

Glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndrome

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Abstract

Glycoprotein IIb/IIIa inhibitors (GPI) block the final common pathway in platelet aggregation. Data from several large randomized clinical trials have demonstrated that glycoprotein IIb/IIIa inhibitors reduce mortality and reinfarction in patients with acute coronary syndrome (ACS), particularly in patients undergoing subsequent percutaneous coronary intervention (PCI). Patients with unstable angina/non-ST-segment elevation myocardial infarction who are troponin-positive, have high-risk features or undergoing an early invasive approach should be initiated on GPI. Glycoprotein IIb/IIIa inhibitors are not recommended in patients with ST-segment elevation myocardial infarction when used in combination with fibrinolytic therapy, either as part of a facilitated regimen prior to primary PCI, or as a pharmacologic reperfusion regimen without planned PCI, due to an increased incidence of bleeding and the lack of improved clinical outcomes. Glycoprotein IIb/IIIa inhibitors appear to be most beneficial in patients with elevated troponin, recurrent ischemia and diabetes. Adequate dose adjustment for creatinine clearance is important to decrease the incidence of side effects such as bleeding and thrombocytopenia. Studies are ongoing to determine the optimal timing of initiation of GPI in patients with ACS and to further identify subgroups who derive greater benefit from GPI.

Key words: antiplatelet, antithrombotic, unstable angina, myocardial infarction, acute coronary syndrome.

Introduction

Platelet aggregation is an important component of acute plaque rupture and thrombosis in acute coronary syndrome (ACS). Glycoprotein IIb/IIIa inhibitors (GPI) block the final common pathway in platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor and fibronectin. Glycoprotein IIb/IIIa inhibitors are among the most extensively studied compounds in cardiovascular medicine, with a large body of evidence derived from randomized clinical trials. In this manuscript, we review the data supporting GPI use in percutaneous coronary intervention (PCI) and across the spectrum of acute coronary syndromes (ACS), key patient population subgroups, and safety issues related to their use.

Glycoprotein IIb/IIIa inhibitors in percutaneous coronary intervention

Elective percutaneous coronary intervention

Glycoprotein IIb/IIIa inhibitors (GPI) were first studied as an adjunct in high-risk patients undergoing percutaneous revascularization. The EPIC study, the first major prospective, double-blind trial of a GPI, assigned 2099 high risk patients to receive one of three regimens: 1) bolus and an infusion of placebo, 2) bolus of abciximab and placebo infusion or 3) bolus and infusion of abciximab [2]. The patients were identified as high risk by clinical features which included: acute evolving MI, early post-infarction angina or unstable angina associated with ECG changes despite medical therapy or high-risk clinical or angiographic characteristics. The primary end point was a 30-day composite of death, nonfatal myocardial infarction, unplanned surgical revascularization, unplanned repeat percutaneous procedure, unplanned implantation of a coronary stent or insertion of an intraaortic balloon pump for refractory ischemia. Abciximab bolus plus infusion reduced the primary endpoint by 35% relative (8.3 vs. 12.8%, $p = 0.008$) to the placebo bolus and infusion group. The primary endpoint occurred in 11.5% of patients on the abciximab bolus with placebo infusion arm. However, bleeding events were greatest in the group treated with abciximab bolus plus infusion (7% placebo vs. 11% abciximab bolus vs. 14% abciximab bolus plus infusion, $p < 0.01$ [placebo vs. abciximab bolus plus infusion]).

Although abciximab was demonstrated to reduce the incidence of adverse cardiac events in patients undergoing PCI, the increased incidence of bleeding events prompted study of shorter-acting GPI. The Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trial randomized 2141 patients undergoing PCI to either receive a bolus and infusion of either placebo or tirofiban [3]. The primary end point was a 30 day composite of death, non-fatal myocardial infarction and need for surgical revascularization, repeat PCI, or stent implantation for threatened or actual thrombotic closure. 10.3% of patients who received tirofiban reached the primary end point compared to 12.2% on placebo ($p = 0.160$). Tirofiban was protective in the early period following angioplasty resulting in a 38% reduction in relative risk at 2 days following PCI (8.7 vs. 5.4%, $p = 0.005$). There was no statistically significant increase in major bleeding (5.3 vs. 3.7%, $p = 0.096$) or thrombocytopenia (1.1 vs. 0.9%, $p = 0.709$) between the tirofiban and placebo groups.

The IMPACT-II trial evaluated another short-acting GPI, eptifibatide, in patients undergoing PCI. Four thousand and ten patients undergoing PCI

were randomized to receive either: bolus and infusion of placebo, 135 $\mu\text{g}/\text{kg}$ bolus and infusion of 0.5 $\mu\text{g}/\text{kg}$ min of eptifibatide (135/0.5) or 135 $\mu\text{g}/\text{kg}$ bolus and infusion of 0.75 $\mu\text{g}/\text{kg}$ min of eptifibatide (135/0.75) [4]. The 30 day composite primary end point of death, myocardial infarction, or unplanned surgical or percutaneous revascularization occurred in 9.2% of patients in the 135/0.5 group ($p = 0.063$) compared with 11.4% on placebo and 9.9% in the 135/0.75 group ($p = 0.22$). By treatment-received analysis, the composite occurred in 9.1% of patients in the 135/0.5 group ($p = 0.035$) compared to 11.6% on placebo and 10% in the 135/0.75 group ($p = 0.18$). There was a more pronounced effect in the first 24 h following PCI with 9.6% of patients reaching the composite end-point compared to 6.6% ($p = 0.006$) in the 135/0.5 group and 6.9% ($p = 0.014$) in the 135/0.75 group. There was no significant increase in major bleeding among the groups (4.8% in placebo vs. 5.1% in the 135/0.5 group vs. 5.2% in the 135/0.75 group).

Karvouni *et al.* performed a meta-analysis on clinical outcomes with GPI in patients undergoing elective or emergent/urgent primary PCI, which included 20,137 patients from 19 randomized clinical trials [5]. Percutaneous intervention in this analysis included: percutaneous transluminal coronary angioplasty (PTCA), stent placement and atherectomy. The primary endpoint was 30-day mortality. Glycoprotein IIb/IIIa inhibitors reduced events by 31% compared to placebo (risk ratio [RR] 0.69, 95% confidential CI 0.0.53-0.90) with a sustained benefit at 6 months (RR 0.79, 95% CI 0.66-0.94). The incidence of bleeding was not higher in trials where heparin was discontinued after PCI (RR 1.02, 95% CI 0.85-1.24) (Figure 1).

