Coronary Artery Disease in Patients with Chronic Kidney Disease - A Review

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Introduction

Cardiovascular diseases (CVD) are the leading causes of death in end-stage renal disease (ESRD) populations. There is increasing recognition that chronic kidney disease (CKD) of any degree portends a worsened prognosis for CAD patients and that long-term outlook in CKD patients is closely related to cardiovascular events. The cardiovascular mortality rate is 20 to 40 times higher for adults on dialysis than for the general population. In treating patients on dialysis, nephrologists contend with the cumulative effects of the processes that cause renal failure, the generic consequences of globally disordered renal function, and the potential adverse effects of treatment or lack of treatment. The value of most therapeutic interventions is less certain for CKD versus non-CKD patients because the former have typically been excluded from randomized trials. This review discusses the epidemiology, pathogenesis, clinical manifestations, diagnostic work-up, treatment, prognosis, and multiple conundrums regarding CAD patients with CKD.

Disease Burden

The prevalence of CAD in CKD patients is high and is a major cause of morbidity and mortality .Chronic kidney disease has reached epidemic proportions. More than 320,000 patients of CKD required dialysis in '98; by 2010, this number may exceed 650,000 patients[1]. Patients with mild to severe decrease in glomerular filtration rate (GFR) constitute a larger group, estimated in 1998 to be 13.3 million. Finally, there are many CKD patients without decreased GFR (5.9 million in 1998).[1] In hemodialysis (HD) or peritoneal dialysis patients, prevalence is estimated at 40% with a 9% annual cardiovascular mortality.[2]

Renal transplant recipients (RTRs) have a lower CAD prevalence (15%) with an annual cardiovascular mortality of 0.54%, twice the general population.[2] This lower prevalence may be due to patients with fewer comorbidities and lower CAD likelihood being chosen for transplantation. The need for nomenclature uniformity has led to a recent CKD classification based on estimated GFR.

Cardiovascular events in CKD

Chronic kidney disease increases cardiovascular event risk and portends a worse outcome if an event occurs. A study of 3,106 acute myocardial infarction (AMI) patients showed in-hospital mortality of 2% in normal renal function, 6% mild CKD, 14% moderate CKD, 21% severe CKD, and 30% in dialysis patients ($p<0.001$) with a similar trend long-term.[3]

Patients with mild to moderate CKD and non–ST-segment elevation acute coronary syndrome (ACS) showed higher 30- and 180-day mortality than non-CKD patients.[4]

One-year mortality after AMI was 59% in dialysis patients and 24% in RTRs. In a post-AMI Medicare cohort comprised of 130,099 patients, one-year mortality was 24% without CKD, 46% with mild CKD, and 66% with moderate CKD.[5]

Metabolic Derangements in CKD

The internal milieu in CKD favors CAD development and raises the question whether renal insufficiency itself is a CAD risk factor.

Diabetes mellitus: Diabetic nephropathy accounts for 40% of new ESRD. The 2001 U.S. Renal Data System reported a progressive rise in diabetic ESRD from 500/million in 1991 to 700/million in 1999 [6]. Moreover, chronic renal failure, independent of diabetes mellitus, is also associated with insulin

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resistance and glucose intolerance. Both are associated with the accumulation of advanced glycation end products that may induce cellular activation and endothelial damage, ultimately contributing to or even accelerating atherogenesis .

The mechanisms of vascular injury being beyond the scope of this review. There is considerable evidence that aggressive glucose control can significantly reduce microvascular and macrovascular complications of diabetes. Therefore, it is important not only to manage diabetes aggressively before the onset of renal disease but also to continue rigorous glycemic control after ESRD has developed. Because hypoglycemic reactions are more common in renal failure, there is a tendency for nephrologists and others who care for diabetics with ESRD to allow blood glucose concentrations to remain at levels that would be unacceptable in the absence of renal failure, thus sustaining the risk for vascular damage and atherogenesis. Sustained rigorous glycemic control before the onset, as well as after the initiation, of renal replacement therapies may be important in reducing cardiovascular morbidity and mortality in diabetic patients as has been shown by Wu *et al.* [7] However, whether such benefits would be offset by excessive hypoglycemic complications needs to be investigated further.

