

ARTICLE

Adjunctive Antiplatelet Treatment in Primary Percutaneous Coronary Intervention

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KEY WORDS: *clopidogrel; prasugrel; ticagrelor; glycoprotein IIb/IIIa inhibitors; abciximab; tirofiban; eptifibatide; antiplatelet treatment; ST elevation myocardial infarction (STEMI); primary percutaneous coronary intervention (PCI)*

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LIST OF ABBREVIATIONS

ACC = American College of Cardiology
ADP P2Y12 = adenosine diphosphate P2Y12 (receptors)
AHA = American Heart Association
CABG = coronary artery bypass grafting
ESC = European Society of Cardiology
FDA = Food and Drug Administration
GPIIb-IIIa = glycoprotein IIb-IIIa (receptors)
LVEF = left ventricular ejection fraction
MACE = major adverse cardiac events
PCI = percutaneous coronary intervention
PPCI = primary percutaneous coronary intervention
SPECT = single-photon emission computed tomography
STEMI = ST segment elevation myocardial infarction
STR = ST segment (elevation) resolution

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ABSTRACT

BACKGROUND: Despite significant advances in the management of coronary heart disease, myocardial infarction is still associated with high mortality. Thienopyridines and glycoprotein IIb/IIIa inhibitors have been used extensively in the management of ST segment elevation myocardial infarction.

OBJECTIVE: This article discusses the evidence from clinical trials and registries concerning the benefits of thienopyridines, reviews the results of published multicenter, randomized controlled trials of the efficacy and safety of platelet GPIIb/IIIa inhibitors in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention (PCI) and presents the recent guidelines.

METHODS: Data for this review were identified by broad searches of MEDLINE, Current Contents and references from relevant articles (1980-2011); numerous articles were identified through searches of the extensive files of the authors and selected based on their importance, opportunity for further reading and up to date information. Search terms included thienopyridines, platelet aggregation inhibitors, percutaneous coronary intervention, antiplatelet therapy, ST elevation myocardial infarction (STEMI), primary percutaneous coronary intervention. Only English language papers were reviewed. No restrictions were set on the type of papers.

RESULTS: Clopidogrel is the most commonly used thienopyridine in patients undergoing primary PCI. Recently new inhibitors of P2Y12 receptors, like prasugrel and ticagrelor, have become available, which have a more potent and rapid onset of action, with similar safety profile, which is specifically targeted to the subgroup of primary PCI. On the other hand, the platelet glycoprotein IIb/IIIa inhibitors have aided and abetted medical management of acute coronary syndromes and proved an important adjunctive therapy in percutaneous coronary interventions. Platelet glycoprotein IIb/IIIa inhibitors, although not recommended for routine therapy, have an important role at the time of primary PCI, particularly in high-risk subgroups, like the diabetics and those with a heavy thrombotic burden.

CONCLUSION: Clopidogrel remains the most used thienopyridine together with aspirin in patients undergoing primary PCI but there are currently available new inhibitors of P2Y12 receptors, like prasugrel and ticagrelor, which have a more potent and rapid onset of action, with similar safety profile. Glycoprotein IIb/IIIa antagonists, although not recommended for routine therapy, can be of use at the time of primary PCI, particularly in high-risk subgroups.

INTRODUCTION

Prompt restoration of blood flow in the infarcted coronary artery and subsequent myocardial tissue reperfusion are fundamental in the treatment of ST-elevation myocardial infarction (STEMI).¹ Irrespectively of how restoration of blood flow is achieved - mechanically or pharmaceutically - addition of dual antiplatelet regimen reduces mortality and the rate of recurrent ischemic events.^{2,3} This is mainly attributed to the primary role of platelets in the activation of hemostasis, when the atherosclerotic plaque ruptures and the vascular endothelium is denuded.⁴ Apart from the well established use of aspirin, other molecular targets of drug therapy on the activated platelet include the adenosine diphosphate (ADP) P2Y12 receptors and the glycoprotein IIb-IIIa (GPIIb-IIIa) receptors, which take part in platelet binding with fibrinogen or von Willebrand's factor.⁵ This review focuses on the use of P2Y12 and GPIIb-IIIa receptor inhibitors in the management of STEMI, treated with primary percutaneous coronary intervention (PPCI).