The current American Heart Association/American College of Cardiology (AHA/ACC) guideline [6] gives GPI a class I indication for patients with unstable (UA)/non-ST-segment elevation myocardial infarction (NSTEMI) undergoing PCI without clopidogrel administration (level of evidence: A) and a class IIa indication GPI in patients with UA/NSTEMI undergoing PCI with clopidogrel administration (level of evidence: B). In elective PCI, GPI received a class IIa indication (level of evidence: B) (Table I).

Adjunct to percutaneous coronary intervention in ST-elevation myocardial infarction

The ADMIRAL (Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up) trial found that initiation of treatment with abciximab prior to coronary stenting improved outcomes compared to stenting alone [7]. Three hundred patients with ST-segment elevation myocardial infarction (STEMI)

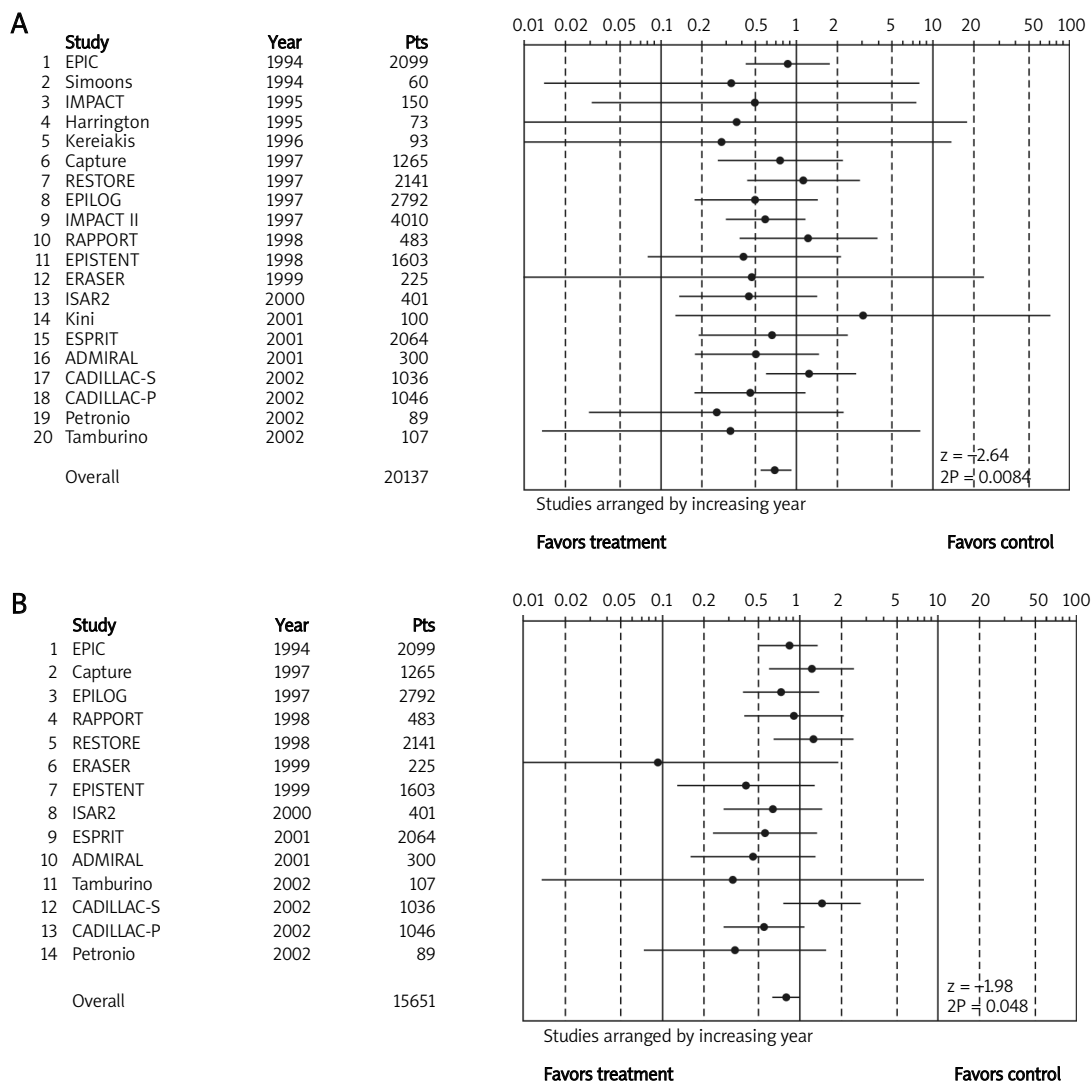


Figure 1. Mortality at 30 days (A) and 6 months (B) among patients who received GPI vs. placebo in PCL RR and 95% CI are shown for each study (reprinted from Karvouni *et al.*)

were randomized to receive either: bolus and infusion of abciximab or placebo bolus and infusion in addition to the standard treatment. The composite primary end point was death, reinfarction or urgent revascularization of the target vessel at 30 days was reduced by abciximab by 8.6% absolute (6.0 vs. 14.6%, $p = 0.01$) compared to placebo. The benefit of abciximab was sustained at 6 months (7.4% on abciximab vs. 15.9% on placebo, $p = 0.02$).

The role of GPI in angioplasty and stenting was evaluated by the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial which enrolled 2,082 patients with symptoms consistent with acute STEMI and ST-segment elevation or left bundle branch block on electrocardiogram or angiography demonstrating high-grade stenosis with associated wall motion

abnormalities. The subjects were randomized to either: percutaneous transluminal coronary angioplasty (PTCA), PTCA plus abciximab, stenting or stenting plus abciximab [8]. The primary endpoint was a 6-month composite of death, reinfarction, stroke and ischemia-driven revascularization of the target vessel. Patients who underwent stenting plus abciximab had the best outcome with the primary endpoint occurring 10.2% of the time compared to 20% after PTCA, 16.5% after PTCA plus abciximab and 11.5% after stenting ($p < 0.001$ in a two-way comparison with PTCA and $p = 0.004$ for the two way comparison with PTCA and abciximab).