Hypertension: Hypertension is a well-established risk factor not only for myocardial ischemia, atherogenesis, and coronary artery calcification but also for the development of left ventricular hypertrophy (LVH). By contributing to LVH, hypertension represents an important risk for sudden cardiac death. Hypertension prevalence in CKD ranges from 60% to 100%, depending on CKD cause and severity and population studied.

Hypertension may cause or be an effect of CKD and confers an increased risk of cardiovascular events in all patient subsets. Forces on arterial and aortic walls produced by increased BP alter vascular endothelial cell function by inciting arterial oxidative stress and inflammatory responses. These effects in turn initiate the atherosclerotic process and stimulate various growth promoting peptides. The attendant endothelial dysfunction can lead to hypertrophy, hyperplasia, lipid incorporation, and calcification of the vascular smooth muscle and to associated reductions in vascular compliance and

thus to tissue ischemia. The reduced elasticity of the aorta and peripheral arteries further contributes to increased cardiac work, LVH, and increased cardiovascular mortality in ESRD patients .

Hyperlipidemia: Hyperlipidemia prevalence is increased in CKD. Lipid abnormalities include increased serum triglycerides, very low-density lipoprotein, and intermediate density lipoprotein and decreased high-density lipoprotein. Elevated total cholesterol is found in 30% of CKD patients without nephrotic syndrome and in 90% with nephritic syndrome compared with 20% of the general population. Low-density lipoprotein cholesterol, calculated by the Friedewald formula, assumes a 5:1 triglyceride/cholesterol ratio in the very low-density lipoprotein particle and ignores intermediate-density lipoprotein. Hemodialysis patients with normal calculated low-density lipoprotein cholesterol may actually have elevated intermediate-density lipoprotein cholesterol measured by ultracentrifugation. Because intermediate-density lipoprotein is atherogenic, the Friedewald formula probably underestimates the amount of atherogenic cholesterol and hence the risk of developing atherosclerosis. Increases in small and dense low-density lipoprotein and oxidized low-density lipoprotein cholesterol have been reported in dialysis patients, which may increase cardiovascular risk. Low serum cholesterol and albumin levels in HD patients probably reflect poor nutritional status and are independent predictors of increased mortality.

Calcium-phosphate product: Hemodialysis patients with hyperphosphatemia for 1 year and an elevated calcium phosphorous product have a higher mortality. Ganesh et al.[8] found that hyperphosphatemic patients had 41% increased risk of cardiovascular death and 20% increased risk of sudden death. Hyperphosphatemia and high calcium phosphate product have been implicated in the pathogenesis of cardiovascular calcification, which may correlate with atherosclerotic plaque burden and increased AMI incidence.

Hyperhomocysteinemia: Hyperhomocysteinemia is associated with an increased incidence of cardiovascular events in ESRD and RTRs.[9] Hyperhomocysteinemia may produce endothelial dysfunction; smooth muscle proliferation; platelet aggregation; activation of factors V, X, and XII; and

modulation of tissue plasminogen activator, all creating a prothrombotic environment. Plasma homocysteine increases, often to very high levels 100 mol/l normal upto 12 mol/l) with GFR 70 ml/min. Homocysteine is metabolized by either transsulfuration with pyridoxine as cofactor or by remethylation with transcobalamin and methyltetrahydrofolate, the active form of folate, as cofactors. Deficiency of these water-soluble vitamins may develop from losses during dialysis and, coupled with poor oral intake and decreased homocysteine renal clearance, promoted hyperhomocysteinemia.

Inflammation and oxidative stress: The role of systemic inflammation and oxidative stress to the atherosclerosis development and cardiac events is currently being investigated, and a discussion is beyond the scope of this review. ESRD patients show activation of systemic inflammation and increased oxidative stress. In nondialysis dependent CKD patients, blood levels of markers of systemic inflammation and oxidative stress increase as renal dysfunction progresses.[10]

Immunosuppressants: Corticosteroids for immunosuppression in RTR may induce insulin resistance and hyperlipoproteinemia. Cyclosporine increases low-density lipoprotein cholesterol level in RTRs.[11]

Is CKD itself a risk factor for CAD?

