitness, increased HDL cholesterol, lowered systolic blood pressure, reduced A1C levels, reduced waist circumference, and reduced need for medications (71). Additionally, several subgroups, including participants who lost at least 10% of baseline body weight at year 1, had improved cardiovascular outcomes (72). Risk factor control was improved with reduced utilization of antihypertensive medications, statins, and insulin (73). In age-stratified analyses, older adults in the trial (60 to early 70s) had similar benefits compared with younger people (74,75). In addition, lifestyle intervention produced benefits on aging-relevant outcomes such as reductions in multimorbidity and improvements in physical function and quality of life (76–79).

PHARMACOLOGIC THERAPY

Recommendations

13.15 In older adults with type 2 diabetes at increased risk of hypoglycemia, medication classes with low risk of hypoglycemia are preferred. **B**

13.16 Overtreatment of diabetes is common in older adults and should be avoided. **B**

13.17 Deintensification of treatment goals is recommended to reduce the risk of hypoglycemia if it can be achieved within the individualized A1C target. **B**

13.18 Simplification of complex treatment plans (especially insulin) is recommended to reduce the risk of hypoglycemia and polypharmacy and decrease the burden of the disease if it can be achieved within the individualized A1C target. **B**

13.19 Consider costs of care and insurance coverage rules when developing treatment plans in order to reduce risk of cost-related barriers to adherence. **B**

Special care is required in prescribing and monitoring pharmacologic therapies in older adults (80). See **Fig. 9.3** for general recommendations regarding glucose-lowering treatment for adults with type 2 diabetes and **Table 9.2** for person- and drug-specific factors to consider when selecting glucose-lowering agents. Cost may be an especially important consideration, as older adults tend to be on many medications and live on fixed incomes (81). Accordingly, the costs of care and insurance coverage rules should be considered when developing treatment plans to reduce the risk of cost-related barriers to adherence (82,83). See **Table 9.3** and **Table 9.4** for median monthly cost in the U.S. of noninsulin glucose-lowering agents and insulin, respectively. It is important to match complexity of the treatment plan to the self-management ability of older adults with diabetes and their available social and medical support. Many older adults with diabetes struggle to maintain the frequent blood glucose monitoring and insulin injection regimens they previously followed, perhaps for many decades, as they develop medical conditions that may impair their ability to follow their treatment plan safely. Individualized glycemic goals should be established (**Fig. 6.2**) and periodically adjusted based on coexisting chronic illnesses, cognitive function, and functional status (2). Intensive glycemic control with regimens including insulin and sulfonylureas in older adults with complex or very complex medical conditions has been identified as overtreatment and found to be very common in clinical practice (84–88). Ultimately, the determination of whether a person is considered overtreated requires an elicitation of the person's perceptions of the current medication burden and preferences for treatments. For those seeking to simplify their diabetes regimen, deintensification of regimens in individuals taking noninsulin glucose-lowering medications can be achieved by either lowering the dose or discontinuing some medications, as long as the individualized glycemic targets are maintained (89). When older adults are found to have an insulin regimen with complexity beyond their self-management abilities, lowering the dose of insulin may not be adequate (90). Simplification of the insulin plan to match an individual's self-management abilities and their available social and medical support in these situations has been shown to reduce hypoglycemia and disease-related distress without worsening glycemic outcomes (91–94). **Figure 13.1** depicts an algorithm that can be used to simplify the insulin regimen (93). There are now multiple studies evaluating deintensification protocols in diabetes as well as hypertension, demonstrating that deintensification is safe and possibly beneficial for older adults (89). **Table 13.2** provides examples of and rationale for situations where deintensification and/or insulin regimen simplification may be appropriate in older adults.

Metformin

Metformin is the first-line agent for older adults with type 2 diabetes. Recent studies have indicated that it may be used safely in individuals with estimated glomerular filtration rate $\geq$30 mL/min/1.73 m^2 (95). However, it is contraindicated in those with advanced renal insufficiency and should be used with caution in those with impaired hepatic function or heart failure because of the increased risk of lactic acidosis. Metformin may be temporarily discontinued before procedures, during hospitalizations, and when acute illness may compromise renal or liver function. Additionally, metformin can cause gastrointestinal side effects and a reduction in appetite that can be problematic for some older adults. Reduction or elimination of metformin may be necessary for those experiencing persistent gastrointestinal side effects. For those taking metformin long-term, monitoring for

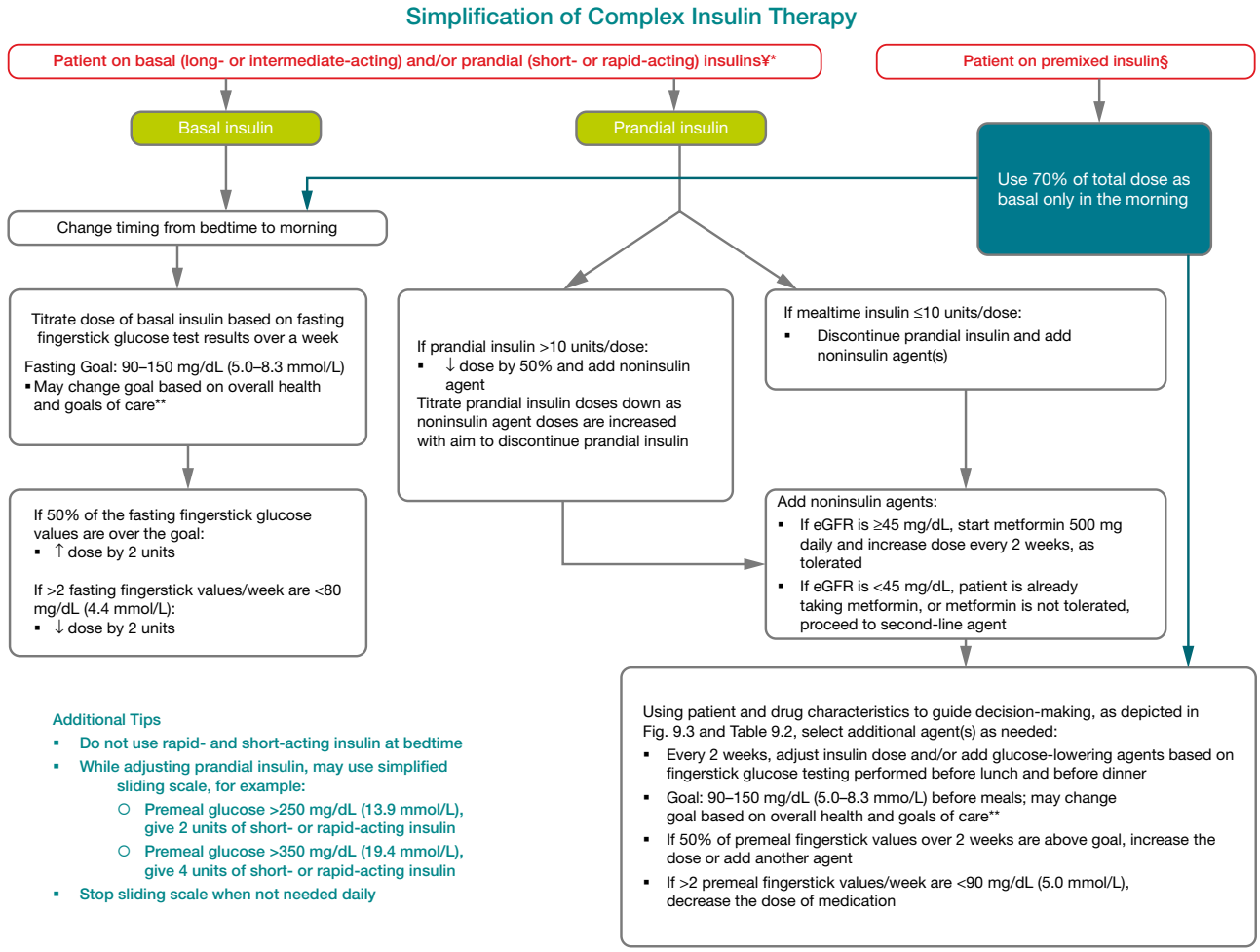

Figure 13.1—Algorithm to simplify insulin regimen for older adults with type 2 diabetes. eGFR, estimated glomerular filtration rate. *Basal insulins: glargine U-100 and U-300, detemir, degludec, and human NPH. **See **Table 13.1**. ¥Prandial insulins: short-acting (regular human insulin) or rapid-acting (lispro, aspart, and glulisine). §Premixed insulins: 70/30, 75/25, and 50/50 products. Adapted with permission from Munshi et al. (93).

vitamin B12 deficiency should be considered (96).

Thiazolidinediones

Thiazolidinediones, if used at all, should be used very cautiously in older adults on insulin therapy as well as in those with or at risk for heart failure, osteoporosis, falls or fractures, and/or macular edema (97,98). Lower doses of a thiazolidinedione in combination therapy may mitigate these side effects.

Insulin Secretagogues

Sulfonylureas and other insulin secretagogues are associated with hypoglycemia and should be used with caution. If used, sulfonylureas with a shorter duration of action, such as glipizide, are preferred. Glyburide is a longer-acting sulfonylurea and should be avoided in older adults (99).

Incretin-Based Therapies

Oral dipeptidyl peptidase 4 (DPP-4) inhibitors have few side effects and minimal risk of hypoglycemia, but their cost may be a barrier to some older adults. DPP-4 inhibitors do not reduce or increase major adverse cardiovascular outcomes (100). Across the trials of this drug class, there appears to be no interaction by age-group (101–103). A challenge of interpreting the age-stratified analyses of this drug class and other cardiovascular outcomes trials is that while most of these analyses were prespecified, they were not powered to detect differences.

GLP-1 receptor agonists have demonstrated cardiovascular benefits among people with diabetes and established atherosclerotic cardiovascular disease (ASCVD) and those at higher ASCVD risk, and newer trials are expanding our understanding of their benefits in other populations (100). See Section 9, "Pharmacologic Approaches to Glycemic Treatment," and Section 10, "Cardiovascular Disease and Risk Management," for a more extensive discussion regarding the specific indications for this class of agents. In a systematic review and meta-analysis of GLP-1 receptor agonist trials, these agents have been found to reduce major adverse cardiovascular events, cardiovascular deaths, stroke, and myocardial infarction to the same degree for people over and under 65 years of age (104). While the evidence for this class of agents for older adults continues to grow, there are a number of practical issues that should be considered specifically for older people. These drugs are injectable agents (with the exception of oral semaglutide) (105), which require visual, motor, and cognitive skills for appropriate administration. Agents with a weekly dosing schedule may reduce the

Table 13.2—Considerations for treatment regimen simplification and deintensification/deprescribing in older adults with diabetes (93,128)

Patient characteristics/ health status	Reasonable A1C/ treatment goal	Rationale/considerations	When may regimen simplification be required?	When may treatment deintensification/ deprescribing be required?
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	<7.0–7.5% (53–58 mmol/mol)	• Patients can generally perform complex tasks to maintain good glycemic control when health is stable • During acute illness, patients may be more at risk for administration or dosing errors that can result in hypoglycemia, falls, fractures, etc.	• If severe or recurrent hypoglycemia occurs in patients on insulin therapy (regardless of A1C) • If wide glucose excursions are observed • If cognitive or functional decline occurs following acute illness	• If severe or recurrent hypoglycemia occurs in patients on noninsulin therapies with high risk of hypoglycemia (regardless of A1C) • If wide glucose excursions are observed • In the presence of polypharmacy
Complex/intermediate (multiple coexisting chronic illnesses or two or more instrumental ADL impairments or mild-to-moderate cognitive impairment)	<8.0% (64 mmol/mol)	• Comorbidities may affect self-management abilities and capacity to avoid hypoglycemia • Long-acting medication formulations may decrease pill burden and complexity of medication regimen	• If severe or recurrent hypoglycemia occurs in patients on insulin therapy (even if A1C is appropriate) • If unable to manage complexity of an insulin regimen • If there is a significant change in social circumstances, such as loss of caregiver, change in living situation, or financial difficulties	• If severe or recurrent hypoglycemia occurs in patients on noninsulin therapies with high risk of hypoglycemia (even if A1C is appropriate) • If wide glucose excursions are observed • In the presence of polypharmacy
Community-dwelling patients receiving care in a skilled nursing facility for short-term rehabilitation	Avoid reliance on A1C, glucose target 100–200 mg/dL (5.55–11.1 mmol/L)	• Glycemic control is important for recovery, wound healing, hydration, and avoidance of infections • Patients recovering from illness may not have returned to baseline cognitive function at the time of discharge • Consider the type of support the patient will receive at home	• If treatment regimen increased in complexity during hospitalization, it is reasonable, in many cases, to reinstate the prehospitalization medication regimen during the rehabilitation	• If the hospitalization for acute illness resulted in weight loss, anorexia, short-term cognitive decline, and/or loss of physical functioning
Very complex/poor health (LTC or end-stage chronic illnesses or moderate-to-severe cognitive impairment or two or more ADL impairments)	Avoid reliance on A1C and avoid hypoglycemia and symptomatic hyperglycemia	• No benefits of tight glycemic control in this population • Hypoglycemia should be avoided • Most important outcomes are maintenance of cognitive and functional status	• If on an insulin regimen and the patient would like to decrease the number of injections and fingerstick blood glucose monitoring events each day • If the patient has an inconsistent eating pattern	• If on noninsulin agents with a high hypoglycemia risk in the context of cognitive dysfunction, depression, anorexia, or inconsistent eating pattern • If taking any medications without clear benefits
At the end of life	Avoid hypoglycemia and symptomatic hyperglycemia	• Goal is to provide comfort and avoid tasks or interventions that cause pain or discomfort • Caregivers are important in providing medical care and maintaining quality of life	• If there is pain or discomfort caused by treatment (e.g., injections or finger sticks) • If there is excessive caregiver stress due to treatment complexity	• If taking any medications without clear benefits in improving symptoms and/or comfort

Treatment regimen simplification refers to changing strategy to decrease the complexity of a medication regimen (e.g., fewer administration times, fewer blood glucose checks) and decreasing the need for calculations (such as sliding-scale insulin calculations or insulin-carbohydrate ratio calculations). Deintensification/deprescribing refers to decreasing the dose or frequency of administration of a treatment or discontinuing a treatment altogether. ADL, activities of daily living; LTC, long-term care.

burden of administration. GLP-1 receptor agonists may also be associated with nausea, vomiting, and diarrhea. Given the gastrointestinal side effects of this class, GLP-1 receptor agonists may not be preferred in older adults who are experiencing unexplained weight loss.

Sodium–Glucose Cotransporter 2 Inhibitors

SGLT2 inhibitors are administered orally, which may be convenient for older adults with diabetes. In those with established ASCVD, these agents have shown cardiovascular benefits (100). This class of agents has also been found to be beneficial for people with heart failure and to slow the progression of chronic kidney disease. See Section 9, "Pharmacologic Approaches to Glycemic Treatment," and Section 10, "Cardiovascular Disease and Risk Management," for a more extensive discussion regarding the indications for this class of agents. The stratified analyses of the trials of this drug class indicate that older adults have similar or greater benefits than younger people (106–108). While understanding of the clinical benefits of this class is evolving, side effects such as volume depletion, urinary tract infections, and worsening urinary incontinence may be more common among older people.

Insulin Therapy

The use of insulin therapy requires that individuals or their caregivers have good visual and motor skills and cognitive ability. Insulin therapy relies on the ability of the older person with diabetes to administer insulin on their own or with the assistance of a caregiver. Insulin doses should be titrated to meet individualized glycemic targets and to avoid hypoglycemia.

Once-daily basal insulin injection therapy is associated with minimal side effects and may be a reasonable option in many older adults (109). When choosing a basal insulin, long-acting insulin analogs have been found to be associated with a lower risk of hypoglycemia compared with NPH insulin in the Medicare population. Multiple daily injections of insulin may be too complex for an older person with advanced diabetes complications, life-limiting coexisting chronic illnesses, or limited functional status. **Figure 13.1** provides a potential approach to insulin regimen simplification.

Other Factors to Consider

The needs of older adults with diabetes and their caregivers should be evaluated to construct a tailored care plan. Impaired social functioning may reduce these individuals' quality of life and increase the risk of functional dependency (7). The person's living situation must be considered as it may affect diabetes management and support needs. Social and instrumental support networks (e.g., adult children, caretakers) that provide instrumental or emotional support for older adults with diabetes should be included in diabetes management discussions and shared decision-making.

The need for ongoing support of older adults becomes even greater when transitions to acute care and long-term care (LTC) become necessary. Unfortunately, these transitions can lead to discontinuity in goals of care, errors in dosing, and changes in nutrition and activity (110). Older adults in assisted living facilities may not have support to administer their own medications, whereas those living in a nursing home (community living centers) may rely completely on the care plan and nursing support. Those receiving palliative care (with or without hospice) may require an approach that emphasizes comfort and symptom management while deemphasizing strict metabolic and blood pressure control.

SPECIAL CONSIDERATIONS FOR OLDER ADULTS WITH TYPE 1 DIABETES

Due in part to the success of modern diabetes management, people with type 1 diabetes are living longer, and the population of these people over 65 years of age is growing (111–113). Many of the recommendations in this section regarding a comprehensive geriatric assessment and personalization of goals and treatments are directly applicable to older adults with type 1 diabetes; however, this population has unique challenges and requires distinct treatment considerations (114). Insulin is an essential life-preserving therapy for people with type 1 diabetes, unlike for those with type 2 diabetes. To avoid diabetic ketoacidosis, older adults with type 1 diabetes need some form of basal insulin even when they are unable to ingest meals. Insulin may be delivered through an insulin pump or injections. CGM is approved for use by Medicare and can play a critical role in improving A1C, reducing glycemic variability, and reducing risk of hypoglycemia (45) (see Section 7, "Diabetes Technology," and Section 9, "Pharmacologic Approaches to Glycemic Treatment"). In older people with type 1 diabetes, administration of insulin may become more difficult as complications, cognitive impairment, and functional impairment arise. This increases the importance of caregivers in the lives of these individuals. Many older people with type 1 diabetes require placement in LTC settings (i.e., nursing homes and skilled nursing facilities) and unfortunately can encounter staff that are less familiar with insulin pumps or CGM. Some staff may be less knowledgeable about the differences between type 1 and type 2 diabetes. In these instances, the individual or the person's family may be more familiar with their diabetes management plan than the staff or health care professionals. Education of relevant support staff and health care professionals in rehabilitation and LTC settings regarding insulin dosing and use of pumps and CGM is recommended as part of general diabetes education (see Recommendations 13.20 and 13.21).

TREATMENT IN SKILLED NURSING FACILITIES AND NURSING HOMES

Recommendations

13.20 Consider diabetes education for the staff of long-term care and rehabilitation facilities to improve the management of older adults with diabetes. **E**

13.21 People with diabetes residing in long-term care facilities need careful assessment to establish individualized glycemic goals and to make appropriate choices of glucose-lowering agents based on their clinical and functional status. **E**

13.22 Consider use of continuous glucose monitoring to assess risk for hypoglycemia in older adults treated with sulfonylureas or insulin. **E**

Management of diabetes in the LTC setting is unique. Individualization of health care is important for all people with diabetes; however, practical guidance is needed for health care professionals as

well as the LTC staff and caregivers (115). Training should include diabetes detection and institutional quality assessment. LTC facilities should develop their own policies and procedures for prevention and management of hypoglycemia. With the increased longevity of populations, the care of people with diabetes and its complications in LTC is an area that warrants greater study.

Resources

Staff of LTC facilities should receive appropriate diabetes education to improve the management of older adults with diabetes. Treatments for each patient should be individualized. Special management considerations include the need to avoid both hypoglycemia and the complications of hyperglycemia (2,116). For more information, see the ADA position statement "Management of Diabetes in Long-term Care and Skilled Nursing Facilities" (115).

Nutritional Considerations

An older adult residing in an LTC facility may have irregular and unpredictable meal consumption, undernutrition, anorexia, and impaired swallowing. Furthermore, therapeutic diets may inadvertently lead to decreased food intake and contribute to unintentional weight loss and undernutrition. Meals tailored to a person's culture, preferences, and personal goals may increase quality of life, satisfaction with meals, and nutrition status (117). It may be helpful to give insulin after meals to ensure that the dose is appropriate for the amount of carbohydrate the individual consumed in the meal.

Hypoglycemia

Older adults with diabetes in LTC are especially vulnerable to hypoglycemia. They have a disproportionately high number of clinical complications and comorbidities that can increase hypoglycemia risk: impaired cognitive and renal function, slowed hormonal regulation and counterregulation, suboptimal hydration, variable appetite and nutritional intake, polypharmacy, and slowed intestinal absorption (118). Oral agents may achieve glycemic outcomes similar to basal insulin in LTC populations (84,119). CGM may be a useful approach to monitoring for hypoglycemia among individuals treated with insulin in LTC, but the data are limited.

Another consideration for the LTC setting is that unlike in the hospital setting, health care professionals are not required to evaluate patients daily. According to federal guidelines, assessments should be done at least every 30 days for the first 90 days after admission and then at least once every 60 days. Although in practice patients may actually be seen more frequently, the concern is that these individuals may have uncontrolled glucose levels or wide excursions without the practitioner being notified. Health care professionals may adjust treatment plans by telephone, fax, or in person directly at the LTC facilities, provided they are given timely notification of blood glucose management issues from a standardized alert system.

The following alert strategy could be considered:

1. **Call health care professional immediately** in cases of low blood glucose levels (<70 mg/dL [3.9 mmol/L]).
2. **Call as soon as possible when**
   a) glucose values are 70–100 mg/dL (3.9–5.6 mmol/L) (treatment plan may need to be adjusted),
   b) glucose values are consistently >250 mg/dL (13.9 mmol/L) within a 24-h period,
   c) glucose values are consistently >300 mg/dL (16.7 mmol/L) over 2 consecutive days,
   d) any reading is too high for the glucose monitoring device, or
   e) the person is sick, with vomiting, symptomatic hyperglycemia, or poor oral intake.

END-OF-LIFE CARE

Recommendations

13.23 When palliative care is needed in older adults with diabetes, health care professionals should initiate conversations regarding the goals and intensity of care. Strict glucose and blood pressure control are not necessary **E**, and simplification of regimens can be considered. Similarly, the intensity of lipid management can be relaxed, and withdrawal of lipid-lowering therapy may be appropriate. **A**

13.24 Overall comfort, prevention of distressing symptoms, and preservation of quality of life and dignity are primary goals for diabetes management at the end of life. **C**

The management of the older adult at the end of life receiving palliative medicine or hospice care is a unique situation. Overall, palliative medicine promotes comfort, symptom control and prevention (pain, hypoglycemia, hyperglycemia, and dehydration), and preservation of dignity and quality of life in older adults with limited life expectancy (116,120). In the setting of palliative care, health care professionals should initiate conversations regarding the goals and intensity of diabetes care; strict glucose and blood pressure control may not be consistent with achieving comfort and quality of life. Avoidance of severe hypertension and hyperglycemia aligns with the goals of palliative care. In a multicenter trial, withdrawal of statins among people with diabetes in palliative care was found to improve quality of life (121–123). The evidence for the safety and efficacy of deintensification protocols in older adults is growing for both glucose and blood pressure control (88,124) and is clearly relevant for palliative care. An individual has the right to refuse testing and treatment, whereas health care professionals may consider withdrawing treatment and limiting diagnostic testing, including a reduction in the frequency of blood glucose monitoring (125,126). Glucose targets should aim to prevent hypoglycemia and hyperglycemia. Treatment interventions need to be mindful of quality of life. Careful monitoring of oral intake is warranted. The decision process may need to involve the individual, family, and caregivers, leading to a care plan that is both convenient and effective for the goals of care (127). The pharmacologic therapy may include oral agents as first line, followed by a simplified insulin regimen. If needed, basal insulin can be implemented, accompanied by oral agents and without rapid-acting insulin. Agents that can cause gastrointestinal symptoms such as nausea or excess weight loss may not be good choices in this setting. As symptoms progress, some agents may be slowly tapered and discontinued.

