ANTIPLATELET THERAPY IN CORONARY ARTERY DISEASE - AN EVOLVING TARGET?
Part 1: Non ST Elevation Acute Coronary Syndrome

Sajan Narayanan MD, DM; *

This journal feature begins with a clinical vignette highlighting common clinical presentation. Evidence supporting use of antiplatelets in such a scenario is mentioned in detail. Guidelines for specific clinical situation is described.

Case:
46 year old gentleman, diabetic since 8 years, currently on combination of glimepiride and metformin, hypertensive since 3 years, on amlodipine, presented with chest pain of 6 hours duration. ECG from referring hospital showed ST depression in II, III,aVF. At the time of presentation, he was hemodynamically stable. Serial ECGs showed T inversions in anterior leads. Trop I peaked at 55.7ng/ml. Echo showed regional wall motion abnormalities in LAD territory. His GRACE score was 79.

Central role of platelets in pathogenesis of coronary artery disease:
The platelet is a mediator of various thrombotic, endothelial and inflammatory processes, and as such, is pivotal in the progression of atherosclerosis. Exposure of platelets to subendothelial collagen and circulating thrombin causes platelet activation which sets entire coagulation cascade into action, culminating in formation of platelet and later fibrin plug. Medical therapies targeting pathways involved in platelet activation and aggregation are fundamental to the treatment of unstable atherosclerotic disease; antiplatelet agents are the mainstay of the treatment of patients with acute coronary syndromes (ACS) because these have been shown to reduce the risk of death, myocardial infarction (MI), and urgent revascularisation.

NSTEACS:
Epidemiological studies have shown three important recent trends in developing economies – 1) Incidence of NSTEMI is less when compared to that of STEMI1 albeit some differences do exist in different regions.2 2) Mean age of patients admitted with ACS tend to be lower when compared to that of patients enrolled in registries in Europe and US. 3) Patients with NSTEMI tend to be older and reach hospitals later than those with STEMI 4) Use of highly sensitive markers of myocardial necrosis has shifted the classification of NSTEMI to NSTEMI

Aspirin – The unchallenged antiplatelet agent
Aspirin acetylates platelet cyclooxygenase -1 (COX-1), which blocks the synthesis and release of thromboxane A2 (TxA2), a platelet activator, thereby decreasing platelet aggregation and arterial thrombus formation. Because the inhibition of COX-1 by aspirin is irreversible, the antiplatelet effects last for the lifetime of the platelets - approximately 7-10 days.

The role of aspirin in the secondary prevention of vascular events was confirmed by the Antithrombotic Trialists' Collaboration Group meta-analysis. Around 140 000 high risk patients for vascular events due to pre-existing disease or a recent vascular event

* Consultant Interventional Cardiologist, Little Flower Hospital & Research Centre, Angamaly, Kerala. Email: sajannarayanan@gmail.com
from 195 trials were included, and the pooled analysis of the general antiplatelet class, with all agents combined, yielded a significant 2.5% absolute reduction in the number of major vascular events (non-fatal MI or stroke, or vascular death).

In addition to reducing adverse clinical events early in the course of treatment, aspirin also reduced the frequency of ischemic events in secondary prevention. It is the cornerstone of antiplatelet therapy in patients with all forms of ACS.

**Dose of Aspirin:** Even though the doses of aspirin in randomised trials have ranged from 50 - 1300mg/day, a dose response effect on efficacy does not seem to exist, while the risk of gastro-intestinal bleeding is increased at higher doses.

CURRENT OASIS - 7 trial - randomised patients with ACS (70% had NSTE ACS) who were referred for an invasive strategy, to either higher-dose aspirin (300 to 325 mg daily) or lower-dose aspirin (75 to 100 mg daily) and either double-dose clopidogrel (a 600 - mg loading dose on day 1, followed by 150 mg daily for 6 days and 75 mg daily thereafter) or standard-dose clopidogrel (a 300-mg loading dose and 75 mg daily thereafter). (2 X 2 factorial design). The primary outcome was cardiovascular death, myocardial infarction, or stroke at 30 days. All patients received loading dose of aspirin (>300mg) before randomisation. No difference in the risk for cardiovascular death, MI or stroke was observed between the doses of aspirin, but GI bleeding increased with higher dose. Guidelines recommend that in patients with NSTE ACS - Aspirin should be prescribed at a loading dose of 162 - 325mg, followed by maintenance dose of 75 - 100 mg daily.