TITAN-TIMI 34 demonstrated that earlier administration of eptifibatid was beneficial in restoring coronary patency before percutaneous intervention for STEMI. Three hundred and forty three patients with STEMI were randomized to either: early

Table I. AHA/ACC guidelines on the use of glycoprotein IIb/IIIa inhibitors (GPI) in ACS

	Class I	Class IIa	Class IIb	Class III
PCI	Initiation of a GPI in patients with UA/NSTEMI undergoing PCI without clopidogrel administration (level of evidence: A) Initiation of a GPI in high-risk and troponin positive patients with UA/NSTEMI who receive PCI when a GPI had been not started prior to diagnostic angiography (level of evidence: A)	Initiation of a GPI in patients undergoing elective PCI with stent placement (level of evidence: B) Initiation of a GPI in patients with UA/NSTEMI undergoing PCI with clopidogrel administration (level of evidence: B)		
STEMI		Treatment with abciximab as early as possible in patients with STEMI undergoing PCI (level of evidence: B)	Treatment with eptifibatide or tirofiban in patients with STEMI undergoing PCI (level of evidence: B) Combination pharmacological reperfusion with abciximab and half-dose reteplase or tenecteplase in patients with STEMI with no plan for PCI who meet the following criteria: anterior location of MI, age less than 75 years, and no risk factors for bleeding (level of evidence: A)	
STEMI – facilitated PCI with fibrinolysis			Facilitated PCI using regimens other than full-dose fibrinolytic therapy reperfusion in situations when all of the following applies (level of evidence: C):	
			<ul style="list-style-type: none"> • high risk patients • PCI is not available within 90 min • low risk of bleeding (younger age, absence of poorly controlled hypertension and normal body weight) 	

initiation of eptifibatide in the emergency department (ED) or in the cardiac catheterization laboratory (CCL) after diagnostic catheterization [9]. The primary end point was the corrected TIMI frame count (CTFC) prior to PCI, which is a measure of epicardial coronary flow and myocardial perfusion with a lower CTFC correlating to faster flow. The pre-PCI CTFC was lower in the group treated with eptifibatide in the ED compared to delayed treatment (77.5 ± 32.2 compared to 84.3 ± 30.7 , $p = 0.049$) suggesting improved coronary patency with earlier administration of eptifibatide.

Montalescot *et al* performed a meta-analysis on the long-term outcomes of abciximab in 1,101 patients with STEMI who undergo primary PCI in 3 European randomized placebo-controlled trials [10]. The primary endpoint was a composite of death or myocardial infarction up to 3 years after randomization. Abciximab reduced the relative risk by 37% compared to placebo (estimated hazard ratio 12.0 vs. 19%, $p = 0.008$) with no statistically significant difference in major bleeding between the two groups (Figure 2).

The AHA/ACC guidelines give a Class IIa indication for treatment with abciximab as early as

Table I. AHA/ACC guidelines on the use of glycoprotein IIb/IIIa inhibitors (GPI) in ACS – cont.

	Class I	Class IIa	Class IIb	Class III
UA/ NSTEMI – early invasive strategy	Use of a GPI with anticoagulation with enoxaparin and UFH in addition to aspirin (level of evidence: A) Uses of a GPI with anticoagulation with bivalirudin and fondaparinux in addition to aspirin (level of evidence: B)	Use of a GPI in patients who receive aspirin, anticoagulation with heparin or enoxaparin and clopidogrel (level of evidence: B) Upstream initiation of abciximab if there is no appreciable delay to angiography and PCI is likely performed; otherwise, eptifibatide or tirofiban is the preferred GPI (level of evidence: B) It is reasonable to omit upstream administration of a GPI before diagnostic angiography if bivalirudin is selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 h prior to planned catheterization		Abciximab is not recommended in patients where PCI is not planned (level of evidence: A)
UA/ NSTEMI – conservative strategy	Patients with high risk features or with continuing ischemia or planned PCI be treated with eptifibatide or tirofiban, in addition to ASA and UFH (level of evidence: A) Treatment with abciximab for 12-24 h in patients with UA/NSTEMI when a PCI is planned within the next 24 h (level of evidence: A)			

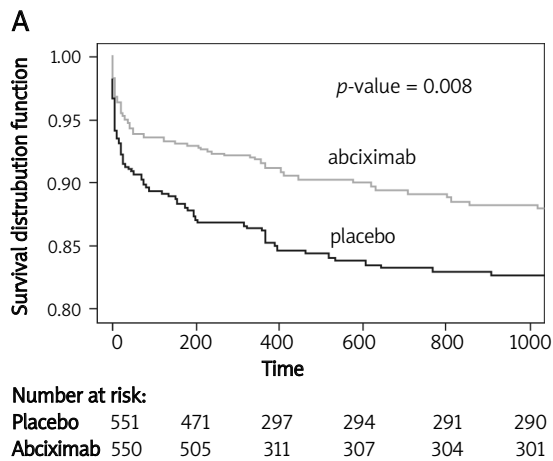
possible in patients with STEMI undergoing PCI (level of evidence: B) [11]. The administration of eptifibatide or tirofiban is a class IIb indication in patients with STEMI undergoing PCI (level of evidence: B), because fewer and smaller trials have been performed with the small molecule GPIs [12].

Glycoprotein IIb/IIIa inhibitors with reduced dose lytic for primary reperfusion in ST-elevation myocardial infarction

As glycoprotein IIb/IIIa inhibitors were found to be effective alone and as an adjunct to fibrinolytic therapy to restore coronary patency in patients with STEMI, further studies were performed to assess the efficacy of GPI + reduced-dose lytic to reduce clinical endpoints. GUSTO-V was a large open-label trial which enrolled 16,588 patients presenting

within 6 hours of symptom onset with STEMI [13]. Patients received standard-dose reteplase or half-dose reteplase with abciximab. The primary endpoint was 30 day mortality, which was 5.9% in the reteplase group compared to 5.6% in the reteplase/abciximab group ($p = 0.43$). However, severe bleeding was more frequent in the combination reteplase and abciximab group compared to reteplase alone (1.1 vs. 0.5%, $p < 0.0001$).

The ASSENT-3 (Assessment of the safety and efficacy of a new thrombolytic regimen) trial randomized 6,095 patients with acute STEMI to one of three regimens: full-dose tenecteplase and enoxaparin (enoxaparin group), half-dose tenecteplase with unfractionated heparin (UFH) and abciximab (abciximab group) or full-dose tenecteplase with UFH (UFH group) [14]. The primary efficacy



of adjunctive antithrombin in a 2 × 2 design to either unfractionated heparin versus enoxaparin [15]. The primary end point was a composite of death or new or worsening heart failure at 30 days, which was higher in the eptifibatide/tenecteplase group (10 vs. 3%, $p = 0.09$) compared to eptifibatide/placebo. Similarly, the BRAVE (Bavarian Reperfusion Alternatives Evaluation) trial randomized 253 patients with STEMI to abciximab with half-dose reteplase or abciximab alone prior to primary PCI [16]. There was no significant difference in the mean infarct size of the left ventricle between the abciximab/reteplase group (13 vs. 11.5%, $p = 0.81$) compared to abciximab alone.