Different patient categories have been proposed for diabetes management in those with advanced disease (59).

1. A stable patient: Continue with the person's previous regimen, with a focus on *1*) the prevention of hypoglycemia and *2*) the management of hyperglycemia using blood glucose testing, keeping levels below the renal threshold of glucose, and hyperglycemia-mediated dehydration. There is no role for A1C monitoring.
2. A patient with organ failure: Preventing hypoglycemia is of greatest significance. Dehydration must be prevented and treated. In people with type 1 diabetes, insulin administration may be reduced as the oral intake of food decreases but should not be stopped. For those with type 2 diabetes, agents that may cause hypoglycemia should be reduced in dose. The main goal is to avoid hypoglycemia, allowing for glucose values in the upper level of the desired target range.
3. A dying patient: For people with type 2 diabetes, the discontinuation of all medications may be a reasonable approach, as these individuals are unlikely to have any oral intake. In people with type 1 diabetes, there is no consensus, but a small amount of basal insulin may maintain glucose levels and prevent acute hyperglycemic complications.

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14. Children and Adolescents: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

The management of diabetes in children and adolescents (individuals <18 years of age) cannot simply be derived from care routinely provided to adults with diabetes. The epidemiology, pathophysiology, developmental considerations, and response to therapy in pediatric diabetes are often different from those of adult diabetes. There are also differences in recommended care for children and adolescents with type 1 diabetes, type 2 diabetes, and other forms of pediatric diabetes. This section is divided into two major parts: the first part addresses care for children and adolescents with type 1 diabetes, and the second part addresses care for children and adolescents with type 2 diabetes. Monogenic diabetes (neonatal diabetes and maturity-onset diabetes in the young [MODY]) and cystic fibrosis–related diabetes, which are often present in youth, are discussed in Section 2, "Classification and Diagnosis of Diabetes." **Table 14.1*A*** and **Table 14.1*B*** provide an overview of the recommendations for screening and treatment of complications and related conditions in pediatric type 1 diabetes and type 2 diabetes, respectively. In addition to comprehensive diabetes care, youth with diabetes should receive age-appropriate and developmentally appropriate pediatric care, including vaccines and immunizations as recommended by the Centers for Disease Control and Prevention (CDC) (1). To ensure continuity of care as an adolescent with diabetes becomes an adult, guidance is provided at the end of this section on the transition from pediatric to adult diabetes care.

Due to the nature of pediatric clinical research, the recommendations for children and adolescents with diabetes are less likely to be based on clinical trial evidence. However, expert opinion and a review of available and relevant experimental data are summarized in the American Diabetes Association (ADA) position statements "Type 1 Diabetes in Children and Adolescents" (2) and "Evaluation and Management of Youth-Onset Type 2 Diabetes" (3). Finally, other sections in the Standards of Care may have recommendations that apply to youth with diabetes and are referenced in the narrative of this section.

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Table 14.1*A*—Recommendations for screening and treatment of complications and related conditions in pediatric type 1 diabetes

	Thyroid disease	Celiac disease	Hypertension	Dyslipidemia	Nephropathy	Retinopathy	Neuropathy
Corresponding recommendations	14.29 and 14.30	14.31–14.33	14.34–14.37	14.38–14.42	14.45 and 14.46	14.47–14.49	14.50
Method	Thyroid-stimulating hormone; consider antithyroglobulin and antithyroid peroxidase antibodies	IgA tTG if total IgA normal; IgG tTG and deamidated gliadin antibodies if IgA deficient	Blood pressure monitoring	Lipid profile, nonfasting acceptable initially	Albumin-to-creatinine ratio; random sample acceptable initially	Dilated fundoscopy or retinal photography	Foot exam with foot pulses, pinprick, 10-g monofilament sensation tests, vibration, and ankle reflexes
When to start	Soon after diagnosis	Soon after diagnosis	At diagnosis	Soon after diagnosis; preferably after glycemia has improved and ≥2 years old	Puberty or >10 years old, whichever is earlier, and diabetes duration of 5 years	Puberty or ≥11 years old, whichever is earlier, and diabetes duration of 3–5 years	Puberty or ≥10 years old, whichever is earlier, and diabetes duration of 5 years
Follow-up frequency	Every 1–2 years if thyroid antibodies negative; more often if symptoms develop or presence of thyroid antibodies	Within 2 years and then at 5 years after diagnosis; sooner if symptoms develop	Every visit	If LDL ≤100 mg/dL, repeat at 9–11 years old; then, if <100 mg/dL, every 3 years	If normal, annually; if abnormal, repeat with confirmation in two of three samples over 6 months	If normal, every 2 years; consider less frequently (every 4 years) if A1C <8% and eye professional agrees	If normal, annually
Target	NA	NA	<90th percentile for age, sex, and height; if ≥13 years old, <120/80 mmHg	LDL <100 mg/dL	Albumin-to-creatinine ratio <30 mg/g	No retinopathy	No neuropathy
Treatment	Appropriate treatment of underlying thyroid disorder	After confirmation, start gluten-free diet	Lifestyle modification for elevated blood pressure (90th to <95th percentile for age, sex, and height or, if ≥13 years old, 120–129/<80 mmHg); lifestyle modification and ACE inhibitor or ARB* for hypertension (≥95th percentile for age, sex, and height or, if ≥13 years old, ≥130/80 mmHg)	If abnormal, optimize glycemia and medical nutrition therapy; if after 6 months LDL >160 mg/dL or >130 mg/dL with cardiovascular risk factor(s), initiate statin therapy (for those aged >10 years)*	Optimize glycemia and blood pressure; ACE inhibitor* if albumin-to-creatinine ratio is elevated in two of three samples over 6 months	Optimize glycemia; treatment per ophthalmology	Optimize glycemia; referral to neurology

ARB, angiotensin receptor blocker; NA, not applicable; tTG, tissue transglutaminase. *Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and medication should be avoided in individuals of childbearing age who are not using reliable contraception.

Table 14.1*B*—Recommendations for screening and treatment of complications and related conditions in pediatric type 2 diabetes

	Hypertension	Nephropathy	Neuropathy	Retinopathy	Nonalcoholic fatty liver disease	Obstructive sleep apnea	Polycystic ovarian syndrome (for adolescent female individuals)	Dyslipidemia
Corresponding recommendations	14.77–14.80	14.81–14.86	14.87 and 14.88	14.89–14.92	14.93 and 14.94	14.95	14.96–14.98	14.100–14.104
Method	Blood pressure monitoring	Albumin-to-creatinine ratio; random sample acceptable initially	Foot exam with foot pulses, pinprick, 10-g monofilament sensation tests, vibration, and ankle reflexes	Dilated fundoscopy	AST and ALT measurement	Screening for symptoms	Screening for symptoms; laboratory evaluation if positive symptoms	Lipid profile
When to start	At diagnosis	At diagnosis	At diagnosis	At/soon after diagnosis	At diagnosis	At diagnosis	At diagnosis	Soon after diagnosis, preferably after glycemia has improved
Follow-up frequency	Every visit	If normal, annually; if abnormal, repeat with confirmation in two of three samples over 6 months	If normal, annually	If normal, annually	Annually	Every visit	Every visit	Annually
Target	<90th percentile for age, sex, and height; if ≥13 years old, <130/80 mmHg	<30 mg/g	No neuropathy	No retinopathy	NA	NA	NA	LDL <100 mg/dL, HDL >35 mg/dL, triglycerides <150 mg/dL
Treatment	Lifestyle modification for elevated blood pressure (90th to <95th percentile for age, sex, and height or, if ≥13 years old, 120–129/<80 mmHg); lifestyle modification and ACE inhibitor or ARB* for hypertension (≥95th percentile for age, sex, and height or, if ≥13 years, ≥130/80 mmHg)	Optimize glycemia and blood pressure; ACE inhibitor* if albumin-to-creatinine ratio is elevated in two of three samples over 6 months	Optimize glycemia; referral to neurology	Optimize glycemia; treatment per ophthalmology	Refer to gastroenterology for persistently elevated or worsening transaminases	If positive symptoms, refer to sleep specialist and polysomnogram	If no contraindications, oral contraceptive pills; medical nutrition therapy; metformin	If abnormal, optimize glycemia and medical nutrition therapy; if after 6 months, LDL >130 mg/dL, initiate statin therapy (for those aged >10 years)*; if triglycerides >400 mg/dL fasting or >1,000 mg/dL nonfasting, begin fibrate

ARB, angiotensin receptor blocker; NA, not applicable. *Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and medication should be avoided in individuals of childbearing age who are not using reliable contraception.

TYPE 1 DIABETES

Type 1 diabetes is the most common form of diabetes in youth (4), although data suggest that it may account for a large proportion of cases diagnosed in adult life (5). The health care professional must consider the unique aspects of care and management of children and adolescents with type 1 diabetes, such as changes in insulin sensitivity related to physical growth and sexual maturation, ability to provide self-care, supervision in the childcare and school environment, neurological vulnerability to hypoglycemia and hyperglycemia in young children, and possible adverse neurocognitive effects of diabetic ketoacidosis (DKA) (6,7). Attention to family dynamics, developmental stages, and physiologic differences related to sexual maturity is essential in developing and implementing an optimal diabetes treatment plan (8).

A multidisciplinary team trained in pediatric diabetes management and sensitive to the challenges of children and adolescents with type 1 diabetes and their families should provide diabetes-specific care for this population. It is essential that diabetes self-management education and support, medical nutrition therapy, and psychosocial support be provided at diagnosis and regularly thereafter in a developmentally appropriate format that builds on prior knowledge by a team of health care professionals experienced with the biological, educational, nutritional, behavioral, and emotional needs of the growing child and family. The diabetes team, taking into consideration the youth's developmental and psychosocial needs, should ask about and advise the youth and parents/caregivers about diabetes management responsibilities on an ongoing basis.

Diabetes Self-Management Education and Support

Recommendation

14.1 Youth with type 1 diabetes and their parents/caregivers (for patients aged <18 years) should receive culturally sensitive and developmentally appropriate individualized diabetes self-management education and support according to national standards at diagnosis and routinely thereafter. **B**

Self-management in pediatric diabetes involves both the youth and their parents/adult caregivers. No matter how sound the medical plan is, it can only be effective if the family and/or affected individuals are able to implement it. Family involvement is a vital component of optimal diabetes management throughout childhood and adolescence. As parents/caregivers are critical to diabetes self-management in youth, diabetes care requires an approach that places the youth and their parents/caregivers at the center of the care model. The pediatric diabetes care team must be capable of evaluating the educational, behavioral, emotional, and psychosocial factors that impact the implementation of a treatment plan and must work with the youth and family to overcome barriers or redefine goals as appropriate. Diabetes self-management education and support requires periodic reassessment, especially as the youth grows, develops, and acquires the need and desire for greater independent self-care skills. The pediatric diabetes team should work with the youth and their parents/caregivers to ensure there is not a premature transfer of self-management tasks to the youth during this time. In addition, it is necessary to assess the educational needs and skills of, and provide training to, day care workers, school nurses, and school personnel who are responsible for the care and supervision of the child with diabetes (9–11).

Nutrition Therapy

Recommendations

14.2 Individualized medical nutrition therapy is recommended for youth with type 1 diabetes as an essential component of the overall treatment plan. **A**

14.3 Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, is a key component to optimizing glycemic management. **B**

14.4 Comprehensive nutrition education at diagnosis, with annual updates, by an experienced registered dietitian nutritionist, is recommended to assess caloric and nutrition intake in relation to weight status and cardiovascular disease risk factors and to inform macronutrient choices. **E**

Nutrition management should be individualized: family habits, food preferences, religious or cultural needs, finances, schedules, physical activity, and the youth's and family's abilities in numeracy, literacy, and self-management should be considered. Visits with a registered dietitian nutritionist should include assessment for changes in food preferences over time, access to food, growth, and development, weight status, cardiovascular risk, and potential for disordered eating. Following recommended nutrition plans is associated with better glycemic outcomes in youth with type 1 diabetes (12).

Physical Activity and Exercise

Recommendations

14.5 Physical activity is recommended for all youth with type 1 diabetes with the goal of 60 min of moderate- to vigorous-intensity aerobic activity daily, with vigorous muscle-strengthening and bone-strengthening activities at least 3 days per week. **C**

14.6 Frequent glucose monitoring before, during, and after exercise, via blood glucose meter or continuous glucose monitoring, is important to prevent, detect, and treat hypoglycemia and hyperglycemia associated with exercise. **C**

14.7 Youth and their parents/caregivers should receive education on targets and management of glycemia before, during, and after physical activity, individualized according to the type and intensity of the planned physical activity. **E**

14.8 Youth and their parents/caregivers should be educated on strategies to prevent hypoglycemia during, after, and overnight following physical activity and exercise, which may include reducing prandial insulin dosing for the meal/snack preceding (and, if needed, following) exercise, reducing basal insulin doses, increasing carbohydrate intake, eating bedtime

snacks, and/or using continuous glucose monitoring. Treatment for hypoglycemia should be accessible before, during, and after engaging in activity. C

Physical activity and exercise positively impact metabolic and psychological health in children with type 1 diabetes (13). While it affects insulin sensitivity, physical fitness, strength building, weight management, social interaction, mood, self-esteem building, and the creation of healthful habits for adulthood, it also has the potential to cause both hypoglycemia and hyperglycemia.

See below for strategies to mitigate hypoglycemia risk and minimize hyperglycemia associated with exercise. For an in-depth discussion, see reviews and guidelines (14–16).

Overall, it is recommended that youth participate in 60 min of moderate-intensity (e.g., brisk walking, dancing) to vigorous-intensity (e.g., running, jumping rope) aerobic activity daily, including resistance and flexibility training (17). Although uncommon in the pediatric population, patients should be medically evaluated for comorbid conditions or diabetes complications that may restrict participation in an exercise program. As hyperglycemia can occur before, during, and after physical activity, it is important to ensure that the elevated glucose level is not related to insulin deficiency that would lead to worsening hyperglycemia with exercise and ketosis risk. Intense activity should be postponed with marked hyperglycemia (glucose ≥350 mg/dL [19.4 mmol/L]), moderate to large urine ketones, and/or β-hydroxybutyrate (B-OHB) >1.5 mmol/L. Caution may be needed when B-OHB levels are ≥0.6 mmol/L (12,14).

The prevention and treatment of hypoglycemia associated with physical activity include decreasing the prandial insulin for the meal/snack before exercise and/or increasing food intake. Youth on insulin pumps can lower basal rates by ∼10–50% or more or suspend for 1–2 h during exercise (18). Decreasing basal rates or long-acting insulin doses by ∼20% after exercise may reduce delayed exercise-induced hypoglycemia (19). Accessible rapid-acting carbohydrates and frequent blood glucose monitoring before, during, and after exercise, with or without continuous glucose monitoring (CGM), maximize safety with exercise. The use of hybrid closed-loop systems may improve time in range (70–180 mg/dL) during exercise, and youth can use "exercise mode" to prevent hypoglycemia (20).

Blood glucose targets prior to physical activity and exercise should be 126–180 mg/dL (7.0–10.0 mmol/L) but should be individualized based on the type, intensity, and duration of activity (14,16). Consider additional carbohydrate intake during and/or after exercise, depending on the duration and intensity of physical activity, to prevent hypoglycemia. For low- to moderate-intensity aerobic activities (30–60 min), and if the youth is fasting, 10–15 g of carbohydrate may prevent hypoglycemia (21). After insulin boluses (relative hyperinsulinemia), consider 0.5–1.0 g of carbohydrates/kg per hour of exercise (∼30–60 g), which is similar to carbohydrate requirements to optimize performance in athletes without type 1 diabetes (22–24).

In addition, obesity is as common in youth with type 1 diabetes as in those without diabetes. It is associated with a higher frequency of cardiovascular risk factors, and it disproportionately affects racial/ethnic minorities in the U.S. (25–29). Therefore, diabetes health care professionals should monitor weight status and encourage a healthy eating pattern, physical activity, and healthy weight as key components of pediatric type 1 diabetes care.

School and Child Care

As a large portion of a youth's day is spent in school and/or day care, training of school or day care personnel to provide care in accordance with the child's individualized diabetes medical management plan is essential for optimal diabetes management and safe access to all school or day care-sponsored opportunities (10,11,30). In addition, federal and state laws require schools, day care facilities, and other entities to provide needed diabetes care to enable the child to safely access the school or day care environment. Refer to the ADA position statements "Diabetes Care in the School Setting" (10) and "Care of Young Children With Diabetes in the Child Care Setting" (11) and ADA's Safe at School website (diabetes.org/resources/know-your-rights/safe-at-school-state-laws) for additional details.

Psychosocial Care

Recommendations

14.9 At diagnosis and during routine follow-up care, screen for psychosocial issues and family stresses that could impact diabetes management and provide appropriate referrals to trained mental health professionals, preferably experienced in childhood diabetes. C

14.10 Mental health professionals should be considered integral members of the pediatric diabetes multidisciplinary team. E

14.11 Encourage developmentally appropriate family involvement in diabetes management tasks for children and adolescents, recognizing that premature transfer of diabetes care responsibility to the youth can result in diabetes burnout, suboptimal diabetes management, and deterioration in glycemia. A

14.12 Health care professionals should screen for food security, housing stability/homelessness, health literacy, financial barriers, and social/community support and apply that information to treatment decisions. E

14.13 Health care professionals should consider asking youth and their parents/caregivers about social adjustment (peer relationships) and school performance to determine whether further intervention is needed. B

14.14 Screen youth with diabetes for psychosocial and diabetes-related distress, generally starting at 7–8 years of age. Refer to a qualified mental health professional for further assessment and treatment if indicated. B

14.15 Offer adolescents time by themselves with their health care professional(s) starting at age 12 years or when developmentally appropriate. E

14.16 Starting at puberty, preconception counseling should be incorporated into routine diabetes care for all individuals of childbearing potential. A

14.17 Begin screening youth with type 1 diabetes for disordered

eating between 10 and 12 years of age. Refer to a qualified mental health professional for further assessment and treatment if indicated. **B**

Rapid and dynamic cognitive, developmental, and emotional changes occur during childhood, adolescence, and emerging adulthood. Diabetes management during childhood and adolescence places substantial burdens on the youth and family, necessitating ongoing assessment of psychosocial status, social determinants of health, and diabetes distress in the youth and the parents/caregivers during routine diabetes visits (31–41). It is important to consider the impact of diabetes on quality of life as well as the development of mental health problems related to diabetes distress, fear of hypoglycemia (and hyperglycemia), symptoms of anxiety, disordered eating behaviors and eating disorders, and symptoms of depression (42). Consider screening youth for diabetes distress, generally starting at 7 or 8 years of age (43). Consider screening for depression and disordered eating behaviors using available screening tools (44,45). Early detection of depression, anxiety, disordered eating, and learning disabilities can facilitate effective treatment options and help minimize adverse effects on diabetes management and disease outcomes (35,43). There are validated tools that can be used in assessing diabetes-specific distress in youth starting at age 8 years and in their parents/caregivers (36,46). Furthermore, the complexities of diabetes management require ongoing parental involvement in care throughout childhood with developmentally appropriate family teamwork between the growing child/teen and parent in order to maintain engagement in self-management behaviors and to prevent deterioration in glycemia (47,48). It is appropriate to inquire about diabetes-specific family conflict during visits and to either help to negotiate a plan for resolution or refer to an appropriate mental health professional (49). Such professionals can conduct further assessment and deliver evidence-based behavioral interventions to support developmentally appropriate, collaborative family involvement in diabetes self-management (50,51). Monitoring of social adjustment (peer relationships) and school performance can facilitate both well-being and academic achievement (52). Elevated A1C is a risk factor for underperformance at school and increased absenteeism (53).

Shared decision-making with youth regarding the adoption of management plan components and self-management behaviors can improve diabetes self-efficacy, participation in diabetes care, and metabolic outcomes (26,54). Although cognitive abilities vary, the ethical position often adopted is the "mature minor rule," whereby children after age 12 or 13 years who appear to be "mature" have the right to consent or withhold consent to general medical treatment, except in cases in which refusal would significantly endanger health (55).

Beginning at the onset of puberty or at diagnosis of diabetes, all individuals with childbearing potential should receive education about the risks of fetal malformations associated with elevated A1C and the use of effective contraception to prevent unplanned pregnancy. Preconception counseling using developmentally appropriate educational and behavioral strategies enables individuals of childbearing potential to make well-informed decisions (56). Preconception counseling resources tailored for adolescents are available at no cost through the ADA (57). Refer to the ADA position statement "Psychosocial Care for People With Diabetes" for further details (43).

Youth with type 1 diabetes have an increased risk of disordered eating behavior as well as clinical eating disorders with serious short-term and long-term negative effects on diabetes outcomes and health in general. It is important to recognize the unique and dangerous disordered eating behavior of insulin omission for weight management in type 1 diabetes (58) using tools such as the Diabetes Eating Problems Survey-Revised (DEPS-R) to allow for early diagnosis and intervention (45,59–61). Given the complexity of treating disordered eating behaviors, collaboration between the diabetes health care team and a mental health professional, ideally with expertise in disordered eating behaviors and diabetes, is recommended.

The presence of a mental health professional on pediatric multidisciplinary teams highlights the importance of attending to the psychosocial issues of diabetes. These psychosocial factors are significantly related to self-management difficulties, elevated A1C, reduced quality of life, and higher rates of acute and chronic diabetes complications.

Glycemic Monitoring, Insulin Delivery, and Targets

Recommendations

14.18 All youth with type 1 diabetes should monitor glucose levels multiple times daily (up to 6–10 times/day by blood glucose meter or continuous glucose monitoring), including prior to meals and snacks, at bedtime, and as needed for safety in specific situations such as physical activity, driving, or the presence of symptoms of hypoglycemia. **B**

14.19 Real-time continuous glucose monitoring **B** or intermittently scanned continuous glucose monitoring **E** should be offered for diabetes management in youth with diabetes on multiple daily injections or insulin pump therapy who are capable of using the device safely (either by themselves or with caregivers). The choice of device should be made based on the individual's and family's circumstances, desires, and needs.

