Recent advances in the use of Glycoprotein (GP) IIb/IIIa receptors inhibitors

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Glycoprotein IIb/IIIa receptors are the most common receptor subtypes on the platelet surface. During vessel injury, the sub-endothelial layer is exposed so that platelets adhere to sub-endothelial collagen via Ia/IIa receptor and to von Willebrand factor via glycoprotein Ib receptor. Adherent platelets are activated by ADP, 5-HT, TXA2 etc which result in the conformational change of platelets, thereby activating nearly 80,000 GP IIb/IIIa receptors on platelet surface. These activated receptors bind fibrinogen to fascilate the formation of a platelet plug.[1,2]

Currently, there are three GP IIb/IIIa inhibitors available for clinical use, Abciximab, Ebtifibatide and Tirofabin. This review article will highlight on the recent trends for the use of GP IIb/IIIa inhibitors in different clinical settings. First of all, the use of GP IIb/IIIa inhibitors is divided into two large groups, during PCI and during. Conservative management. During PCT, its use is again categorized into three subgroups: PCI for stable CAD, in the setting of Non-ST segment elevation acute coronary syndrome(NSTE-ACS, that is, unstable angina and Non-ST elevation MI) and, ST segment elevation MI (STEMI). Similarly, during conservative management, its use is discussed in two subgroups: in the setting of NSTE-ACS and in STEMI. This article will also discuss on specific situations like diabetics patients undergoing PCI and high risk NSTE-ACS.

1. GP IIb/IIIa inhibitors during PCI

A. Role during PCI in Stable CAD

The role of GP IIb/IIIa receptors inhibitors during PCI was first studied in three large randomized trials total enrolling more than 7,000 patients: EPIC [3], EPILOG [4] and EPISTENT[5] trials. EPIC trial[3] (Evaluation of 7E-3 for the Prevention of Ischemic Complications) was a prospective, randomized double blinded trial including 2,099 patients with severe unstable angina, evolving MI and high risk coronary morphology in 56 centers and found that there was 35% reduction in the composite end point of death, MI and TVR in Abciximab bolus+

IV infusion (P=0.008) and 10% reduction in Abciximab bolus + placebo infusion (P=0.43), There was a 20% reduction in composite end point in 6 month follow up (P=0.001) with doubling of major bleeds. The EPILOG trial[4] (Evaluation in PTCA to Improve Long term Outcome with abciximab GPIIb/IIIa blockade) randomized 2,792 patients undergoing urgent or elective PCI, At 30 days follow up, it was found that there were 11.7%, 5.4% and 5.2% incidences of composite end point (death, MI and TVR) in placebo, abciximab+ low dose heparin and Abciximab+ standard dose heparin, respectively. Similarly the EPISTENT trial[5] (Evaluation of Platelet IIb/ IIIa Inhibitor for stenting) randomized 2,399 patients undergoing elective or urgent PCI and found that there was 5.5% reduction of death or MI at 30 days.

This benefit sustained at 6 months follow up too, with 5.8% reduction of death or Mi in the favor of Abciximab. In pooled analysis of above 3 trials, percentage risk reduction in primary end point at 30 days was 57%, 58% and 44% in low, moderate and high risk patients respectively. There was 22% relative reduction in mortality with abciximab at 3 years.[33]Although the treatment effect was present in both low risk and high risk group, patients with complex coronary lesions achieved greater benefit, one year reduction of composite end point of death and MI by 50% in the complex lesion group.[34] However, the above trials enrolled the mixed population of stable and unstable CAD. So, its role during elective PCI for stable CAD cannot be concluded fully on the basis of above trials. The ISAR-REACT trial (Intra- coronary Stenting and Anti thrombotic Regimen-Rapid Early Action for Coronary Treatment)[6] highlight this issue. This trial enrolled more than 2,000 patients with stable CAD to receive either Abciximab or placebo during low-intermediate risk PCI. All patients were pretreated with a 600 mg dose of clopidogrel at least 2 hours before the procedure. Administration of Abciximab failed to provide any additional clinical benefit with respect to the composite end point ol death, MI and TVR. Even at the follow up of 1 year, no trends of clinical benefit was observed. Thus, at present, as per the data available from the ISAR-REACT trial, stable CAD with low to intermediate risk PCI can be managed adequately with loading high dose of clopidogrel. Whether this benefit of pre-loading high dose clopidogrel can also be seen in high risk ACS, is being addressed in ISAR-REACT-2 and BRAVE-3 trials. The 2005 ESC guidelines recommend the use of GP IIb/IIIa during PCI in stable CAD if there is complex angiographic lesions, threatened / actual vessel closure, visible thrombus and no/slow reflow phenomenon,[35]