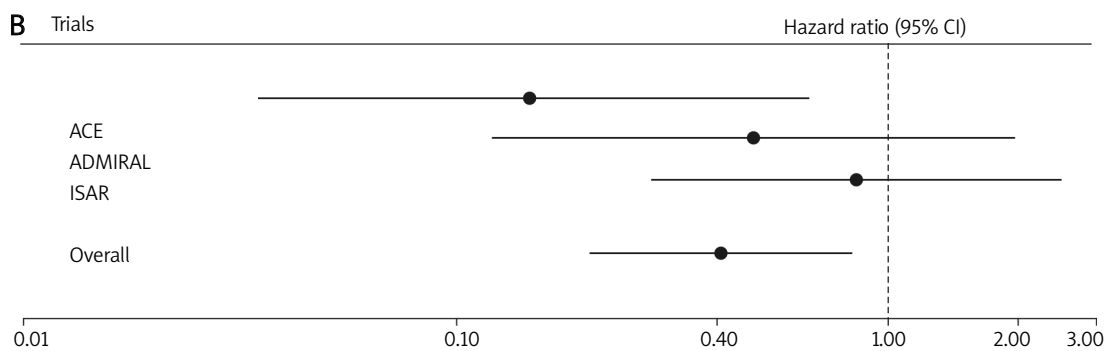


Figure 2A – Freedom from death or re-infarction over 3 years of follow-up of STEMI treated with abciximab (light gray) vs. placebo (dark). **B** – Individual study results and meta-analysis results are presented with hazard ratio and 95% confidence intervals (reprinted from Montelese *et al.* with permission)

endpoint was a 30-day composite of mortality, in-hospital reinfarction and in-hospital refractory ischemia. The event rate was 11.4% in the enoxaparin group vs. 15.4% in the UFH group ($p = 0.0002$) vs. 11.1% in the abciximab group ($p < 0.0001$).

The AHA/ACC guidelines make a class IIb recommendation for combination pharmacological reperfusion with abciximab and half-dose reteplase or tenecteplase in patients with STEMI with no plan for PCI who meet the following criteria: anterior location of MI, age less than 75 years, and no risk factors for bleeding (level of evidence: A) [11].

Glycoprotein IIb/IIIa inhibitors with reduced dose lytic facilitating primary percutaneous coronary intervention

The mixed results with GPI + reduced-dose fibrinolytic as a pharmacologic reperfusion regimen led to studies exploring this combination for facilitation of primary PCI in the hope that restoring infarct artery patency prior to PCI might improve outcomes. ADVANCE MI assigned 146 patients with ST-elevation MI to receive eptifibatide plus half dose tenecteplase or eptifibatide plus placebo prior to primary PCI. There was a second randomization

The FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial is the most recent study on facilitated PCI in combination with fibrinolysis [16]. FINESSE was a large, double-blind randomized control trial of 2,452 patients which compared facilitated PCI with abciximab and half-dose reteplase, facilitated PCI with abciximab alone or abciximab just prior to PCI in patients in the first 6 h of an evolving STEMI. The primary end point was a 90-day composite of death, ventricular fibrillation, cardiogenic shock and CHF. There was no statistically significant difference in the primary endpoint which occurred in 9.8% of patients in the combination-facilitated PCI group, 10.5% in the abciximab-facilitated PCI group and 10.7% in the primary PCI only group ($p = 0.55$) (Figure 3).

Most recently, the On-TIME 2 (Ongoing tirofiban in myocardial infarction evaluation 2) trial randomized 984 patients with STEMI to pre-hospital initiation of bolus tirofiban compared to placebo in addition to standard therapy [18]. The primary endpoint was residual ST-segment deviation one hour after PCI. Treatment with tirofiban significantly decreased mean residual ST-segment deviation

compared to placebo (3.6 mm [SD 4.6] vs. 4.8 mm [SD 6.3], $p = 0.003$). There was no significant difference in major bleeding (4 vs. 3%, $p = 0.36$).

The current American Heart Association/ American College of Cardiology (AHA/ACC) guidelines give a Class IIb recommendation (level of evidence: C) for facilitated PCI using regimens other than full-dose fibrinolytic therapy reperfusion in situations when all of the following applies: patients are high risk, PCI is not available within 90 min and there is low risk of bleeding (younger age, absence of poorly controlled hypertension and normal body weight) [11].

Glycoprotein IIb/IIIa inhibitors in unstable angina/non-ST-elevation myocardial infarction

Patients managed with an early invasive approach

Following trials that demonstrated a reduction in acute ischemic complications in patients undergoing PCI, further studies were performed to assess the role of GPI in the management of UA and NSTEMI. The CAPTURE trial studied 1,265 patients with refractory unstable angina who underwent angiography and were randomized to abciximab or placebo infusion for 18-24 h prior to and 1 h after percutaneous coronary angioplasty (PTCA) [19]. The primary end point was a 30-day composite of death, MI, or urgent intervention for recurrent ischemia. Abciximab reduced the relative risk by 29% compared to placebo (11.3 vs. 15.9%, $p = 0.012$). There was more major bleeding with abciximab than with placebo (3.8 vs. 1.9%, $p = 0.043$).

PRISM-PLUS assigned 1,915 patients with unstable angina and NSTEMI to three treatment groups: tirofiban, heparin or tirofiban plus heparin [20]. The primary end point was a 7-day composite of death, myocardial infarction or refractory ischemia. Tirofiban plus heparin reduced the absolute risk by 5% compared to heparin alone (12.9 vs. 17.9%, $p = 0.004$). This effect was sustained at 30 days (18.5 vs. 22.3%, $p = 0.03$) and 6 months (27.7 vs. 32.1%, $p = 0.02$). However, the tirofiban alone arm was discontinued early due to excess mortality compared to heparin alone (4.6 vs. 1.1%). This study demonstrated that the additive combination of tirofiban with standard antithrombotic therapies (aspirin, heparin) is associated with improved outcomes in patients with UA and NSTEMI, although tirofiban alone without heparin was associated with increased mortality.