14.20 Automated insulin delivery systems should be offered for diabetes management to youth with type 1 diabetes who are capable of using the device safely (either by themselves or with caregivers). The choice of device should be made based on the individual's and family's circumstances, desires, and needs. **A**

14.21 Insulin pump therapy alone should be offered for diabetes management to youth on multiple daily injections with type 1 diabetes who are capable of using the device safely (either by themselves or with caregivers). The choice of device should be made based on the individual's and family's circumstances, desires, and needs. **A**

14.22 Students must be supported at school in the use of diabetes

technology, including continuous glucose monitors, insulin pumps, connected insulin pens, and automated insulin delivery systems as prescribed by their diabetes care team. E

14.23 A1C goals must be individualized and reassessed over time. An A1C of <7% (53 mmol/mol) is appropriate for many children and adolescents. B

14.24 Less stringent A1C goals (such as <7.5% [58 mmol/mol]) may be appropriate for youth who cannot articulate symptoms of hypoglycemia; have hypoglycemia unawareness; lack access to analog insulins, advanced insulin delivery technology, and/or continuous glucose monitoring; cannot check blood glucose regularly; or have nonglycemic factors that increase A1C (e.g., high glycators). B

14.25 Even less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for individuals with a history of severe hypoglycemia, limited life expectancy, or where the harms of treatment are greater than the benefits. B

14.26 Health care professionals may reasonably suggest more stringent A1C goals (such as <6.5% [48 mmol/mol]) for selected individuals if they can be achieved without significant hypoglycemia, negative impacts on well-being, or undue burden of care or in those who have nonglycemic factors that decrease A1C (e.g., lower erythrocyte life span). Lower targets may also be appropriate during the honeymoon phase. B

14.27 Continuous glucose monitoring metrics derived from continuous glucose monitor use over the most recent 14 days (or longer for youth with more glycemic variability), including time in range (70–180 mg/dL), time below target (<70 and <54 mg/dL), and time above target (>180 and >250 mg/dL), are recommended to be used in conjunction with A1C whenever possible. E

Current standards for diabetes management reflect the need to minimize hyperglycemia as safely as possible. The Diabetes Control and Complications Trial (DCCT), which did not enroll children <13 years of age, demonstrated that near normalization of blood glucose levels was more difficult to achieve in adolescents than in adults. Nevertheless, the increased use of basal-bolus regimens, insulin pumps, frequent blood glucose monitoring, CGM, automated insulin delivery systems, goal setting, and improved patient education has been associated with more children and adolescents reaching the blood glucose targets recommended by the ADA (62–64), particularly in families in which both the parents/caregivers and the child with diabetes participate jointly to perform the required diabetes-related tasks.

Lower A1C in adolescence and young adulthood is associated with a lower risk and rate of microvascular and macrovascular complications (65–68) and demonstrates the effects of metabolic memory (69–72).

In addition, type 1 diabetes can be associated with adverse effects on cognition during childhood and adolescence (6,73–75), and neurocognitive imaging differences related to hyperglycemia in children provide another motivation for achieving glycemic targets (6). DKA has been shown to cause adverse effects on brain development and function. Additional factors (76–79) that contribute to adverse effects on brain development and function include young age, severe hypoglycemia at <6 years of age, and chronic hyperglycemia (80–82). However, meticulous use of therapeutic modalities such as rapid- and long-acting insulin analogs, technological advances (e.g., CGM, sensor-augmented pump therapy, and automated insulin delivery systems), and intensive self-management education now make it more feasible to achieve glycemic goals while reducing the incidence of severe hypoglycemia (83–106). Please refer to Section 7, "Diabetes Technology," for more information on technology to support people with diabetes.

In selecting individualized glycemic targets, the long-term health benefits of achieving a lower A1C should be balanced against the risks of hypoglycemia and the developmental burdens of intensive treatment plans in youth (107). Recent data with newer devices and insulins indicate that the risk of hypoglycemia with lower A1C is less than it was before (108–117). Some data suggest that there could be a threshold where lower A1C is associated with more hypoglycemia (118,119); however, the confidence intervals were large, suggesting great variability. In addition, achieving lower A1C levels is likely facilitated by setting lower A1C targets (120,121). Lower goals may be possible during the "honeymoon" phase of type 1 diabetes. Special consideration should be given to the risk of hypoglycemia in young children (aged <6 years) who are often unable to recognize, articulate, and/or manage hypoglycemia.However, registry data indicate that A1C targets can be achieved in children, including those aged <6 years, without increased risk of severe hypoglycemia (109,120). Recent data have demonstrated that the use of real-time CGM lowered A1C and increased time in range in adolescents and young adults and, in children aged <8 years old, was associated with a lower risk of hypoglycemia (122,123). Please refer to Section 6, "Glycemic Targets," for more information on glycemic assessment.

A strong relationship exists between the frequency of blood glucose monitoring and glycemic management (84–86, 124–130). Glucose levels for all children and adolescents with type 1 diabetes should be monitored multiple times daily by blood glucose monitoring and/or CGM. In the U.S., real-time CGM is approved for nonadjunctive use in children aged 2 years and older and intermittently scanned CGM is approved for nonadjunctive use in children aged 4 years and older. Parents/caregivers and youth should be offered initial and ongoing education and support for CGM use. Behavioral support may further improve ongoing CGM use (123). Metrics derived from CGM include percent time in target range, below target range, and above target range (131). While studies indicate a relationship between time in range and A1C (132, 133), it is still uncertain what the ideal target time in range should be for children, and further studies are needed.

Please refer to Section 7, "Diabetes Technology," for more information on the use of blood glucose meters, CGM, and insulin pumps. More information on insulin injection technique can be found in Section 9, "Pharmacologic Approaches to Glycemic Treatment."

Key Concepts in Setting Glycemic Targets

- Targets should be individualized, and lower targets may be reasonable based on a benefit–risk assessment.
- Blood glucose targets should be modified in children with frequent hypoglycemia or hypoglycemia unawareness.
- Postprandial blood glucose values should be measured when there is a discrepancy between preprandial blood glucose values and A1C levels and to assess preprandial insulin doses in those on basal-bolus or pump regimens.

Autoimmune Conditions

Recommendation

14.28 Assess for additional autoimmune conditions soon after the diagnosis of type 1 diabetes and if symptoms develop. **B**

Because of the increased frequency of other autoimmune diseases in type 1 diabetes, screening for thyroid dysfunction and celiac disease should be considered (134–138). Periodic screening in asymptomatic individuals has been recommended, but the optimal frequency of screening is unclear.

Although much less common than thyroid dysfunction and celiac disease, other autoimmune conditions, such as Addison disease (primary adrenal insufficiency), autoimmune hepatitis, autoimmune gastritis, dermatomyositis, and myasthenia gravis, occur more commonly in the population with type 1 diabetes than in the general pediatric population and should be assessed and monitored as clinically indicated. In addition, relatives of youth with type 1 diabetes should be offered testing for islet autoantibodies through research studies (e.g., TrialNet) and national programs for early diagnosis of preclinical type 1 diabetes (stages 1 and 2).

Thyroid Disease

Recommendations

14.29 Consider testing children with type 1 diabetes for antithyroid peroxidase and antithyroglobulin antibodies soon after diagnosis. **B**

14.30 Measure thyroid-stimulating hormone concentrations at diagnosis when clinically stable or soon after optimizing glycemia. If normal, suggest rechecking every 1–2 years or sooner if the youth has positive thyroid antibodies or develops symptoms or signs suggestive of thyroid dysfunction, thyromegaly, an abnormal growth rate, or unexplained glycemic variability. **B**

Autoimmune thyroid disease is the most common autoimmune disorder associated with diabetes, occurring in 17–30% of individuals with type 1 diabetes (135,139,140). At the time of diagnosis, ~25% of children with type 1 diabetes have thyroid autoantibodies (141), the presence of which is predictive of thyroid dysfunction—most commonly hypothyroidism, although hyperthyroidism occurs in ~0.5% of people with type 1 diabetes (142,143). For thyroid autoantibodies, a study from Sweden indicated that antithyroid peroxidase antibodies were more predictive than antithyroglobulin antibodies in multivariate analysis (144). Thyroid function tests may be misleading (euthyroid sick syndrome) if performed at the time of diagnosis owing to the effect of previous hyperglycemia, ketosis or ketoacidosis, weight loss, etc. Therefore, if performed at diagnosis and slightly abnormal, thyroid function tests should be repeated soon after a period of metabolic stability and achievement of glycemic targets. Subclinical hypothyroidism may be associated with an increased risk of symptomatic hypoglycemia (145) and a reduced linear growth rate. Hyperthyroidism alters glucose metabolism and usually causes deterioration of glycemia.

Celiac Disease

Recommendations

14.31 Screen youth with type 1 diabetes for celiac disease by measuring IgA tissue transglutaminase (tTG) antibodies, with documentation of normal total serum IgA levels, soon after the diagnosis of diabetes, or IgG tTG and deamidated gliadin antibodies if IgA is deficient. **B**

14.32 Repeat screening within 2 years of diabetes diagnosis and then again after 5 years and consider more frequent screening in youth who have symptoms or a first-degree relative with celiac disease. **B**

14.33 Individuals with confirmed celiac disease should be placed on a gluten-free diet for treatment and to avoid complications; they should also have a consultation with a registered dietitian nutritionist experienced in managing both diabetes and celiac disease. **B**

Celiac disease is an immune-mediated disorder that occurs with increased frequency in people with type 1 diabetes (1.6–16.4% of individuals compared with 0.3–1% in the general population) (134, 137,138,146–150). Screening people with type 1 diabetes for celiac disease is further justified by its association with osteoporosis, iron deficiency, growth failure, and potential increased risk of retinopathy and albuminuria (151–154).

Screening for celiac disease includes measuring serum levels of IgA and tissue transglutaminase (tTG) IgA antibodies, or, with IgA deficiency, screening can include measuring tTG IgG antibodies or deamidated gliadin peptide IgG antibodies. Because most cases of celiac disease are diagnosed within the first 5 years after the diagnosis of type 1 diabetes, screening should be considered at the time of diagnosis and repeated at 2 and then 5 years (148) or if clinical symptoms indicate, such as poor growth or increased hypoglycemia (149,151).

Although celiac disease can be diagnosed more than 10 years after diabetes diagnosis, there are insufficient data after 5 years to determine the optimal screening frequency. Measurement of tTG antibody should be considered at other times in individuals with symptoms suggestive of celiac disease (148). Monitoring for symptoms should include an assessment of linear growth and weight gain (149,151). A small bowel biopsy in antibody-positive children is recommended to confirm the diagnosis

(155). European guidelines on screening for celiac disease in children (not specific to children with type 1 diabetes) suggest that biopsy may not be necessary in symptomatic children with high antibody titers (i.e., greater than 10 times the upper limit of normal) provided that further testing is performed (verification of endomysial antibody positivity on a separate blood sample) (156). Whether this approach may be appropriate for asymptomatic children in high-risk groups remains an open question, though evidence is emerging (157). It is also advisable to check for celiac disease-associated HLA types in patients who are diagnosed without a small intestinal biopsy. In symptomatic children with type 1 diabetes and confirmed celiac disease, gluten-free diets reduce symptoms and rates of hypoglycemia (158). The challenging dietary restrictions associated with having both type 1 diabetes and celiac disease place a significant burden on individuals. Therefore, a biopsy to confirm the diagnosis of celiac disease is recommended, especially in asymptomatic children, before establishing a diagnosis of celiac disease (159) and endorsing significant dietary changes. A gluten-free diet was beneficial in asymptomatic adults with positive antibodies confirmed by biopsy (160).

Management of Cardiovascular Risk Factors

Hypertension Screening

Recommendation

14.34 Blood pressure should be measured at every routine visit. In youth with high blood pressure (blood pressure ≥90th percentile for age, sex, and height or, in adolescents aged ≥13 years, blood pressure ≥120/80 mmHg) on three separate measurements, ambulatory blood pressure monitoring should be strongly considered. **B**

Hypertension Treatment

Recommendations

14.35 Treatment of elevated blood pressure (defined as 90th to <95th percentile for age, sex, and height or, in adolescents aged ≥13 years, 120–129/<80 mmHg) is lifestyle modification focused on healthy nutrition, physical activity, sleep, and, if appropriate, weight management. **C**

14.36 In addition to lifestyle modification, ACE inhibitors or angiotensin receptor blockers should be started for treatment of confirmed hypertension (defined as blood pressure consistently ≥95th percentile for age, sex, and height or, in adolescents aged ≥13 years, ≥130/80 mmHg). Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and ACE inhibitors and angiotensin receptor blockers should be avoided in individuals of childbearing age who are not using reliable contraception. **B**

14.37 The goal of treatment is blood pressure <90th percentile for age, sex, and height or, in adolescents aged ≥13 years, <130/80 mmHg. **C**

Blood pressure measurements should be performed using the appropriate size cuff with the youth seated and relaxed. Elevated blood pressure should be confirmed on at least three separate days, and ambulatory blood pressure monitoring should be considered. Evaluation should proceed as clinically indicated (161,162). Treatment is generally initiated with an ACE inhibitor, but an angiotensin receptor blocker can be used if the ACE inhibitor is not tolerated (e.g., due to cough) (163).

Dyslipidemia Screening

Recommendations

14.38 Initial lipid profile should be performed soon after diagnosis, preferably after glycemia has improved and age is ≥2 years. If initial LDL cholesterol is ≤100 mg/dL (2.6 mmol/L), subsequent testing should be performed at 9–11 years of age. **B** Initial testing may be done with a nonfasting lipid level with confirmatory testing with a fasting lipid panel.

14.39 If LDL cholesterol values are within the accepted risk level (<100 mg/dL [2.6 mmol/L]), a lipid profile repeated every 3 years is reasonable. **E**

Dyslipidemia Treatment

Recommendations

14.40 If lipids are abnormal, initial therapy should consist of optimizing glycemia and medical nutrition therapy to limit the amount of calories from fat to 25–30% and saturated fat to <7%, limit cholesterol to <200 mg/day, avoid *trans* fats, and aim for ∼10% calories from monounsaturated fats. **A**

14.41 After the age of 10 years, addition of a statin may be considered in youth with type 1 diabetes who, despite medical nutrition therapy and lifestyle changes, continue to have LDL cholesterol >160 mg/dL (4.1 mmol/L) or LDL cholesterol >130 mg/dL (3.4 mmol/L) and one or more cardiovascular disease risk factors. **E** Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and statins should be avoided in individuals of childbearing age who are not using reliable contraception. **B**

14.42 The goal of therapy is an LDL cholesterol value <100 mg/dL (2.6 mmol/L). **E**

Population-based studies estimate that 14–45% of children with type 1 diabetes have two or more atherosclerotic cardiovascular disease (ASCVD) risk factors (164–166), and the prevalence of cardiovascular disease (CVD) risk factors increase with age (166) and among racial/ethnic minorities (25), with girls having a higher risk burden than boys (165).

Pathophysiology. The atherosclerotic process begins in childhood, and although ASCVD events are not expected to occur during childhood, observations using a variety of methodologies show that youth with type 1 diabetes may have subclinical CVD within the first decade of diagnosis (167–169). Studies of carotid intima-

media thickness have yielded inconsistent results (162,163).

Screening. Diabetes predisposes to the development of accelerated arteriosclerosis. Lipid evaluation for these patients contributes to risk assessment and identifies an important proportion of those with dyslipidemia. Therefore, initial screening should be done soon after diagnosis. If the initial screen is normal, subsequent screening may be done at 9–11 years of age, which is a stable time for lipid assessment in children (170). Children with a primary lipid disorder (e.g., familial hyperlipidemia) should be referred to a lipid specialist. Non-HDL cholesterol level has been identified as a significant predictor of the presence of atherosclerosis—as powerful as any other lipoprotein cholesterol measure in children and adolescents. For both children and adults, non-HDL cholesterol level seems to be more predictive of persistent dyslipidemia and, therefore, atherosclerosis and future events than total cholesterol, LDL cholesterol, or HDL cholesterol levels alone. A major advantage of non-HDL cholesterol is that it can be accurately calculated in a nonfasting state and therefore is practical to obtain in clinical practice as a screening test (171). Youth with type 1 diabetes have a high prevalence of lipid abnormalities (164,172).

Even if normal, screening should be repeated within 3 years, as A1C and other cardiovascular risk factors can change dramatically during adolescence (173).

Treatment. Pediatric lipid guidelines provide some guidance relevant to children with type 1 diabetes and secondary dyslipidemia (162,170,174,175); however, there are few studies on modifying lipid levels in children with type 1 diabetes. A 6-month trial of dietary counseling produced a significant improvement in lipid levels (176); likewise, a lifestyle intervention trial with 6 months of exercise in adolescents demonstrated improvement in lipid levels (177). Data from the SEARCH for Diabetes in Youth (SEARCH) study show that improved glucose over a 2-year period is associated with a more favorable lipid profile; however, improved glycemia alone will not normalize lipids in youth with type 1 diabetes and dyslipidemia (173).

Although intervention data are sparse, the American Heart Association categorizes children with type 1 diabetes in the highest tier for cardiovascular risk and recommends both lifestyle and pharmacologic treatment for those with elevated LDL cholesterol levels (175,178). Initial therapy should include a nutrition plan that restricts saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day (170). Data from randomized clinical trials in children as young as 7 months of age indicate that this diet is safe and does not interfere with normal growth and development (179).

Neither long-term safety nor cardiovascular outcome efficacy of statin therapy has been established for children; however, studies have shown short-term safety equivalent to that seen in adults and efficacy in lowering LDL cholesterol levels in familial hypercholesterolemia or severe hyperlipidemia, improving endothelial function and causing regression of carotid intimal thickening (180,181). Statins are not approved for children aged <10 years, and statin treatment should generally not be used in children with type 1 diabetes before this age. Statins are contraindicated in pregnancy; therefore, the prevention of unplanned pregnancies is of paramount importance. Statins should be avoided in individuals of childbearing age who are not using reliable contraception (see Section 15, "Management of Diabetes in Pregnancy," for more information). The multicenter, randomized, placebo-controlled Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) provides safety data on pharmacologic treatment with an ACE inhibitor and statin in adolescents with type 1 diabetes (162).

Smoking

Recommendations

14.43 Elicit a smoking history at initial and follow-up diabetes visits; discourage smoking in youth who do not smoke and encourage smoking cessation in those who do smoke. **A**

14.44 Electronic cigarette use should be discouraged. **A**

The adverse health effects of smoking are well recognized with respect to future cancer and CVD risk. Despite this, smoking rates are significantly higher among youth with diabetes than among youth without diabetes (182,183). In youth with diabetes, it is important to avoid additional CVD risk factors. Smoking increases the risk of the onset of albuminuria; therefore, smoking avoidance is important to prevent both microvascular and macrovascular complications (170,184). Discouraging cigarette smoking, including electronic cigarettes (185, 186), is an important part of routine diabetes care. In light of CDC evidence of deaths related to electronic cigarette use (187,188), no individuals should be advised to use electronic cigarettes, either as a way to stop smoking tobacco or as a recreational drug. In younger children, it is important to assess exposure to cigarette smoke in the home because of the adverse effects of secondhand smoke and to discourage youth from ever smoking.

Microvascular Complications

Nephropathy Screening

Recommendation

14.45 Annual screening for albuminuria with a random (morning sample preferred to avoid effects of exercise) spot urine sample for albumin-to-creatinine ratio should be considered at puberty or at age >10 years, whichever is earlier, once the child has had diabetes for 5 years. **B**

Nephropathy Treatment

Recommendation

14.46 An ACE inhibitor or an angiotensin receptor blocker, titrated to normalization of albumin excretion, may be considered when elevated urinary albumin-to-creatinine ratio (>30 mg/g) is documented (two of three urine samples obtained over a 6-month interval following efforts to improve glycemia and normalize blood pressure). **E** Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and ACE inhibitors and angiotensin receptor blockers should be avoided in individuals of

childbearing age who are not using reliable contraception. B

Data from 7,549 participants <20 years of age in the T1D Exchange clinic registry emphasize the importance of meeting glycemic and blood pressure goals, particularly as diabetes duration increases, in order to reduce the risk of diabetic kidney disease. The data also underscore the importance of routine screening to ensure early diagnosis and timely treatment of albuminuria (189). An estimation of glomerular filtration rate (GFR), calculated using GFR estimating equations from the serum creatinine, height, age, and sex (190), should be considered at baseline and repeated as indicated based on clinical status, age, diabetes duration, and therapies. Improved methods are needed to screen for early GFR loss since estimated GFR is inaccurate at GFR >60 mL/min/1.73 m^2 (190,191). The AdDIT study in adolescents with type 1 diabetes demonstrated the safety of ACE inhibitor treatment, but the treatment did not change the albumin-to-creatinine ratio over the course of the study (162).

Retinopathy

Recommendations

14.47 An initial dilated and comprehensive eye examination is recommended once youth have had type 1 diabetes for 3–5 years, provided they are aged ≥11 years or puberty has started, whichever is earlier. B

14.48 After the initial examination, repeat dilated and comprehensive eye examination every 2 years. Less frequent examinations, every 4 years, may be acceptable on the advice of an eye care professional and based on risk factor assessment, including a history of A1C <8%. B

14.49 Programs that use retinal photography (with remote reading or use of a validated assessment tool) to improve access to diabetic retinopathy screening can be appropriate screening strategies for diabetic retinopathy. Such programs need to provide pathways for timely referral for a comprehensive eye examination when indicated. E

Retinopathy (like albuminuria) most commonly occurs after the onset of puberty and after 5–10 years of diabetes duration (192). It is currently recognized that there is a low risk of development of vision-threatening retinal lesions prior to 12 years of age (193,194). A 2019 publication based on the follow-up of the DCCT adolescent cohort supports a lower frequency of eye examinations than previously recommended, particularly in adolescents with A1C closer to the target range (195,196). Referrals should be made to eye care professionals with expertise in diabetic retinopathy and experience in counseling pediatric patients and families on the importance of prevention, early detection, and intervention.

Neuropathy

Recommendation

14.50 Consider an annual comprehensive foot exam at the start of puberty or at age ≥10 years, whichever is earlier, once the youth has had type 1 diabetes for 5 years. The examination should include inspection, assessment of foot pulses, pinprick, and 10-g monofilament sensation tests, testing of vibration sensation using a 128-Hz tuning fork, and ankle reflex tests. B

Diabetic neuropathy rarely occurs in prepubertal children or after only 1–2 years of diabetes (192), although data suggest a prevalence of distal peripheral neuropathy of 7% in 1,734 youth with type 1 diabetes and association with the presence of CVD risk factors (197,198). A comprehensive foot exam, including inspection, palpation of dorsalis pedis and posterior tibial pulses, and determination of proprioception, vibration, and monofilament sensation, should be performed annually along with an assessment of symptoms of neuropathic pain (198). Foot inspection can be performed at each visit to educate youth regarding the importance of foot care (see Section 12, "Retinopathy, Neuropathy, and Foot Care").

TYPE 2 DIABETES

For information on risk-based screening for type 2 diabetes and prediabetes in children and adolescents, please refer to Section 2, "Classification and Diagnosis of Diabetes." For additional support for these recommendations, see the ADA position statement "Evaluation and Management of Youth-Onset Type 2 Diabetes" (3).

The prevalence of type 2 diabetes in youth has continued to increase over the past 20 years (4). The CDC published projections for type 2 diabetes prevalence using the SEARCH database; assuming a 2.3% annual increase, the prevalence in those under 20 years of age will quadruple in 40 years (199,200).

Evidence suggests that type 2 diabetes in youth is different not only from type 1 diabetes but also from type 2 diabetes in adults and has unique features, such as a more rapidly progressive decline in β-cell function and accelerated development of diabetes complications (3,201). Long-term follow-up data from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study showed that a majority of individuals with type 2 diabetes diagnosed as youth had microvascular complications by young adulthood (202). Type 2 diabetes disproportionately impacts youth of ethnic and racial minorities and can occur in complex psychosocial and cultural environments, which may make it difficult to sustain healthy lifestyle changes and self-management behaviors (26,203–206). Additional risk factors associated with type 2 diabetes in youth include adiposity, family history of diabetes, female sex, and low socioeconomic status (201).

As with type 1 diabetes, youth with type 2 diabetes spend much of the day in school. Therefore, close communication with and the cooperation of school personnel are essential for optimal diabetes management, safety, and maximal academic opportunities.

Screening and Diagnosis

Recommendations

14.51 Risk-based screening for prediabetes and/or type 2 diabetes should be considered after the onset of puberty or ≥10 years of age, whichever occurs earlier, in youth with overweight (BMI ≥85th percentile) or obesity (BMI ≥95th percentile) and who have one or more additional risk factors for diabetes (see **Table 2.4** for evidence grading of other risk factors).