The question of whether specific factors in CKD accelerate atherosclerosis is unanswered, but clues suggest that this may be so. CKD may accelerate atherosclerosis further in the presence of type 2 DM. In one study, diabetic RTRs had a lower ACS incidence after transplantation compared with pretransplantation.[12] Vascular disease in young ESRD patients was related to inflammatory markers, hyperparathyroidism, hyperphosphatemia, and hyperhomocysteinemia but not traditional risk factors . Asymptomatic mild CKD patients in the Cardiovascular Health Study showed elevated proinflammatory and prothrombotic parameters [10]. These data emphasize the adverse internal environment and potential contribution of novel risk factors in the development and progression of CAD in CKD patients.

Morphology of atherosclerotic plaque in CKD.

Postmortem data of CKD vessels showed increased medial thickness and smaller lumen area compared with age- and gender-matched control subjects. Control plaques were mostly fibroatheromatous, whereas CKD plaques were calcified. An electron beam computed tomography study in ESRD adults showed coronary calcification in 92%; on average, calcium scores exceeded 10-fold the 95th percentile, the severity related to ESRD duration.[13]

Special Issues in CKD Patients

Diagnosing ischemia and CAD symptoms

Chest pain specificity for CAD is reduced in CKD as a result of ischemia from anemia, poorly controlled hypertension, and/or left ventricular hypertrophy, as well as, CAD. Conversely, CKD patients with CAD may not experience chest pain owing to diabetic or uremic neuropathy. Dyspnea on exertion is also less specific for angina as it may be secondary to anemia, volume overload, diastolic dysfunction or respiratory compensation for metabolic acidosis.

Non invasive evaluation: The electrocardiogram in CKD may display widened QRS and ST-T changes of left ventricular hypertrophy, volume overload, and electrolyte abnormalities. Peak exercise capacity may be limited by physical deconditioning, musculoskeletal problems, poorly controlled blood pressure, and anemia. Baseline electrocardiographic abnormalities and an inability to reach target heart rate in exercise electrocardiographic testing lowers sensitivity and specificity in CKD patients. Dobutamine stress-echocardiography in dialysis patients has a sensitivity of 75% to 95% and specificity of 76% to 86%. Dipyridamole radionuclide stress testing has a sensitivity of 80% and specificity of 37% to 73%.[14]

Invasive evaluation and contrast-induced nephropathy (CIN)

The invasive evaluation of CAD in CKD patients is complicated by an increased CIN risk, defined as an absolute serum creatinine (sCr) increase 0.5 mg/dl or relative increase 25% above baseline after contrast administration.

The most important CIN risk factors are (i) age $\geq$ 70 years, (ii) pre-existing CKD, and (iii) DM. In DM patients with CKD, the CIN rate may exceed 25%. Most studies comparing ionic high-osmolar with nonionic low-osmolar contrast in patients without high-risk features have shown no difference in renal outcome. Data suggest that non-ionic low-osmolar or isoosmolar contrast decreases

nephrotoxicity in diabetics and CKD patients, but the effect is relatively small. One controlled randomized trial comparing normal saline hydration alone with saline and mannitol or furosemide showed that saline alone was most successful in preventing CIN.[15] Several agents have been shown to be ineffective in CIN prevention, including dopamine, mannitol, furosemide, atrial natriuretic peptide, calcium channel blockers, aminophylline, and fenoldopam . Isotonic saline appears superior to hypotonic saline. Some trials in CKD patients have shown *N*-acetylcysteine (an antioxidant) decreasing CIN incidence. In a meta-analysis of 805 patients, *N*-acetylcysteine reduced CIN risk by 56% (p=0.02) [16]. Based on low cost, simple regimen, low adverse effect incidence, and clinical trial results, *N*-acetylcysteine may be used for CIN prevention. There still remains a need for a large trial to definitively demonstrate efficacy.

