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Editorial

Glycoprotein IIb-IIIa inhibitors – Do we still need them?

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Platelets play central role in thrombotic events in acute coronary syndromes (ACS) and during percutaneous coronary interventions (PCI). Platelet activation occurs through various mechanisms and all culminate in expression of the surface GP IIb-IIIa receptors which mediate their aggregation and thrombosis. Glycoprotein IIb-IIIa inhibitors (GPI) remain the most powerful antiplatelet agents by inhibiting this final common pathway of platelet activation. The role of GPI in the treatment of coronary ischemic events has evolved through the past 20 years. Given their potent antiplatelet activity and consistent anti-ischemic benefit in major trials, they were an integral part of antiplatelet – antithrombin portfolio in the treatment of ACS and during PCI over a decade. However, the advent of stents and thienopyridine ticlopidine and later clopidogrel made periprocedural ischemic complications less common and GPI had slowly lost its importance in routine low-risk PCI. Though GPI reduced periprocedural ischemic complications, increased bleeding events continued to be a major problem. In the recent years, bleeding has increasingly been recognized as a major determinant of clinical outcomes both with ACS and PCI. Recently, the availability of bivalirudin as an equally effective and safer periprocedural anticoagulant, heparin and GPI have slowly been pushed to second place over the entire spectrum of coronary interventions. The newer antiplatelets which provide rapid and more consistent antiplatelet action further reduced the role of GPI to a very small subset of patients where ischemic risk far exceeds the thrombotic risk.[1–3] This editorial briefly evaluates the current role of GPI in the background of recent major studies with newer antiplatelets and bivalirudin.

1. Elective PCI

GPI ruled the era of plain balloon angioplasty where acute closure was the main threat to the interventionist. The paradigm shift happened when stents and thienopyridines were introduced into the interventional practice. Though this brought down GPI usage substantially, they continued to be an important part of periprocedural antithrombin-antiplatelet treatment. Two major trials in the last decade questioned the practice of routine periprocedural use of GPI in non-acute PCI where effective platelet inhibition can be achieved with optimal clopidogrel loading. The ISAR-REACT trial tested the role of abciximab in 2159 patients undergoing elective low-risk PCI after preloading with 600 mg of clopidogrel. Abciximab failed to show any reduction in the primary end point of 30-day incidence of major adverse cardiac events compared with placebo. Further, it increased the incidence of thrombocytopenia and blood transfusions.[4] The ISAR-SWEET trial examined the same strategy in 701 diabetic patients. Again abciximab did not improve outcomes in the setting of clopidogrel loading at least 2 h prior to the procedure.[5] In contrast, a recent meta-analysis of 22 studies involving 10,123 patients showed significant reduction in non-fatal myocardial infarction at the expense of significant increase in minor bleeding events with GPI over and above dual antiplatelets.[6] With the available evidence, the current guidelines do not recommend routine use of GPI in elective low and intermediate risk PCI if the patients are optimally preloaded with clopidogrel.[7]

2. Unstable angina and non-ST-segment elevation myocardial infarction

GPI had consistently been shown to be beneficial in patients with unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI). This led to wide spread use of these agents both in medically treated patients and upstream to the planned procedure. However, a meta-analysis of 29,570 patients by Roffi et al,[8] in 2002 showed that the utility of GPI

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0019-4832/$ – see front matter
http://dx.doi.org/10.1016/j.ihj.2013.04.032

was mainly for patients who had invasive strategy. Again, this practice was re-evaluated in two recent trials, ACUITY – timing[9] and EARLY ACS[10]; they did show any advantage with routine upstream therapy with GPI compared to selective administration in the catheterization laboratory in the background of optimal dual antiplatelet preloading. In addition, upstream therapy was associated with increased bleeding events. Further, ISAR-REACT-2 trial investigated the utility of abciximab given in catheterization laboratory in patients optimally loaded with dual antiplatelets. There was a 25% statistically significant relative reduction in the primary endpoint of death, myocardial infarction or urgent revascularization and this benefit was confined to only patients with elevated troponin levels.[11] The current guidelines recommends GPI only in patients with high risk features such as elevated troponin and angiographically visible thrombus and those not pre-treated with thienopyridines. Upstream therapy may be considered only in patients with on-going ischemia and the risk of bleeding is low.[12,13]