14.52 If screening is normal, repeat screening at a minimum of 3-year intervals **E**, or more frequently if BMI is increasing. **C**

14.53 Fasting plasma glucose, 2-h plasma glucose during a 75-g oral glucose tolerance test, and A1C can be used to test for prediabetes or diabetes in children and adolescents. **B**

14.54 Children and adolescents with overweight or obesity in whom the diagnosis of type 2 diabetes is being considered should have a panel of pancreatic autoantibodies tested to exclude the possibility of autoimmune type 1 diabetes. **B**

In the last decade, the incidence and prevalence of type 2 diabetes in adolescents has increased dramatically, especially in racial and ethnic minority populations (170, 207). A few studies suggest oral glucose tolerance tests or fasting plasma glucose values as more suitable diagnostic tests than A1C in the pediatric population, especially among certain ethnicities (208), although fasting glucose alone may overdiagnose diabetes in children (209,210). In addition, many of these studies do not recognize that diabetes diagnostic criteria are based on long-term health outcomes, and validations are not currently available in the pediatric population (211). An analysis of National Health and Nutrition Examination Survey (NHANES) data suggests using A1C for screening of high-risk youth (212).

The ADA acknowledges the limited data supporting A1C for diagnosing type 2 diabetes in children and adolescents. Although A1C is not recommended for diagnosis of diabetes in children with cystic fibrosis or symptoms suggestive of acute onset of type 1 diabetes, and only A1C assays without interference are appropriate for children with hemoglobinopathies, the ADA continues to recommend A1C for diagnosis of type 2 diabetes in this population (213,214).

Diagnostic Challenges

Given the current obesity epidemic, distinguishing between type 1 and type 2 diabetes in children can be difficult. Overweight and obesity are common in children with type 1 diabetes (27), and diabetes-associated autoantibodies and ketosis may be present in pediatric individuals with clinical features of type 2 diabetes (including obesity and acanthosis nigricans) (209). The presence of islet autoantibodies has been associated with faster progression to insulin deficiency (209). At the onset, DKA occurs in ~6% of youth aged 10–19 years with type 2 diabetes (215). Although uncommon, type 2 diabetes has been observed in prepubertal children under the age of 10 years, and thus it should be part of the differential in children with suggestive symptoms (216). Finally, obesity contributes to the development of type 1 diabetes in some individuals (217), which further blurs the lines between diabetes types. However, accurate diagnosis is critical, as treatment plans, educational approaches, dietary advice, and outcomes differ markedly between patients with the two diagnoses. The significant diagnostic difficulties posed by MODY are discussed in Section 2, "Classification and Diagnosis of Diabetes." In addition, there are rare and atypical diabetes cases that represent a challenge for clinicians and researchers.

Management

Lifestyle Management

Recommendations

14.55 All youth with type 2 diabetes and their families should receive comprehensive diabetes self-management education and support that is specific to youth with type 2 diabetes and is culturally appropriate. **B**

14.56 Youth with overweight/obesity and type 2 diabetes and their families should be provided with developmentally and culturally appropriate comprehensive lifestyle programs that are integrated with diabetes management to achieve a 7–10% decrease in excess weight. **C**

14.57 Given the necessity of long-term weight management for youth with type 2 diabetes, lifestyle intervention should be based on a chronic care model and offered in the context of diabetes care. **E**

14.58 Youth with prediabetes and type 2 diabetes, like all children and adolescents, should be encouraged to participate in at least 60 min of moderate to vigorous physical activity daily (with muscle and bone strength training at least 3 days/week) **B** and to decrease sedentary behavior. **C**

14.59 Nutrition for youth with prediabetes and type 2 diabetes, like for all children and adolescents, should focus on healthy eating patterns that emphasize consumption of nutrient-dense, high-quality foods and decreased consumption of calorie-dense, nutrient-poor foods, particularly sugar-added beverages. **B**

Glycemic Targets

Recommendations

14.60 Blood glucose monitoring should be individualized, taking into consideration the pharmacologic treatment of the patient. **E**

14.61 Real-time continuous glucose monitoring or intermittently scanned continuous glucose monitoring should be offered for diabetes management in youth with type 2 diabetes on multiple daily injections or insulin pumps who are capable of using the device safely (either by themselves or with a caregiver). The choice of device should be made based on an individual's and family's circumstances, desires, and needs. **E**

14.62 Glycemic status should be assessed every 3 months. **E**

14.63 A reasonable A1C target for most children and adolescents with type 2 diabetes is <7% (53 mmol/mol). More stringent A1C targets (such as <6.5% [48 mmol/mol]) may be appropriate for selected individuals if they can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate individuals might include those with a short duration of diabetes and lesser degrees of β-cell dysfunction and individuals treated with

lifestyle or metformin only who achieve significant weight improvement. E

14.64 Less stringent A1C goals (such as 7.5% [58 mmol/mol]) may be appropriate if there is an increased risk of hypoglycemia. E

14.65 A1C targets for individuals on insulin should be individualized, taking into account the relatively low rates of hypoglycemia in youth-onset type 2 diabetes. E

Pharmacologic Management

Recommendations

14.66 Initiate pharmacologic therapy, in addition to behavioral counseling for healthful nutrition and physical activity changes, at diagnosis of type 2 diabetes. A

14.67 In individuals with incidentally diagnosed or metabolically stable diabetes (A1C <8.5% [69 mmol/mol] and asymptomatic), metformin is the initial pharmacologic treatment of choice if renal function is normal. A

14.68 Youth with marked hyperglycemia (blood glucose ≥250 mg/dL [13.9 mmol/L], A1C ≥8.5% [69 mmol/mol]) without acidosis at diagnosis who are symptomatic with polyuria, polydipsia, nocturia, and/or weight loss should be treated initially with long-acting insulin while metformin is initiated and titrated. B

14.69 In individuals with ketosis/ketoacidosis, treatment with subcutaneous or intravenous insulin should be initiated to rapidly correct the hyperglycemia and the metabolic derangement. Once acidosis is resolved, metformin should be initiated while subcutaneous insulin therapy is continued. A

14.70 In individuals presenting with severe hyperglycemia (blood glucose ≥600 mg/dL [33.3 mmol/L]), consider assessment for hyperglycemic hyperosmolar nonketotic syndrome. A

14.71 If glycemic targets are no longer met with metformin (with or without long-acting insulin), glucagon-like peptide 1 receptor agonist therapy approved for youth with type 2 diabetes should be considered in children 10 years of age or older if they have no past medical history or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2. A

14.72 Individuals treated with metformin, a glucagon-like peptide 1 receptor agonist, and long-acting insulin who do not meet glycemic targets should be moved to multiple daily injections with long-acting and prandial insulins or insulin pump therapy. E

14.73 In individuals initially treated with insulin and metformin who are meeting glucose targets based on blood glucose monitoring, insulin can be tapered over 2–6 weeks by decreasing the insulin dose 10–30% every few days. B

14.74 Use of medications not approved by the U.S. Food and Drug Administration for youth with type 2 diabetes is not recommended outside of research trials. B

Treatment of youth-onset type 2 diabetes should include lifestyle management, diabetes self-management education and support, and pharmacologic treatment. Initial treatment of youth with obesity and diabetes must take into account that diabetes type is often uncertain in the first few weeks of treatment due to overlap in presentation and that a substantial percentage of youth with type 2 diabetes will present with clinically significant ketoacidosis (218). Therefore, initial therapy should address the hyperglycemia and associated metabolic derangements irrespective of ultimate diabetes type, with adjustment of therapy once metabolic compensation has been established and subsequent information, such as islet autoantibody results, becomes available. **Figure 14.1** provides an approach to the initial treatment of new-onset diabetes in youth with overweight or obesity with clinical suspicion of type 2 diabetes.

Glycemic targets should be individualized, taking into consideration the long-term health benefits of more stringent targets and risk for adverse effects, such as hypoglycemia. A lower target A1C in youth with type 2 diabetes when compared with those recommended in type 1 diabetes is justified by a lower risk of hypoglycemia and higher risk of complications (202,219–222).

Self-management in pediatric diabetes involves both the youth and their parents/adult caregivers. Individuals and their families should receive education and support for healthful nutrition and physical activity such as a balanced meal plan, achieving and maintaining a healthy weight, and regular physical activity. Physical activity should include aerobic, muscle-strengthening, and bone-strengthening activities (17). A family-centered approach to nutrition and lifestyle modification is essential in children and adolescents with type 2 diabetes, and nutrition recommendations should be culturally appropriate and sensitive to family resources (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes"). Given the complex social and environmental context surrounding youth with type 2 diabetes, individual-level lifestyle interventions may not be sufficient to target the complex interplay of family dynamics, mental health, community readiness, and the broader environmental system (3).

A multidisciplinary diabetes team, including a physician, diabetes care and education specialist, registered dietitian nutritionist, and psychologist or social worker, is essential. In addition to achieving glycemic targets and self-management education (223–225), initial treatment must include management of comorbidities such as obesity, dyslipidemia, hypertension, and microvascular complications.

Current pharmacologic treatment options for youth-onset type 2 diabetes are limited to three approved drugs classes: insulin, metformin, and glucagon-like peptide 1 receptor agonists. Presentation with ketoacidosis or marked ketosis requires a period of insulin therapy until fasting and postprandial glycemia have been restored to normal or near-normal levels. Insulin pump therapy may be considered as an option for those on long-term multiple daily injections who are able

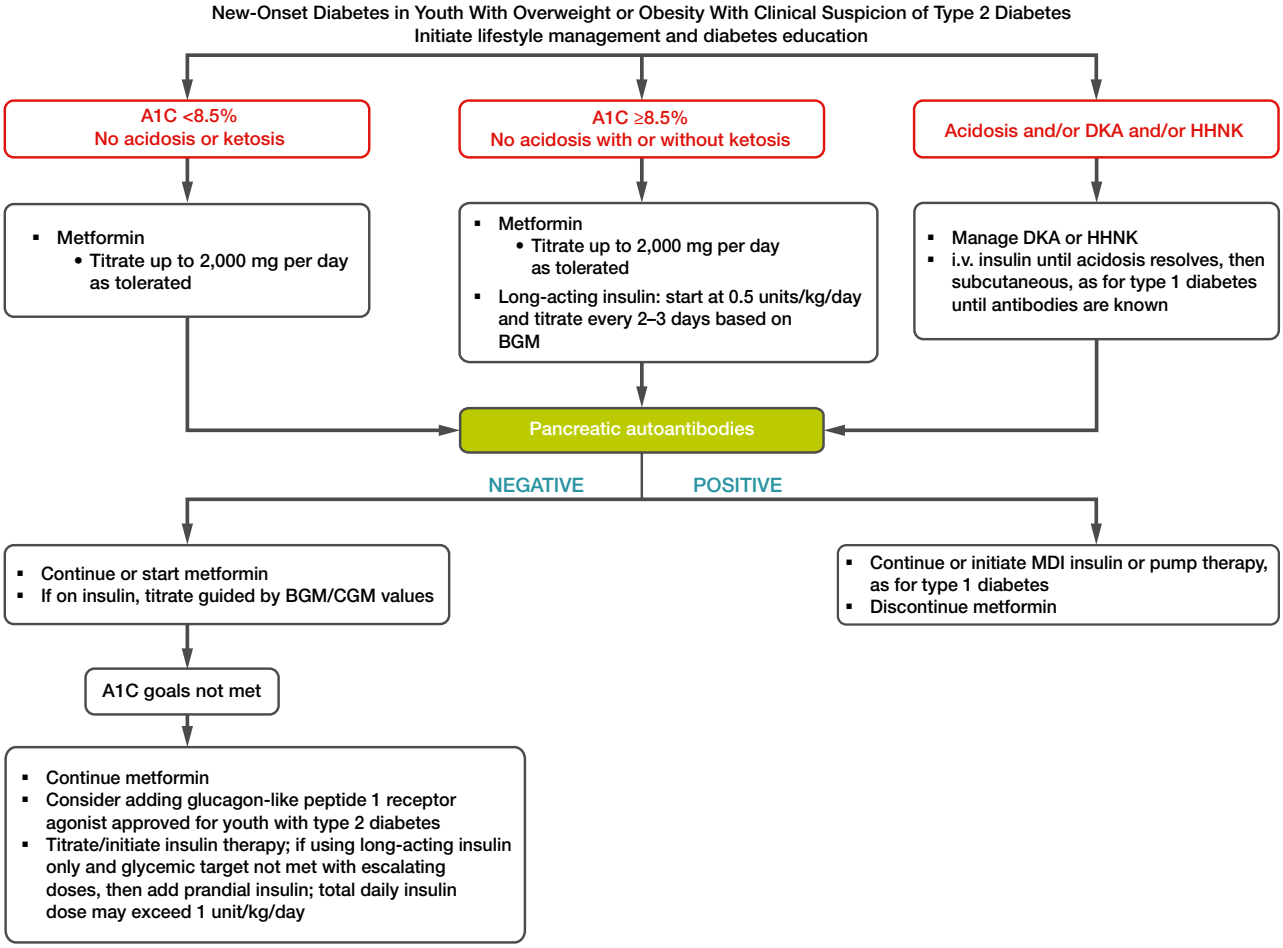

Figure 14.1—Management of new-onset diabetes in youth with overweight or obesity with clinical suspicion of type 2 diabetes. A1C 8.5% = 69 mmol/mol. Adapted from the ADA position statement "Evaluation and Management of Youth-Onset Type 2 Diabetes" (3). BGM, blood glucose monitoring; CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; HHNK, hyperosmolar hyperglycemic nonketotic syndrome; i.v., intravenous; MDI, multiple daily injections.

to safely manage the device. Initial treatment should also be with insulin when the distinction between type 1 diabetes and type 2 diabetes is unclear and in patients who have random blood glucose concentrations ≥250 mg/dL (13.9 mmol/L) and/or A1C ≥8.5% (69 mmol/mol) (226). Metformin therapy should be added after resolution of ketosis/ketoacidosis.

When initial insulin treatment is not required, initiation of metformin is recommended. The TODAY study found that metformin alone provided durable glycemic control (A1C ≤8% [64 mmol/mol] for 6 months) in approximately half of the subjects (227). The Restoring Insulin Secretion (RISE) Consortium study did not demonstrate differences in measures of glucose or β-cell function preservation between metformin and insulin, but there was more weight gain with insulin (228).

To date, the TODAY study is the only trial combining lifestyle and metformin therapy in youth with type 2 diabetes; the combination did not perform better than metformin alone in achieving durable glycemic control (227).

A randomized clinical trial in youth aged 10–17 years with type 2 diabetes demonstrated the addition of subcutaneous liraglutide (up to 1.8 mg daily) to metformin (with or without long-acting insulin) as safe and effective to decrease A1C (estimated decrease of 1.06 percentage points at 26 weeks and 1.30 percentage points at 52 weeks), although it did increase the frequency of gastrointestinal side effects (229). Liraglutide and once-weekly exenatide extended release are approved for the treatment of type 2 diabetes in youth aged 10 years or older (230–232).

Blood glucose monitoring plans should be individualized, taking into consideration the pharmacologic treatment of the person. Although data on CGM in youth with type 2 diabetes are sparse (233), CGM could be considered in individuals requiring frequent blood glucose monitoring for diabetes management.

Metabolic Surgery

Recommendations

14.75 Metabolic surgery may be considered for the treatment of adolescents with type 2 diabetes who have severe obesity (BMI >35 kg/m^2) and who have elevated A1C and/or serious comorbidities despite lifestyle and pharmacologic intervention. **A**

14.76 Metabolic surgery should be performed only by an experienced surgeon working as part of a well-organized and engaged multidisciplinary team, including a

surgeon, endocrinologist, registered dietitian nutritionist, behavioral health specialist, and nurse. A

The results of weight loss and lifestyle interventions for obesity in children and adolescents have been disappointing, and treatment options as adjuncts to lifestyle therapy are limited. Recent U.S. Food and Drug Administration–approved medications for youth ages 12 and older include phentermine and topiramate extended-release capsules and liraglutide (234–236). Over the last decade, weight loss surgery has been increasingly performed in adolescents with obesity. Small retrospective analyses and a prospective multicenter, nonrandomized study suggest that bariatric or metabolic surgery may have benefits in adolescents with obesity and type 2 diabetes similar to those observed in adults. Teenagers experience similar degrees of weight loss, diabetes remission, and improvement of cardiometabolic risk factors for at least 3 years after surgery (237). A secondary data analysis from the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) and TODAY studies suggests surgical treatment of adolescents with severe obesity and type 2 diabetes is associated with improved glycemia (238); however, no randomized trials have yet compared the effectiveness and safety of surgery to those of conventional treatment options in adolescents (239). The guidelines used as an indication for metabolic surgery in adolescents generally include BMI >35 kg/m^2 with comorbidities or BMI >40 kg/m^2 with or without comorbidities (240–251). A number of groups, including the Pediatric Bariatric Study Group and Teen-LABS study, have demonstrated the effectiveness of metabolic surgery in adolescents (244–250).

Prevention and Management of Diabetes Complications

Hypertension

Recommendations

14.77 Blood pressure should be measured at every visit. In youth with high blood pressure (blood pressure ≥90th percentile for age, sex, and height or, in adolescents aged ≥13 years, ≥120/80 mmHg) on three separate measurements, ambulatory blood pressure monitoring should be strongly considered. B

14.78 Treatment of elevated blood pressure (defined as 90th to <95th percentile for age, sex, and height or, in adolescents aged ≥13 years, 120–129/<80 mmHg) is lifestyle modification focused on healthy nutrition, physical activity, sleep, and, if appropriate, weight management. C

14.79 In addition to lifestyle modification, ACE inhibitors or angiotensin receptor blockers should be started for treatment of confirmed hypertension (defined as blood pressure consistently ≥95th percentile for age, sex, and height or, in adolescents aged ≥13 years, ≥130/80 mmHg). Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and ACE inhibitors and angiotensin receptor blockers should be avoided in individuals of childbearing age who are not using reliable contraception. B

14.80 The goal of treatment is blood pressure <90th percentile for age, sex, and height or, in adolescents aged ≥13 years, <130/80 mmHg. C

Nephropathy

Recommendations

14.81 Protein intake should be at the recommended daily allowance of 0.8 g/kg/day. E

14.82 Urine albumin-to-creatinine ratio should be obtained at the time of diagnosis and annually thereafter. An elevated urine albumin-to-creatinine ratio (>30 mg/g creatinine) should be confirmed on two of three samples. B

14.83 Estimated glomerular filtration rate should be determined at the time of diagnosis and annually thereafter. E

14.84 In youth with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin-to-creatinine ratio (30–299 mg/g creatinine) and is strongly recommended for those with urinary albumin-to-creatinine ratio >300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. E Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and ACE inhibitors and angiotensin receptor blockers should be avoided in individuals of childbearing age who are not using reliable contraception. B

14.85 For those with nephropathy, continued monitoring (yearly urinary albumin-to-creatinine ratio, estimated glomerular filtration rate, and serum potassium) may aid in assessing engagement and detecting progression of disease. E

14.86 Referral to nephrology is recommended in case of uncertainty of etiology, worsening urinary albumin-to-creatinine ratio, or decrease in estimated glomerular filtration rate. E

Neuropathy

Recommendations

14.87 Youth with type 2 diabetes should be screened for the presence of neuropathy by foot examination at diagnosis and annually. The examination should include inspection, assessment of foot pulses, pinprick and 10-g monofilament sensation tests, testing of vibration sensation using a 128-Hz tuning fork, and ankle reflex tests. C

14.88 Prevention should focus on achieving glycemic targets. C

Retinopathy

Recommendations

14.89 Screening for retinopathy should be performed by dilated fundoscopy at or soon after diagnosis and annually thereafter. C

14.90 Optimizing glycemia is recommended to decrease the risk

or slow the progression of retinopathy. B

14.91 Less frequent examination (every 2 years) may be considered if achieving glycemic targets and a normal eye exam. C

14.92 Programs that use retinal photography (with remote reading or use of a validated assessment tool) to improve access to diabetic retinopathy screening can be appropriate screening strategies for diabetic retinopathy. Such programs need to provide pathways for timely referral for a comprehensive eye examination when indicated. E

Nonalcoholic Fatty Liver Disease

Recommendations

14.93 Evaluation for nonalcoholic fatty liver disease (by measuring AST and ALT) should be done at diagnosis and annually thereafter. B

14.94 Referral to gastroenterology should be considered for persistently elevated or worsening transaminases. B

Obstructive Sleep Apnea

Recommendation

14.95 Screening for symptoms of sleep apnea should be done at each visit, and referral to a pediatric sleep specialist for evaluation and a polysomnogram, if indicated, is recommended. Obstructive sleep apnea should be treated when documented. B

Polycystic Ovary Syndrome

Recommendations

14.96 Evaluate for polycystic ovary syndrome in female adolescents with type 2 diabetes, including laboratory studies, when indicated. B

14.97 Oral contraceptive pills for treatment of polycystic ovary syndrome are not contraindicated for female individuals with type 2 diabetes. C

14.98 Metformin, in addition to lifestyle modification, is likely to improve the menstrual cyclicity and hyperandrogenism in female individuals with type 2 diabetes. E

Cardiovascular Disease

Recommendation

14.99 Intensive lifestyle interventions focusing on weight loss, dyslipidemia, hypertension, and dysglycemia are important to prevent overt macrovascular disease in early adulthood. E

Dyslipidemia

Recommendations

14.100 Lipid screening should be performed initially after optimizing glycemia and annually thereafter. B

14.101 Optimal goals are LDL cholesterol <100 mg/dL (2.6 mmol/L), HDL cholesterol >35 mg/dL (0.91 mmol/L), and triglycerides <150 mg/dL (1.7 mmol/L). E

14.102 If lipids are abnormal, initial therapy should consist of optimizing glycemia and medical nutritional therapy to limit the amount of calories from fat to 25–30% and saturated fat to <7%, limit cholesterol to <200 mg/day, avoid *trans* fats, and aim for ~10% calories from monounsaturated fats for elevated LDL. For elevated triglycerides, medical nutrition therapy should also focus on decreasing simple sugar intake and increasing dietary n-3 fatty acids in addition to the above changes. A

14.103 If LDL cholesterol remains >130 mg/dL after 6 months of dietary intervention, initiate therapy with statin, with a goal of LDL <100 mg/dL. Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and statins should be avoided in individuals of childbearing age who are not using reliable contraception. B

14.104 If triglycerides are >400 mg/dL (4.7 mmol/L) fasting or >1,000 mg/dL (11.6 mmol/L) nonfasting, optimize glycemia and begin fibrate, with a goal of <400 mg/dL (4.7 mmol/L) fasting to reduce risk for pancreatitis. C

Cardiac Function Testing

Recommendation

14.105 Routine screening for heart disease with electrocardiogram, echocardiogram, or stress testing is not recommended in asymptomatic youth with type 2 diabetes. B

Comorbidities may already be present at the time of diagnosis of type 2 diabetes in youth (201,252). Therefore, blood pressure measurement, a fasting lipid panel, assessment of random urine albumin-to-creatinine ratio, and a dilated eye examination should be performed at diagnosis. Additional medical conditions that may need to be addressed include polycystic ovary disease and other comorbidities associated with pediatric obesity, such as sleep apnea, hepatic steatosis, orthopedic complications, and psychosocial concerns. The ADA position statement "Evaluation and Management of Youth-Onset Type 2 Diabetes" (3) provides guidance on the prevention, screening, and treatment of type 2 diabetes and its comorbidities in children and adolescents.

Youth-onset type 2 diabetes is associated with significant microvascular and macrovascular risk burden and a substantial increase in the risk of cardiovascular morbidity and mortality at an earlier age than in those diagnosed later in life (202,253). The higher complication risk in earlier-onset type 2 diabetes is likely related to prolonged lifetime exposure to hyperglycemia and other atherogenic risk factors, including insulin resistance, dyslipidemia, hypertension, and chronic inflammation. There is a low risk of hypoglycemia in youth with type 2 diabetes, even if they are being treated with insulin (254), and there are high rates of complications (219–222).