Contrast-induced nephropathy is usually non-oliguric. Treatment includes fastidious maintenance of fluid balance, avoidance of nephrotoxic agents, and monitoring of renal function and electrolyte status. Dialysis is necessary in only a small percentage (0.4% to 0.8% of patients undergoing percutaneous coronary intervention PCI.[17] Most patients recover by one to three weeks, but a small percent do not, or only partially. Patients with mild to moderate CKD who develop CIN after PCI show increased one-year mortality (45% if dialysis is required, 35% if dialysis is not required, and 19% if sCr does not rise, $p < 0.001$).[18]

Reliability of Biomarkers for Diagnosing AMI in CKD: Creatine kinase-myocardial band (CK-MB) elevations have been found on routine testing in dialysis patients without clinical or electrocardiographic evidence of AMI. It is unclear whether these elevations represent false positives, ongoing myocardial damage, or reduced CK-MB clearance. Troponin measurement may have similar limitations. In one study, cardiac troponin was found to be the most consistent AMI marker in all CKD strata including dialysis patients and was more sensitive and had a higher negative predictive value than myoglobin and CK-MB. However, sporadic or persistent elevations have also been seen in troponin T and I in asymptomatic patients.

Predicting prognosis with biomarkers: Studies have evaluated the relationship of biomarkers to prognosis in ACS, post-PCI, and asymptomatic CKD patients. In 7,033 ACS patients in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) IV trial, troponin T predicted increased AMI or death risk at one month regardless of creatinine clearance (CCr).[19] The CK-MB elevation after PCI in CKD patients is associated with increased mortality and in-hospital complications.

An increase in predialysis serum troponin T and/or I was associated with a twofold to fivefold increase in two-year mortality in asymptomatic HD patients. In HD patients without ACS, troponin T correlated with left ventricular mass and all-cause and cardiovascular mortality. Further, in such patients, increasing troponin T and C-reactive protein levels were independently associated with an increased risk of death, and their combination predicted the highest death risk. The exact role of troponin testing for risk stratification of asymptomatic HD patients is attractive but undefined. Also unclear is the appropriate evaluation and management of CKD patients with asymptomatic serum CK-MB and/or troponin elevation.

CAD screening in renal transplant candidates: Cardiovascular events cause 35% to 50% of all deaths after renal transplantation.[20] The purpose of CAD screening is two-fold:

1) To determine surgical risk, and

2) To estimate survival after transplantation.

It should be noted that there are no large-scale trials demonstrating that "prophylactic" revascularization improves long-term outcome after transplantation. Because there is a limited organ supply and patients without CAD are likely to have better long-term outcome, should screening exclude CAD patients from transplantation ?

Alternatively, should aggressive screening and coronary revascularization be performed to optimize long-term outcome after transplantation for patients who survive the revascularization procedure? What is clear is that patients who manifest ischemia on pre-transplant stress testing have a higher cardiac event and mortality risk in long-term post-

transplantation follow-up.[21] These data emphasize the quandary on how to evaluate and treat these patients.

The American Society of Transplant Physicians has formulated CAD screening guidelines. Transplant candidates with angina and diabetics with evidence of ischemia should usually undergo pre-transplant coronary angiography without prior noninvasive testing. Routine pre-transplant coronary angiography in asymptomatic diabetics is uncertain. For asymptomatic patients with CAD by history or multiple risk factors, noninvasive testing may help in assessing the post-transplant cardiac risk. If the stress test is abnormal, coronary angiography is recommended. American Society of Transplant Physicians guidelines suggest revascularization before transplantation in patients with "critical" lesions based on a small randomized trial in 26 asymptomatic diabetics.[21]

Optimizing medical management.
There is underutilization of aspirin, beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), glycoprotein IIb/IIIa receptor antagonists, diagnostic coronary angiography, thrombolytic therapy, and PCI in CKD patients with AMI or ACS. This may relate to physician concern regarding bleeding risk, worsening of renal function, lack of evidence for use of certain drugs, associated co-morbidities, and generally worsened outcomes in CKD patients. Dose adjustment in cardiac medications may be necessary.

