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Original Article

Clopidegrol Resistance in Patients Undergoing Percutaneous Coronary Intervention (PCI): our experiences at Apollo Hospitals Dhaka

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Key Words : *PCI, IHD CYP2C19, Clopidegrol*

Abstract:

Background: *Dual antiplatelet (DAPT) treatment with Clopidegrol and Aspirin after percutaneous coronary intervention(PCI) is common practice for the interventionist to prevent thrombotic event after coronary stent placement. In spite of this, significant number of thrombotic events still occur. Exact data on our population regarding the thrombotic events after successful PCI and uses of DAPT not yet available. Therefore, we have carried out this study to see sensitivity resistance in our population by measuring Clopidegrol resistance test (CYP2C19 assay).*

Methods: *Total 351 patients were enrolled in this observation non randomized prospective cohort. Patient who had percutaneous coronary intervention (PCI) at our center or elsewhere, and on Clopidegrol with Aspirin, were selected for the study. Clopidegrol resistance were measured by PCR assay for CYP2C19 at our hospital molecular lab.*

Results: *Among the 351 patients, male 292 and female 59. Average age for the male: female was 59:61years. Clopidegrol resistant test was performed by Real Time PCR for CYP2C19. Total 57%(200) patients are Clopidegrol resistant or positive and 43%(151) patients are Negative. Among the resistant case 9.1%(32) patients are Homozygous Positive with probable genotype CYP2C19*2 (*2/*2) and 168 (47.8%) patients were Heterozygous positive with probable genotype CYP2C19(*1/*2). Among the CAD risk factors, Dyslipidemia were more, followed by HTN, DM, FH and smoking. Among the studied group; PCI territory Left Anterior Descending (LAD), total number of Percutaneous Coronary Intervention (PCI) and number of vessel that is Single Vessel Disease (SVD) were more in Heterozygous, Homozygous and CYP2C19 Negative group.*

Conclusion: *In this single center, observational prospective cohort, we found quiet a significant (57%) number of patients are Clopidegrol resistant. Therefore, we may need to double the Clopidegrol dose and or to start other antiplatelet such as Ticagrelor or prasugrel in addition to Aspirin. Thus, to prevent stent thrombosis or restenosis.*

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Introduction:

Prevalence of coronary artery disease has been recognized as one of the important cause of morbidity and mortality in our Bangladeshi patient population. Advent of interventional procedure, improved technical skill and expertise of individual interventionist with the availability of various drug eluting stents, has improved the morbidity and reduced mortality. In addition of uses of dual antiplatelet therapy with the addition of Clopidogrel to Aspirin has reduced the symptoms with improved long term efficacy of PCI.[1]

It has been recommended individual patient should receive DAPT for up to 12 months. Despite this guideline directed regimen, stent thrombosis remained a significant drawback in intervention resulting in recurrence of ischemic events.

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Dual Antiplatelet treatment combining Clopidegrol and aspirin is the standard of care for patients having acute coronary syndromes or undergoing percutaneous coronary intervention (PCI), according to current ACC/AHA and ESC guidelines.[2-4] However, despite the administration of DAPT, some patient develops recurrent cardiovascular events with stent thrombosis[5] This acute re-occlusion of the artery may Cause acute myocardial infarction and is associated with increased morbidity and mortality.[6]

Clopidegrol is an antiplatelet drug used by approximately 40 million patients worldwide to treat or to prevent atherothrombotic events after PCI.[7] It is well stablished that the antiplatelet response to Clopidegrol varies widely among patients.[8-9] Patients who develop little attenuation of platelet reactivity under Clopidegrol therapy are recognized as low or non-responder or Clopidegrol resistance. [1] Although, the standard 75mg daily maintenance dose of Clopidegrol has proven to be clinically adequate for patent's, in some cases some different pharmacodynamics response to Clopidegrol were detected. Therefore, patients with higher platelet reactivity while receiving Clopidegrol are at risk of cardiovascular events.[11]

Clopidegrol, an active prodrug is metabolized by the hepatic cytochrome P450 (CYP) system to generate its active thiol metabolite. Patients with mutations in CYP2C19 gene, have more adverse clinical events after PCI.[12] Also it has been suggested that Clopidegrol may be less effective in reducing the rate of cardiovascular events in patients who are carriers of loss of function CYP2C19 like CYP2C19*2 and *3, are associated with reduced conversion of Clopidegrol to its active metabolite.[13-14]