These diabetes comorbidities also appear to be higher than in youth with type 1 diabetes despite shorter diabetes duration and lower A1C (252). In addition, the progression of vascular abnormalities appears to be more pronounced in youth-onset type 2 diabetes than with type 1 diabetes of similar duration, including ischemic heart disease and stroke (255).

Psychosocial Factors

Recommendations

14.106 Health care professionals should screen for food insecurity, housing instability/homelessness, health literacy, financial barriers, and social/community support and apply that information to treatment decisions. **E**

14.107 Use age-appropriate standardized and validated tools to screen for diabetes distress, depressive symptoms, and mental/behavioral health in youth with type 2 diabetes, with attention to symptoms of depression and disordered eating, and refer to a qualified mental health professional when indicated. **B**

14.108 When choosing glucose-lowering or other medications for youth with overweight or obesity and type 2 diabetes, consider medication-taking behavior and the medications' effect on weight. **E**

14.109 Starting at puberty, preconception counseling should be incorporated into routine diabetes clinic visits for all individuals of childbearing potential because of the adverse pregnancy outcomes in this population. **A**

14.110 Adolescents and young adults should be screened for tobacco, electronic cigarettes, and alcohol use at diagnosis and regularly thereafter. **C**

Most youth with type 2 diabetes come from racial/ethnic minority groups, have low socioeconomic status, and often experience multiple psychosocial stressors (26,43,205,206). Consideration of the sociocultural context and efforts to personalize diabetes management are of critical importance to minimize barriers to care, enhance participation, and maximize response to treatment.

Evidence about psychiatric disorders and symptoms in youth with type 2 diabetes is limited (256–260), but given the sociocultural context for many youth and the medical burden and obesity associated with type 2 diabetes, ongoing surveillance of mental health/behavioral health is indicated. Symptoms of depression and disordered eating are common and associated with poorer glycemic control (39,257,261,262).

Many of the medications prescribed for diabetes and psychiatric disorders are associated with weight gain and can increase concerns about eating, body shape, and weight (263,264).

The TODAY study documented high rates of maternal complications during pregnancy and low rates of preconception counseling and contraception use (265).

TRANSITION FROM PEDIATRIC TO ADULT CARE

Recommendations

14.111 Pediatric diabetes care teams should begin to prepare youth for transition to adult health care in early adolescence and, at the latest, at least 1 year before the transition. **E**

14.112 Both pediatric and adult diabetes care professionals should provide support and resources for transitioning young adults. **E**

14.113 Youth with type 2 diabetes should be transferred to an adult-oriented diabetes specialist when deemed appropriate by the young adult and health care professional. **E**

Care and close supervision of diabetes management are increasingly shifted from parents and other adults to the youth with type 1 or type 2 diabetes throughout childhood and adolescence. The shift from pediatric to adult health care professionals, however, often occurs abruptly as the older teen enters the next developmental stage, referred to as emerging adulthood (266), which is a critical period for young people who have diabetes. During this period of major life transitions, youth may begin to move out of their parents' homes and become increasingly responsible for their diabetes care. Their new responsibilities include self-management of their diabetes, making medical appointments, and financing health care once they are no longer covered by their parents' health insurance plans (ongoing coverage until age 26 years is currently available under provisions of the U.S. Affordable Care Act). In addition to lapses in health care, this is also a period associated with deterioration in glycemic stability; increased occurrence of acute complications; psychosocial, emotional, and behavioral challenges; and the emergence of chronic complications (267–272). The transition period from pediatric to adult care is prone to fragmentation in health care delivery, which may adversely impact health care quality, cost, and outcomes (273). Worsening diabetes health outcomes during the transition to adult care and early adulthood have been documented (274,275).

Although scientific evidence is limited, it is clear that comprehensive and coordinated planning that begins in early adolescence is necessary to facilitate a seamless transition from pediatric to adult health care (267,268,276,277). New technologies and other interventions are being tried to support the transition to adult care in young adulthood (278–282). Given the behavioral, psychosocial, and developmental factors that relate to this transition, diabetes care teams addressing transition should include social workers, psychologists, and other behavioral health professionals, as available (51,283). A comprehensive discussion regarding the challenges faced during this period, including specific recommendations, is found in the ADA position statement "Diabetes Care for Emerging Adults: Recommendations for Transition From Pediatric to Adult Diabetes Care Systems" (268).

The Endocrine Society, in collaboration with the ADA and other organizations, has developed transition tools for clinicians and youth and families (277).

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15. Management of Diabetes in Pregnancy: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

DIABETES IN PREGNANCY

The prevalence of diabetes in pregnancy has been increasing in the U.S. in parallel with the worldwide epidemic of obesity. Not only is the prevalence of type 1 diabetes and type 2 diabetes increasing in individuals of reproductive age, but there is also a dramatic increase in the reported rates of gestational diabetes mellitus (GDM). Diabetes confers significantly greater maternal and fetal risk largely related to the degree of hyperglycemia but also related to chronic complications and comorbidities of diabetes. In general, specific risks of diabetes in pregnancy include spontaneous abortion, fetal anomalies, preeclampsia, fetal demise, macrosomia, neonatal hypoglycemia, hyperbilirubinemia, and neonatal respiratory distress syndrome, among others. In addition, diabetes in pregnancy may increase the risk of obesity, hypertension, and type 2 diabetes in offspring later in life (1,2).

Preconception Counseling

Recommendations

15.1 Starting at puberty and continuing in all people with diabetes and reproductive potential, preconception counseling should be incorporated into routine diabetes care. **A**

15.2 Family planning should be discussed, and effective contraception (with consideration of long-acting, reversible contraception) should be prescribed and used until an individual's treatment plan and A1C are optimized for pregnancy. **A**

15.3 Preconception counseling should address the importance of achieving glucose levels as close to normal as is safely possible, ideally A1C $<6.5\%$ (48 mmol/mol), to reduce the risk of congenital anomalies, preeclampsia, macrosomia, preterm birth, and other complications. **A**

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All individuals with diabetes and reproductive potential should be informed about the importance of achieving and maintaining as near euglycemia as safely possible prior to conception and throughout pregnancy. Observational studies show an increased risk of diabetic embryopathy, especially anencephaly, microcephaly, congenital heart disease, renal anomalies, and caudal regression, directly proportional to elevations in A1C during the first 10 weeks of pregnancy (3). Although observational studies are confounded by the association between elevated periconceptional A1C and other engagement in self-care behaviors, the quantity and consistency of data are convincing and support the recommendation to optimize glycemia prior to conception, given that organogenesis occurs primarily at 5–8 weeks of gestation, with an A1C <6.5% (48 mmol/mol), which is associated with the lowest risk of congenital anomalies, preeclampsia, and preterm birth (3–7). A systematic review and meta-analysis of observational studies of preconception care for pregnant individuals with preexisting diabetes demonstrated lower A1C and reduced risk of birth defects, preterm delivery, perinatal mortality, small-for-gestational-age births, and neonatal intensive care unit admission (8).

There are opportunities to educate all adults and adolescents with diabetes and reproductive potential about the risks of unplanned pregnancies and about improved maternal and fetal outcomes with pregnancy planning (8). Effective preconception counseling could avert substantial health and associated cost burdens in offspring (9). Family planning should be discussed, including the benefits of long-acting, reversible contraception, and effective contraception should be prescribed and used until the individual is prepared and ready to become pregnant (10–14).

To minimize the occurrence of complications, beginning at the onset of puberty or at diagnosis, all adults and adolescents with diabetes of childbearing potential should receive education about *1*) the risks of malformations associated with unplanned pregnancies and even mild hyperglycemia and *2*) the use of effective contraception at all times when preventing a pregnancy. Preconception counseling using developmentally appropriate educational tools enables adolescent girls to make well-informed decisions (8). Preconception counseling resources tailored for adolescents are available at no cost through the American Diabetes Association (ADA) (15).

Preconception Care

Recommendations

15.4 Individuals with preexisting diabetes who are planning a pregnancy should ideally begin receiving care in preconception at a multidisciplinary clinic including an endocrinologist, maternal-fetal medicine specialist, registered dietitian nutritionist, and diabetes care and education specialist, when available. **B**

15.5 In addition to focused attention on achieving glycemic targets **A**, standard preconception care should be augmented with extra focus on nutrition, diabetes education, and screening for diabetes comorbidities and complications. **B**

15.6 Individuals with preexisting type 1 or type 2 diabetes who are planning a pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. Dilated eye examinations should occur ideally before pregnancy or in the first trimester, and then pregnant individuals should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy and as recommended by the eye care health care professional. **B**

The importance of preconception care for all pregnant people is highlighted by American College of Obstetricians and Gynecologists (ACOG) Committee Opinion 762, "Prepregnancy Counseling" (16). Preconception counseling for pregnant people with preexisting type 1 or type 2 diabetes is highly effective in reducing the risk of congenital malformations and decreasing the risk of preterm delivery and admission to neonatal intensive care units. Preconception counseling likely also reduces perinatal mortality and small-for-gestational-age birth weight (17). A key point is the need to incorporate a question about plans for pregnancy into the routine primary and gynecologic care of people with diabetes. Preconception care for people with diabetes should include the standard screenings and care recommended for any person planning pregnancy (16). Prescription of prenatal vitamins with at least 400 μg of folic acid and 150 μg of potassium iodide (18) is recommended prior to conception. Review and counseling on the use of nicotine products, alcohol, and recreational drugs, including marijuana, is important. Standard care includes screening for sexually transmitted diseases and thyroid disease, recommended vaccinations, routine genetic screening, a careful review of all prescription and nonprescription medications and supplements used, and a review of travel history and plans with special attention to areas known to have Zika virus, as outlined by ACOG. See **Table 15.1** for additional details on elements of preconception care (16,19).

Counseling on the specific risks of obesity in pregnancy and lifestyle interventions to prevent and treat obesity, including referral to a registered dietitian nutritionist (RDN), is recommended.

Diabetes-specific counseling should include an explanation of the risks to mother and fetus related to pregnancy and the ways to reduce risk, including glycemic goal setting, lifestyle and behavioral management, and medical nutrition therapy (17). The most important diabetes-specific component of preconception care is the attainment of glycemic goals prior to conception. In addition, the presence of microvascular complications is associated with higher risk of disease progression and adverse pregnancy outcomes (20). Diabetes-specific testing should include A1C, creatinine, and urinary albumin-to-creatinine ratio. Special attention should be paid to the review of the medication list for potentially harmful drugs, i.e., ACE inhibitors (21,22), angiotensin receptor blockers (21), and statins (22,23). A referral for a comprehensive eye exam is recommended. Individuals with preexisting diabetic retinopathy will need close monitoring during pregnancy to assess for the progression of retinopathy and provide treatment if indicated (24).

GLYCEMIC TARGETS IN PREGNANCY

Recommendations

15.7 Fasting and postprandial blood glucose monitoring are recommended in both gestational diabetes mellitus and preexisting diabetes in pregnancy to achieve optimal glucose levels. Glucose targets are fasting plasma glucose <95 mg/dL (5.3 mmol/L) and either 1-h postprandial glucose <140 mg/dL (7.8 mmol/L) or 2-h postprandial glucose <120 mg/dL (6.7 mmol/L). Some individuals with preexisting diabetes should also check blood glucose preprandially. **B**

15.8 Due to increased red blood cell turnover, A1C is slightly lower during pregnancy in people with and without diabetes. Ideally, the A1C target in pregnancy is <6% (42 mmol/mol) if this can be achieved without significant hypoglycemia, but the target may be relaxed to <7% (53 mmol/mol) if necessary to prevent hypoglycemia. **B**

15.9 When used in addition to pre- and postprandial blood glucose monitoring, continuous glucose monitoring can help to achieve the A1C target in diabetes and pregnancy. **B**

15.10 When used in addition to blood glucose monitoring, targeting traditional pre- and postprandial targets, real-time continuous glucose monitoring can reduce macrosomia and neonatal hypoglycemia in pregnancy complicated by type 1 diabetes. **B**

15.11 Continuous glucose monitoring metrics may be used in addition to but should not be used as a substitute for blood glucose monitoring to achieve optimal pre- and postprandial glycemic targets. **E**

15.12 Commonly used estimated A1C and glucose management indicator calculations should not be used in pregnancy as estimates of A1C. **C**

15.13 Nutrition counseling should endorse a balance of macronutrients

Table 15.1—Checklist for preconception care for people with diabetes (16,19)

Preconception education should include:

- ☐ Comprehensive nutrition assessment and recommendations for:
  - Overweight/obesity or underweight
  - Meal planning
  - Correction of dietary nutritional deficiencies
  - Caffeine intake
  - Safe food preparation technique
- ☐ Lifestyle recommendations for:
  - Regular moderate exercise
  - Avoidance of hyperthermia (hot tubs)
  - Adequate sleep
- ☐ Comprehensive diabetes self-management education
- ☐ Counseling on diabetes in pregnancy per current standards, including natural history of insulin resistance in pregnancy and postpartum; preconception glycemic targets; avoidance of DKA/severe hyperglycemia; avoidance of severe hypoglycemia; progression of retinopathy; PCOS (if applicable); fertility in people with diabetes; genetics of diabetes; risks to pregnancy including miscarriage, still birth, congenital malformations, macrosomia, preterm labor and delivery, hypertensive disorders in pregnancy, etc.
- ☐ Supplementation
  - Folic acid supplement (400 μg routine)
  - Appropriate use of over-the-counter medications and supplements

Health assessment and plan should include:

- ☐ General evaluation of overall health
- ☐ Evaluation of diabetes and its comorbidities and complications, including DKA/severe hyperglycemia; severe hypoglycemia/hypoglycemia unawareness; barriers to care; comorbidities such as hyperlipidemia, hypertension, NAFLD, PCOS, and thyroid dysfunction; complications such as macrovascular disease, nephropathy, neuropathy (including autonomic bowel and bladder dysfunction), and retinopathy
- ☐ Evaluation of obstetric/gynecologic history, including a history of: cesarean section, congenital malformations or fetal loss, current methods of contraception, hypertensive disorders of pregnancy, postpartum hemorrhage, preterm delivery, previous macrosomia, Rh incompatibility, and thrombotic events (DVT/PE)
- ☐ Review of current medications and appropriateness during pregnancy

Screening should include:

- ☐ Diabetes complications and comorbidities, including comprehensive foot exam; comprehensive ophthalmologic exam; ECG in individuals starting at age 35 years who have cardiac signs/symptoms or risk factors and, if abnormal, further evaluation; lipid panel; serum creatinine; TSH; and urine protein-to-creatinine ratio
- ☐ Anemia
- ☐ Genetic carrier status (based on history):
  - Cystic fibrosis
  - Sickle cell anemia
  - Tay-Sachs disease
  - Thalassemia
  - Others if indicated
- ☐ Infectious disease
  - *Neisseria gonorrhoeae/Chlamydia trachomatis*
  - Hepatitis C
  - HIV
  - Pap smear
  - Syphilis

Immunizations should include:

- ☐ Rubella
- ☐ Varicella
- ☐ Hepatitis B
- ☐ Influenza
- ☐ Others if indicated

Preconception plan should include:

- ☐ Nutrition and medication plan to achieve glycemic targets prior to conception, including appropriate implementation of monitoring, continuous glucose monitoring, and pump technology
- ☐ Contraceptive plan to prevent pregnancy until glycemic targets are achieved
- ☐ Management plan for general health, gynecologic concerns, comorbid conditions, or complications, if present, including hypertension, nephropathy, retinopathy; Rh incompatibility; and thyroid dysfunction

DKA, diabetic ketoacidosis; DVT/PE, deep vein thrombosis/pulmonary embolism; ECG, electrocardiogram; NAFLD, nonalcoholic fatty liver disease; PCOS, polycystic ovary syndrome; TSH, thyroid-stimulating hormone.

including nutrient-dense fruits, vegetables, legumes, whole grains, and healthy fats with n-3 fatty acids that include nuts and seeds and fish in the eating pattern. E

Pregnancy in people with normal glucose metabolism is characterized by fasting levels of blood glucose that are lower than in the nonpregnant state due to insulin-independent glucose uptake by the fetus and placenta and by mild postprandial hyperglycemia and carbohydrate intolerance as a result of diabetogenic placental hormones. In people with preexisting diabetes, glycemic targets are usually achieved through a combination of insulin administration and medical nutrition therapy. Because glycemic targets in pregnancy are stricter than in nonpregnant individuals, it is important that pregnant people with diabetes eat consistent amounts of carbohydrates to match with insulin dosage and to avoid hyperglycemia or hypoglycemia. Referral to an RDN is important to establish a food plan and insulin-to-carbohydrate ratio and determine weight gain goals. The quality of the carbohydrates should be evaluated. A subgroup analysis of the Continuous Glucose Monitoring in Pregnant Women With Type 1 Diabetes Trial (CONCEPTT) study demonstrated that the diets of individuals planning pregnancy and currently pregnant assessed during the run-in phase prior to randomization were characterized by high-fat, low-fiber, and poor-quality carbohydrate intakes. Fruit and vegetable consumption was inadequate, with one in four participants at risk for micronutrient deficiencies, highlighting the importance of medical nutrition therapy (25). An expert panel on nutrition in pregnancy recommends a balance of macronutrients. A diet that severely restricts any macronutrient class should be avoided, specifically the ketogenic diet that lacks carbohydrates, the Paleo diet because of dairy restriction, and any diet characterized by excess saturated fats. Nutrient-dense, whole foods are recommended, including fruits, vegetables, legumes, whole grains, and healthy fats with n-3 fatty acids that include nuts and seeds and fish, which are less likely to promote excessive weight gain. Processed foods, fatty red meat, and sweetened foods and beverages should be limited (26).

Insulin Physiology

Given that early pregnancy is a time of enhanced insulin sensitivity and lower glucose levels, many people with type 1 diabetes will have lower insulin requirements and an increased risk for hypoglycemia (27). Around 16 weeks, insulin resistance begins to increase, and total daily insulin doses increase linearly ~5% per week through week 36. This usually results in a doubling of daily insulin dose compared with the prepregnancy requirement. The insulin requirement levels off toward the end of the third trimester with placental aging. A rapid reduction in insulin requirements can indicate the development of placental insufficiency (28). In people with normal pancreatic function, insulin production is sufficient to meet the challenge of this physiological insulin resistance and to maintain normal glucose levels. However, in people with diabetes, hyperglycemia occurs if treatment is not adjusted appropriately.

Glucose Monitoring

Reflecting this physiology, fasting and postprandial blood glucose monitoring is recommended to achieve metabolic control in pregnant people with diabetes. Preprandial testing is also recommended when using insulin pumps or basal-bolus therapy so that premeal rapid-acting insulin dosage can be adjusted. Postprandial monitoring is associated with better glycemic outcomes and a lower risk of preeclampsia (29–31). There are no adequately powered randomized trials comparing different fasting and postmeal glycemic targets in diabetes in pregnancy.

Similar to the targets recommended by ACOG (upper limits are the same as for GDM, described below) (32), the ADA-recommended targets for pregnant people with type 1 or type 2 diabetes are as follows:

- Fasting glucose 70–95 mg/dL (3.9–5.3 mmol/L) and either
- One-hour postprandial glucose 110–140 mg/dL (6.1–7.8 mmol/L) or
- Two-hour postprandial glucose 100–120 mg/dL (5.6–6.7 mmol/L)

Lower limits are based on the mean of normal blood glucose in pregnancy (33). Lower limits do not apply to individuals with type 2 diabetes treated with nutrition alone. Hypoglycemia in pregnancy is as defined and treated in Recommendations 6.10–6.15 (Section 6, "Glycemic Targets"). These values represent optimal control if they can be achieved safely. In practice, it may be challenging for a person with type 1 diabetes to achieve these targets without hypoglycemia, particularly those with a history of recurrent hypoglycemia or hypoglycemia unawareness. If an individual cannot achieve these targets without significant hypoglycemia, the ADA suggests less-stringent targets based on clinical experience and individualization of care.

A1C in Pregnancy

In studies of individuals without preexisting diabetes, increasing A1C levels within the normal range are associated with adverse outcomes (34). In the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, increasing levels of glycemia were also associated with worsening outcomes (35). Observational studies in preexisting diabetes and pregnancy show the lowest rates of adverse fetal outcomes in association with A1C <6–6.5% (42–48 mmol/mol) early in gestation (4–6,36). Clinical trials have not evaluated the risks and benefits of achieving these targets, and treatment goals should account for the risk of maternal hypoglycemia in setting an individualized target of <6% (42 mmol/mol) to <7% (53 mmol/mol). Due to physiological increases in red blood cell turnover, A1C levels fall during normal pregnancy (37,38). Additionally, as A1C represents an integrated measure of glucose, it may not fully capture postprandial hyperglycemia, which drives macrosomia. Thus, although A1C may be useful, it should be used as a secondary measure of glycemic outcomes in pregnancy, after blood glucose monitoring.

In the second and third trimesters, A1C <6% (42 mmol/mol) has the lowest risk of large-for-gestational-age infants (36,39,40), preterm delivery (41), and preeclampsia (1,42). Taking all of this into account, a target of <6% (42 mmol/mol) is optimal during pregnancy if it can be achieved without significant hypoglycemia. The A1C target in a given individual

should be achieved without hypoglycemia, which, in addition to the usual adverse sequelae, may increase the risk of low birth weight (43). Given the alteration in red blood cell kinetics during pregnancy and physiological changes in glycemic parameters, A1C levels may need to be monitored more frequently than usual (e.g., monthly).

Continuous Glucose Monitoring in Pregnancy

CONCEPTT was a randomized controlled trial (RCT) of real-time continuous glucose monitoring (CGM) in addition to standard care, including optimization of pre- and postprandial glucose targets versus standard care for pregnant people with type 1 diabetes. It demonstrated the value of real-time CGM in pregnancy complicated by type 1 diabetes by showing a mild improvement in A1C without an increase in hypoglycemia and reductions in large-for-gestational-age births, length of stay, and neonatal hypoglycemia (44). An observational cohort study that evaluated the glycemic variables reported using CGM found that lower mean glucose, lower standard deviation, and a higher percentage of time in target range were associated with lower risk of large-for-gestational-age births and other adverse neonatal outcomes (45). Use of the CGM-reported mean glucose is superior to the use of estimated A1C, glucose management indicator, and other calculations to estimate A1C, given the changes to A1C that occur in pregnancy (46). CGM time in range (TIR) can be used for assessment of glycemic outcomes in people with type 1 diabetes, but it does not provide actionable data to address fasting and postprandial hypoglycemia or hyperglycemia. The cost of CGM in pregnancies complicated by type 1 diabetes is offset by improved maternal and neonatal outcomes (47).

There are insufficient data to support the use of CGM in people with type 2 diabetes or GDM (48,49).

The international consensus on TIR (50) endorses pregnancy target ranges and goals for TIR for people with type 1 diabetes using CGM as reported on the ambulatory glucose profile; however, it does not specify the type or accuracy of the device or need for alarms and alerts. A prospective, observational study including 20 pregnant people with type 1 diabetes simultaneously monitored with intermittently scanning CGM (isCGM) and real-time CGM (rtCGM) for 7 days in early pregnancy demonstrated a higher percentage of time below range in the isCGM group. Asymptomatic hypoglycemia measured by isCGM should therefore not necessarily lead to a reduction of insulin dose and/or increased carbohydrate intake at bedtime unless these episodes are confirmed by blood glucose meter measurements (51). Selection of CGM device should be based on an individual's circumstances, preferences, and needs.