**P2Y12 Inhibitors:** Management of non ST elevation ACS now routinely includes dual antiplatelet therapy (DAPT), which consists of aspirin and a P2Y12 inhibitor. The latter falls into two groups: thienopyridines (ticlopidine,clopidogrel & prasugrel) and a cyclopylentyl-triazolopyrimidine ( ticagrelor) . All of them act on P2Y12 component of the ADP receptor on the surface of platelet and block platelet activation by ADP, thereby inhibiting the final expression of GpIIb/IIa receptor. Clopidogrel and Prasugrel are irreversible inhibitors of ADP receptor while ticagrelor is a reversible inhibitor.

**Important pharmacokinetic and pharmacodynamics differences do exist among the three agents. Ticagrelor is rapidly absorbed in the intestine. The absorbed drug does not require further biotransformation for activation. It directly and reversibly binds to the platelet adenosine diphosphate (ADP) receptor P2Y12. The half-life of ticagrelor is 7 to 8 hours. The thienopyridines - Clopidogrel & prasugrel are prodrugs. Their active metabolites irreversibly bind to P2Y12 for the platelet's life span. After intestinal absorption,
Clopidogrel Pretreatment in CURE : (PCI CURE substudy)

In patient group who underwent PCI, clopidogrel pretreatment significantly reduced composite cardiovascular outcomes. Individually, patients pretreated with clopidogrel had significantly fewer MIIs by 30 days than patients given placebo.1

Caveats:

1) Only 20% of patients enrolled in CURE trial eventually underwent PCI (PCI CURE analysis). The trial was conducted at a time when angiography and intervention were not common practice
2) Median time interval of catheterisation after loading dose of clopidogrel was 10 days - which by present standards is too late. Although, the benefit of pretreatment with clopidogrel was seen regardless of time delay in performance of PCI
3) CURE was not designed to test the hypothesis of pretreatment versus no pretreatment. Subsequently, trials like Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty (ARMYDA 5 PRELOAD) trial showed that a strategy of 600-mg in-lab clopidogrel load pre-PCI may have similar clinical outcomes as routine 4- to 8-h pre-load.6 Large systematic reviews also confirmed lack of benefit of clopidogrel pretreatment in patients who present with NSTEMI and increased bleeding risks associated with this strategy.9

Pretreatment with clopidogrel and outcomes in patients undergoing CABG (CURE CABG):

In patients who underwent CABG, those who received clopidogrel had fewer cardiovascular events; consistent with overall treatment effect seen with use of clopidogrel in CURE trial.10 However, it was noted that, incidence of bleeding including life threatening bleeds were more common in clopidogrel group.10

Caveats:

1) Benefits of clopidogrel were primarily observed in the period before CABG; i.e., from day of presentation to actual performance of CABG - clopidogrel ‘protects’ the patient while awaiting surgery
2) CABG was performed median 25.5 days after randomisation in CURE trial - late by present standards.
3) Whether clopidogrel pretreatment provides same clinical benefit with acceptable bleeding outcomes with current practice of early CABG; much shorter than time frame in CURE trial - is not known.

Dose of clopidogrel:

Dose of clopidogrel used in landmark CURE trial was 300mg loading dose, followed by 75mg once daily. It was found that, maximal platelet inhibition after 300mg does not start atleast 3 hours following the loading dose administration and clinical benefits were observed only when at least 6 hours have elapsed after the loading dose. A 600mg loading dose has been tested in large number of later trials, which showed that platelet inhibition can be achieved as early as 2 hours following the loading dose. Trials that enrolled high risk NSTEMI patients consistently proved benefit of 600mg loading dose.11

CURRENT OASIS - 7 trial prospectively randomised high risk ACS patients referred for invasive evaluation to high dose clopidogrel (600mg loading followed by 150mg maintenance dose from day 2 - day 7 and then 75mg daily thereafter) versus standard dose clopidogrel (300mg loading, followed by 75mg daily). The trial also had high dose and low dose ASA arms as discussed previously.

CURRENT OASIS 7 - Conclusions:

1) Overall, double dose clopidogrel did not reduce the composite of cardiovascular death, MI or stroke in patients with NSTEMI, although it increased major bleeding and need for red cell transfusions.
2) Of 25,086 patients enrolled in this study and who underwent angiogram, 17,263 patients (69%) underwent PCI. Sub analysis of this cohort showed that primary composite of Cardiovascular death, MI or stroke was significantly less in double dose group.12
3) Incidence of definite stent thrombosis was less regardless of stent type in patients who received double dose clopidogrel.