PURSUIT was a large double-blinded trial which assigned 10,948 patients with non-ST-segment elevation ACS to treatment with either eptifibatide or placebo [21]. The primary end point was a 30-day composite of death and nonfatal MI, which was 14.2% in the eptifibatide group and 15.7% in placebo

($p = 0.04$). Major bleeding was higher in the eptifibatide group compared to placebo (10.6 vs. 9.1%, $p = 0.02$) although there was no significant difference in intracranial hemorrhage. Subgroup analyses, however, showed that although the difference in reaching the composite end point among men treated with eptifibatide was significant (16.2% in the placebo group vs. 12.4% in the eptifibatide group, $p = 0.006$), this was not sustained among women (12.9% in the placebo group vs. 10.6% in the eptifibatide group, $p = 0.19$).

A subgroup analysis of the PURSUIT trial evaluated 2,430 patients who were treated with either eptifibatide or placebo in conjunction with an early invasive strategy [22]. Patients who underwent PCI within 30 days were divided into four groups based on the timing of their intervention: day 1, days 2 or 3, days 4 to 7 or days 8 to 30. The primary endpoint was a 30-day composite event rate of death or MI. There was no significant difference in the event rates among patients treated with placebo (15.9% day 1, 17.5% day 2-3, 15% day 4-7, 18.2% day 8-30, $p = 0.11$). Event rates were lowest among patients treated with eptifibatide who underwent PCI on day 1 (9.2 vs. 14.0% day 2-3, 15.0% day 4-7, 17.4% day 8-30, $p < 0.05$). This suggests that eptifibatide in conjunction with an early invasive approach results in improved outcomes.

TACTICS TIMI-18 (Treat angina with aggrastat and determine cost of therapy with an invasive or

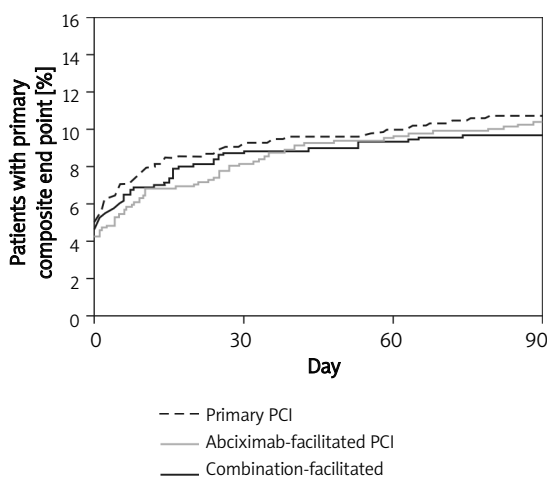


Figure 3. Kaplan-Meier estimates of proportion of patients with the composite end point between primary PCI, abciximab-facilitated PCI and combination (abciximab plus reteplase)-facilitated PCI. The composite end point included death from all causes and complications of MI (reprinted from Ellis *et al.* with permission)
 $p = 0.55$ for the comparison of primary percutaneous coronary intervention (PCI) with combination-facilitated PCI
 $p = 0.86$ for the comparison of primary PCI with abciximab-facilitated PCI
 $p = 0.68$ for the comparison of abciximab-facilitated PCI with combination-facilitated PCI

conservative strategy Thrombolysis in Myocardial Infarction-18) randomized 2,200 patients with UA/NSTEMI to either an early invasive or conservative strategy after treatment with aspirin, heparin and tirofiban for 48 h [23]. The primary endpoint was a 6-month composite of death, MI or rehospitalization for ACS. The early invasive strategy decreased the relative risk by 18% compared to a conservative approach (15.9 vs. 19.4%, $p = 0.025$).

A meta-analysis by Boersma *et al.* included a subgroup analysis on GPI and the early use of coronary revascularization [24]. Among patients who underwent PCI or CABG within 5 days, the 30-day composite of death or MI was lower in patients who received GPI compared to placebo (14.3 vs. 17.3%, OR 0.79, 95% CI 0.68-0.91). This effect was most prominent in patients undergoing early revascularization, however there was a reduction in composite events among all patients randomized to GPI (Figure 4).

The current AHA/ACC guidelines give a class IIa indication for abciximab upstream if there is no appreciable delay to angiography and PCI is likely performed; otherwise, eptifibatide or tirofiban is the preferred GPI (level of evidence: B) [25]. Abciximab is given a class I recommendation in patients with UA/NSTEMI when a PCI is planned within the next 24 h (level of evidence: A). Abciximab is not recommended in patients where PCI is not planned (class III, level of evidence: A).

The EARLY ACS (Early Front-Loaded Eptifibatide in the Treatment of Patients with Non-ST-Segment Elevation Acute Coronary Syndrome) trial enrolled 9,492 high – risk patients with non-STE ACS in

a prospective, randomized, double-blind comparison of early double-bolus eptifibatide given 12 h or more prior to PCI vs. placebo with provisional use of eptifibatide after angiography (delayed eptifibatide) in patients managed with an early invasive strategy [26]. There was no significant difference in the primary end point which was a composite of death, myocardial infarction, recurrent ischemia necessitating urgent revascularization or the occurrence of a thrombotic complication during PCI requiring bolus therapy at 96 h between the two groups (9.3% in the early-eptifibatide group vs. 10% in the delayed-eptifibatide group, $p = 0.23$). However, there was a trend toward fewer deaths or reinfarctions through 30 days (the key secondary endpoint) with early, routine eptifibatide (11.2 vs. 12.3%, $p = 0.08$). The early-eptifibatide group also experienced more bleeding complications and required more transfusions. In an invasive approach, the routine, upstream use of eptifibatide 12 h or more prior PCI in patients with non-STE ACS did not result in improved outcomes as compared to the selective use of eptifibatide after angiography.

Medical management in patients not planning to undergo early revascularization

The Platelet Receptor Inhibition in Ischemic Syndrome Management Study (PRISM) trial randomized 3,232 patients with unstable angina who were treated with aspirin to either tirofiban or heparin for 48 prior to angiography and possible revascularization [27]. The primary composite endpoint included death, myocardial infarction or refractory ischemia within 48 h. Tirofiban reduced the relative risk by 32% compared to heparin (3.8 vs. 5.6%, $p = 0.01$). This study suggests that tirofiban in addition to aspirin offered more benefit than aspirin and heparin alone in the medical management of UA.