ADP P2Y12 RECEPTOR INHIBITORS

There are three thienopyridines and a nucleoside analogue that inhibit the ADP P2Y12 receptors in clinical use;

ticlopidine, clopidogrel, prasugrel and ticagrelor. Ticlopidine has been almost abandoned because of side-effects, including hemorrhagic diathesis, leucopenia, thrombocytopenia, aplastic anemia and Moskowitz syndrome.⁶ Hence, clopidogrel and prasugrel that present a safer profile remain of option, while most recently ticagrelor has also become available. The site of action of the P2Y12 inhibitors is shown in Figure 1.

Clopidogrel

Clopidogrel is an oral, irreversible inhibitor of ADP P2Y12 receptors on the platelet surface. Following absorption of a large proportion from the intestine, it follows two pathways of metabolism. The first is related to the conversion of the 85% of the clopidogrel intake to an inactive metabolite by esterases in the intestine, portal circulation and the liver. The remaining 15% is metabolized in a two-step process at the level of hepatic CYP-450.⁷ The final result is the presence of only 2% of the total clopidogrel intake on the specific platelet receptors.

Even though clopidogrel administration is recommended as soon as possible before or during PPCI, exact timing of use has not been yet established by any large randomized trial (class of recommendation, level of evidence IC).^{1,8} In the COMMIT/CCS 2 trial (Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study), Chen et al² observed a reduction of the relative risk of death

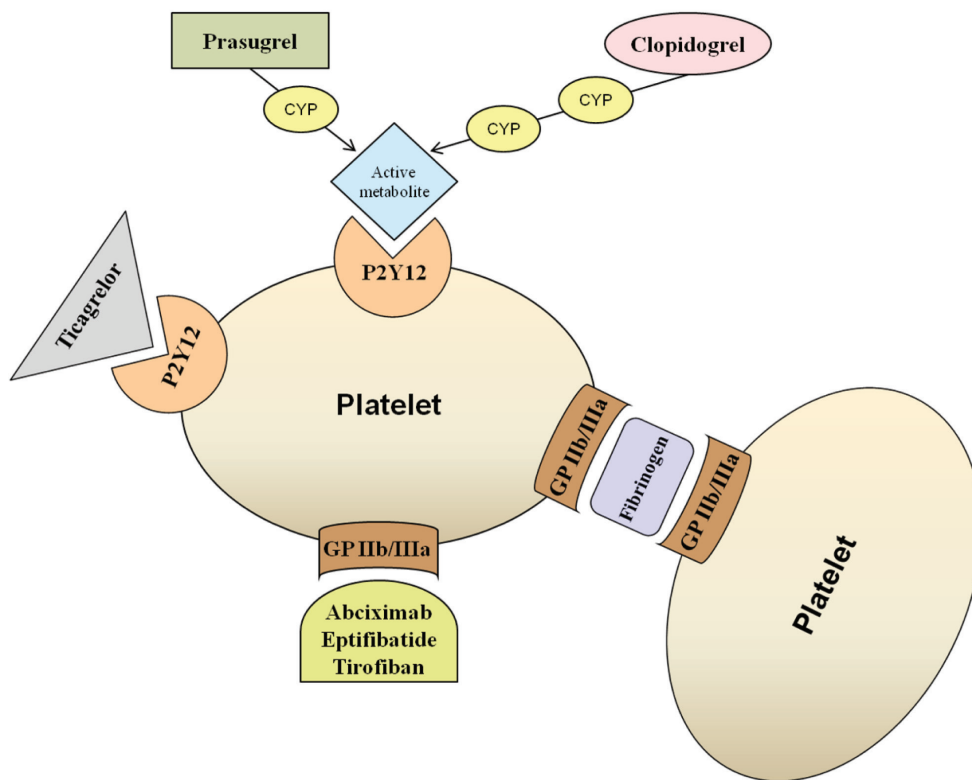


FIGURE 1. Molecular targets of drug therapy on the activated platelet. CYP: Cytochrome P-450; P2Y12: Purinergic receptor P2Y, G-protein coupled, 12; GP IIb/IIIa: glycoprotein IIb/IIIa

by 7% during the scheduled treatment period in hospital (mean 15 days), in patients who had not undergone PPCI, after adding clopidogrel 75 mg per day to the aspirin regimen. Sabatine et al³ also found a 20% reduction of the relative risk of cardiovascular death, recurrent ischemic events or urgent revascularization, in a 30-day follow up, using a 300 mg clopidogrel loading dose followed by 75 mg daily on top of aspirin administration, in STEMI patients who underwent angioplasty in a median of three days after thrombolysis. Additionally, results from registries support the use of clopidogrel, either pre-, or post- revascularization.^{9,10}