Hence in conclusion, a 600mg loading dose, followed by 150mg maintenance for a week may benefit in patients who undergo PCI, while this strategy doesn’t confer an overall benefit in patients with ACS.

Drawbacks of clopidogrel:

1) Only 15% of drug administered orally reaches the circulation
2) Requires two step oxidation process to generate active moiety
3) Oxidation process involves CYP 2C and 3A systems in hepatocytes which are prone for two important issues - a) genetic polymorphisms b) interference with other drugs which are metabolised by same system.

PRASUGREL:

Prasugrel is a thienopyridine and is a prodrug like clopidogrel. Its active metabolite is an irreversible inhibitor of platelet P2Y12 receptor.
However, unlike clopidogrel, prasugrel is oxidised rapidly in one step to its active metabolite and becomes active within 30 minutes of ingestion, when compared to 2 hours with 600mg clopidogrel. Although the active metabolites of clopidogrel and prasugrel exert equal antiplatelet effects when studied in vitro, generation of the prasugrel metabolite is approximately 10 times as great as generation of the clopidogrel metabolite, which results in roughly 10 times greater potency.

**Evidence for prasugrel:**

Trial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet Inhibition with Prasugrel - Thrombolysis in Myocardial Infarction (TRITON TIMI 38) randomly assigned 13608 patients with ACS - in whom PCI was planned - to receive prasugrel - 60mg loading dose, followed by 10mg daily maintenance dose or clopidogrel - 300mg loading dose followed by 75mg maintenance dose. All patients received aspirin.

The primary efficacy end point (a composite of the rate of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke during the follow-up period) was observed to favour prasugrel. Major bleeding was observed in 2.4% of patients receiving prasugrel and in 1.8% of patients receiving clopidogrel (P = 0.03). Life threatening bleed was also more common in prasugrel group. Benefit was particularly striking in patients with diabetes. In 12844 patients who received coronary stents at the time of PCI, prasugrel reduced the incidence of stent thrombosis (regardless of stent type) by half in comparison to clopidogrel.

**Risk of bleeding was particularly high in three subsets of patients:**

1) age > 75 years
2) low body weight (<60Kg)
3) those with history of stroke/TIA.

Sub analysis of this trial confirmed that patients with genetic polymorphisms of P glycoprotein ABCB1 (which determines drug absorption from intestine) & cytochrome 2C have increased cardiovascular events when on clopidogrel. While those on prasugrel were unaffected by genetic variations.

**Pretreatment with prasugrel in NSTEACS – does this strategy work?**

ACCOAST trial enrolled 4033 patients with non-STEMI who were scheduled to undergo coronary angiography within 2 to 48 hours after randomization. Patients were randomly assigned to receive prasugrel (a 30-mg loading dose) before the angiography or placebo. When PCI was indicated, an additional 30 mg prasugrel was given in the pretreatment group at the time of PCI, and 60mg prasugrel was given in the control group. A pharmacodynamic substudy involving 23 patients was performed to evaluate the effect of prasugrel on the inhibition of platelet aggregation relative to the time of administration.

The rate of the primary efficacy end point, a composite of death from cardiovascular causes, myocardial infarction, stroke, urgent revascularization, or glycoprotein IIb/IIIa inhibitor rescue therapy (glycoprotein IIb/IIIa bailout) through day 7, did not differ significantly between the two groups (P = 0.81). The rate of the key safety end point of all Thrombolysis in Myocardial Infarction (TIMI) major bleeding episodes, whether related or not related to coronary-artery bypass grafting (CABG), through day 7 was increased with pretreatment (P = 0.006). Pretreatment did not reduce the rate of the primary outcome among patients undergoing PCI (69% of the patients) but increased the rate of TIMI major bleeding at 7 days. All the results were confirmed at 30 days and in prespecified subgroups. These results were surprising, in that, the pharmacodynamic substudy did confirm adequate platelet inhibition at the time of angiography in pretreatment group.