The GUSTO-IV trial evaluated the use of abciximab in the medical management of patients with UA and NSTEMI when early revascularization was not planned [28]. GUSTO-IV randomized 7,800 patients on standard therapy to either: bolus and 24-h infusion of abciximab, bolus and 48-h infusion of abciximab or placebo. The primary endpoint was a 30-day composite of death or MI. There was no statistical difference in the occurrence of the primary endpoint between the three groups (8.0% patients on placebo vs. 8.2% patients on 24 h abciximab vs. 9.1% on 48 h abciximab, $p = 0.190$). The GUSTO-IV trial suggests that abciximab is not superior to placebo in the medical management of UA and NSTEMI, when early coronary revascularization is not planned.

The clinical efficacy and safety of glycoprotein IIb/IIIa inhibitors in patients with non-ST-segment elevation ACS not routinely scheduled for early revascularization was evaluated in a meta-analysis

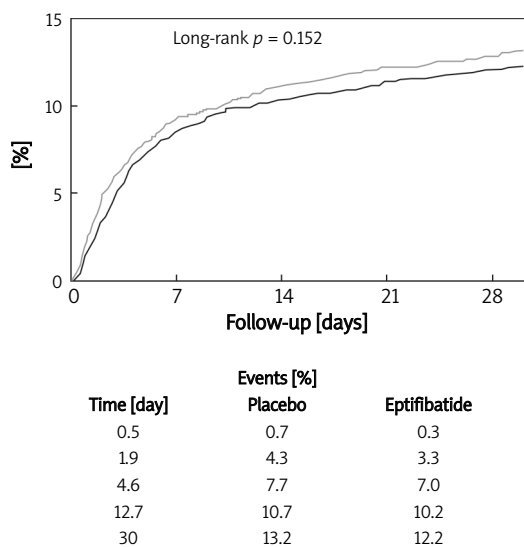


Figure 4. Kaplan-Meier curves showing cumulative incidence of death or non-fatal MI during period of medical treatment alone in patients with UA/ACS assigned to GPI vs. placebo for 72 h (reprinted from Ronner *et al.* with permission)

done by Boersma *et al.* of 6 trials (PRISM, PRISM-PLUS, PURSUIT, GUSTO-IV, PARAGON-A and PARAGON-B) which included 31,402 patients [24]. The primary endpoint was a 30 day composite of death or MI. Glycoprotein IIb/IIIa inhibitors reduced the relative risk by 9% compared to placebo (10.8 vs. 11.8%, $p = 0.015$). The incidence of major bleeding was found to be higher in patients treated with GPI (2.4 vs. 1.4%, $p < 0.0001$) although there was not increase in intracranial bleeding (0.09 vs. 0.06%, $p = 0.40$) (Figure 5).

For UA/NSTEMI patients in whom an initial conservative approach is elected, the current AHA/ACC guidelines give a class IIb recommendation for the addition of eptifibatide or tirofiban to anti-coagulant and oral antiplatelet therapy (level of evidence: B) [25]. Diagnostic angiography is indicated if there are high-risk features such as recurrent symptoms of ischemia, heart failure or serious arrhythmias (class I, level of evidence: A) with upstream administration of either eptifibatide or tirofiban (class I, level of evidence: A) or clopidogrel loading plus daily maintenance (class I, level of evidence: A) prior to angiography.

Comparison of glycoprotein IIb/IIIa inhibitors

TARGET (Do Tirofiban and ReoPro Give Similar Efficacy Trial) is the first large trial which directly compares the efficacy and safety of two GPI, tirofiban and eptifibatide [29]. This trial assigned 4809 patients undergoing either elective or urgent PCI (excluding primary PCI for STEMI) to receive either tirofiban (10 $\mu\text{g}/\text{kg}$ bolus plus infusion of 0.15 $\mu\text{g}/\text{kg}/\text{min}$ for 18-24 h) or abciximab (0.25 mg/kg bolus plus infusion of 0.125 $\mu\text{g}/\text{kg}/\text{min}$ for 12 h). The primary endpoint was a 30-day composite of death, nonfatal MI or urgent revascularization. The primary endpoint occurred in 7.6% of patients in the tirofiban group compared to 6.0% in the abciximab group ($p = 0.038$). Major bleeding events were similar between the two groups.

The STRATEGY (Single High Dose Bolus Tirofiban and Sirolimus Eluting Stent vs Abciximab and Bare Metal Stent in Myocardial Infarction) trial compared tirofiban and abciximab in stenting for STEMI [30]. One hundred and seventy 5 patients with STEMI or new left bundle-branch block were randomized to either a high-dose bolus of tirofiban in conjunction with sirolimus-eluting stenting or standard-dose abciximab with bare-metal stenting. The primary endpoint was a composite of death, non-fatal MI, stroke or binary restenosis at 8 months, which occurred in 19% of patients in the tirofiban plus sirolimus-eluting stenting compared to 50% of patients in the abciximab plus bare-metal stenting group ($p < 0.04$). This trial supports other similar data suggesting that high-dose bolus of tirofiban

can achieve results that are at least as good as abciximab and eptifibatide.

Use of glycoprotein IIb/IIIa inhibitors with other antiplatelet and anticoagulation agents

Earlier studies evaluated the use of GPI with unfractionated heparin (UFH). The INTERACT (Integrilin and Enoxaparin Randomized Assessment of Acute Coronary syndrome Treatment) trial evaluated combination therapy with GPI with LMWH in ACS [31]. Seven hundred and forty six patients with UA or NSTEMI were assigned to open-label treatment with either enoxaparin or UFH in addition to eptifibatide. The enoxaparin group experienced less frequent recurrent ischemia (14.3 vs. 25.4%, $p = 0.0002$) compared to UFH in the initial and subsequent 48-h periods (12.7 vs. 25.9%, $p < 0.0001$). A secondary endpoint of death or MI at 30 days demonstrated a 4% absolute risk reduction with enoxaparin compared to UFH (5 vs. 9%, $p = 0.031$). The primary safety endpoint of major non-coronary artery bypass surgery-related bleeding at 96 h also supported the use of LMWH over UFH (1.8 vs. 4.6%, $p = 0.03$). The INTERACT trial supports the use of enoxaparin over UFH when given in combination with eptifibatide for the management of non-ST segment elevation ACS when PCI is not performed early.