- Target range 63–140 mg/dL (3.5–7.8 mmol/L): TIR, goal >70%
- Time below range (<63 mg/dL [3.5 mmol/L]), goal <4%
- Time below range (<54 mg/dL [3.0 mmol/L]), goal <1%
- Time above range (>140 mg/dL [7.8 mmol/L]), goal <25%

MANAGEMENT OF GESTATIONAL DIABETES MELLITUS

Recommendations

15.14 Lifestyle behavior change is an essential component of management of gestational diabetes mellitus and may suffice as treatment for many individuals. Insulin should be added if needed to achieve glycemic targets. **A**

15.15 Insulin is the preferred medication for treating hyperglycemia in gestational diabetes mellitus. Metformin and glyburide should not be used as first-line agents, as both cross the placenta to the fetus. **A** Other oral and noninsulin injectable glucose-lowering medications lack long-term safety data.

15.16 Metformin, when used to treat polycystic ovary syndrome and induce ovulation, should be discontinued by the end of the first trimester. **A**

15.17 Telehealth visits for pregnant people with gestational diabetes mellitus improve outcomes compared with standard in-person care. **A**

GDM is characterized by an increased risk of large-for-gestational-age birth weight and neonatal and pregnancy complications and an increased risk of long-term maternal type 2 diabetes and abnormal glucose metabolism of offspring in childhood. These associations with maternal oral glucose tolerance test (OGTT) results are continuous with no clear inflection points (35,52). Offspring with exposure to untreated GDM have reduced insulin sensitivity and β-cell compensation and are more likely to have impaired glucose tolerance in childhood (53). In other words, short-term and long-term risks increase with progressive maternal hyperglycemia. Therefore, all pregnant people should be screened as outlined in Section 2, "Classification and Diagnosis of Diabetes." Although there is some heterogeneity, many RCTs and a Cochrane review suggest that the risk of GDM may be reduced by diet, exercise, and lifestyle counseling, particularly when interventions are started during the first or early in the second trimester (54–56). There are no intervention trials in offspring of mothers with GDM. A meta-analysis of 11 RCTs demonstrated that metformin treatment in pregnancy does not reduce the risk of GDM in high-risk individuals with obesity, polycystic ovary syndrome, or preexisting insulin resistance (57). A meta-analysis of 32 RCTs evaluating the effectiveness of telehealth visits for GDM demonstrated reduction of incidences of cesarean delivery, neonatal hypoglycemia, premature rupture of membranes, macrosomia, pregnancy-induced hypertension or preeclampsia, preterm birth, neonatal asphyxia, and polyhydramnios compared with standard in-person care (58).

Lifestyle and Behavioral Management

After diagnosis, treatment starts with medical nutrition therapy, physical activity, and weight management, depending on pregestational weight, as outlined in the section below on preexisting type 2 diabetes, as well as glucose monitoring aiming for the targets recommended by the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (59):

- Fasting glucose <95 mg/dL (5.3 mmol/L) and either
- One-hour postprandial glucose <140 mg/dL (7.8 mmol/L) or

- Two-hour postprandial glucose <120 mg/dL (6.7 mmol/L)

The glycemic target lower limits defined above for preexisting diabetes apply for GDM treated with insulin. Depending on the population, studies suggest that 70–85% of people diagnosed with GDM under Carpenter-Coustan criteria can manage GDM with lifestyle modification alone; it is anticipated that this proportion will be even higher if the lower International Association of the Diabetes and Pregnancy Study Groups (60) diagnostic thresholds are used.

Medical Nutrition Therapy

Medical nutrition therapy for GDM is an individualized nutrition plan developed between the pregnant person and an RDN familiar with the management of GDM (61,62). The food plan should provide adequate calorie intake to promote fetal/neonatal and maternal health, achieve glycemic goals, and promote weight gain, according to the 2009 Institute of Medicine recommendations (63). There is no definitive research that identifies a specific optimal calorie intake for people with GDM or suggests that their calorie needs are different from those of pregnant individuals without GDM. The food plan should be based on a nutrition assessment with dietary reference intake guidance from the National Institute of Medicine. The recommended dietary reference intake for all pregnant people is a minimum of 175 g of carbohydrate, a minimum of 71 g of protein, and 28 g of fiber (64). The nutrition plan should emphasize monounsaturated and polyunsaturated fats while limiting saturated fats and avoiding *trans* fats. As is true for all nutrition therapy in people with diabetes, the amount and type of carbohydrate will impact glucose levels. The current recommended amount of carbohydrates is 175 g, or ~35% of a 2,000-calorie diet. Liberalizing higher quality, nutrient-dense carbohydrates results in controlled fasting/postprandial glucose, lower free fatty acids, improved insulin action, and vascular benefits and may reduce excess infant adiposity. Individuals who substitute fat for carbohydrates may unintentionally enhance lipolysis, promote elevated free fatty acids, and worsen maternal insulin resistance (65,66). Fasting urine ketone testing may be useful to identify those who are severely restricting carbohydrates to control blood glucose. Simple carbohydrates will result in higher postmeal excursions.

Physical Activity

A systematic review demonstrated improvements in glucose control and reductions in need to start insulin or insulin dose requirements with an exercise intervention. There was heterogeneity in the types of effective exercise (aerobic, resistance, or both) and duration of exercise (20–50 min/day, 2–7 days/week of moderate intensity) (67).

Pharmacologic Therapy

Treatment of GDM with lifestyle and insulin has been demonstrated to improve perinatal outcomes in two large randomized studies, as summarized in a U.S. Preventive Services Task Force review (68). Insulin is the first-line agent recommended for the treatment of GDM in the U.S. While individual RCTs support limited efficacy of metformin (69,70) and glyburide (71) in reducing glucose levels for the treatment of GDM, these agents are not recommended as the first-line treatment for GDM because they are known to cross the placenta and data on long-term safety for offspring is of some concern (32). Furthermore, in separate RCTs, glyburide and metformin failed to provide adequate glycemic outcomes in 23% and 25–28% of participants with GDM, respectively (72,73).

Sulfonylureas

Sulfonylureas are known to cross the placenta and have been associated with increased neonatal hypoglycemia. Concentrations of glyburide in umbilical cord plasma are approximately 50–70% of maternal levels (72,73). In meta-analyses and systematic reviews, glyburide was associated with a higher rate of neonatal hypoglycemia, macrosomia, and increased neonatal abdominal circumference than insulin or metformin (74,75).

Glyburide failed to be found noninferior to insulin based on a composite outcome of neonatal hypoglycemia, macrosomia, and hyperbilirubinemia (76). Long-term safety data for offspring exposed to glyburide are not available (76).

Metformin

Metformin was associated with a lower risk of neonatal hypoglycemia and less maternal weight gain than insulin in systematic reviews (74,77–79). However, metformin readily crosses the placenta, resulting in umbilical cord blood levels of metformin as high or higher than simultaneous maternal levels (80,81). In the Metformin in Gestational Diabetes: The Offspring Follow-Up (MiG TOFU) study's analyses of 7- to 9-year-old offspring, the 9-year-old offspring exposed to metformin for the treatment of GDM in the Auckland cohort were heavier and had a higher waist-to-height ratio and waist circumference than those exposed to insulin (82). This difference was not found in the Adelaide cohort. In two RCTs of metformin use in pregnancy for polycystic ovary syndrome, follow-up of 4-year-old offspring demonstrated higher BMI and increased obesity in the offspring exposed to metformin (83,84). A follow-up study at 5–10 years showed that the offspring had higher BMI, weight-to-height ratios, waist circumferences, and a borderline increase in fat mass (84,85). A recent meta-analysis concluded that metformin exposure resulted in smaller neonates with an acceleration of postnatal growth, resulting in higher BMI in childhood (84).

Randomized, double-blind, controlled trials comparing metformin with other therapies for ovulation induction in individuals with polycystic ovary syndrome have not demonstrated benefit in preventing spontaneous abortion or GDM (86), and there is no evidence-based need to continue metformin in these individuals (87–89).

There are some people with GDM requiring medical therapy who may not be able to use insulin safely or effectively during pregnancy due to cost, language barriers, comprehension, or cultural influences. Oral agents may be an alternative for these individuals after discussing the known risks and the need for more long-term safety data in offspring. However, due to the potential for growth restriction or acidosis in the setting of placental insufficiency, metformin should not be used in pregnant people with hypertension or preeclampsia or those at risk for intrauterine growth restriction (90,91).

Insulin

Insulin use should follow the guidelines below. Both multiple daily insulin injections and continuous subcutaneous insulin infusion are reasonable delivery strategies, and neither has been shown to be superior to the other during pregnancy (92).

MANAGEMENT OF PREEXISTING TYPE 1 DIABETES AND TYPE 2 DIABETES IN PREGNANCY

Insulin Use

Recommendations

15.18 Insulin should be used to manage type 1 diabetes in pregnancy. **A** Insulin is the preferred agent for the management of type 2 diabetes in pregnancy. **B**

15.19 Either multiple daily injections or insulin pump technology can be used in pregnancy complicated by type 1 diabetes. **C**

The physiology of pregnancy necessitates frequent titration of insulin to match changing requirements and underscores the importance of daily and frequent blood glucose monitoring. Due to the complexity of insulin management in pregnancy, referral to a specialized center offering team-based care (with team members including a maternal-fetal medicine specialist, endocrinologist or other health care professional experienced in managing pregnancy and preexisting diabetes, RDN, diabetes care and education specialist, and social worker, as needed) is recommended if this resource is available.

None of the currently available human insulin preparations have been demonstrated to cross the placenta (92–97). Insulins studied in RCTs are preferred (98–101) over those studied in cohort studies (102), which are preferred over those studied in case reports only.

While many health care professionals prefer insulin pumps in pregnancy, it is not clear that they are superior to multiple daily injections (103,104). None of the current hybrid closed-loop insulin pump systems approved by the U.S. Food and Drug Administration (FDA) achieve pregnancy targets. However, predictive low-glucose suspend (PLGS) technology has been shown in nonpregnant people to be better than sensor-augmented insulin pumps (SAP) for reducing low glucose values (105). It may be suited for pregnancy because the predictive low-glucose threshold for suspending insulin is in the range of premeal and overnight glucose value targets in pregnancy and may allow for more aggressive prandial dosing. See SENSOR-AUGMENTED PUMPS and AUTOMATED INSULIN DELIVERY SYSTEMS in Section 7, "Diabetes Technology," for more information on these systems.

Type 1 Diabetes

Pregnant individuals with type 1 diabetes have an increased risk of hypoglycemia in the first trimester and, like all pregnant people, have altered counterregulatory response in pregnancy that may decrease hypoglycemia awareness. Education for people with diabetes and family members about the prevention, recognition, and treatment of hypoglycemia is important before, during, and after pregnancy to help prevent and manage hypoglycemia's risks. Insulin resistance drops rapidly with the delivery of the placenta.

Pregnancy is a ketogenic state, and people with type 1 diabetes, and to a lesser extent those with type 2 diabetes, are at risk for diabetic ketoacidosis (DKA) at lower blood glucose levels than in the nonpregnant state. Pregnant people with type 1 diabetes should be prescribed ketone strips and receive education on DKA prevention and detection. DKA carries a high risk of stillbirth. Those in DKA who are unable to eat often require 10% dextrose with an insulin drip to adequately meet the higher carbohydrate demands of the placenta and fetus in the third trimester in order to resolve their ketosis.

Retinopathy is a special concern in pregnancy. The necessary rapid implementation of euglycemia in the setting of retinopathy is associated with worsening of retinopathy (106).

Type 2 Diabetes

Type 2 diabetes is often associated with obesity. Recommended weight gain during pregnancy for people with overweight is 15–25 lb and for those with obesity is 10–20 lb (63). There are no adequate data on optimal weight gain versus weight maintenance in pregnant people with BMI >35 kg/m^2.

Optimal glycemic targets are often easier to achieve during pregnancy with type 2 diabetes than with type 1 diabetes but can require much higher doses of insulin, sometimes necessitating concentrated insulin formulations. Insulin is the preferred treatment for type 2 diabetes in pregnancy. An RCT of metformin added to insulin for the treatment of type 2 diabetes found less maternal weight gain and fewer cesarean births. There were fewer macrosomic neonates, but there was a doubling of small-for-gestational-age neonates (107). As in type 1 diabetes, insulin requirements drop dramatically after delivery.

The risk for associated hypertension and other comorbidities may be as high or higher with type 2 diabetes as with type 1 diabetes, even if diabetes is better managed and of shorter apparent duration, with pregnancy loss appearing to be more prevalent in the third trimester in those with type 2 diabetes, compared with the first trimester in those with type 1 diabetes (108,109).

PREECLAMPSIA AND ASPIRIN

Insulin Use

Recommendation

15.20 Pregnant individuals with type 1 or type 2 diabetes should be prescribed low-dose aspirin 100–150 mg/day starting at 12 to 16 weeks of gestation to lower the risk of preeclampsia. **E** A dosage of 162 mg/day may be acceptable **E**; currently, in the U.S., low-dose aspirin is available in 81-mg tablets.

Diabetes in pregnancy is associated with an increased risk of preeclampsia (110). The U.S. Preventive Services Task Force recommends using low-dose aspirin (81 mg/day) as a preventive medication at 12 weeks of gestation in individuals at high risk for preeclampsia (111). However, a meta-analysis and an additional trial demonstrate that low-dose aspirin <100 mg is not effective in reducing preeclampsia. Low-dose aspirin >100 mg is required (112–114). A cost-benefit analysis has concluded that this approach would reduce morbidity, save lives, and lower health care costs (115). However, there is insufficient data regarding benefits of aspirin in pregnant people with preexisting diabetes (116,117). More

studies are needed to assess the long-term effects of prenatal aspirin exposure on offspring (116).

PREGNANCY AND DRUG CONSIDERATIONS

Recommendations

15.21 In pregnant individuals with diabetes and chronic hypertension, a blood pressure threshold of 140/90 mmHg for initiation or titration of therapy is associated with better pregnancy outcomes than reserving treatment for severe hypertension, with no increase in risk of small-for-gestational-age birth weight. **A** There are limited data on the optimal lower limit, but therapy should be lessened for blood pressure <90/60 mmHg. **E** A blood pressure target of 110–135/85 mmHg is suggested in the interest of reducing the risk for accelerated maternal hypertension. **A**

15.22 Potentially harmful medications in pregnancy (i.e., ACE inhibitors, angiotensin receptor blockers, statins) should be stopped prior to conception and avoided in sexually active individuals of childbearing potential who are not using reliable contraception. **B**

In normal pregnancy, blood pressure is lower than in the nonpregnant state. The Chronic Hypertension and Pregnancy (CHAP) Trial Consortium's RCT on treatment for mild chronic hypertension during pregnancy demonstrated that a blood pressure of 140/90 mmHg, as the threshold for initiation or titration of treatment, reduces the incidence of adverse pregnancy outcomes without compromising fetal growth (118). The CHAP Consortium's study mitigates concerns about small-for-gestational-age birth weight. Attained mean ± SD blood pressure measurements in the treated versus untreated groups were systolic 129.5 ± 10.0 vs. 132.6 ± 10.1 mmHg (between-group difference −3.11 [95% CI −3.95 to 2.28]) and diastolic 79.1 ± 7.4 vs. 81.5 ± 8.0 mmHg (−2.33 [−2.97 to 0.04]) (118). Individuals with diabetes had an even better composite outcome score than those without diabetes (118).

As a result of the CHAP study, ACOG issued a Practice Advisory recommending a blood pressure of 140/90 mmHg as the threshold for initiation or titration of medical therapy for chronic hypertension in pregnancy (119) rather than their previously recommended threshold of 160/110 mmHg (120).

The CHAP study provides additional guidance for the management of hypertension in pregnancy. Data from the previously published Control of Hypertension in Pregnancy Study (CHIPS) supports a target blood pressure goal of 110–135/85 mmHg to reduce the risk of uncontrolled maternal hypertension and minimize impaired fetal growth (120–122). The 2015 study (121) excluded pregnancies complicated by preexisting diabetes, and only 6% of participants had GDM at enrollment. There was no difference in pregnancy loss, neonatal care, or other neonatal outcomes between the groups with tighter versus less tight control of hypertension (121).

During pregnancy, treatment with ACE inhibitors and angiotensin receptor blockers is contraindicated because they may cause fetal renal dysplasia, oligohydramnios, pulmonary hypoplasia, and intrauterine growth restriction (21).

A large study found that after adjusting for confounders, first trimester ACE inhibitor exposure does not appear to be associated with congenital malformations (123). However, ACE inhibitors and angiotensin receptor blockers should be stopped as soon as possible in the first trimester to avoid second and third trimester fetopathy (123). Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, nifedipine, labetalol, diltiazem, clonidine, and prazosin. Atenolol is not recommended, but other β-blockers may be used, if necessary. Chronic diuretic use during pregnancy is not recommended as it has been associated with restricted maternal plasma volume, which may reduce uteroplacental perfusion (124). On the basis of available evidence, statins should also be avoided in pregnancy (125).

See pregnancy and antihypertensive medications in Section 10, "Cardiovascular Disease and Risk Management," for more information on managing blood pressure in pregnancy.

POSTPARTUM CARE

Recommendations

15.23 Insulin resistance decreases dramatically immediately postpartum, and insulin requirements need to be evaluated and adjusted as they are often roughly half the prepregnancy requirements for the initial few days postpartum. **C**

15.24 A contraceptive plan should be discussed and implemented with all people with diabetes of reproductive potential. **A**

15.25 Screen individuals with a recent history of gestational diabetes mellitus at 4–12 weeks postpartum, using the 75-g oral glucose tolerance test and clinically appropriate nonpregnancy diagnostic criteria. **B**

15.26 Individuals with overweight/obesity and a history of gestational diabetes mellitus found to have prediabetes should receive intensive lifestyle interventions and/or metformin to prevent diabetes. **A**

15.27 Breastfeeding is recommended to reduce the risk of maternal type 2 diabetes and should be considered when choosing whether to breastfeed or formula feed. **B**

15.28 Individuals with a history of gestational diabetes mellitus should have lifelong screening for the development of type 2 diabetes or prediabetes every 1–3 years. **B**

15.29 Individuals with a history of gestational diabetes mellitus should seek preconception screening for diabetes and preconception care to identify and treat hyperglycemia and prevent congenital malformations. **E**

15.30 Postpartum care should include psychosocial assessment and support for self-care. **E**

Gestational Diabetes Mellitus

Initial Testing

Because GDM often represents previously undiagnosed prediabetes, type 2 diabetes, maturity-onset diabetes of the young, or even developing type 1 diabetes, individuals with GDM should be

tested for persistent diabetes or prediabetes at 4–12 weeks postpartum with a fasting 75-g OGTT using nonpregnancy criteria as outlined in Section 2, "Classification and Diagnosis of Diabetes," specifically **Table 2.2**. In the absence of unequivocal hyperglycemia, a positive screen for diabetes requires two abnormal values. If both the fasting plasma glucose (≥126 mg/dL [7.0 mmol/L]) and 2-h plasma glucose (≥200 mg/dL [11.1 mmol/L]) are abnormal in a single screening test, then the diagnosis of diabetes is made. If only one abnormal value in the OGTT meets diabetes criteria, the test should be repeated to confirm that the abnormality persists. OGTT testing immediately postpartum, while still hospitalized, has demonstrated improved engagement in testing but also variably reduced sensitivity to the diagnosis of impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes (126,127).

Postpartum Follow-up

The OGTT is recommended over A1C at 4–12 weeks postpartum because A1C may be persistently impacted (lowered) by the increased red blood cell turnover related to pregnancy, by blood loss at delivery, or by the preceding 3-month glucose profile. The OGTT is more sensitive at detecting glucose intolerance, including both prediabetes and diabetes. Individuals of childbearing potential with prediabetes may develop type 2 diabetes by the time of their next pregnancy and will need preconception evaluation. Because GDM is associated with an increased lifetime maternal risk for diabetes estimated at 50–60% (128,129), individuals should also be tested every 1–3 years thereafter if the 4–12 weeks postpartum 75-g OGTT is normal. Ongoing evaluation may be performed with any recommended glycemic test (e.g., annual A1C, annual fasting plasma glucose, or triennial 75-g OGTT using nonpregnant thresholds).

Gestational Diabetes Mellitus and Type 2 Diabetes

Individuals with a history of GDM have a greatly increased risk of conversion to type 2 diabetes over time (129), and those with GDM have a 10-fold increased risk of developing type 2 diabetes compared with those without GDM (128). Absolute risk of developing type 2 diabetes after GDM increases linearly through a person's lifetime, being approximately 20% at 10 years, 30% at 20 years, 40% at 30 years, 50% at 40 years, and 60% at 50 years (129). In the prospective Nurses' Health Study II (NHS II), subsequent diabetes risk after a history of GDM was significantly lower in those who followed healthy eating patterns (130). Adjusting for BMI attenuated this association moderately, but not completely. Interpregnancy weight gain is associated with increased risk of adverse pregnancy outcomes (131) and higher risk of GDM, while in people with BMI >25 kg/m^2, weight loss is associated with lower risk of developing GDM in the subsequent pregnancy (132). Development of type 2 diabetes is 18% higher per unit of BMI increase from prepregnancy BMI at follow-up, highlighting the importance of effective weight management after GDM (133). In addition, postdelivery lifestyle interventions are effective in reducing risk of type 2 diabetes (134).

Both metformin and intensive lifestyle intervention prevent or delay progression to diabetes in individuals with prediabetes and a history of GDM. Only five to six individuals with prediabetes and a history of GDM need to be treated with either intervention to prevent one case of diabetes over 3 years (135). In these individuals, lifestyle intervention and metformin reduced progression to diabetes by 35% and 40%, respectively, over 10 years compared with placebo (136). If the pregnancy has motivated the adoption of healthy nutrition, building on these gains to support weight loss is recommended in the postpartum period. (See Section 3, "Prevention or Delay of Type 2 Diabetes and Associated Comorbidities.")

Preexisting Type 1 and Type 2 Diabetes

Insulin sensitivity increases dramatically with the delivery of the placenta. In one study, insulin requirements in the immediate postpartum period are roughly 34% lower than prepregnancy insulin requirements (137). Insulin sensitivity then returns to prepregnancy levels over the following 1–2 weeks. For individuals taking insulin, particular attention should be directed to hypoglycemia prevention in the setting of breastfeeding and erratic sleep and eating schedules (138).

Lactation

Considering the immediate nutritional and immunological benefits of breastfeeding for the baby, all mothers, including those with diabetes, should be supported in attempts to breastfeed. Breastfeeding may also confer longer-term metabolic benefits to both mother (139) and offspring (140). Breastfeeding reduces the risk of developing type 2 diabetes in mothers with previous GDM. It may improve the metabolic risk factors of offspring, but more studies are needed (141). However, lactation can increase the risk of overnight hypoglycemia, and insulin dosing may need to be adjusted.

Contraception

A major barrier to effective preconception care is the fact that the majority of pregnancies are unplanned. Planning pregnancy is critical in individuals with preexisting diabetes to achieve the optimal glycemic targets necessary to prevent congenital malformations and reduce the risk of other complications. Therefore, all individuals with diabetes of childbearing potential should have family planning options reviewed at regular intervals to make sure that effective contraception is implemented and maintained. This applies to individuals in the immediate postpartum period. Individuals with diabetes have the same contraception options and recommendations as those without diabetes. Long-acting, reversible contraception may be ideal for individuals with diabetes and childbearing potential. The risk of an unplanned pregnancy outweighs the risk of any currently available contraception option.