**Why did pretreatment with prasugrel fail in ACCOAST?**

1) Various studies have shown that only 35% of NSTEACS patients ultimately undergo PCI. So treating rest 65% with a powerful antiplatelet agent like prasugrel may only contribute to bleeding risk
2) Time delay in performance of angiogram was mean 4.4 hours after randomisation - such early intervention could've largely underestimated efficacy of pretreatment - with definition of MI used in the trial
3) ACCOAST trial enrolled patients before TRITON TIMI 38 was published. Hence they didn’t exclude elderly, low body weight patients and those with history of stroke (comprised 23% of study population) - which could’ve contributed to high bleeding risk observed in pretreatment arm
4) Femoral access was used in 56% of population - a variable consistently associated with elevated bleeding risk - non CABG related bleeding episodes were low in radial access group in ACCOAST trial.

**Prasugrel in medically managed patients: is there a place at all?**

TRILOGY ACS trial enrolled 7243 patients younger than 75 years, who were being managed medically following NSTEACS. All patients received aspirin. Trial compared prasugrel (10mg) versus clopidogrel (75mg) for up to 30 months.
At a median follow-up of 17 months, the primary end point of death from cardiovascular causes, myocardial infarction, or stroke among patients under the age of 75 years occurred in 13.9% of the prasugrel group and 16.0% of the clopidogrel group (P = 0.21). Similar results were observed in the overall population. The prespecified analysis of multiple recurrent ischemic events (all components of the primary end point) suggested a lower risk for prasugrel among patients under the age of 75 years (P = 0.04). Rates of severe and intracranial bleeding were similar in the two groups in all age groups.

Overall trial results showed that NSTEACS patients managed medically - prasugrel may not offer added advantage over using clopidogrel.20

However, a subanalysis of this trial showed that those patients who underwent angiography before enrolment, had fewer events while on prasugrel when compared to clopidogrel.21 How could this explain this finding? How can just performance of angiogram reduce events while on prasugrel?

Benefit of prasugrel when compared to clopidogrel was confined to patients enrolled after angiography - probably explained by selection:

a) First, coronary angiography would clarify the cause of the index event as being plaque rupture rather than a non-acute coronary syndrome process, thereby reducing the chance of enrolment for an event that would not be affected by a different intensity of antiplatelet treatment

b) Second - patients with either modest coronary disease (lesions <30%) or anatomy suitable for percutaneous coronary intervention or coronary artery bypass graft would be excluded. Therefore, most patients enrolled after angiography had moderate or severe coronary disease probably not suitable for percutaneous coronary intervention or were in centres without access to percutaneous coronary intervention and had a definitive cause of acute coronary syndrome.

c) Third - favourable characteristics for reduced bleeding (age <75 years, weight >60 kg, and no previous stroke) with prasugrel in this prespecified subgroup - probably contributed to beneficial effect.22

**PRESCRIBING PRASUGREL IN NSTEACS - NAVIGATING BETWEEN SCYLLA & CHARYBDIS**

In Greek mythology, Scylla was a ferocious beast and Charybdis was a monstrous whirlpool. The wily Odysseus successfully navigated between these two dangers by steering closer to Scylla, though he did lose a few crew members to her.

1) Prasugrel to be initiated only after angiogram - after a decision to proceed for PCI is taken

2) Avoid in 3 subsets - 1) patients aged >75 years 2) previous history of stroke / TIA 3) low body weight (<60 Kg)

3) Probably, patients who have most severe coronary lesions, not suitable for any form of revascularisation and who have low bleeding risk may probably benefit from long term prasugrel

**TICAGRELORETHE NEW PLAYER**

The Study of Platelet Inhibition and Patient Outcomes (PLATO) - phase III pivotal trial compared ticagrelor (180mg loading dose, followed by 90 mg twice daily) with clopidogrel (300 or 600 mg loading dose, followed by 75mg daily maintenance dose) ; both groups also received aspirin.

A significant reduction in primary endpoints - MI, cardiovascular death and relative risk reduction in total mortality was observed in ticagrelor group. The rate of stent thrombosis was reduced significantly from 1.9% to 1.3%.22 Benefit was consistent across all subgroups, including those who were pretreated with 300mg loading dose of clopidogrel. Sub analysis among biomarker positive patients showed that those patients with elevated hs-Troponin T, derived maximum benefit from ticagrelor.23 Ticagrelor was more effective than clopidogrel irrespective of CYP2C19 and ABCB1 polymorphisms.24

PLATO showed no benefit of ticagrelor in subgroup of patients enrolled in US, in whom dose of aspirin was higher on average than in other countries.25 Whether this finding is related to chance, to more frequent use of aspirin at 325mg daily, or to some other aspect of care in US remains uncertain. FDA recommends low dose aspirin - 75 - 100mg as maintenance with ticagrelor.