Anticoagulation
Management of ACS in CKD patients is the same as in the general population with few exceptions. Aspirin is recommended, although no prospective efficacy or safety data have dealt specifically with CKD patients. Unfractionated heparin is preferred over low molecular-weight-heparin, which may accumulate in renal failure and for which adequate data are unavailable. Direct thrombin inhibitors are cleared partially by the kidney, urging caution until more data are available. A metaanalysis suggests that at least for bivalirudin, the drug is equally, or more, effective than unfractionated heparin and produces less bleeding.[22] Safety data on glycoprotein IIb/IIIa inhibitors are limited as a result of the exclusion of CKD patients from most clinical trials. Among mild to moderate CKD patients in the

Platelet-Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial, tirofiban plus heparin was well tolerated and effective in reducing ACS complications.

Among mild CKD patients in the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial, bleeding risk and treatment effect with eptifibatide were similar to that in patients with normal renal function.[23]

Management of Hypertension
The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure recommends that CKD patients should have a blood pressure 130/80 mm Hg.[24] The National Kidney Foundation recommends 125/75 mm Hg for CKD patients with proteinuria 1 g/day. However, the relationship between blood pressure and mortality in HD patients may exhibit a "U"-shaped distribution wherein not only high (180 mm Hg) but also low (110 mm Hg) systolic blood pressure is associated with increased mortality.[25]

Hypertension in CKD patients, especially those on dialysis, is volume-dependent. Hence maintenance of fluid balance is paramount. Examination of neck veins, edema, and body weight can aid in managing fluid status.

ACEI Angiotensin-converting enzyme inhibitors decreased 30-day mortality (relative risk 0.64) in dialysis patients with AMI, an effect similar to non-dialysis patients. Angiotensin-converting enzyme inhibitors decrease the progression of nephropathy in type 1 and 2 diabetes and non-diabetic renal disease.[26] In the Heart Outcomes Prevention Evaluation (HOPE) trial, risk reduction for cardiovascular death, all-cause mortality, and heart failure hospitalizations with ramipril was greater for CKD than non-CKD patients.[27] These agents should be used cautiously because they may induce hyperkalemia in nondialysis patients with mild to severe CKD.

Angiotensin Receptor Blockers: Renoprotection from angiotensin receptor blockers has been demonstrated in CKD patients but cardioprotection has not. Renoprotection appears to be independent of blood pressure reduction. In a randomized trial of 1,513 CKD patients with type 2 DM, nephropathy

progression was reduced by losartan but cardiovascular death incidence was similar to placebo[28]. In a trial of irbesartan, amlodipine, or placebo in 1,715 CKD patients with hypertension and type 2 DM, irbesartan afforded renoprotection but not cardioprotection.[29] Based on lack of proven cardioprotective effect of angiotensin receptor blockers in CKD patients, ACEI are preferred when possible.

Beta-Blockers: Beta-blockers appear to retain their cardioprotective effects in CKD patients. In an analysis of a Medicare database of over 200,000 mild CKD patients, there was a 35% reduction in mortality with beta-blockers .

Treatment of Hyperlipidemia: Target serum low-density lipoprotein cholesterol in CAD patients is 100 mg/dl. Statin dose reduction is required in RTRs taking cyclosporine or tacrolimus. It is not clear whether isolated hypertriglyceridemia or low levels of high-density lipoprotein cholesterol should be treated with drugs in CKD patients.

Treatment of Hyperhomocysteinemia: Recommended daily allowances of folate (5 mg/day), transcobalamin (0.4 mg/day), and pyridoxine (50 mg/day) normalize homocysteine level in mild to moderate CKD patients and RTRs, but only mildly affect homocysteine levels in dialysis patients. It seems reasonable to normalize plasma homocysteine if possible.