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16. Diabetes Care in the Hospital: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Among hospitalized patients, hyperglycemia, hypoglycemia, and glucose variability are associated with adverse outcomes, including increased morbidity and mortality (1). Careful management of people with diabetes during hospitalization has direct and immediate benefits. Diabetes management in the inpatient setting is facilitated by preadmission treatment of hyperglycemia in people with diabetes, having elective procedures, a dedicated inpatient diabetes service applying well-developed and validated standards of care, and careful transition to prearranged outpatient management. These steps can shorten hospital stays, reduce the need for readmission and emergency department visits, and improve outcomes. Some in-depth reviews of in-hospital care and care transitions for adults with diabetes have been published (2–4). For older hospitalized patients or for patients in long-term care facilities, please see Section 13, "Older Adults."

HOSPITAL CARE DELIVERY STANDARDS

Recommendations

16.1 Perform an A1C test on all people with diabetes or hyperglycemia (blood glucose >140 mg/dL [7.8 mmol/L]) admitted to the hospital if not performed in the prior 3 months. **B**

16.2 Insulin should be administered using validated written or computerized protocols that allow for predefined adjustments in the insulin dosage based on glycemic fluctuations. **B**

Considerations on Admission

High-quality hospital care for diabetes requires standards for care delivery, which are best implemented using structured order sets and quality improvement strategies for process improvement. Unfortunately, "best practice" protocols, reviews, and guidelines (2,4) are inconsistently implemented within hospitals. To correct this, medical centers striving for optimal inpatient diabetes treatment should establish protocols and structured order sets, which include computerized provider order entry (CPOE).

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Initial orders should state the type of diabetes (i.e., type 1, type 2, gestational diabetes mellitus, pancreatogenic diabetes) when it is known. Because inpatient treatment and discharge planning are more effective if based on preadmission glycemia, A1C should be measured for all people with diabetes or hyperglycemia admitted to the hospital if an A1C test has not been performed in the previous 3 months (5–8). In addition, diabetes self-management knowledge and behaviors should be assessed on admission, and diabetes self-management education provided, especially if a new treatment plan is being considered. Diabetes self-management education should include appropriate skills needed after discharge, such as medication dosing and administration, glucose monitoring, and recognition and treatment of hypoglycemia (9,10). Evidence supports preadmission treatment of hyperglycemia in people scheduled for elective surgery as an effective means of reducing adverse outcomes (11–14).

The National Academy of Medicine recommends CPOE to prevent medication-related errors and increase medication administration efficiency (15). Systematic reviews of randomized controlled trials using computerized advice to improve glycemic outcomes in the hospital found significant improvement in the percentage of time individuals spent in the target glucose range, lower mean blood glucose levels, and no increase in hypoglycemia (16,17). Where feasible, there should be structured order sets that provide computerized guidance for glycemic management. Electronic insulin order templates also improve mean glucose levels without increasing hypoglycemia in people with type 2 diabetes, so structured insulin order sets incorporated into the CPOE can facilitate glycemic management (18,19). Insulin dosing algorithms using machine learning and data in the electronic health record (EHR) currently in development show great promise to more accurately predict insulin requirements during hospitalization compared with existing clinical practices (20).

Diabetes Care Specialists in the Hospital

Recommendation

16.3 When caring for hospitalized people with diabetes, consult with a specialized diabetes or glucose management team when possible. **C**

Appropriately trained specialists or specialty teams may reduce the length of stay and improve glycemic and other clinical outcomes (21–23). In addition, the increased risk of 30-day readmission following hospitalization that has been attributed to diabetes can be reduced, and costs saved when inpatient care is provided by a specialized diabetes management team (21,24,25). In a cross-sectional study comparing usual care to specialists reviewing diabetes cases and making recommendations virtually through the EHR, rates of both hyperglycemia and hypoglycemia were reduced by 30–40% (26). Providing inpatient diabetes education and developing a diabetes discharge plan that includes continued access to diabetes medications and supplies and ongoing education and support are key strategies to improve outcomes (27–29). Details of diabetes care team composition are available in the Joint Commission standards for programs and from the Society of Hospital Medicine (30,31).

Even the most efficacious orders may not be carried out in a way that improves quality, nor are they automatically updated when new evidence arises. The Joint Commission accreditation program for the hospital care of diabetes (31), the Society of Hospital Medicine workbook for program development (30), and the Joint British Diabetes Societies (JBDS) for Inpatient Care Group (32) are valuable resources.

GLYCEMIC TARGETS IN HOSPITALIZED ADULTS

Recommendations

16.4 Insulin therapy should be initiated for the treatment of persistent hyperglycemia starting at a threshold ≥180 mg/dL (10.0 mmol/L) (checked on two occasions). Once insulin therapy is started, a target glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for most critically ill and noncritically ill patients. **A**

16.5 More stringent goals, such as 110–140 mg/dL (6.1–7.8 mmol/L) or 100–180 mg/dL (5.6–10.0 mmol/L), may be appropriate for selected patients and are acceptable if they can be achieved without significant hypoglycemia. **C**

Standard Definitions of Glucose Abnormalities

Hyperglycemia in hospitalized patients is defined as blood glucose levels >140 mg/dL (7.8 mmol/L) (33). Blood glucose levels persistently above this level warrant prompt interventions, such as alterations in nutrition or changes to medications that cause hyperglycemia. An admission A1C value ≥6.5% (48 mmol/mol) suggests that the onset of diabetes preceded hospitalization (see Section 2, "Classification and Diagnosis of Diabetes") (33,34). Hypoglycemia in hospitalized patients is categorized by blood glucose concentration and clinical correlates (**Table 6.4**) (35). Level 1 hypoglycemia is defined as a glucose concentration of 54–70 mg/dL (3.0–3.9 mmol/L). Level 2 hypoglycemia is defined as a blood glucose concentration <54 mg/dL (3.0 mmol/L), which is typically the threshold for neuroglycopenic symptoms. Level 3 hypoglycemia is defined as a clinical event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery. Levels 2 and 3 require immediate correction of low blood glucose. Prompt treatment of level 1 hypoglycemia can prevent progression to more significant level 2 and level 3 hypoglycemia.

Glycemic Targets

In a landmark clinical trial conducted in a surgical intensive care unit, Van den Berghe et al. (36) demonstrated that an intensive intravenous insulin protocol with a target glycemic range of 80–110 mg/dL (4.4–6.1 mmol/L) reduced mortality by 40% compared with a standard approach targeting blood glucose of 180–215 mg/dL (10–12 mmol/L) in critically ill hospitalized patients with recent surgery. This study provided robust evidence that active treatment to lower blood glucose in hospitalized patients could have immediate benefits. However, a large, multicenter follow-up study in critically ill hospitalized patients, the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial (37), led to a reconsideration of the optimal target range for glucose lowering in critical illness. In this trial, critically ill patients randomized to intensive glycemic management (80–110 mg/dL) derived no significant treatment advantage compared with a group with more moderate glycemic targets (140–180 mg/dL [7.8–10.0 mmol/L]) and had slightly but

significantly higher mortality (27.5% vs. 25%). The intensively treated group had 10- to 15-fold greater rates of hypoglycemia, which may have contributed to the adverse outcomes noted. The findings from NICE-SUGAR are supported by several meta-analyses and a randomized controlled trial, some of which suggest that tight glycemic management increases mortality compared with more moderate glycemic targets and generally causes higher rates of hypoglycemia (38–40).

Based on these results, insulin therapy should be initiated for the treatment of persistent hyperglycemia ≥180 mg/dL (10.0 mmol/L) and targeted to a glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) for the majority of critically ill patients. Although not as well supported by data from randomized controlled trials, these recommendations have been extended to hospitalized patients without critical illness. More stringent goals, such as 110–140 mg/dL (6.1–7.8 mmol/L), may be appropriate for selected patients (e.g., critically ill postsurgical patients or patients with cardiac surgery) as long as they can be achieved without significant hypoglycemia (41–43). For inpatient management of hyperglycemia in noncritical care, the expert consensus recommends a target range of 100–180 mg/dL (5.6–10.0 mmol/L) for noncritically ill patients with "new" hyperglycemia as well as people with known diabetes prior to admission. It has been found that fasting glucose levels <100 mg/dL are predictors of hypoglycemia within the next 24 h (44). Glycemic levels >250 mg/dL (13.9 mmol/L) may be acceptable in terminally ill patients with short life expectancy. In these individuals, less aggressive insulin regimens to minimize glucosuria, dehydration, and electrolyte disturbances are often more appropriate. Clinical judgment combined with ongoing assessment of clinical status, including changes in the trajectory of glucose measures, illness severity, nutritional status, or concomitant medications that might affect glucose levels (e.g., glucocorticoids), may be incorporated into the day-to-day decisions regarding insulin dosing (42).

BLOOD GLUCOSE MONITORING

In hospitalized individuals with diabetes who are eating, point-of-care (POC) glucose monitoring should be performed before meals; in those not eating, glucose monitoring is advised every 4–6 h (33). More frequent POC blood glucose monitoring ranging from every 30 min to every 2 h is the required standard for safe use of intravenous insulin. Safety standards for blood glucose monitoring that prohibit sharing lancing devices, other testing materials, and needles are mandatory (45).

The vast majority of hospital glucose monitoring is performed with FDA-approved prescription POC glucose monitoring systems with and capillary blood taken from finger sticks, similar to the process performed by outpatients for home blood glucose monitoring (46). POC blood glucose meters are not as accurate or as precise as laboratory glucose analyzers, and capillary blood glucose readings are subject to artifacts due to perfusion, edema, anemia/erythrocytosis, and several medications commonly used in the hospital (47) (**Table 7.1**). The U.S. Food and Drug Administration (FDA) has established standards for capillary (fingerstick) blood glucose meters used in the ambulatory setting, as well as standards to be applied for POC measures in the hospital (47). The balance between analytic requirements (e.g., accuracy, precision, interference) and clinical requirements (rapidity, simplicity, point of care) has not been uniformly resolved (46,48), and most hospitals have arrived at their own policies to balance these parameters. It is critically important that devices selected for in-hospital use, and the workflow through which they are applied, have careful analysis of performance and reliability and ongoing quality assessments. Recent studies indicate that POC measures provide adequate information for usual practice, with only rare instances where care has been compromised (49,50). Best practice dictates that any glucose result that does not correlate with the patient's clinical status should be confirmed by measuring a serum sample in the clinical laboratory.

Continuous Glucose Monitoring

Real-time continuous glucose monitoring (CGM) provides frequent measurements of interstitial glucose levels and the direction and magnitude of glucose trends. Even though CGM has theoretical advantages over POC glucose monitoring in detecting and reducing the incidence of hypoglycemia, it has not been approved by the FDA for inpatient use. Some hospitals with established glucose management teams allow the use of CGM in selected people with diabetes on an individual basis, mostly in noncritical care settings, provided both the individual and the glucose management team are well educated in the use of this technology. CGM is not currently approved for intensive care unit use due to accuracy concerns such as hypovolemia, hypoperfusion, and use of therapies such as vasopressor agents.

During the coronavirus disease 2019 (COVID-19) pandemic, many institutions were able to use CGM to minimize contact between health care professionals and people with diabetes, especially those in the intensive care unit under an FDA policy of enforcement discretion during the pandemic (51–59). This approach has been helpful in that regard, as well as in minimizing the use of personal protective equipment. The availability of data about the safe and effective use of CGM in the inpatient setting is evolving. Preliminary data suggest that CGM can significantly improve glycemic management and other hospital outcomes (57,60–63).

For more information on CGM, see Section 7, "Diabetes Technology."

GLUCOSE-LOWERING TREATMENT IN HOSPITALIZED PATIENTS

Recommendations

16.6 Basal insulin or a basal plus bolus correction insulin regimen is the preferred treatment for noncritically ill hospitalized patients with poor oral intake or those who are taking nothing by mouth. **A**

16.7 An insulin regimen with basal, prandial, and correction components is the preferred treatment for most noncritically ill hospitalized patients with adequate nutritional intake. **A**

16.8 Use of a correction or supplemental insulin without basal insulin (often referred to as a sliding scale) in the inpatient setting is discouraged. **A**

Insulin Therapy

Critical Care Setting

Continuous intravenous insulin infusion is the most effective method for achieving glycemic targets in the critical care setting. Intravenous insulin infusions should be administered based on validated

written or computerized protocols that allow for predefined adjustments in the infusion rate, accounting for glycemic fluctuations and insulin dose (64).

Noncritical Care Setting

In most instances, insulin is the preferred treatment for hyperglycemia in hospitalized patients. However, in certain circumstances, it may be appropriate to continue home therapies, including oral glucose-lowering medications (64,65). If oral medications are held in the hospital but will be reinstated after discharge, there should be a protocol for guiding resumption of home medications 1–2 days prior to discharge. For people taking insulin, several reports indicate that inpatient use of insulin pens is safe and may be associated with improved nurse satisfaction compared with the use of insulin vials and syringes with safety protocols in place (66–68). Insulin pens have been the subject of an FDA warning because of potential blood-borne diseases if inadvertently shared with more than one person; the warning "For single patient use only" should be rigorously followed using strict safety measures such as barcoding to prevent errors (69,70).

Outside of critical care units, scheduled insulin orders are recommended to manage hyperglycemia in people with diabetes. Orders for insulin analogs or human insulin result in similar glycemic outcomes in the hospital setting (71). The use of subcutaneous rapid- or short-acting insulin before meals, or every 4–6 h if no meals are given or if the individual is receiving continuous enteral/parenteral nutrition, is indicated to correct or prevent hyperglycemia. Basal insulin, or a basal plus bolus correction schedule, is the preferred treatment for noncritically ill hospitalized patients with inadequate oral intake or those restricted from oral intake. An insulin schedule with basal, prandial, and correction components is the preferred treatment for most noncritically ill hospitalized people with diabetes with adequate nutritional intake (72). In people with diabetes with blood glucose $<$240 mg/dL, consider alternatives to basal-bolus therapy as discussed below (72,73).

For individuals who are eating, insulin injections should align with meals. In such instances, POC glucose monitoring should be performed immediately before meals. If oral intake is inadequate, a safer procedure is administering prandial insulin immediately after eating, with the dose adjusted to be appropriate for the amount of carbohydrates ingested (71).

A randomized controlled trial has shown that basal-bolus treatment improved glycemic outcomes and reduced hospital complications compared with a correction or supplemental insulin without basal insulin (formerly known as sliding scale) in general surgery for people with type 2 diabetes (74). Prolonged use of correction or supplemental insulin without basal insulin as the sole treatment of hyperglycemia is strongly discouraged in the inpatient setting, with the exception of people with type 2 diabetes in noncritical care with mild hyperglycemia (23,75,76).

While there is evidence for using premixed insulin formulations in the outpatient setting (77), an inpatient study of 70/30 NPH/regular insulin versus basal-bolus therapy showed comparable glycemic outcomes but significantly increased hypoglycemia in the group receiving insulin mixtures (78). Therefore, insulin mixtures such as 75/25 or 70/30 insulins are not routinely recommended for in-hospital use.

Type 1 Diabetes

For people with type 1 diabetes, dosing insulin based solely on premeal glucose levels does not account for basal insulin requirements or caloric intake, increasing the risk of both hypoglycemia and hyperglycemia. Typically, basal insulin dosing is based on body weight, with some evidence that people with renal insufficiency should be treated with lower doses (79,80). An insulin schedule with basal and correction components is necessary for all hospitalized individuals with type 1 diabetes, even when taking nothing by mouth, with the addition of prandial insulin when eating.

Transitioning From Intravenous to Subcutaneous Insulin

When discontinuing intravenous insulin, a transition protocol is associated with less morbidity and lower costs of care (81,82) and is therefore recommended. A person with type 1 or type 2 diabetes being transitioned to a subcutaneous regimen should receive a dose of subcutaneous basal insulin 2 h before the intravenous infusion is discontinued. Prior to discontinuing an insulin infusion, initiation of subcutaneous basal insulin may help minimize hyperglycemia and avoid rebound hypoglycemia (83,84). The dose of basal insulin is best calculated on the basis of the insulin infusion rate during the last 6 h when stable glycemic goals were achieved (85). For people being transitioned to concentrated insulin (U-200, U-300, or U-500) in the inpatient setting, it is important to ensure correct dosing by utilizing an individual pen or cartridge for each person and by meticulous pharmacy and nursing supervision of the dose administered (85,86).

Noninsulin Therapies

The safety and efficacy of noninsulin glucose-lowering therapies in the hospital setting is an area of active research (73,87–89). Several recent randomized trials have demonstrated the potential effectiveness of glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase 4 inhibitors in specific groups of hospitalized people with diabetes (90–93). However, an FDA bulletin states that health care professionals should consider discontinuing saxagliptin and alogliptin in people who develop heart failure (94).

Sodium–glucose cotransporter 2 (SGLT2) inhibitors should be avoided in cases of severe illness, in people with ketonemia or ketonuria, and during prolonged fasting and surgical procedures (4). Until safety and efficacy are established, SGLT2 inhibitors are not recommended for routine in-hospital use for diabetes management, although they may be considered for the treatment of people with type 2 diabetes who have or are at risk for heart failure (95). Furthermore, the FDA has warned that SGLT2 inhibitors should be stopped 3 days before scheduled surgeries (4 days in the case of ertugliflozin) (96).

HYPOGLYCEMIA

Recommendations

16.9 A hypoglycemia management protocol should be adopted and implemented by each hospital or hospital system. A plan for preventing and treating hypoglycemia should be established for each individual. Episodes of hypoglycemia in the hospital should be documented in the medical record and tracked for quality improvement/quality assessment. **E**

16.10 Treatment regimens should be reviewed and changed as necessary to prevent further hypoglycemia when a blood glucose value of <70 mg/dL (3.9 mmol/L) is documented. **C**

People with or without diabetes may experience hypoglycemia in the hospital setting. While hypoglycemia is associated with increased mortality (97), in many cases, it is a marker of an underlying disease rather than the cause of fatality. However, hypoglycemia is a severe consequence of dysregulated metabolism and/or diabetes treatment, and it is imperative that it be minimized during hospitalization. Many episodes of inpatient hypoglycemia are preventable. Therefore, a hypoglycemia prevention and management protocol should be adopted and implemented by each hospital or hospital system. A standardized hospital-wide, nurse-initiated hypoglycemia treatment protocol should be in place to immediately address blood glucose levels of <70 mg/dL (3.9 mmol/L) (98,99). In addition, individualized plans for preventing and treating hypoglycemia for each individual should also be developed. An American Diabetes Association consensus statement recommends that an individual's treatment plan be reviewed any time a blood glucose value of <70 mg/dL (3.9 mmol/L) occurs, as such readings often predict subsequent level 3 hypoglycemia. Episodes of hypoglycemia in the hospital should be documented in the medical record and tracked (1,2).

Triggering Events and Prevention of Hypoglycemia

Insulin is one of the most common drugs causing adverse events in hospitalized patients, and errors in insulin dosing and/or administration occur relatively frequently (97,100,101). Beyond insulin dosing errors, common preventable sources of iatrogenic hypoglycemia are improper prescribing of other glucose-lowering medications, inappropriate management of the first episode of hypoglycemia, and nutrition–insulin mismatch, often related to an unexpected interruption of nutrition (102). A recent study describes acute kidney injury as an important risk factor for hypoglycemia in the hospital (103), possibly as a result of decreased insulin clearance. Studies of "bundled" preventive therapies, including proactive surveillance of glycemic outliers and an interdisciplinary data-driven approach to glycemic management, showed that hypoglycemic episodes in the hospital could be prevented. Compared with baseline, two such studies found that hypoglycemic events fell by 56–80% (99,104,105). The Joint Commission recommends that all hypoglycemic episodes be evaluated for a root cause and the episodes be aggregated and reviewed to address systemic issues (31).

In addition to errors with insulin treatment, iatrogenic hypoglycemia may be induced by a sudden reduction of corticosteroid dose, reduced oral intake, emesis, inappropriate timing of short- or rapid-acting insulin in relation to meals, reduced infusion rate of intravenous dextrose, unexpected interruption of enteral or parenteral feedings, delayed or missed blood glucose checks, and altered ability of the individual to report symptoms (106).

Recent inpatient CGM studies show promise for CGM as an early warning system to alert of impending hypoglycemia, offering an opportunity to mitigate it before it happens (60–63). The use of personal CGM and automated insulin delivery devices, such as insulin pumps that can automatically deliver correction doses and change basal delivery rates in real time, should be supported for ongoing use during hospitalization for individuals who are capable of using devices safely and independently when proper supervision is available. Hospitals should be encouraged to develop policies and protocols to support inpatient use of individual- and hospital-owned diabetes technology and have expert staff available for safe implementation. Hospital information technology teams are beginning to integrate CGM data into the electronic health record. The ability to download and interpret diabetes device data during hospitalization can inform insulin dosing during hospitalization and care transitions (107).

For more information on CGM, see Section 7, "Diabetes Technology."

Predictors of Hypoglycemia

In people with diabetes in the ambulatory setting, it is well established that an episode of severe hypoglycemia increases the risk for a subsequent event, partly because of impaired counterregulation (108,109). This relationship also holds true for people with diabetes in the inpatient setting. For example, in a study of hospitalized individuals treated for hyperglycemia, 84% who had an episode of "severe hypoglycemia" (defined in the study as <40 mg/dL [2.2 mmol/L]) had a preceding episode of hypoglycemia (<70 mg/dL [3.9 mmol/L]) during the same admission (110). In another study of hypoglycemic episodes (defined in the study as <50 mg/dL [2.8 mmol/L]), 78% of patients were using basal insulin, with the incidence of hypoglycemia peaking between midnight and 6:00 A.M. Despite recognition of hypoglycemia, 75% of individuals did not have their dose of basal insulin changed before the next insulin administration (111).

Recently, several groups have developed algorithms to predict episodes of hypoglycemia in the inpatient setting (112,113). Models such as these are potentially important and, once validated for general use, could provide a valuable tool to reduce rates of hypoglycemia in the hospital. In one retrospective cohort study data, a fasting blood glucose of <100 mg/dL was shown to be a predictor of next-day hypoglycemia (44).

MEDICAL NUTRITION THERAPY IN THE HOSPITAL

The goals of medical nutrition therapy in the hospital are to provide adequate calories to meet metabolic demands, optimize glycemic outcomes, address personal food preferences, and facilitate the creation of a discharge plan. The American Diabetes Association does not endorse any single meal plan or specified percentages of macronutrients. Current nutrition recommendations advise individualization based on treatment goals, physiological parameters, and medication use. Consistent carbohydrate meal plans are preferred by many hospitals as they facilitate matching the prandial insulin dose to the amount of carbohydrate given (114). Orders should also indicate that the meal delivery and nutritional insulin coverage should be coordinated, as their variability often creates the possibility of hyperglycemic and hypoglycemic events (28). Many hospitals offer "meals on demand," where individuals may order meals from

the menu at any time during the day. This option improves patient satisfaction but complicates meal-insulin coordination. Finally, if the hospital food service supports carbohydrate counting, this option should be made available to people with diabetes counting carbohydrates at home (115,116).

SELF-MANAGEMENT IN THE HOSPITAL

Diabetes self-management in the hospital may be appropriate for specific individuals who wish to continue to perform self-care while acutely ill (117,118). Candidates include children with parental supervision, adolescents, and adults who successfully perform diabetes self-management at home and whose cognitive and physical skills needed to successfully self-administer insulin and perform glucose monitoring are not compromised (9,119). In addition, they should have adequate oral intake, be proficient in carbohydrate estimation, take multiple daily insulin injections or use insulin pumps, have stable insulin requirements, and understand sick-day management. If self-management is supported, a policy should include a requirement that people with diabetes and the care team agree that self-management is appropriate on a daily basis during hospitalization. Hospital personal medication policies may include guidance for people with diabetes who wish to take their own or hospital-dispensed diabetes medications during their hospital stay. A hospital policy for personal medication may consider a pharmacy exception on a case-by-case basis along with the care team. Pharmacy must verify any home medication and require a prescriber order for the individual to self-administer home or hospital-dispensed medication under the supervision of the registered nurse. If an insulin pump or CGM is worn, hospital policy and procedures delineating guidelines for wearing an insulin pump and/or CGM device should be developed according to consensus guidelines, including the changing of infusion sites and glucose sensors (107,120,121). As outlined in Recommendation 7.30, people with diabetes wearing diabetes devices should be supported to continue them in an inpatient setting when they are competent to perform self-care and proper supervision is available.