The result of PCI in diabetic patients is not as good as non-diabetic patients. This is perhaps due to enhanced platelet activation, aggregability and greater expression of GP IIb/IIIa receptors. So, there might be hypothesis that diabetic patients need to be managed more aggressively using GP IIb/IIIa inhibitors during PCI. The retrospective analysis of diabetic subgroups in EPISTENT study showed that there is prognostic benefit of Abciximab in diabetic groups.[36] But as stated earlier this study had mixed population of stable and unstable CAD and the subgroup analysis was retrospective not prospective. This issue has been highlighted in ISAR- SWEET trial.[7] ISAR-SWEET (is abciximab Superior Way to Eliminate Thrombotic risk in diubetes) was a prospective trial enrolling diabetic patients undergoing elective PCI with pre-treatment by 600 mg clopidogrel. The result showed that Abciximab did not provide extra benefit in terms of death and MI. Thus, whether Abciximab should be routinely used in all diabetic patients undergoing elective PCI is not yet proved.

In comparision to Abciximab, the benefits were less marked with the use of small molecules GP IIb/IIIa inhibitors (Ebtifibatide and tirofabin) as observed in IMPACT-II trial[9] with Ebtifibatide and RESTORE trial[12] with Tirofiban.

B. Role during PCT for NSTE-ACS (Unstable angina and NSTEMI)

Although benefit of GP IIb/IIIa inhibitors is seen across all groups, this benefit is more prominent in ACS patients. There are several trials showing the usefulness of GP IIb/IIIa inhibitors in patients with stable angina or NSTE-ACS. Among three GP IIb/IIIa inhibitors, Abciximab has been extensively studied as in EPIC, EPILOG, EPISTENT and CAPTURE trial[8]. The role of ebtifibatide has been studied in IMPACT-II and ESPIRIT [10,11] trials and that of Tirofiban in RESTORE[12] and TARGET trials,[13] There is prominent role of Abciximab during PCI in ACS patients as shown in EPIC, EPILOG and EPISTENT trial. But it should be noted that these trial comprised the mixed population of stable and unstable CAD, The CAPTURE trial[8] (Chimeric 7E3 AntiPlatelet Therapy in Unstable angina refractory to standard treatment) has been especially designed to observe the usefulness of Abciximab during PCI in unstable angina .The 30 day composite end point of death, MI or TVR was significantly reduced in the favour of Abciximab therapy (15.95 vs 11.3%, p=0.012).

Whether the small molecule GP IIb/IIIa was also useful during PCI in NSTE- ACS was studied in IMPACT-II[9] and ESPIRIT[10,11] trials for Ebtifibatide and in RESTORE[12] and TARGET[13] trials for Tirofiban.

The IMPACT trial[9] (Integrilin to Manage Platelet Aggregation to prevent Coronary Thrombosis) was a double blind multi-centers trial enrolling 4,010 patients undergoing PCI which was randomized into 3 groups: placebo, 135 ug/kg bolus Ebtifibatide + low dose infusion (0.5 ug/kg/min) for 20 to 24 hours and 135 ug/kg bolus Ebtifibatide + high dose infusion (0.75 ug/kg/min for 20 to 24 hours. The 30 day composite end point of death, MI, unplanned surgical or repeat PCI or coronary stent implantation for abrupt closure occurred in 11.4%, 9.2%(p=0.0630 and 9.9% (p=0.22) respectively, As the benefit of Ebtifibatide was not observed in IMPACT- II trial, perhaps due to low dose, another trial with higher dose of Ebtifibatide was conducted, the ESPIRIT[10,11] trial (Enhanced Suppression of platelet IIb/IIIa Receptor with Integrilin Therapy). A total of 2,064 patients were enrolled with a double bolus regimen of Ebtifibatide (180ug/kg bolus followed by 2ug/kg/min infusion with a second bolus of 180 ug/kg given 10 min after the first bolus) compared to placebo treatment. The 48 hour primary composite end point of death, MI, urgent TVR or bailout treatment with Ebtifibatide was reduced 37% from 10.5 to 6.65 (p=0.0015). There was a consistent treatment benefit across all components of the end point as well as across all subgroups of patients. At 30 days, the secondary composite end point of death, MI or urgent TVR was improved by 35% from 10.4 to 6.85 (p= 0.0034)