The CRUSADE registry analyzed 11,358 patients with UA or NSTEMI treated with early GPI who received either UFH or LMWH (the choice of heparin

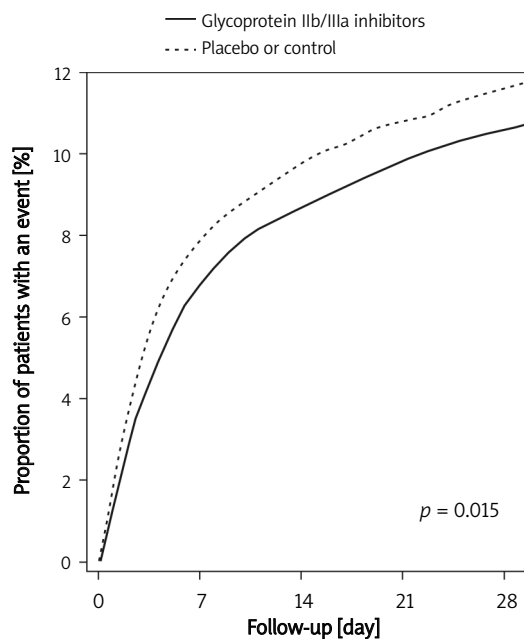


Figure 5. Kaplan-Meier estimates of cumulative occurrence of death or MI within 30 days comparing GPI vs. placebo in patients with non-ST-segment elevation ACS (reprinted from Boersma *et al.* with permission)

was at the discretion of the treating physician) [32]. Similar to INTERACT, this analysis found that patients who received LMWH had improved outcomes [adjusted odds ratio (AOR) of 0.81 95% confidence interval (CI) 0.67-0.99 in in-hospital death or reinfarction] and this effect was even more pronounced in patients undergoing PCI more than 48 h after hospitalization. There were similar bleeding outcomes in the two groups. These data from CRUSADE support the use of LMWH in combination with early glycoprotein IIb/IIIa inhibitors in patients with non-ST segment elevation ACS.

The initial studies on GPI were performed prior to clopidogrel became standard therapy in ACS. The ISAR-REACT 2 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2) trial assessed the role of abciximab in patients with ACS undergoing PCI after clopidogrel pretreatment [33]. ISAR-REACT 2 randomized 2,022 patients with non-ST-segment elevation ACS undergoing PCI to receive either placebo or abciximab in addition to oral clopidogrel 600 mg and standard therapy. The primary endpoint was a 30-day composite of death, myocardial infarction or urgent revascularization. Abciximab reduced the relative risk by 25% (8.9 vs. 11.9%, $p = 0.03$) compared to placebo. Subgroup analysis revealed that this difference was accounted for only in patients with elevated troponin (13.1% in the abciximab group vs. 18.3% in the placebo group, $p = 0.02$), whereas there was no difference in troponin-negative patients at 30 days (4.6% in both groups). The incidence of major bleeding and intracranial bleeding was the same in both the abciximab and placebo groups (14 vs. 14%). The combined primary endpoint at one year showed that abciximab reduced the relative risk by 17% (23.3 vs. 28%, $p = 0.012$) compared to placebo, however subgroup analysis demonstrated that abciximab improved outcomes compared to placebo regardless of troponin status (28.6 vs. 33.3% in troponin-positive patients and 17.8 vs. 22% in troponin-negative patients) [34]. This trial demonstrates that abciximab improves outcomes in patients with non-ST-segment elevation ACS pretreated with heparin and clopidogrel without any increase in the rate of major bleeding.

The REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced clinical Events) trial evaluated the use of bivalirudin with GPI during PCI [35]. Six thousand and ten patients undergoing PCI were randomized to bivalirudin and GPI or heparin and GPI. The primary endpoint was a 30-day composite of death, MI, urgent repeat revascularization or major bleeding. Bivalirudin with GPI was found to be non-inferior compared to heparin with GPI (9.2 vs. 10.0%, OR 0.92; 95% CI 0.77-1.09, $p = 0.32$). Bivalirudin reduced the absolute risk of major

in-hospital bleeding by 1.7% (2.4 vs. 4.1%, $p < 0.001$) compared to heparin.

The ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial randomized 13,819 patients with non-ST-segment elevation ACS to either: unfractionated heparin or enoxaparin plus GPI, bivalirudin plus GPI or bivalirudin alone [36]. One of the primary end points was a net clinical outcome composite of ischemia or major bleeding. Bivalirudin plus GPI was found to be non-inferior to heparin plus GPI (11.8 vs. 11.7%). Bivalirudin alone demonstrated an improved net clinical outcome (10.1 vs. 11.7%, $p = 0.02$) compared to heparin plus a GPI.

The current AHA/ACC guidelines on patients with UA/NSTEMI make a class I recommendation for GPI in troponin-positive and high risk patients who undergo PCI (level of evidence: A) in addition to aspirin and anticoagulation [25]. Class I recommendations for anticoagulation include: enoxaparin and UFH (level of evidence: A) and bivalirudin and fondaparinux (level of evidence: B). Glycoprotein IIb/IIIa inhibitors is a class IIa recommendation in patients who receive aspirin, anticoagulation with heparin or enoxaparin and clopidogrel (level of evidence: B). However, in patients managed with an initial invasive strategy, upstream of treatment with a GPI can be omitted in circumstances where bivalirudin is used and treatment with at least 300 mg of clopidogrel is given at least 6 h prior to angiography.

Use of glycoprotein IIb/IIIa inhibitors in special groups

Glycoprotein IIb/IIIa inhibitors in women

Although GPI have been shown to portend improved outcomes in ACS, subgroup analyses have not shown the same benefit in women. The aggregate data of all women treated with GPI for non-ST-segment elevation ACS in the Boersma *et al.* meta-analysis demonstrated an odds ratio (OR) of death or MI at 30 days of 1.15 for women compared to an OR of 0.81 for men ($p < 0.0001$) [24]. However, women fared as well as, if not better than, men in EARLY ACS [37] with a relative risk reduction of 7% compared with 8% in men for the primary endpoint, and 20% compared with 6% in men for the key secondary endpoint.

Glycoprotein IIb/IIIa inhibitors in diabetic patients

A meta-analysis performed by Roffi *et al.* compiled the diabetic populations from six trials on GPI in the medical management of non-ST-segment ACS [38]. Using the primary endpoint of mortality at 30 days, the authors found a greater than 25% relative risk reduction in patients given GPI compared to placebo (4.6 vs. 6.2%, $p = 0.000$). This

relationship is even more pronounced in diabetic patients who underwent PCI, where GPI reduced the relative risk of death at 30 days by 30% compared to placebo (1.2 vs. 4.0%, $p = 0.002$). This demonstrates that GPI are associated with improved outcomes, particularly in diabetic patients with ACS.