Case: A Young 44year old Bangladeshi gentleman with h/o FH positive for CAD, HTN, Dyslipidemia underwent CAG on 12/4/2017 for exertional chest tightness, revealed LM with TVD and recommended for PCI. PCI done on 17/4/2017 with LM-LAD: Resolute 3 x 38mm, LCX-OM: Resolute 2.75 x 24mm; RCA-PDA: Biomatrix 2.5x33. He was on DAPT and statin. On 21/5/2017 again he visited his primary physician for similar chest tightness, reassured and advised to continue medication. On 27/12/17, again he visited his primary physician with the same chest discomfort, this time advised for check CAG. Later, he went to center outside country of residence. On, 13/2/18 CAG revealed: Significant ISR of all three stents; LM-LAD 40-50% mid segment ISR, LCX 90% ostial lesion and RCA-PDA 80-90% ISR. His Clopidogrel Resistance test found Heterozygous Positive with high Homocysteine level. Considering his ongoing symptoms with restenosis with very short time, recommended for CABG. He put on Prasurel and Ecosprin with Folison in addition to other medication. He is doing well.

Methods:

Total 351 patients (Male 292, Female 59) were enrolled in this non randomized prospective cohort study Patients were enrolled in this study, who underwent clopidogrel resistance test by PCR assay for CYP2C19. Most of the studied patient had their PCI or CABG done here or somewhere else and kept on DAPT with Aspirin and Clopidogrel. Among, the CABG group of patient, either they had prior PCI and later went for CABG due to stent thrombosis, ISR or new lesion development or PCI after CABG due to development of new lesion or graft failure. For those in our center, all Patient were routinely loaded with pre-procedural Clopidogrel 300mg and Aspirin 300mg with post procedural maintenance doses Clopidogrel 150mg and Aspirin 150mg.

Blood sampling and Genotyping:

Whole blood for genotyping was obtained from the arterial sheath of all patients directly after diagnostics angiography and PCI. Genomic DNA were extracted from 200mL of blood using commercially available kits according to manufacturer's instruction. Clopidogrel Resistance were analyzed post PCI stage when patient come into OPD follow up by Real time PCR reactions for CYP2C19. If the patient were found to be heterozygotes or homozygotes, clopidogrel were changed to Prasugrel or Ticarel and continued with aspirin.

Results:

Total 351 patients (M 292: Female 59) were studied in this prospective non randomized cohort. Based on clopidogrel resistance assessed by real time PCR reactions for CYP2C19 and found as heterozygous 47.9%(168) homozygous 9.1%(32) and negative were (43%(151) and studied. Table1. shows the profile of studied patient. Female were older than in male (F60:M59) and more obese than male (F29:M27.5)

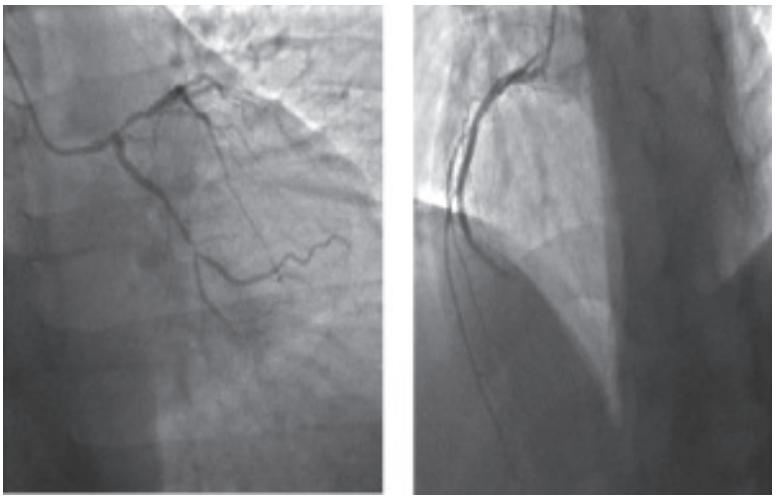
and poorly controlled diabetes (F 8.5; M 7.6). Fig 1 shows the baseline Coronary angiogram (CAG) with stenosis in patients before PCI, Fig 2 shows PCI 2 months after diagnostic CAG and Fig 3. Shows Re-Look CAG after 8 months of PCI. Significant ISR of RCA-PDA stent, LM-LAD stent and new plaque development at LCX ostium. Fig 4. Shows distribution of male and female patients. Fig 5 shows distribution of CAD risk factors. Dyslipidemia were more (76.1%) followed by HTN (70.1%) DM 48.1%), FH for CAD 24.2%, Smoking 23.3%. Fig 6 shows distribution of Clopidogrel resistance based on PCR assay for CYP219C. Heterozygous 47.9%, Homozygous 9.1% and CYP2C19 Negative 43%. Fig 7 shows distribution of CABG, Primary PCI (pPCI) and PCI in the studied group. Total PCI were more in Heterozygous group and homozygous group. Primary PCI and CABG were more in CYP2c19 negative group. Fig 8 shows total number vessel in all three groups, and found that SVD is more in all three group, followed by DVD and TVD. Fig 9 shows territory wise distribution shows Heterozygous and CYP2C19 were more in LAD, followed by all three in RCA and LCX.