Nonetheless, a wide range of patients' response to clopidogrel's action exists. Response to clopidogrel shows a normal distribution following 300 mg loading and 75 mg/day dose, with 31% of patients being resistant to its action, 24 hours and 5 days after its administration.¹¹ Similarly, the rate of clopidogrel resistance approaches 20%, the latter being associated with higher rates of stent thrombosis.¹² In a recent meta-analysis, analyzing both acute and stable patients with coronary artery disease, clopidogrel resistance was followed by a higher risk of death or ischemic events.¹³

Clopidogrel resistance is multifactorial, with genetic and clinical factors being implicated in its pathogenesis. CYP2C19*2 loss-of-function polymorphism seems to be associated with high platelet reactivity despite clopidogrel administration.¹⁴ Age >70 years, obesity and diabetes mellitus have similarly an adverse impact on platelet reactivity.^{14,15} However, all of the above mentioned factors cannot explain more than 11.5% of clopidogrel low responsiveness.¹⁴ Furthermore, clopidogrel resistance could be enhanced due to low dosing or drug-drug interaction, especially when co-administered with proton pump inhibitors.¹⁶ In contrast, the COGENT study (Clopidogrel and the Optimization of Gastrointestinal Events Trial)¹⁷ not only did not support the drug-drug interaction theory between clopidogrel and omeprazole, but found that the omeprazole group had lower rate of gastrointestinal bleeding.

Finally, the drug's absorption from the gut seems to be affected in states of stress, such as STEMI, due to reduced perfusion, activation of the sympathetic nervous system and release of atrial natriuretic peptide that inhibits gut permeability.¹⁸⁻²⁰ In addition to the extremely augmented platelet activation,²¹ patients suffering from STEMI absorbed less clopidogrel and achieved maximum drug concentration in blood later than healthy controls.²² The latter is independent of CYP3A4 and CYP3A5 activity, as the conversion rate of clopidogrel to its active metabolite remained unchanged in both groups. These facts resulted in an inadequate inhibition of platelet reactivity, even 24 hours after drug administration, due to its impaired bioavailability.

A number of pharmacological studies have been conducted in order to investigate clopidogrel resistance and its dose dependence. According to the ISAR-CHOICE study (Intracoronary Stenting and Antithrombotic Regimen: Choose Between

3 High Oral Doses for Immediate Clopidogrel Effect), clopidogrel loading dose of 600 mg achieved significantly greater platelet inhibition 4 hours later, compared to the loading dose of 300 mg, in patients with coronary artery disease.²³ On the contrary, a dose of 900 mg did not show further inhibition, possibly due to limited clopidogrel absorption.^{23,24} Usage of the enhanced loading dose of 600 mg is critical in states with increased thrombotic burden, such as STEMI. Matetzky et al reloaded a low clopidogrel response group of patients, suffering an acute myocardial infarction (15% of total population), who were initially administered 300 mg of clopidogrel, with 600 mg clopidogrel, followed by 150 mg daily dose. Of note, the clopidogrel responders were under the classic regimen of 300 mg/75 mg).²⁵ The study resulted in a great decrease of platelet reactivity in just 4 hours after reloading, remaining low as long as double dose of clopidogrel was administered. An additional interesting observation of this study was that patients presenting with STEMI were more likely to be nonresponders to clopidogrel (90% vs 74%, $p = 0.06$).

The large, multicenter study CURRENT-OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions),²⁶ compared double dose of clopidogrel (600 mg loading/150 mg daily for the next 6 days /75 mg daily thereafter) with standard dose (300 mg loading/75 mg daily), in patients with acute coronary syndromes, and the clinical outcome at 30 days was evaluated. The results referring to the overall population not only did not show any clinical value of the double dose, but an increase of major bleeding rate was observed.²⁷ Interestingly, in the subgroup undergoing PPCI because of STEMI (7327 patients), higher clopidogrel dose significantly reduced stent thrombosis and myocardial infarction rates, without any increase of bleeding events. In the HORIZONS-AMI trial (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction), the impact of clopidogrel loading 600 mg versus 300 mg on the 30- day clinical outcomes was evaluated in patients suffering a STEMI, undergoing PPCI and assigned either in unfractionated heparine plus glycoprotein IIb-IIIa inhibitors or bivalirudin monotherapy. A 600-mg compared with a 300-mg loading dose of clopidogrel was associated with lower 30-day rates of mortality, reinfarction, and stent thrombosis, without any association with increased rates of bleeding.²⁸

Regarding the timing of loading dose administration, Vlaar et al²⁹ studied the effects of clopidogrel when given pre- or post- initial angiography. This meta-analysis included patients who underwent PPCI following STEMI. The group of early, pre-PCI clopidogrel administration showed better patency angiographically (TIMI flow 2-3), and significantly lower rate of clinical outcome of death or death and recurrent infarction compared to those in whom clopidogrel was administered after PCI.