Side effects

Bleeding

Glycoprotein IIb/IIIa inhibitors have been associated with increased bleeding in clinical practice. A meta-analysis by Labinaz *et al.* evaluated the bleeding risk of GPI in PCI, which included 23,941 patients from 21 randomized trials [39]. There was a higher incidence of thrombocytopenia (OR 1.41, 95% CI 1.10 to 1.81) and minor bleeding (OR 1.80, 95% CI 1.47 to 2.21) in patients treated with a GPI, but no statistically significant increase major bleeding (OR 1.29, 95 CI 0.98 to 1.68) compared to the control group. This suggests that GPI do not cause a significant increase in major bleeding. Glycoprotein IIb/IIIa inhibitors is contraindicated in patients with active bleeding. Relative contraindications for GPI include: uncontrolled hypertension with a systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg, severe anemia, severe thrombocytopenia, major surgery in the past 3 months, stroke within the past 6 months and recent trauma [39].

Alexander *et al.* evaluated gender differences in major bleeding with glycoprotein IIb/IIIa inhibitors from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines) initiative [40]. This analysis included 18,436 subjects who were treated with either full or reduced dose eptifibatide or full or reduced dose tirofiban. A creatinine clearance < 30 for tirofiban and a creatinine clearance < 50 for eptifibatide was an indication for reduced dosing. Major bleeding occurred more frequently among women compared to men, regardless of whether they were treated with glycoprotein IIb/IIIa inhibitors (15.7% of women vs. 7.3% of men, $p < 0.0001$) or not (8.5% of women vs. 5.4% of men, $p < 0.0001$). However, women were 3.8 times more likely to receive excess dosing of glycoprotein IIb/IIIa inhibitors based on their creatinine clearance than men (46.4% of women vs. 17.2% of men, $p < 0.0001$). There was a significant association between excess dosing and increased risk of bleeding [OR 1.72 (CI 1.3-2.28) in women and OR 1.27 (CI 0.97-1.66) in men]. This analysis suggests that women are more likely to receive excessive dosing for their given creatinine clearance which is associated with an increased risk of major bleeding.

Thrombocytopenia

Dasgupta *et al.* compiled data from eight placebo-controlled randomized studies evaluating the use of GPI in ACS and PCI to assess the incidence of thrombocytopenia and its relation to significant bleeding [41]. Patients treated with abciximab and heparin had a higher incidence of mild thrombocytopenia ($< 50,000/\mu\text{l}$, 4.2 vs. 2.0%, $p < 0.001$) and severe thrombocytopenia ($< 20,000/\mu\text{l}$, 1.0 vs. 0.4%, $p = 0.01$) compared to placebo and heparin. The aggregate of patients who received small molecule GPI (tirofiban and eptifibatide) and heparin did not have any increased incidence of mild or severe thrombocytopenia. The patients who did have profound or severe thrombocytopenia did not experience any major bleeding sequelae. This suggests that although the combination of abciximab and heparin did increase the mild and severe thrombocytopenia, this did not result in any clinically relevant bleeding.

Dosing in renal failure

Analysis of the PROTECT-TIMI 30 (Randomized trial to evaluate the relative protection against post-PCI microvascular dysfunction and post-PCI ischemia among anti-platelet and anti-thrombotic agents – Thrombosis and Thrombolysis In Myocardial Infarction-30) trial found that among patients with a creatinine clearance (CrCl) ≤ 50 [33], who met the criteria for reduced-dose eptifibatide, 45% [15] were given the full-dose eptifibatide [42].

None of the bleeding events occurred in patients who were received the appropriate reduced dose, however the incidence of bleeding was 20% [15] in patients with a CrCl ≤ 50 who were given full-dose eptifibatide.

In order to minimize bleeding risks and complications, appropriate dosing of glycoprotein inhibitors based on creatinine clearance is important. The recommended dosing for eptifibatide is in ACS is a bolus of 180 $\mu\text{g}/\text{kg}$ (maximum: 22.6 mg) followed by an intravenous infusion of 2 $\mu\text{g}/\text{kg}/\text{min}$ (maximum: 15 mg/h). For patients with a creatinine clearance of < 50 , the infusion dose of eptifibatide should be decreased to 1 $\mu\text{g}/\text{kg}/\text{min}$ infusion. Dose recommendations for tirofiban is an initial rate of 0.4 $\mu\text{g}/\text{kg}/\text{min}$ for 30 min followed by 0.1 $\mu\text{g}/\text{kg}/\text{min}$ with a dose reduction of 50% for a creatinine clearance of < 30 . Abciximab is not renally-cleared so there is no need for adjustment for renal function. It is dosed at 0.25 mg/kg intravenous bolus followed intravenous infusion of 10 $\mu\text{g}/\text{min}$.

Conclusions

Glycoprotein IIb/IIIa inhibitors (GPI) have been demonstrated to reduce mortality and reinfarction

in patients with ACS, particularly in patients undergoing subsequent PCI. Glycoprotein IIb/IIIa inhibitors should be started in troponin-positive and high-risk patients with UA/NSTEMI who receive PCI when a GPI has not been initiated prior to diagnostic angiography. In patients with STEMI, the use of GPI in combination with fibrinolytic therapy, either as part of a facilitated regimen prior to primary PCI, or as a pharmacologic reperfusion regimen without planned PCI, is associated with increased bleeding and no improvement in clinical outcomes.

Eptifibatide and tirofiban are recommended in patients with non-STE ACS undergoing an early invasive approach and in those with high-risk features or continuing ischemia. In patients with UA/NSTEMI where PCI is planned within the next 24 h, abciximab is another reasonable option. Enoxaparin, UFH, bivalirudin or fondaparinux are all appropriate anticoagulants for use in conjunction with GPI, although less data are available with fondaparinux.

Glycoprotein IIb/IIIa inhibitors appear to be most beneficial in patients with elevated troponin, recurrent ischemia and diabetes. The incidence of bleeding while on GPI is higher in women, which may in part be attributed to inadequate dose adjustment for creatinine clearance. Future areas of study in GPI remain with regards to its use in end-stage renal failure, further identification of subgroups who derive greater benefit from GPI and the optimal timing of initiation of GPI in patients with ACS.

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