Table-I

Demographic Profile of patient

	Male	Female
Number	292	59
Age (yrs)	59.0±11	60.0±11
BMI(kg/m^2)	27.5±3.5	29.0±5.4
SBP(mmHg)	125.3±12.2	126.0±11.3
DBP(mmHg)	74.6±9.3	74.6±6.9
FBS	7.6±2.7	8.5±3.2
HbA1C	7.5±1.7	8.7±2.3
Creat	1.3±0.7	1.2±0.6

Data were presented as Mean ± SD



(a) (b)

Fig.-1: *(a) Coronary Angiogram on Feb 2017; Shows Significant LM 50% distal, LAD 90-95% proximal, 80-85% LCX-OM lesion and 1 (b)& 1(c): occluded from distal segment*

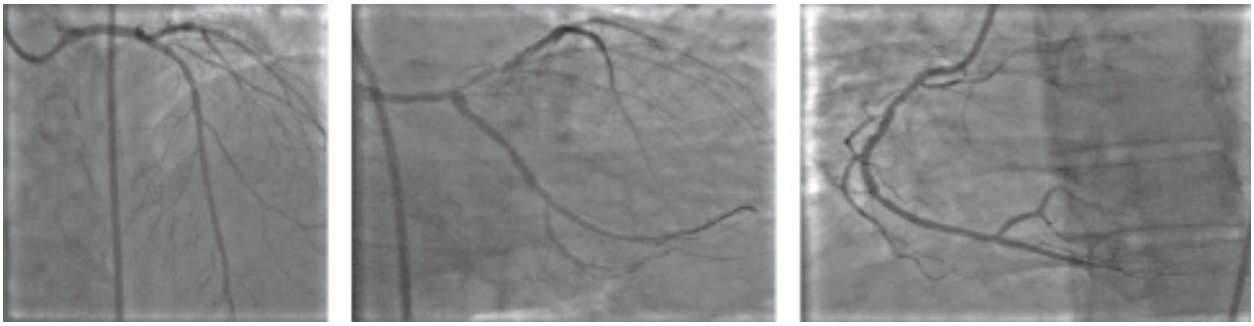


Fig.-2: *(a): on April 2017; PCI of LM-LAD with DES 3 x 38 mm at 16 ATM. Post dilated with 3.5x10, 4.0x10mm balloon at 16 ATMFigure 2(b): PCI of LCX-OM: DES 2.75 x 15 mm at 16 ATMFigure 2(c): PCI of RCA-PDA DES 2.75 x 15 mm at 12 ATM*