Following the above data, the 2011 American College of

Cardiology (ACC) and American Heart Association (AHA), as well as European Society of Cardiology (ESC) guidelines on myocardial revascularization recommend administration of 600 mg of clopidogrel in every STEMI patient scheduled for PCI, as soon as possible, followed by 75 mg daily (recommendation IC and IB in ESC and ACC/AHA guidelines respectively).^{8,30}

Prasugrel

Prasugrel is a novel, 10 times more potent than clopidogrel, thienopyridine anti-platelet agent. Similar to clopidogrel, prasugrel is extensively hydrolyzed by intestinal plasma esterases to an inactive terminal metabolite, with the residual unhydrolyzed drug metabolized in a single step (instead of two in the case of clopidogrel) to the active sulfhydryl compound, mainly by cytochrome P450 3A4 (CYP3A4) and 2B6 (CYP2B6) enzymes. As a result, about 80% of an orally absorbed dose of prasugrel is converted to active drug, compared with only 10% to 20% of absorbed clopidogrel. Finally, the active metabolite irreversibly connects and inhibits the platelet receptors ADP P2Y12.^{31,32}

Brandt's pharmacodynamic study,³³ in healthy volunteers, showed that 60 mg of prasugrel, compared to 300 mg of clopidogrel, achieved greater and faster platelet inhibition, in just 15 minutes from its administration, maintaining its action during the whole 24 hours of study time. Jernberg et al reached the same results for prasugrel loading dose either 60 mg or 40 mg and this enhanced action was retained with daily dose of 10 or 15 mg of prasugrel when compared with 75 mg of clopidogrel.³⁴ In another pharmacodynamic study, conducted by Varenhorst,³⁵ 60 mg of prasugrel had a more potent action even than 600 mg of clopidogrel, which actually remained even with the daily dose (10 mg prasugrel versus 75 mg clopidogrel). Finally, switching from maintenance clopidogrel to prasugrel offers further platelet inhibition in just 2 hours from a loading dose of 60 mg or in 7 days if the loading dose is omitted and 10 mg/day are used.³⁶

Contrary to clopidogrel, neither specific genetic traits nor pharmacokinetic drug interactions seem to interfere with prasugrel antiplatelet activity. As opposed to clopidogrel, administered prasugrel is practically completely activated. Even though, at first sight with a similar two-step process, this activation shows distinct differences. The first metabolic step is mediated by carboxylesterases and the second reaction is catalyzed by five different CYP isoenzymes, with no pivotal role for CYP 2C19 or any other CYP isoform. Unfolding evidence, including a lack of interference by genotype and CYP 2C19 or CYP 3A4 inhibitors, has confirmed this expectation.³⁷

The greater and faster platelet inhibition has been translated into clinical benefit.^{38,39} Administration of prasugrel in STEMI patients (3534 patients, 69% PPCI) in the TRITON-TIMI 38 trial (Trials to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction) reduced the primary

endpoint (death, myocardial infarction, stroke) after 30 days and kept it low until the 15th month, compared to that of clopidogrel group.³⁹ The stent thrombosis rate was also lowered ($p=0.0084$), whilst it was observed that the anterior myocardial infarction subgroup was particularly favoured by the use of prasugrel. Bleeding event rate has not shown any increase, apart from the patients who underwent coronary artery bypass grafting (CABG). The prasugrel group exhibited increased risk of TIMI major bleeding after CABG. Overall, major, minor, intracranial and life-threatening bleeding event rates were similar in both groups. Thus, with regards to net clinical outcome, prasugrel administration is beneficial in STEMI patients, while in the overall population of the trial, mortality did not differ significantly between treatment groups. Of note, until now there exists no direct comparison assessing clinical endpoints between 600 mg/150 mg of clopidogrel and 60 mg/10 mg of prasugrel.