The beneficial effect of Tirofiban is less robust as shown in RESTORE and TARGET trials. In RESTORE trial[12] (Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis), the composite end point of death, MI, urgent TVR or bailout treatment was 12.2% in placebo vs 10.3% in Tirofiban group, which was not statistically significant. Further, Tirofiban was directly compared with Abciximab in TARGET trial[13] (Do Tirofiban And Reopro Give similar Efficacy). It was found that Abciximab was superior to Tirofiban in reducing composite end point of death, MI or TVR at 30 days in the subgroup of patients with ACS (6.35 vs 9.3 %, p=0.002). The TENACITY trial will study a higher dose of Tirofiban than in TARGET and compare it head to head with Abciximab.

In conclusion, when PCI is planned, Abciximab is the best tested drug, as shown in EPIC, EPILOG, EPISTENT and CAPTURE trials. In such setting, high dose Ebtifibatide is also better alternative as shown in ESPIRIT trial but the role of Tirofiban is still controversial.

C. Role during PCI in ST segment elevation MI (during primary PCI)

Despite successful revascularization in primary PCI, there might be sub-optimal microvascular reperfusion due to distal embolization with platelet aggregrgates which necessitate the use of potent anuplitelet agent. The role of GP IIb/IIIa inhibitors, especially Abciximab has been well studied in the setting of primary PCI. Abciximab has been studied in five randomized trials[14,18] (RAPPORT, ISAR- 2, CADILLAC, ADMIRAL and ACE trials) total enrolling more than 3,000 patients undergoing primary PCI. At 30 days and 6 months follow up, all the trials demonstrated beneficial effect in terms of a composite end point of death, reinfarction or TVR, however when only death or death + reinfarction was evaluated, none of the tial showed the clear cut benefit.Thus, Abciximab was especially benefit in terms of TVR. The pooled analysis of the five trials revealed that Abciximab was not only better in terms of TVR but also re-infarction, however not in mortility, 10.5/4.5 ($P<0.05$), 8.5/4.0 ($p<0.05$) and 4/3.5 (not significant) for placebo Abciximab respectively, The 2005 ESC guideline recommend the use of Abciximab during primary PCI as class IIa indication. The role of other small molecule GPIIb/IIIa is well investigated in the setting of primary PCI.

2. Role during conservative management

A, In Non-ST segment elevation acute coronary syndrome(Unstable angina and NSTEMI)

Clinical efficacy of GP IIb/IIIa inhibitors in patients with NSTE-ACS who are not routinely scheduled to undergo revascularization is less obvious. Six major randomized trials[19-24]: Platelet Receptor Inhibition in ischemic Syndrome Management (PRISM). Platelet Receptor Inhibition in ischemic Syndrome Management in Patients Limited by Unstable Signs and symptoms (PRISM-PLUS), Platelet IIb/IIIa Antagonism for the Reduction of acute coronary syndrome events in a Global Organization network (PARAGON-A), PARAGON-B, Platelet glycoprotein IIb/IIIa in Unstable angina;Receptor Suppression Using Integrilin Therapy (PURSUIT) and the Global Utilization of Strategies To Open occluded coronary arteries (GUSTO-IV ACS) enrolling more than 30,000 patients have addressed this issue. The PCI was not scheduled and even discouraged in these trials so that the PCI rates are low ranging from 1-6% to 30.5%. Ebtfibatide showed benefit in terms of death and MI in PERSUIT trial and Tirofiban in terms of death, MI or TVR in PRISM and PRISM-PLUS trials. But Abciximab failed to show benefit in GUSTO-4 ACS trial and similarly Lamifabin in PARAGON and PARAGON: B trials. Ebtifibatide was studied in PERSUIT trial enrolling

10,948 patients, the biggest trial among the six trials, showed the composite end point of death and MI of 15.7% in placebo arm vs 14.2% in Ebtifibatide arm ($p< 0.05$). In PRISM trial which enrolled 3,332 unstable angina patients, had incidence of death, MI or TVR of 5.6% in placebo arm compared to 3.8% in Tirofiban arm ($p< 0.05$). PRISM-PLUS trial showed the similar result. However, in GUSTO IV-ACS trial, the composite end point of death and MI was 8%, 8.2% and 9.1% respectively in placebo, Abciximab for 24 hr and Abciximab for 48 hr respectively which was not statistically significant.