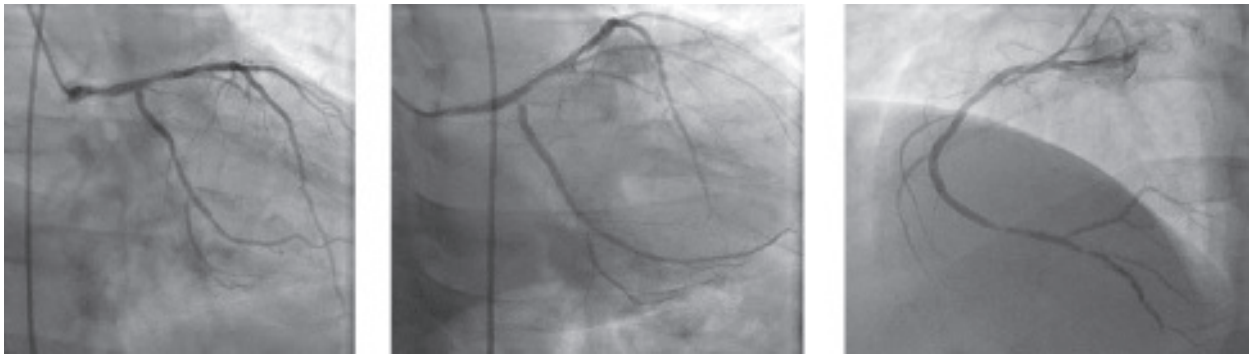


Fig.-3: *Re-look CAG 10 months after PCI*

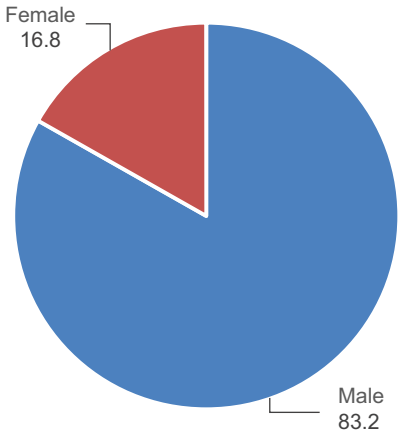


Fig.-4: *Shows distribution of male and female in the studied group*

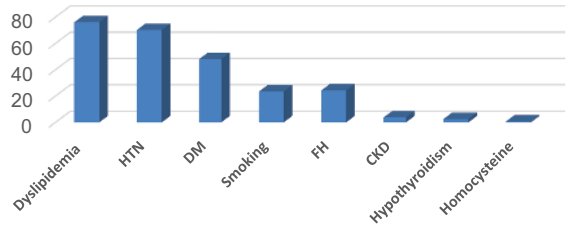


Fig.-5: *Shows distribution of CAD risk factors*

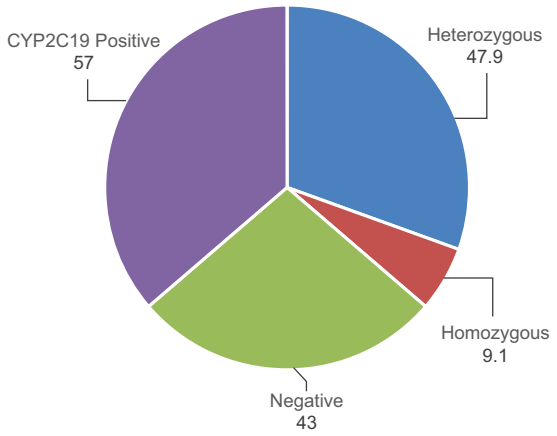


Fig.-6: *shows the distribution of patient based on CYP2C19 assay*

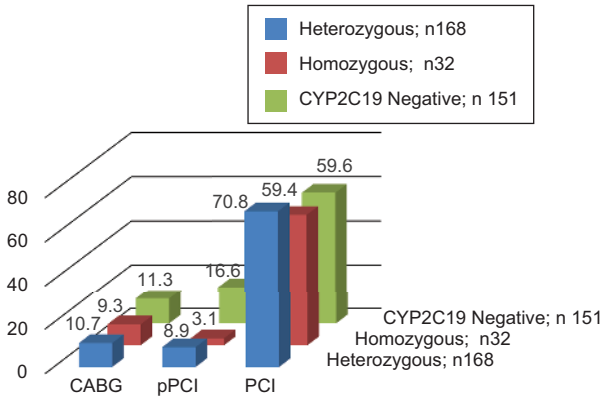


Fig.-7: *shows distribution of CABG, Primary PCI (pPCI) and PCI*

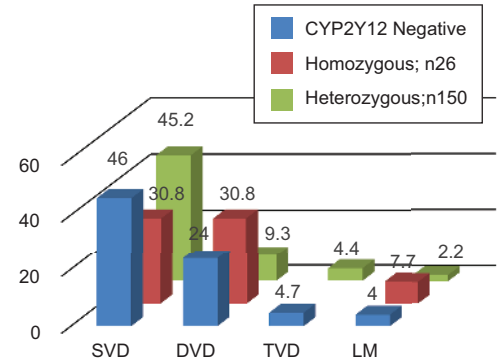


Fig.-8: *shows distribution of number of vessel with CAD*

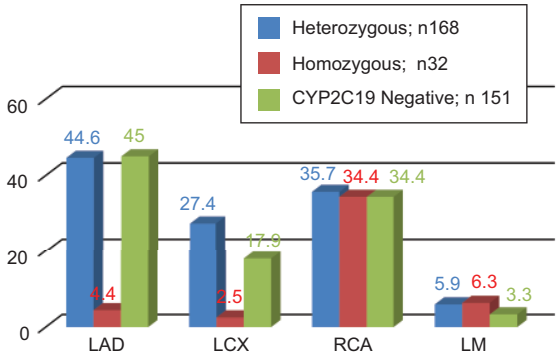


Fig.-9: *Shows territory wised distributions vessels*

Discussion:

Oral antiplatelet agents are the cornerstone of modern pharmacotherapy in the prevention and management of cardiovascular atherothrombotic disease according to the ACC/AHA and

ESC guideline. [2-3] Antiplatelet response to Clopidegrol is not uniform and it varies widely among patients.[8,15] When combined with Aspirin, Clopidegrol is the gold standard for the prevention of ST in subjects going for PCI and thus reducing major cardiovascular events in patients with NSTMI acute coronary syndrome.[16] Stent thrombosis is considered as a multifactorial problem related to patients, procedure, lesion, factors relate to blood coagulation and response to antiplatelet therapy.[17]

Besides medication. Noncompliance (pseudo resistance), pharmacodynamics and pharmacokinetics mechanism are involved in variability in responsiveness to antiplatelet agents, and these includes drug bioavailability, drug-drug interactions, Cytochrome-P-450 (CYP 450) activity acetic polymorphism.

Various clinical studies have demonstrated that the patients with high residual platelet reactivity on clopidogrel were at increased risk for stent thrombosis.[18-19] Multiple studies have demonstrated that both homozygotes and heterozygotes for loss-of-function CYP2C19 alleles have lower level of active clopidogrel metabolite,[20] diminished platelet response to clopidogrel[21] and higher rates of adverse cardiovascular events when compared with non-carriers.[22]

In Bangladeshi interventional era, many of the patients of ACS or STEMI are being treated by percutaneous coronary intervention either by Drug Eluting stent (DES) or Coronary Artery Bypass Graf(CABG) and kept on DAPT either Aspirin and Clopidogrel. Exact data on Clopidogrel resistance in our patient population not yet available. Therefore, we performed this single center non randomized prospective cohort of patients with DAPT with Aspirin and Clopidogrel either after PCI with DES or CABG. In our 351 patients 83% (292) were male and 17(59) patients were female. Dyslipidemia is one of the common CAD risk factors followed by HTN, DM Smoking and FH for CAD.

Among the studied patients, total 57%(200) patients were Clopidogrel Resistance by PCR Assay of CYP2C19, of which Heterogeneous was 47.9%(168) and 9.1%(homozygous), indicating a large proportion of patient of our population are resistant to clopidogrel. Thus, increasing the chances of stent thrombosis as it happened in our presented case in the text. Total percentage distribution of PCI was more in all three groups. Interestingly, among the Primary PCI, 16.6%(25) patients were CYP2C19 negative, indicating better outcome or less chance of stent thrombosis or development of acute or late stent thrombosis among these group of population if treated with Clopidegrol with ASA. On the other hand, 70.8%(119) patient who had PCI with DES are heterozygous, indicating chances of stent thrombosis or ISR. Thus, may need double doses of clopidogrel or change to Ticarel or Prasurel.

Among the territory involvement wise analysis showed, Heterozygous positive were more ion LAD followed by RCA, then LCX and Homozygous positive in RCA followed by LCX and LAD. On the contrary, Homozygous are more in LM stem PCI patient, may suggest that this group of patient are in high risk of stent thrombosis or ISR and may need to start Ticarel or Prasurel with ASA at the beginning.

Numerous randomized trials have indicated the benefits of Clopidegrol either as an alternative or as an adjunct to aspirin.[23-25] Despite proved efficacy, antiplatelet protection with clopidogrel has several potential limitations. Delayed onset of platelet inhibition even after loading regimens, substantial response variability in acute setting, remaining risk for the development of vascular thrombosis and higher rate of perioperative bleeding complications during cardiac and non-cardiac surgery.[26-29]

By definition; insufficient platelet inhibition with clopidogrel has been termed clopidogrel resistance. However, it remains a laboratory research finding rather than approved, despite low response to worsened vascular outcomes in general and the development of stent thrombosis.[30] Different methods report different prevalence's depending on the test used, the cut-off value used to define resistance, the timing with respect to medication and population studied. Indeed, if clopidogrel resistance is a real meaningful finding, then higher loading and maintenance doses of clopidogrel and new much more potent prasugrel or Ticarel will

result in better outcomes. In certain groups of patient higher loading and maintenance doses of clopidogrel; with drug eluting stents, promoting clopidogrel resistance, and exposing to higher risk of bleeding and stent thrombosis.