No significant difference in the rates of major bleeding was found between the ticagrelor and clopidogrel groups but ticagrelor was associated with a higher rate of major bleeding not related to coronary-artery bypass grafting (4.5% vs. 3.8%, P = 0.03), including more instances of fatal intracranial bleeding and fewer of fatal bleeding of other types.25

Because ticagrelor is a reversible agent, it can be started at the time of arrival at the emergency department and be continued for 1 year in medically managed patients and in those undergoing PCI. Ticagrelor achieves a higher level of platelet inhibition than clopidogrel and has a shorter half life (12 hours). Ticagrelor should be discontinued 5 days before CABG.

**Intravenous P2Y12 blockade:**

CHAMPION PLATFORM26 & CHAMPION PCI27 tested efficacy of cangrelor - ultrashort acting (Half life 3-6 minutes) intravenous directly acting P2 Y12 antagonist in patients with ACS scheduled for PCI.
Comparitor arm received clopidogrel. Both trials differed on timing of clopidogrel. Former enrolled patients to receive 600mg loading dose of clopidogrel at end of PCI, while cangrelor was started before PCI. While in latter, both drugs were given at least 30 minutes prior to PCI. Bot trials didn't show significant benefit for cangrelor.

**ALGORITHM FOR ORAL ANTIPLATELET STRATEGY IN NSTEACS**

![Algorithm Diagram]

**Glycoprotein IIb/IIIa Inhibitors in NSTEACS: A Lost Paradise?**

The three GP IIb/IIIa receptor inhibitors approved for clinical use are intravenously administered agents belonging to different classes: abciximab is a monoclonal antibody fragment; eptifibatide is a cyclic peptide; and tirofiban is a peptidomimetic molecule.

Tirofiban plus UFH and aspirin (PRISM PLUS) significantly reduced rate of death, MI or refractory ischemia at 7 days when compared with aspirin plus UFH. In a trial involving 10,948 patients, eptifibatide also significantly reduced the rate of death or MI at 30 days (PURSUIT). However, no benefit and higher mortality were found with use of abciximab in patients with NSTEACS in whom an early conservative strategy was planned (GUSTO IV ACS). A meta-analysis of patients initially medically managed and planned for PCI showed a 9% RRR in death or non-fatal MI with GP IIb/IIIa receptor inhibitors. However above trials and meta-analysis were performed in an era when routine use of P2Y12 inhibitors were not in place.

ISAR REACT 2 trial enrolled patients with NSTEACS who received aspirin and 600mg loading dose of clopidogrel - scheduled for PCI were randomised to IV abciximab or placebo. Abciximab significantly reduced primary end point (composite of death, MI and need for urgent target vessel revascularisation within 30 days) in patients who had elevated troponin levels, while offered no significant advantage for troponin negative individuals. In ACUITY timing study, it was found that those patients who didn't receive pretreatment with clopidogrel had better outcomes with UFH + GpIIb/IIIa inhibitors.

**EARLY ACS trial** randomized patients assigned to an invasive strategy to early eptifibatide or placebo, with provisional use of eptifibatide after angiography for PCI at discretion of operator. All patients received loading dose (300mg - 600mg) of clopidogrel prior to PCI. This trial demonstrated no advantage with a routine upstream use of eptifibatide in an invasive strategy compared with a delayed provisional strategy. Consistently, it was found in most of the trials that upstream use of GpIIb/IIIa inhibitors is associated with excessive bleeding episodes. In TRITON TIMI 38, patients who received GpIIb/IIIa inhibitors had consistently higher bleeding episodes.

**Key points:**

1. Routine use of GpIIb/IIIa inhibitors in patients who are pretreated with thienopyridines is of no definite advantage unless patient has refractory symptoms and a GRACE score of more than 140
2. In lab use - in cases with high thrombus load, persistent no reflow or as a bail out strategy may improve outcomes
3. When patient is not pretreated with thienopyridines, GpIIb/IIIa inhibitors improve outcomes after PCI.
4. Abciximab to be used only in cath lab after a decision to proceed to PCI is taken.
5. Small molecules - tirofiban & eptifibatide may offer advantages in patients who are not pretreated with thienopyridines.

**Protease-Activated Receptor-1 Antagonists**

The oral protease activated receptor - PAR-1 antagonist voraxapar did not improve primary efficacy outcomes, and was associated with increased bleeding episodes.