Thus, as per the data available from PERSUIT trial, Ebtifibatide is recommended in NSTE-ACS when PCI is not planned, Similarly, Tirofiban is also recommended in this setting as per the data available from PRISM and PRISM-PLUS trials, But Abciximab, which is the best tested drug during PCI, is not recommended when PCI is not planned on the basis of data available from GUSTO-V ACS trial.

Although, the benefit of GPIIb/IIIa was observed in all NSTE-ACS, this benefit was markedly enhanced when viewed according to risk stratification (TIMI risk score, tropinin level, ST segment changes, diabetes etc). Use of GP IIb/IIIa inhibitors was associated with 15% relative risk reduction in the 30 days end point in troponin positive patients (10.3% vs 12%).[21] In comparision, in patients with negative tropinins, no risk reduction was seen (7% vs 6.2%). This differential treatment with respect to tropinin level was significant (P=0.045). Meta analysis of diabetic patients in these six trials revealed a 26% mortality reduction with the use of these agents as compared to placebo.[37] Thus, use of GP IIb/IIIa should be a standard practice in high risk NSTE-ACS.

B. In ST segment elevation MI:

The role of GP IIb/IIIa is not obvious in the patients undergoing thrombolysis. Although the combination therapy of thrombolysis and GP IIb/IIIa was encouraging in several pilot studies, the initial trials with the combination of streptokinase and abCiximab or ebtifibatide was discontinued due to excessive bleeding complications. Two 6 phase trials[25-30]: TIMI 14, SPEED, INTRO-AMI, INTREGITI, TIMI 20, ENTIRE TIMI 23, FASTER TIMI 24 tested the optimal combination of reduced dose(50-75%) of thrombolytic agents(Tpa,r-pa,TNK) with GP IIb/IIIa inhibitors(Abciximab, Ebtifibatide, Tirofiban) as compared to full dose thrombolytic therapy. The TIMI perfusion grade. The blush score and ST segment resolution was significantly enhanced in the favor of combination therapy, however the clinical impact

of thies benefit was not tested in the above trials, The two large trials, GUSTO V[31] and ASSENT- 3)[32] trial tested the clinical impact of combination therapy. In GUSTO V trial, although there was significant reduction in the rate of non fatal ischemic events, these benefits was not translated into mortality benefit. Similarly, in ASSENT-3 trial, no mortality benefit was seen. Thus, combination therapy, although provides reduction in secondary end points, is not associated with mortality benefit over standard thrombolytic therapy, 50 at present, the combination therapy cannot be used as routine management in our clinical settings.

Conclusion:

GP IIb/IIIa inhibitors should not be routinely used during elective low-intermediate risk PCT, as per data available from ISAR-REACT trial, Its use during elective low risk PCI for diabetic patients is controversial as Abciximab failed to show extra benefit in ISAR-SWEET trial, especially designed for diabetic patients. During PCI for NSTE-ACS, abciximab is the best tested drug (EPIC, EPILOG, EPISTENT, CAPTURE trials), The role of Ebtifibatide in this setting is evident from ESPIRIT trial. However, current data does not support the use of Tirofiban (TARGET, RESTORE trials) in this clinical setting, During primary PCI, the role of Abciximab is supported by RAPPORT, ISAR-2, CADILLAC, ADMIRAL and ACE trials, but of note, neither of the trials showed mortality benefits, Ebtifibatide and Tirofiban are less investigated during primary PCI, When PCI is not planned, both Ebtifibatide or Tirofiban can be used (PERSUIT, PRISM, PRISM-PLUS irials), But data from GUSTO IV ACS does not support Abciximab, when PCT is not planned. During thrombolysis, although few trials showed that GP IIb/IIIa is beneficial in terms of reducing secondary end points, there was no mortility benefit, and so, until further data can be obtained the use of GP IIb/IIIa during. thrombolysis should be avoided.

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