Prompt administration of 60 mg of prasugrel following STEMI, and its continuation with 10 mg daily, has recently received a IB recommendation when STEMI is managed with PPCI by both the European Society of Cardiology (ESC) and the American Heart Association (AHA).^{8,30} The STEMI subgroup, in the TRITON-TIMI 38 study,³⁹ did not appear to be at higher risk of major bleeding, irrespectively of the patients' demographics. The contraindications of prasugrel usage, i.e. history of stroke / transient ischemic attack and special precautions for its use (age ≥ 75 or weight < 60 kg) remain valid, as arose from the overall trial population.³⁸

Ticagrelor

Ticagrelor is a new oral inhibitor of P2Y12 platelet receptor. This new agent competes with ADP, reversibly binding to target receptor. Contrary to regimens described above, ticagrelor does not require metabolic activation and directly acts on its receptor.⁴⁰

The recent ONSET-OFFSET study has revealed that ticagrelor (180 mg loading dose/90 mg bid maintenance dose) inhibits platelet aggregation much stronger and faster than clopidogrel (600 mg/75 mg). Interestingly, following discontinuation of treatment, platelet reactivity was restored faster in the ticagrelor group.⁴¹

Ticagrelor's properties make it ideal in situations of great thrombogenicity, like STEMI, irrespectively of whether angioplasty is performed or CABG is recommended. In the PLATO (Platelet Inhibition and Patient Outcomes) trial (18624 patients with acute coronary syndrome), ticagrelor reduced the primary endpoint (death from vascular causes, myocardial infarction or stroke) by 16% compared to clopidogrel.⁴² These results were achieved without any compromise in drug's safety profile, if minor bleeding events are excluded. In the STEMI subgroup (7544 patients, 1.3 hours delay from admission to PCI), being managed with PPCI, the results remained the same with those of the main study.⁴³ Ticagrelor's impressive

outcomes are attributed, apart from the strong, reversible platelet inhibition, to the inhibition of adenosine reuptake from red cells, that improves myocardial microcirculation⁴⁴ and, possibly, suggestive of a pleiotropic action.⁴⁵

In 2010, ticagrelor (180 mg loading dose/90 mg bid maintenance dose) received a recommendation of IB for STEMI management, when combined with PPCI, according to the ESC guidelines on myocardial revascularization.³⁰ Recently, USA Food and Drug Administration (FDA) approved its use that was pending due to its non-efficacy in the North America subgroup (hazard ratio-HR 1.25; confidence intervals- CI (0.93, 1.67), $p=0.05$).⁴² Following the latter development, late in 2011, AHA also recommended (Class IB) the use of ticagrelor in STEMI patients.⁸

Conclusion

To sum up, it appears that clopidogrel may not be the only antiplatelet agent of choice in the management of STEMI. In a recent meta-analysis, Bellemain et al compared newer inhibitors of P2Y12 receptors with clopidogrel in patients that had undergone PCI.⁴⁶ In the STEMI subgroup, newer agents exhibit reduced mortality, without any significant change in major bleeding incidents. The increased thrombotic state encountered in STEMI makes these new, more potent agents, even more effective than clopidogrel. In parallel, this thrombogenicity contributes to the safety of the increased

platelet inhibition that newer agents achieve.⁴⁶ It seems that new established agents like prasugrel and ticagrelor, as well as, other under trial inhibitors of P2Y12 receptors,^{47,48} have much to contribute in the antiplatelet management of the STEMI patient in the near future. A synopsis of the use of P2Y12 inhibitors in PPCI is shown in Table 1.

GLYCOPROTEIN IIB/IIIA RECEPTORS INHIBITORS

The intravenously administrated glycoprotein IIB/IIIA inhibitors (GPIIb/IIIA), abciximab, tirofiban, and eptifibatide, have a principal role in the adjunctive pharmacotherapy of STEMI because they seem to improve tissue-level reperfusion, restoration of blood flow in the infarct-related artery and improve the impaired left ventricular function.⁴⁹ The site of action of IIB/IIIA inhibitors is shown in Figure 1.