STANDARDS FOR SPECIAL SITUATIONS

Enteral/Parenteral Feedings

For individuals receiving enteral or parenteral feedings who require insulin, the insulin orders should include coverage of basal, prandial, and correctional needs (115,122,123). It is essential that people with type 1 diabetes continue to receive basal insulin even if feedings are discontinued.

Most adults receiving basal insulin should continue with their basal dose, while the insulin dose for the total daily nutritional component may be calculated as 1 unit of insulin for every 10–15 g carbohydrate in the enteral and parenteral formulas. Commercially available cans of enteral nutrition contain variable amounts of carbohydrates and may be infused at different rates. All of this must be considered while calculating insulin doses to cover the nutritional component of enteral nutrition (116). Giving NPH insulin two or three times daily (every 8 or 12 h) to cover individual requirements is a reasonable option. Adjustments in insulin doses should be made frequently. Correctional insulin should also be administered subcutaneously every 6 h with human regular insulin or every 4 h with a rapid-acting insulin analog. If enteral nutrition is interrupted, a 10% dextrose infusion should be started immediately to prevent hypoglycemia and to allow time to select more appropriate insulin doses.

For adults receiving enteral bolus feedings, approximately 1 unit of regular human insulin or rapid-acting insulin per 10–15 g carbohydrate should be given subcutaneously before each feeding. Correctional insulin coverage should be added as needed before each feeding.

In individuals receiving nocturnal tube feeding, NPH insulin administered with the initiation of the feeding represents a reasonable approach to cover this nutritional load.

For individuals receiving continuous peripheral or central parenteral nutrition, human regular insulin may be added to the solution, particularly if >20 units of correctional insulin have been required in the past 24 h. A starting dose of 1 unit of human regular insulin for every 10 g dextrose has been recommended (115) and should be adjusted daily in the solution. Adding insulin to the parenteral nutrition bag is the safest way to prevent hypoglycemia if the parenteral nutrition is stopped or interrupted. Correctional insulin should be administered subcutaneously to address any hyperglycemia. For full enteral/parenteral feeding guidance, please refer to review articles detailing this topic (122,124,125).

Because continuous enteral or parenteral nutrition results in a continuous postprandial state, efforts to bring blood glucose levels to below 140 mg/dL (7.8 mmol/L) substantially increase the risk of hypoglycemia in these patients.

Glucocorticoid Therapy

The prevalence of consistent use of glucocorticoid therapy in hospitalized patients can approach 10%, and these medications can induce hyperglycemia in 56–86% of these individuals with and without preexisting diabetes (126,127). If left untreated, this hyperglycemia increases mortality and morbidity risk, e.g., infections and cardiovascular events. Glucocorticoid type and duration of action must be considered in determining appropriate insulin treatments. Daily-ingested intermediate-acting glucocorticoids such as prednisone reach peak plasma levels in 4–6 h (128) but have pharmacologic actions that can last through the day. Individuals placed on morning steroid therapy have disproportionate hyperglycemia during the day but frequently reach target blood glucose levels overnight regardless of treatment (126). In subjects on once- or twice-daily steroids, administering intermediate-acting (NPH) insulin is a standard approach. NPH is usually administered in addition to daily basal-bolus insulin or in addition to oral glucose-lowering medications. Because NPH action peaks at 4–6 h after administration, it is recommended to administer it concomitantly with intermediate-acting steroids (129). For long-acting glucocorticoids such as dexamethasone and multidose or continuous glucocorticoid use, long-acting basal insulin may be required to manage fasting blood glucose levels (65,130). For higher doses of glucocorticoids, increasing doses of prandial (if eating) and correctional insulin, sometimes as much as 40–60% or more, are often needed in addition to basal insulin (72,131,132). A single-center retrospective study found that increasing the ratio of insulin to steroids was positively associated with

improved time in range (70–180 mg/dL); however, there was an increase in hypoglycemia (133). Whatever insulin orders are initiated, daily adjustments based on levels of glycemia and anticipated changes in type, doses, and duration of glucocorticoids, along with POC blood glucose monitoring, are critical to reducing rates of hypoglycemia and hyperglycemia.

Perioperative Care

It is estimated that up to 20% of general surgery patients have diabetes, and 23–60% have prediabetes or undiagnosed diabetes. Surgical stress and counterregulatory hormone release increase the risk of hyperglycemia as well as mortality, infection, and length of stay (134). There is little data available to guide care of people with diabetes through the perioperative period. To reduce surgical risk in people with diabetes, some institutions have A1C cutoffs for elective surgeries, and some have developed optimization programs to lower A1C before surgery (135).

The following approach (136–138) may be considered:

1. A preoperative risk assessment should be performed for people with diabetes who are at high risk for ischemic heart disease and those with autonomic neuropathy or renal failure.
2. The A1C target for elective surgeries should be <8% (63.9 mmol/L) whenever possible (139,140).
3. The target range for blood glucose in the perioperative period should be 100–180 mg/dL (5.6–10.0 mmol/L) (139) within 4 h of the surgery (1).
4. Metformin should be held on the day of surgery.
5. SGLT2 inhibitors must be discontinued 3–4 days before surgery.
6. Hold any other oral glucose-lowering agents the morning of surgery or procedure and give half of NPH dose or 75–80% doses of long-acting analog or insulin pump basal insulin based on the type of diabetes and clinical judgment.
7. Monitor blood glucose at least every 2–4 h while the individual takes nothing by mouth and dose with short- or rapid-acting insulin as needed.
8. There are no data on the use and/or influence of glucagon-like peptide 1 receptor agonists or ultra-long-acting insulin analogs on glycemia in perioperative care.

A recent review concluded that perioperative glycemic targets tighter than 80–180 mg/dL (4.4–10.0 mmol/L) did not improve outcomes and was associated with more hypoglycemia (137); therefore, in general, stricter glycemic targets are not advised. Evidence from a recent study indicates that compared with usual dosing, a reduction of insulin given the evening before surgery by ~25% was more likely to achieve perioperative blood glucose levels in the target range with a lower risk for hypoglycemia (141).

In noncardiac general surgery patients, basal insulin plus premeal short- or rapid-acting insulin (basal-bolus) coverage has been associated with improved glycemic outcomes and lower rates of perioperative complications compared with the reactive, correction-only short- or rapid-acting insulin coverage alone with no basal insulin dosing (74,134,142).

Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

There is considerable variability in the presentation of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic states, ranging from euglycemia or mild hyperglycemia and acidosis to severe hyperglycemia, dehydration, and coma; therefore, individualization of treatment based on a careful clinical and laboratory assessment is needed (83,143–145).

Management goals include restoration of circulatory volume and tissue perfusion, resolution of hyperglycemia, and correction of electrolyte imbalance and acidosis. It is also essential to treat any correctable underlying cause of DKA, such as sepsis, myocardial infarction, or stroke. In critically ill and mentally obtunded individuals with DKA or hyperosmolar hyperglycemia, continuous intravenous insulin is the standard of care. Successful transition from intravenous to subcutaneous insulin requires administration of basal insulin 2–4 h before the intravenous insulin is stopped to prevent recurrence of ketoacidosis and rebound hyperglycemia (143). There is no significant difference in outcomes for intravenous human regular insulin versus subcutaneous rapid-acting analogs when combined with aggressive fluid management for treating mild or moderate DKA (146). Individuals with uncomplicated DKA may sometimes be treated with subcutaneous insulin in the emergency department or step-down units (147). This approach may be safer and more cost-effective than treatment with intravenous insulin. If subcutaneous insulin administration is used, it is important to provide an adequate fluid replacement, frequent POC blood glucose monitoring, treatment of any concurrent infections, and appropriate follow-up to avoid recurrent DKA. Several studies have shown that the use of bicarbonate in patients with DKA made no difference in the resolution of acidosis or time to discharge, and its use is generally not recommended (148). For further treatment information, refer to recent in-depth reviews (4,106,149).

TRANSITION FROM THE HOSPITAL TO THE AMBULATORY SETTING

Recommendation

16.11 A structured discharge plan should be tailored to the individual with diabetes. **B**

A structured discharge plan tailored to the individual may reduce the length of hospital stay and readmission rates and increase satisfaction with the hospital experience (150). Multiple strategies are key, including diabetes education prior to discharge, diabetes medication reconciliation with attention to access, and scheduled virtual and/or face-to-face follow-up visits after discharge. Discharge planning should begin at admission and be updated as individual needs change (3,151).

The transition from the acute care setting presents risks for all people with diabetes. Individuals may be discharged to varied settings, including home (with or without visiting nurse services), assisted living, rehabilitation, or skilled nursing facilities. For individuals discharged to home or assisted living, the optimal discharge plan will need to consider diabetes type and severity, effects of the illness on blood glucose levels, and the individual's capabilities and preferences (29,152,153). See Section 13, "Older Adults," for more information.

An outpatient follow-up visit with the primary care clinician, endocrinologist, or diabetes care and education specialist

within 1 month of discharge is advised for all individuals experiencing hyperglycemia in the hospital. If glycemic medications are changed or glucose management is not optimal at discharge, an earlier appointment (in 1–2 weeks) is preferred, and frequent contact may be needed to avoid hyperglycemia and hypoglycemia. A discharge algorithm for glycemic medication adjustment based on admission A1C, diabetes medications before admission, and insulin usage during hospitalization was found useful to guide treatment decisions and significantly improved A1C after discharge (6). If an A1C from the prior 3 months is unavailable, measuring the A1C in all people with diabetes or hyperglycemia admitted to the hospital is recommended upon admission.

Clear communication with outpatient health care professionals directly or via hospital discharge summaries facilitates safe transitions to outpatient care. Providing information regarding the root cause of hyperglycemia (or the plan for determining the cause), related complications and comorbidities, and recommended treatments can assist outpatient health care professionals as they assume ongoing care.

The Agency for Healthcare Research and Quality recommends that, at a minimum, discharge plans include the following (154):

Medication Reconciliation

- Home and hospital medications must be cross-checked to ensure that no chronic medications are stopped and to ensure the safety of new and old prescriptions.
- Prescriptions for new or changed medication should be filled and reviewed with the individual and care partners at or before discharge.

Structured Discharge Communication

- Information on medication changes, pending tests and studies, and follow-up needs must be accurately and promptly communicated to outpatient health care professionals.
- Discharge summaries should be transmitted to the primary care clinician as soon as possible after discharge.
- Scheduling follow-up appointments prior to discharge with people with diabetes agreeing to the time and place increases the likelihood that they will attend.

It is recommended that the following areas of knowledge be reviewed and addressed before hospital discharge:

- Identification of the health care professionals who will provide diabetes care after discharge.
- Level of understanding related to the diabetes diagnosis, glucose monitoring, home glucose goals, and when to call the health care professionals.
- Definition, recognition, treatment, and prevention of hyperglycemia and hypoglycemia.
- Information on making healthy food choices at home and referral to an outpatient registered dietitian nutritionist or diabetes care and education specialist to guide individualization of the meal plan, if needed.
- When and how to take blood glucose-lowering medications, including insulin administration.
- Sick-day management (29,153).
- Proper use and disposal of diabetes supplies, e.g., insulin pen, pen needles, syringes, and lancets.

People with diabetes must be provided with appropriate durable medical equipment, medications, supplies (e.g., blood glucose test strips or CGM sensors), prescriptions, and appropriate education at the time of discharge to avoid a potentially dangerous hiatus in care.

PREVENTING ADMISSIONS AND READMISSIONS

In people with diabetes, the hospital readmission rate is between 14 and 20%, nearly twice that in people without diabetes (151,155). This may result in increased diabetes distress and has significant financial implications. Of people with diabetes who are hospitalized, 30% have two or more hospital stays, and these admissions account for over 50% of hospital costs for diabetes (156). Factors contributing to readmission include male sex, longer duration of prior hospitalization, number of previous hospitalizations, number and severity of comorbidities, and lower socioeconomic and/or educational status; scheduled home health visits and timely ambulatory follow-up care reduce readmission rates (151,155). While there is no standard to prevent readmissions, several successful strategies have been reported (151). These include targeting ketosis-prone people with type 1 diabetes (157), insulin treatment of individuals with admission A1C >9% (75 mmol/mol) (158), and the use of a transitional care model (159). For people with diabetic kidney disease, collaborative patient-centered medical homes may decrease risk-adjusted readmission rates (160). A 2018 published algorithm based on demographic and clinical characteristics of people with diabetes had only moderate predictive power but identified a promising future strategy (161).

Age is also an important risk factor in hospitalization and readmission among people with diabetes (refer to Section 13, "Older Adults," for detailed criteria).

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17. Diabetes Advocacy: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Managing the daily health demands of diabetes can be challenging. People living with diabetes should not have to face discrimination due to diabetes. By advocating for the rights of those with diabetes at all levels, the American Diabetes Association (ADA) can help to ensure that they live a healthy and productive life. A strategic goal of the ADA is for more children and adults with diabetes to live free from the burden of discrimination. The ADA is also focused on making sure cost is not a barrier to successful diabetes management.

One tactic for achieving these goals has been to implement the ADA Standards of Care through advocacy-oriented position statements. The ADA publishes evidence-based, peer-reviewed statements on topics such as diabetes and employment, diabetes and driving, insulin access and affordability, and diabetes management in certain settings such as schools, childcare programs, and detention facilities. In addition to the ADA's clinical documents, these advocacy statements are important tools in educating schools, employers, licensing agencies, policy makers, and others about the intersection of diabetes management and the law and for providing scientifically supported policy recommendations.

ADVOCACY STATEMENTS

The following is a partial list of advocacy statements ordered by publication date, with the most recent statement appearing first. A comprehensive list of advocacy statements is available at professional.diabetes.org/content/key-statements-and-reports.

Insulin Access and Affordability

The ADA's Insulin Access and Affordability Working Group compiled public information and convened a series of meetings with stakeholders throughout the insulin supply chain to learn how each entity affects the cost of insulin for the consumer. Their conclusions and recommendations are published in an ADA statement (1).

Diabetes Care in the School Setting

A sizable portion of a child's day is spent in school, so close communication with and training and cooperation of school personnel are essential to optimize diabetes

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management, safety, and access to all school-sponsored opportunities. Refer to the published ADA position statement for diabetes management information for students with diabetes in elementary and secondary school settings (2).

Care of Young Children With Diabetes in the Childcare Setting

Very young children (aged <6 years) with diabetes have legal protections and can be safely cared for by childcare professionals with appropriate training, access to resources, and a communication system with parents and the child's diabetes health care professional. Refer to the published ADA position statement for information on young children aged <6 years in settings such as daycare centers, preschools, camps, and other programs (3).

Diabetes and Driving

People with diabetes who wish to operate motor vehicles are subject to various licensing requirements applied by both state and federal jurisdictions. For an overview of existing licensing rules for people with diabetes, factors that impact driving for this population, and general guidelines for assessing driver fitness and determining appropriate licensing restrictions, refer to the published ADA position statement (4).

Editor's note: Federal commercial driving rules for individuals with insulin-treated diabetes changed on 19 November 2018. These changes will be reflected in a future updated ADA statement.

Diabetes and Employment

Any person with diabetes, whether insulin treated or noninsulin treated, should be eligible for any employment for which they are otherwise qualified. Employment decisions should never be based on generalizations or stereotypes regarding the effects of diabetes. For a general set of guidelines for evaluating individuals with diabetes for employment, including how an assessment should be performed and what changes (accommodations) in the workplace may be needed for an individual with diabetes, refer to the published ADA position statement (5).

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Disclosures: *Standards of Care in Diabetes—2023*

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Committee members disclosed the following financial or other conflicts of interest (COI) covering the period 12 months before December 2022

Member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Ownership interest	Consultant/ advisory board	Other
American Diabetes Association Professional Practice Committee							
Nuha A. ElSayed (Chair)§	American Diabetes Association	None	None	None	None	Expert, World Health Organization	Endocrinologist, Joslin Diabetes Center Chair, Diabetes Education for All
Grazia Aleppo	Northwestern University Feinberg School of Medicine Division of Endocrinology, Metabolism and Molecular Medicine	Dexcom#, Eli Lilly#, Fractyl Health#, Insulet/Self#, Emmes#	Emmes, Fractyl, Welldoc	Dexcom, Insulet/Self	None	Bayer, Dexcom, Eli Lilly, Insulet, Medscape	Associate Editor, *Diabetes Technology & Therapeutics*
Vanita R. Aroda	Brigham and Women's Hospital Faculty, Harvard Medical School	Applied Therapeutics#, Eli Lilly#, Fractyl#, Novo Nordisk#	None	None	None	Applied Therapeutics, Fractyl, Novo Nordisk*, Pfizer, Sanofi	Spouse Sandip Datta, MD, Senior Medical Director, Early Development, Infectious Diseases, May 2020 to present, Janssen Pharmaceutical Companies of Johnson & Johnson Consultant/educational activities: Associate Editor, *Diabetes Care*; Member of the Writing Group for "Management of Hyperglycemia in Type 2 Diabetes, 2022. Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)" Novo Nordisk* (received other Industry benefits, such as travel)
Raveendhara R. Bannuru (Chief Methodologist)§	American Diabetes Association	None	None	None	None	None	None
Florence M. Brown	Joslin Diabetes Center	None	Dexcom	None	None	None	None

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Member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Ownership interest	Consultant/ advisory board	Other
Dennis Bruemmer	Cleveland Clinic Lerner College of Medicine, Case Western Reserve University	Novartis	None	None	None	Intellisphere, Esperion (advisory board)	HCPLive/sponsored continuing medical education
Billy S. Collins	CDR, U.S. Public Health Service	None	None	None	None	None	None
Marisa E. Hilliard	Baylor College of Medicine Texas Children's Hospital	None	JDRF	None	None	None	Springer Publishing (book royalties) Associate Editor, American Psychological Association Member, Clinical & Research Advisory Committee; College Diabetes Network Member, External Registry & Research Committee; T1D Exchange Mental Health Diabetes Education Program
Diana Isaacs	Cleveland Clinic Endocrinology & Metabolism Institute	None	None	Abbott, Dexcom, Medtronic, Novo Nordisk, Bayer	None	Insulet, Eli Lilly, Sanofi, Klinio, Undermyfork	Board of Directors, Association of Diabetes Care and Education Specialists Clinical Practice Guideline Oversight Committee, American Association of Clinical Endocrinology
Eric L. Johnson	University of North Dakota School of Medicine and Health Sciences Altru Health System	None	None	None	None	None	Editorial Board, *Clinical Diabetes*
Scott Kahan	George Washington University Milken Institute School of Public Health National Center for Weight and Wellness	None	None	None	None	Vivus, Eli Lilly, Novo Nordisk, Currax, Gelesis, Medscape	(All without compensation) Board of Directors, The Obesity Society Board of Directors, Obesity Action Coalition Advocacy and Public Outreach Core Committee, Endocrine Society
Kamlesh Khunti	University of Leicester Leicester Diabetes Centre Leicester General Hospital	Boehringer Ingelheim#, Applied Therapeutics, AstraZeneca#, Novartis#, Novo Nordisk#, Oramed Pharmaceuticals, Sanofi#, Eli Lilly#, Merck Sharp & Dohme#	None	None	None	AstraZeneca, Bayer, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Boehringer Ingelheim	None
Jose Leon	National Center for Health in Public Housing	None	None	None	None	None	None

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Member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Ownership interest	Consultant/ advisory board	Other
Sarah K. Lyons	Baylor College of Medicine Texas Medical Center Diabetes and Endocrinology	None	None	None	Eli Lilly (parent stockholder)†	None	Unpaid Board Member, Epic's Pediatric Endocrinology Steering Board Volunteer member, Clinical and Research Advisor Committee of College Diabetes Network Volunteer member, Publications Committee on the T1D Exchange Quality Improvement Collaborative
Mary Lou Perry	UVA Heart and Vascular Center-Morrison's Compass Group	None	None	None	None	LifeScan Diabetes Institute	Editorial Board Member, *Diabetes Spectrum*
Priya Prahalad	Stanford Hospital and Clinics Lucile Packard Children's Hospital	None	None	None	None	None	Unpaid Board Member on Epic's Pediatric Endocrinology Steering Board
Richard E. Pratley	Advent Health Translational Research Institute	Novo Nordisk#	None	Novo Nordisk#	None	Bayer AG#, Gasherbrum Bio#, Hanmi Pharmaceutical#, Hengrui (USA)#, Merck#, Novo Nordisk#, Rivus Pharmaceuticals#, Sun Pharmaceutical Industries#	Editorial Board Member, *Diabetes Care* Board Member, International Geriatric Diabetes Society
Jane Jeffrie Seley	Weill Cornell Medicine	None	None	None	None	None	Director of Strategy, Diabetes Technology Society Associate Editor, *Diabetes Spectrum* Section Co-editor, *Current Diabetes Reports* Editor, *Journal of Diabetes Science and Technology* Editor, *BMJ Open Diabetes Research & Care* LifeScan Diabetes Institute
Robert C. Stanton	Joslin Diabetes Center	None	None	None	None	None	None
Robert A. Gabbay§	American Diabetes Association	None	None	None	None	Onduo*, HealthReveal, Lark, Vida Health*	Spouse Christi Gabbay, CHSE, Managing Director, Major Gifts and Philanthropy at American Diabetes Association Senior volunteer, Joslin Diabetes Center
American College of Cardiology Designated Representatives and Staff (Section 10 "Cardiovascular Disease and Risk Management")							
Sandeep R. Das	University of Texas Southwestern Medical Center	None	None	None	None	None	Associate Editor, *Circulation*

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Member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Ownership interest	Consultant/ advisory board	Other
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American Diabetes Association Staff							
Malaika I. Hill	American Diabetes Association	None	None	None	None	None	None
Laura S. Mitchell	American Diabetes Association	None	None	None	None	None	None
Designated Subject Matter Experts							
Kenneth Cusi	University of Florida	Echosens#, Inventiva#, Novo Nordisk#, Poxel#, Labcorp#, and Zydus#	None	None	None	Altimmune, Arrowhead, AstraZeneca, 89Bio, Bristol-Myers Squibb, Lilly, Madrigal, Merck, Novo Nordisk, ProSciento, Quest, Sagimet Biosciences, Sonic Incytes, Terns	None
Christopher H. Gibbons	Beth Israel Deaconess Medical Center	Grifols	Grifols	None	CND Life Sciences	None	None
John M. Giurini	Beth Israel Deaconess Medical Center	None	None	None	None	None	None
Lisa Murdock	American Diabetes Association	None	None	None	None	None	None
Jennifer K. Sun	Joslin Diabetes Center		Novo Nordisk, Boehringer Ingelheim, Genentech/Roche	Jaeb Center for Health Research/ National Eye Insitute, JDRF	Genentech/ Roche	None	None
Crystal C. Woodward	American Diabetes Association	None	None	None	None	None	None
Deborah Young-Hyman	Office of Behavioral Health and Social Sciences Research, National Institutes of Health	None	None	None	None	None	None

*≥$10,000 per year from company to individual. #Grant or contract is to university or other employer. †Disclosure made after committee member began work on the SOC 2022 update. §Nuha A. ElSayed, Raveendhara R. Bannuru, and Robert A. Gabbay are also American Diabetes Association staff.

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