3. ST-segment elevation myocardial infarction

The trials of 'pre dual antiplatelet' era showed clinical benefit of routine GPI, both upstream and periprocedural, in the setting of primary PCI. However, recent data does not support this practice. The upstream administration of GPI was evaluated in two trials. In the On-TIME 2 trial, the patients were pre-treated with a loading dose of clopidogrel and randomized to prehospital administration of tirofiban infusion vs placebo. Tirofiban infusion improved ST-segment resolution at 1 h after PCI. Though it fails to demonstrate improvement in survival or rate of reinfarction, there was reduction in the incidence of early stent thrombosis and urgent PCI.[14] In the BRAVE-3 trial, upstream administration of abciximab was evaluated against placebo in patients pre-treated with 600 mg of clopidogrel loading and heparin. There was no difference in the primary endpoint of reduction in infarct size or in the secondary end point of 30-day incidence of death, myocardial infarction or urgent revascularization.[15] In addition, there was increased incidence of thrombocytopenia and minor bleeding in the abciximab arm. With this background, the current guidelines recommended GPI for selected patients with high risk angiographic features and those not optimally loaded with dual antiplatelets.[16,17]

4. Bivalirudin vs heparin + GPI

Bivalirudin is a synthetic, direct thrombin inhibitor that binds specifically and reversibly to both clot-bound and free thrombin. It has been evaluated as an alternative to heparin + GPI in patients undergoing both urgent and elective PCI. In the REPLACE-2 trial, bivalirudin with provisional use of GPI (abciximab) was tested against low-dose unfractionated heparin (UFH) plus planned GPI in both stable and acute coronary syndromes. At 30-day follow-up, bivalirudin with provisional GPI not only met the non-inferiority primary composite endpoint but was also associated with significantly lower rate of bleeding.[18] The ACUITY trial evaluated bivalirudin in 13,819 patients with NSTEMI–ACS. It enrolled patients into three arms: unfractionated or low molecular weight heparin + GPI (UFH/LMWH + GPI), bivalirudin + GPI and bivalirudin alone. The composite ischemic endpoint was not different among the three arms. However, the bivalirudin alone arm was associated lower rate of bleeding and significantly better net clinical outcome compared to UFH/LMWH + GPI arm.[19] The ISAR-REACT 4 trial, compared bivalirudin alone with UFH + GPI in 1721 NSTEMI patients in the background of optimal dual antiplatelet loading. The UFH + abciximab arm failed to reduce the primary endpoint and in addition, was associated with increased bleeding.[20] The 3602 patient HORIZONS-AMI trial evaluated bivalirudin with provisional GPI against UFH and planned GPI in the setting of primary PCI.[21] The bivalirudin arm was associated with reduced rate of primary endpoint of net clinical outcome, primarily linked to lower incidence of bleeding. In addition bivalirudin arm was associated with lower mortality that remained significant at 3-year follow-up. Bivalirudin arm was associated with increased incidence of acute stent thrombosis, especially in patients who did not receive clopidogrel loading.[22] However, at the end of three years, the incidence was similar between both the arms. With this superior clinical outcomes, bivalirudin has been given Class I (Level of evidence – B) recommendation during PCI.[7,13,16,17]

5. GPI and newer antiplatelets

Clopidogrel is limited by its slow onset and less potent platelet inhibition. Even with 600 mg of loading dose, it takes at least a few hours to achieve adequate platelet inhibition which is associated with increased periprocedural ischemic complications. This led to the introduction of three newer P_2Y_{12} inhibitors: prasugrel, ticagrelor and cangrelor.[23] Prasugrel and ticagrelor are thienopyridines and administered orally. The additional benefit of GPI in the background of these drugs is largely unknown. In TRITON–TIMI 38 trial, a 55% of patients received GPI. GPI usage over all increased the rates of TIMI major and minor non-CABG bleeding and however this did not influence both clinical benefit and the risk of bleeding with prasugrel compared with clopidogrel.[24] In the PLATO trial, 27% of patients received GPI. Similar to prasugrel, ticagrelor also reduced rates of death, MI, or stroke independent of GPI use.[25] Cangrelor is a non-thienopyridine reversible P_2Y_{12} inhibitor, administered intravenously and provides instant protection against ischemic events. It also has the advantage of disappearance of antiplatelet activity at cessation of infusion. This is advantageous in case of major bleeding or emergency surgery. This might further reduce the need for adjunctive GPI use. However, in the major CHAMPION – PHOENIX trial, none of the patients received GPI.[26] It remains to be seen whether it gives the same level of protection against ischemic events in the acute setting. As there have been no randomized studies specifically evaluating the role of GPI in the background of newer drugs, current guidelines do not give any definite recommendations.