A key issue with the use of GPIIb/IIIA inhibitors is whether they can improve the prognosis of patients with STEMI who are managed with PPCI.^{50,51} A meta-analysis of 11 randomized trials, involving 27115 patients, showed a significant reduction in short-term (30 days) mortality (2.4% vs. 3.4%, $p=0.047$) and long-term (6-12 months) mortality (4.4% vs. 6.2%, $p=0.01$) in patients treated with abciximab when compared with a control group. Abciximab resulted in a significant reduction in 30-day reinfarction rate (1.0% vs. 1.9%, $p=0.03$) but also in an increased risk of major bleeding complications (4.7%

TABLE 1. P2Y12 Receptor Inhibitors in Primary Percutaneous Coronary Intervention (PCI)

Study	Population	Study Design	Primary End-Points
CURRENT OASIS 7 2010 ²⁶	Patients with STEMI mostly treated with primary PCI N= 6346	2x2 factorial design, double dose clopidogrel vs standard dose and either higher or lower dose aspirin	Cardiovascular death, MI, stroke at 30 days
HORIZONS AMI 2009 ²⁸	Patients with STEMI undergoing PCI N= 3602	Randomization to bivalirudin or unfractionated heparin plus glycoprotein IIB-IIa inhibitors, stratified by clopidogrel loading dose (600 mg vs 300 mg)	Major bleeding and combined adverse clinical events, defined as the combination of major bleeding or major adverse cardiovascular events including death, reinfarction, target-vessel revascularization for ischemia, and stroke within 30 days.
TRITON-TIMI 38 2009 ³⁹	Patients with STEMI N= 3534	Assigned either prasugrel (60 mg LD/ 10 mg MD) or clopidogrel (300 mg LD/75 mg MD)	Cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke in the following 15 months
PLATO STEMI subgroup analysis 2010 ⁴³	Acute coronary syndrome patients with STEMI or left bundle branch block N= 7544	Randomized, double blind trial, comparing ticagrelor (180 mg LD/90 mg bid MD) with clopidogrel (300 mg LD/75mg MD)	Composite of death from vascular causes, myocardial infarction, or stroke at 12 months

LD = loading dose; MD = maintenance dose; MI = myocardial infarction; STEMI = ST elevation myocardial infarction

vs. 4.1%, $p=0.36$).^{50,52} In another meta-analysis including 3266 patients with acute myocardial infarction, the early reduction in ischemic events was partly balanced by an increased likelihood of major bleeding with abciximab therapy (odds ratio-OR, 0.73; 95% confidence intervals-CI, 1.11-2.72). In that sense, benefits of abciximab must be balanced against the bleeding risk in individual patients, and attention must be paid to appropriate dosing of antithrombin therapies.⁵³⁻⁵⁷ It is important to mention that in the above meta-analysis, patients did not receive clopidogrel loading before PCI. Therefore, a logical question arises whether abciximab has a benefit for PPCI patients who received loading with clopidogrel. This was tested in the 800 patients of the Bavarian Reperfusion Alternatives Evaluation (BRAVE)-3 trial, pre-treated with 600 mg of clopidogrel, whereby abciximab was not associated with a reduction in infarct size and no clinical benefit at 30 days and at 1 year was observed. There was a trend towards a benefit with abciximab in patients who were enrolled <180 min from the onset of symptoms.⁵⁸

The Ongoing Tirofiban in Myocardial Evaluation (ON-TIME) 2 trial⁵⁹ assessed whether pre-hospital initiation of tirofiban in patients with STEMI undergoing PPCI has beneficial results in addition to dual antiplatelet therapy.^{60,61} Results of the double-blind phase noted that at 1 hour post-PCI, the rate of residual ST-segment deviation (>3 mm) was significantly reduced (43.3% vs. 36.0%, $p=0.02$) and lower rate TIMI flow 0/1 or distal embolisation after PCI (6.2% vs. 10.3%, $p=0.029$) was observed with tirofiban. At 30 days, the combined rate of death, recurrent myocardial infarction, or major adverse cardiac events (MACE) was significantly lower in the tirofiban arm (5.8% vs. 8.6%, $p=0.043$). There was a strong trend towards a significant decrease in mortality with tirofiban with respect to all-cause mortality (2.2% vs. 4.1%, $p=0.051$). Patients who presented early after symptom onset (≤ 75 min) demonstrated a significant reduction in MACE with tirofiban therapy (4.3% vs. 8.1%). The clinical benefit was sustained at 1 year since a post hoc analysis indicated a significantly lower mortality with tirofiban therapy (2.4% vs. 5.5%, $p=0.007$) and a significantly lower occurrence of stroke (0.3% vs. 1.4, $p=0.031$).⁶¹ In the ON-TIME 2 study the median time from the onset of symptoms until the initiation of tirofiban was only 90 min, while in the BRAVE-3 study the abciximab was started rather late (>200 min) after the onset of symptoms. Early administration of GPIIb/IIIa inhibitors seems to have clear advantage, compared with delayed administration, as it improves the clinical outcome of patients who have been preloaded with high-dose clopidogrel (600 mg) in addition to aspirin and unfractionated heparin after PPCI with no increased risk of major bleeding. In contrast, in the Safety and Efficacy Study of Integriilin-Facilitated PCI Versus PPCI in STEMI (ASSIST), there was no difference between heparin plus eptifibatide vs heparin alone in patients referred for PPCI. At 30 days, the primary end point - the composite of death from