Management of Anemia:
Anemia may increase angina severity and left ventricular hypertrophy and decrease exercise tolerance, and its correction improves these abnormalities. The Normal Hematocrit Trial showed that patients with ESRD and CAD or heart failure treated with erythropoietin to a target hematocrit of 42% had a higher risk ratio (RR) (1.3) for the end points of death or nonfatal AMI compared with a targeted hematocrit of 30%.[30] Alternatively, a large Medicare study of HD patients using erythropoietin demonstrated decreased risk of cardiac mortality with a hematocrit of 30% to 33%, and an even lower risk with 33% to 36%.[31]

Role of Antioxidants:
Antioxidants for cardioprotection have demonstrated conflicting results. The Secondary Prevention with Antioxidants of Cardiovascular disease in end stage renal disease (SPACE) trial demonstrated that vitamin E use in HD patients was associated with a 54% decrease in the combined end point of AMI, ischemic stroke, symptomatic peripheral vascular disease, and unstable angina.[32] Other studies have not demonstrated a beneficial effect of vitamin E. *N*-acetylcysteine in HD patients decreased the composite end point of fatal/nonfatal AMI, cardiovascular death, need for revascularization, ischemic stroke, and symptomatic peripheral vascular disease versus placebo (28% vs. 47%, p 0.03).[33] Although efficacy trials with antioxidants have been disappointing in non-CKD patients, the increased oxidant stress in CKD may provide the environment for antioxidants to be cardioprotective. Clearly more data are required before any antioxidant can be recommended.

Revascularizing CKD patients with PCI
There is a striking lack of comparison of CAD treatments in CKD patients. Small studies using balloon angioplasty in HD patients have shown initial angiographic success of 56% to 96% with high re-stenosis rates (60% to 81%). Procedural advances and stent use have produced better angiographic success rates (90%) and lower re-stenosis rates (31% to 36%).[34] Drug-eluting stents may reduce re-stenosis rates further, although data are currently unavailable.

Mortality risk during PCI hospitalization increases with CKD as well as DM and appears additive. The CKD patients have higher one-year mortality after PCI than non-CKD patients, a trend observed through four-year follow-up.[35] Percutaneous coronary intervention use in AMI showed a higher 30-day death rate (7.5%) in CKD versus non-CKD patients (0.8%, p 0.0001).[36] The CKD patients undergoing saphenous vein graft interventions also show a higher in-hospital and one-year mortality.[37] Chronic kidney disease patients with ST-segment elevation AMI showed a lower 30-day mortality with thrombolysis (8.3%) than PCI (37.1%, p 0.04),[38] emphasizing the uncertainty of the preferred AMI treatment in CKD patients.

Coronary Artery Bypass Graft Surgery (CABG):
Coronary artery bypass graft surgery perioperative mortality in dialysis patients is approximately 7% to 10%, at least three to four times non-CKD patients, and five-year mortality is estimated at 48% versus 15% in non-CKD patients.[39] Most studies are retrospective, have small sample size, and are

unadjusted. In studies with adjustment, CKD remains a highly significant predictor for decreased long-term survival.[40] Not unexpectedly, HD-dependent diabetics suffer worse long-term outcomes after CABG than non-diabetics. Coronary artery bypass graft surgery outcomes in mild or moderate CKD patients are limited. Chronic kidney disease patients (vs. non-CKD patients) had longer in-hospital and intensive care unit stay and more frequent postoperative dialysis.[41] In a prospective study of 2,222 mild CKD patients, 7.7% had postoperative renal dysfunction associated with prolonged intensive care unit and hospital stays and increased mortality.[42] In another analysis of mild to moderate CKD patients, inhospital CABG mortality was 11% and actuarial survival at 10 years was 32%, similar to dialysis patients.[43]

Comparison of CABG and PCI:
Studies comparing CABG with PCI in HD patients are all non-randomized and retrospective. There may be an increased perioperative mortality but better long-term survival and freedom from angina with CABG compared with balloon angioplasty. A preliminary report from a large prospective trial comparing stenting and CABG in patients with multi-vessel disease suggests similar outcomes. A non-randomized study in CKD patients with estimated GFR 60 ml/min with ACS showed that PCI was associated with improved survival compared with CABG or medical therapy .

Conclusions:
Patients with ESRD have more than CAD risk equivalent status in their baseline CAD risk assessment.This review has highlighted that CAD is widely prevalent in CKD and that CAD patients with CKD have a worsened prognosis. The current challenge is to study the CAD patient with CKD in prospective randomized trials to provide an evidence-based approach to therapy. In the absence of such information, aggressive control of CAD risk factors and timely intervention for symptomatic CAD is suggested.

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