**ANALYSING THE GUIDELINES:**

**Aspirin:**
- Aspirin should be given to all patients without contraindications at an initial loading dose of 150-300 mg, and at a maintenance dose of 75-100 mg daily, long-term regardless of treatment strategy. (Class I Evidence A) - ESC Recommendation
- Non-enteric-coated aspirin to all patients promptly after presentation 162 mg-325 mg
- Aspirin maintenance dose continued
indefinitely 81 mg/d-325 mg/d (specifically recommends dose of 81mg/d in combination with ticagrelor (Class I evidence A) - ACC/AHA guidelines

- ACC/AHA guidelines specifically recommends continuing aspirin in patients undergoing CABG (Class I Evidence B)

**P2Y12 inhibitors:**

- Both ESC & ACC/AHA guidelines recommend adding a P2Y12 inhibitor to aspirin in patients with NSTEACS; albeit with some difference
  
a) ACC / AHA guidelines recommend either clopidogrel or ticagrelor in all patients presenting with NSTEACS regardless of initial treatment strategy (early invasive vs conservative) - Class I Evidence B
  
b) ESC recommends Ticagrelor in all patients who present with moderate to high risk NSTEACS (like positive troponins), including patients who are preloaded (300mg) with clopidogrel (Class I Evidence B). Clopidogrel (300mg loading followed by 75mg maintanence) - only if patient cannot receive ticagrelor or prasugrel (class I Evidence A) While ACC/AHA gives Class IIa recommendation (Evidence B) for this strategy of preferential use of ticagrelor to clopidogrel
  
c) ESC also adds - 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option. (Class I Evidence B)
  
d) ESC recommends Prasugrel (60-mg loading dose, 10-mg daily dose) for P2Y12-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life threatening bleeding or other contraindications (Class I Evidence B)
  
e) ACC/AHA recommends Prasugrel (60mg loading, followed by 10mg daily) in patients with NSTEACS who undergo stenting (Evidence B)
  
f) In patients pre-treated with P2Y12 inhibitors who need to undergo non-emergent major surgery (including CABG), postponing surgery at least for 5 days after cessation of ticagrelor or clopidogrel, and 7 days for prasugrel, if clinically feasible and unless the patient is at high risk of ischaemic events should be considered - ESC & ACC/AHA guidelines

Both ESC & ACC/AHA guidelines agree on 12 month duration of aspirin + P2Y12 regardless of treatment strategy

**GpIIb/IIIa Inhibitors:**

1) ESC - GpIIb/IIIa inhibitors are not recommended routinely before angiography (Class III Evidence A)

2) ESC - GpIIb/IIIa Inhibitors are not recommended routinely along with DAPT in patients treated conservatively (Class III Evidence A)

3) Addition of GpIIb/IIIa Inhibitors to DAPT in patients who present with high risk features like elevated troponins and visible thrombus receive Class Ib recommendation from ESC, while its IIb in ACC/AHA guidelines.

4) ESC - Eptifibatide or tirofiban may be added to patients who present with high risk features, along with ASA who are not preloaded with P2Y12 inhibitor (Class Ia Evidence C) - while ACC/AHA don't address this issue

5) ESC - Eptifibatide or tirofiban may be added to DAPT, prior to early angiography, if there is ongoing ischemia and risk of bleeding is low (class IIb Evidence C)

**Management of the case:**

The patient presenting with high risk NSTEACS was started on loading dose of Aspirin 325mg, fondaparinux, metoprolol, Ramipril and intravenous nitroglycerine. He underwent coronary angiogram 6 hours after admission which revealed critical lesions in LAD and large OM. Since patient was low bleeding risk and being a diabetic, he was administered loading dose of prasugrel (60mg) after angiogram on table, and underwent PCI to LAD & OM with drug eluting stents. He was discharged with an advice to continue DAPT for 12 months and assessment thereafter.

**POINTS TO REMEMBER: NSTE ACS**

1) Aspirin (non-enteric coated) should be loaded at dose of 300mg at the first contact

2) Recommended maintanence dose of aspirin is 75 - 100mg/ day

3) Initiation of P2Y12 receptor antagonist depends on general treatment strategy (early invasive v conservative) adopted.

4) Prasugrel has to be initiated only after coronary anatomy is defined and a decision to proceed with PCI is taken

5) Ticagrelor is superior to clopidogrel in patients with NSTE ACS, regardless of treatment strategy adopted

6) GpIIb/IIIa inhibitors are to be initiated only in cath lab under specific situations.