any cause, recurrent myocardial infarction, or recurrent severe ischemia - was 6.47% in the heparin plus eptifibatide group, and 5.53% in the heparin-alone group ($p=0.69$). Similarly, at 6 months, there was no difference in the incidence of the primary end point between the two groups (7.96% vs. 7.11%, $p=0.75$). However, the rates of bleeding (major or minor) were significantly higher in patients assigned to heparin plus eptifibatide (22.4% vs. 14.6%, $p=0.04$).⁶²

An important factor that determines the benefit from administration of GPIIb/IIIa inhibitors seems to be the basic risk of each patient. There is a linear relationship between the baseline risk of the patient cohort and the effects of GPIIb/IIIa on mortality. Particularly, the higher patients' mortality who received placebo or bivalirudin, the higher the reduction in mortality achieved from the GPIIb/IIIa inhibitors administration.⁶³

Another important question concerns the timing that is better to administer the GPIIb/IIIa inhibitor in the ambulance or in the catheterization laboratory. In the Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) study neither facilitation of PCI with reteplase plus abciximab nor facilitation with abciximab alone significantly improved the clinical outcomes, as compared with abciximab given at the time of PCI.⁶⁴ In a post hoc analysis of the FINESSE study, patients with TIMI risk score ≥ 3 and presentation to a spoke site with a symptom-to-randomization time ≤ 4 hours had a significantly better 1-year survival if treated with combination-facilitated PCI (hazard ratio [HR]: 0.0351, $p=0.01$) as well as 90-day composite outcome (HR:0.45, $p=0.009$).⁶⁵

In the EUROTRANSFER Registry, 1650 patients were randomized to receive abciximab, either before admission to the catheterization laboratory, immediately before or during PCI in the catheterization laboratory. Analysis according to the risk profile showed significant difference only in high-risk patients. Particularly 1-year mortality was significantly lower with early abciximab administration compared to late administration (8.7% vs. 15.8%, $p=0.01$) at 1-year follow-up. Early abciximab administration strategy did not result in a significant increase in bleeding rate and provided a better benefit to harm profile than standard therapy in high-risk patients.⁶⁶

In the MISSION study, patients who received abciximab in the ambulance, within a median time of 63 min (golden period) from the onset of symptoms, presented higher infarct-related artery patency at the onset of the PCI compared to the in-hospital group (odds ratio=4.9; 95% CI 2.4-10.1), smaller infarct size, higher left ventricular function at 90 days post-PPCI (59% vs. 54%, $p=0.01$), and lower incidence of heart failure through a median of 210 days of clinical follow-up (3% vs.11%, $p=0.04$).⁶⁷

Another important question is whether all GPIIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) offer the same benefit to the patient for whom PPCI is planned. In the Ep-

tifibatide Versus Abciximab in PPCI for Acute Myocardial Infarction (EVA-AMI) trial, the incidence of complete ST segment resolution (STR) at 60 min after PCI was 62.6% after eptifibatide and 56.3% after abciximab. All-cause mortality was 6.2% vs 4.5% (p=0.50), reinfarction 0.4% vs.3.5% (p=0.03), target vessel revascularization 4.4% vs. 6.5% (p=0.40) and the combined end-point of death, nonfatal reinfarction, and target vessel revascularization 10.6% vs. 10.9% (p=0.90).⁶⁸ The Swedish Coronary Angiography and Angioplasty Registry (SCAAR) suggested that eptifibatide is non-inferior to abciximab in 11479 patients with STEMI undergoing PPCI

with an odds ratio 0.94 (95% CI: 0.82 to 1.09) and this non-inferiority was also shown at the secondary end points of death and myocardial infarction separately with odds ratio 0.99 (95% CI: 0.82 to 1.19) and 0.88 (95% CI: 0.73 to 1.05), respectively.⁶⁹ The MULTISTRATEGY trial compared the effect of high-dose bolus tirofiban (25 µg/Kg) with abciximab infusion in 745 patients with STEMI undergoing PCI. At 30 days, the incidence of the primary clinical end point- a composite of death, reinfarction, or revascularization of the target vessel- was 4.3% vs. 4.0% (p=0.85) in the abciximab and tirofiban groups respectively, while the incidence of major and minor