There is a need to have a simple, affordable, near patient test useful in clinical (not just laboratory) setting to validate large clinical trial to identify Clopidegrol resistance. Uses of higher loading or maintenance doses of Clopidegrol or new and more potent P2Y12 receptor blockers is a potential alternative strategy although benefits need to be balanced with increased bleeding risk. In addition to other factors, genetic polymorphism and patient risk profile also be taken in to account to detect Clopidegrol resistance. Moreover, this might be seen on top of uses of GPIIb/IIIa inhibitors, fibrinolytic and bivaluridins.[31]

In our present non randomized observational study, we found quiet a significant number of patient 57%(200) are Clopidogrel Resistance by PCR assay of CYP2c19. Heterozygous was 47.9%(168) and Homozygous 9.1%(32) and Negative 43%(151). Indicating, the necessity to increase the Clopidogrel doses increase to double the needs or start Ticarel 90mg BD or Prasugrel 10mg od with ASA 75mg. For Homozygous positive group of patients (9.1%) are in increase risk stent thrombosis or subsequent development of in stent restenosis. Thus, warranted to start Ticarel or Prasurel along with ASA, not the Clopidogrel.

Acute or sub-acute stent thrombosis are not very uncommon in our daily practices, possibly due to double doses of Clopidegrol uses as loading and maintenance. Ticagrelor or Prasurel are effective alternative to those Clopidegrol non-responder of positive substances. Due to cost pricing, simply rule out if the person is sensitive or resistance. Then, if yes, then only it can be started or we can start Ticarel or Prasurel at procedure, do the test, if negative or non-responder, then can switch to Clopidegrol Thus it can save al of financial burden in our individual patient None of the method fulfils ideal criteria

In addition, Noncompliance is a major and the most logical practical reason for nonresponse to Clopidegrol. Although the rate of non-compliances is higher than Clopidegrol resistance. However, should resistance be a laboratory artifact frequently observed in noncompliant patients, then higher doses and or more aggressive antiplatelet regimens are harmful and cause harmful bleeding and regime discontinuation, rebound platelet activation and worsened vascular outcomes.

Therefore, the hysteria of clopidogrel resistance is developing on top of GPIIb/IIIa receptor blocker which are also potent antiplatelet agents. Therefore, the hypothesis that Clopidegrol resistance causes vascular thrombosis is widespread and is far from being conclusive without a definitive outcome study is and not supported by randomized clinical trial. Thus, Combined appropriate antiplatelet therapies may be required for pharmacologic management of high risk for arterial thrombotic events but not as a primary prevention modality or as an alternative to anticoagulants.

Expansion of DES per se is more likely a trade-off between restenosis and thrombosis. Higher rate of late ISR may need more aggressive antiplatelet regimen, but ISR is probably caused by prothrombotic properties of slow-released eluting agents and has nothing to do with Clopidegrol Resistance. Despite the controversy over DES, rate of stent thrombosis is 0.5 to 1.27%.[32-33] In contrast, rate of Clopidegrol resistance are higher 4.2 to 30%, depending on the platelet test used, patient selection and compliance. Therefore, only a small portion of Resistant patient develop stent thrombosis.[34-35]

Conclusion:

The uses of Clopidegrol has tremendously increased over the last few years, following its effectiveness together with aspirin in greatly reducing clinical adverse events in patients having acute syndrome or undergoing PCI. There is a need to have a simple, affordable, near patient test useful in the clinical setting should have been validated in the large trial based in our population in Bangladesh. However, uses of higher pre-PCI loading doses or maintenance doses clopidogrel or new or more potent P2Y12 receptor blockers is a potential beneficial effects need to balance with increased risk of bleeding.

In addition, genetic polymorphism and patient risk profile should account to detect clopidogrel resistance. Combined appropriate antiplatelet therapies may be required for the pharmacologic management of high risk patients.

Future perspectives:

In our present study, it is quite evident, that a reasonable number of patient who underwent CABG or PCI and kept on DAPT with Clopidogrel and Aspirin, might develop resistance to clopidogrel due to abnormal genetic allele for CYP2C19. Thus, may develop early stent thrombosis or graft occlusion. We need to find out the problem early by genetic study, if not possible then can double the dose of clopidogrel. In this regards we need more patient inclusion, if possible multicenter involvement. These could prevent stent thrombosis and graft failure as it was happening in my above case patient who had CABG within 10 months of PCI due to ISR and new lesion development. Interestingly, he was heterozygous for CYP2C19 allele.

Study Limitations: In our present study we did not perform coronary angiogram to check thrombotic status if any.

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Conflict of Interest - None.

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