TABLE 2. GPIIb/IIIa Receptor Inhibitors in Primary Percutaneous Coronary Intervention

Study	Population	Study Design	Primary End-Points
MULTISTRATEGY 2008 ⁶⁶	Patients with STEMI or new LBBB undergoing PCI N= 745	Open –label, 2x2 factorial trial, high dose bolus tirofiban vs abciximab infusion	8-month combined death from any cause, reinfarction, and clinically driven target-vessel revascularization
ON-TIME 2 2008 ⁵⁵	Patients with STEMI scheduled for PCI N= 984	Randomized double blind high bolus tirofiban vs placebo	The extent of residual ST-segment deviation 1hour after PCI
BRAVE-3 2009 ⁵⁴	Patients with acute MI presenting <24 h after the onset of symptoms N= 1285	Randomized double-blind trial, abciximab vs placebo group	Infarct size in the single –photon emission computed tomography
ASSIST 2009 ⁵⁸	Patients with STEMI referred for primary PCI N=414	Randomized trial, heparin+eptifibatide vs heparin alone	Composite death from any cause, recurrent myocardial infarction, or recurrent severe ischemia during the first 30 days after randomization
FINESSE 2009 ⁶¹	Patients who presented within 6h of the onset of STEMI stratified by TIMI risk score N=2452	Randomized double blind trial, half dose reteplase+abciximab vs abciximab alone vs placebo	Composite of all-cause mortality, ventricular fibrillation occurring >48 h after randomization, cardiogenic shock, and congestive heart failure requiring hospital stay or emergency department visit within 90 days
EUROTRANSFER 2009 ⁶²	Patients with STEMI who were scheduled for primary PCI N =1650	Not randomized registry, abciximab early vs abciximab late	Composite of all cause death, reinfarction and bleeding complications at 30 days after PCI
EVA-AMI 2010 ⁶⁴	Patients with STEMI and planned primary PCI N=427	Randomized open parallel group study, double-bolus eptifibatide vs single-bolus abciximab	Incidence of complete ST-segment resolution 60 min after PCI
SCAAR 2010 ⁶⁵	Patients with STEMI who underwent primary PCI N=11479	Not randomized registry, eptifibatide vs abciximab	Death or myocardial infarction during 1-year follow-up

LBBB = left bundle branch block; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST elevation myocardial infarction

bleedings did not differ (7.8% in the abciximab vs 7.2 in the tirofiban group, $p=0.89$).⁷⁰

The more recent guidelines for STEMI patients of the American College of the Cardiology Foundation/American Heart Association (2011) suggest that it is reasonable to start treatment with a GPIIb/IIIa receptor antagonist at the time of PPCI (with or without stenting) in selected patients with STEMI (class IIa), while the usefulness of these agents before the arrival of patients in the cardiac catheterization laboratory is uncertain (class IIb).⁸ The ESC/European Association of Cardiothoracic Surgery (EACTS) guidelines (2010) suggest that an indication for GPIIb/IIIa administration have all the patients with STEMI undergoing PPCI and present high intracoronary thrombus burden. Particularly, abciximab and eptifibatid are class IIa, while tirofiban is class IIb. Finally, the administration of these agents before patients' arrival in the catheterization laboratory is not considered beneficial (class III).⁷¹ A synopsis of the use of IIb/IIIa inhibitors in PPCI is presented in Table 2.

CONCLUSION

The ADP P2Y₁₂ receptor inhibitors have been proven to be beneficial in reducing mortality in patients suffering from STEMI. Newer antiplatelet agents, such as prasugrel and ticagrelor, seem to offer greater efficacy than clopidogrel, with comparable safety, especially when combined with PPCI. In addition, GPIIb/IIIa antagonists can be of use at the time of PPCI but are not recommended as routine therapy. Many times the benefit of these agents depends on the timing of administration and patients' risk profile. Patients with the highest ischemic risk seem to have the highest benefit from these agents, while they offer comparable benefit in PPCI patients.

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