

REVIEW

The Current Role of Glycoprotein IIb/IIIa Inhibitors in Percutaneous Coronary Intervention

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Abstract

The central role of platelets in acute coronary syndromes (ACS) and percutaneous coronary interventions (PCI) is well appreciated. The various platelet activation mechanisms finally lead to expression and activation of surface glycoprotein IIb/IIIa receptors that mediate platelet aggregation and thrombus formation. Glycoprotein IIb/IIIa inhibitors (GPIs) are the most potent antiplatelet agents and their role in ACS treatment and PCI has been dominant in the recent past. The advent of stents and thienopyridines minimized ischemic complications and in parallel the role of GPIs in low risk PCI. Despite being effective in decreasing PCI-related ischemic complications, the major drawback of GPI use is a relative increase of bleeding that can adversely affect prognosis. The availability of bivalirudin, which is regarded as an equally effective but safer antithrombotic agent when compared to the combination of heparin and GPIs, despite an ongoing controversy, has also led to a decrease of GPI use in PCI for ACS. Finally the advent of novel potent antiplatelet agents (prasugrel, ticagrelor and soon cangrelor) further contained GPI use in patients with ischemic – thrombotic risk that clearly exceeds bleeding risk and mainly for bail-out in case of a thrombotic event during PCI. A concise overview of accumulated data regarding optimal use of GPIs as determined by large clinical trials and recent guidelines is herein attempted. (*Rhythm* 2016;11(2):39-48).

**Key words:** glycoprotein IIb/IIIa inhibitors; percutaneous coronary intervention; acute coronary syndrome; myocardial infarction; coronary stents; abciximab; eptifibatide; tirofiban

**Abbreviations:** ACS = acute coronary syndromes, CAD = coronary artery disease, GPI = glycoprotein IIb/IIIa inhibitor, MI = myocardial infarction, NSTEMI = non ST-segment elevation, PCI = percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction

Introduction

The glycoprotein IIb/IIIa receptor is an integrin, a heterodimer consisting of  $\alpha$ IIb and  $\beta_3$  subunits, which mediates the final common pathway of platelet aggregation. Glycoprotein IIb/IIIa inhibitors (GPIs) compete with fibrinogen and von Willebrand factor for glycoprotein IIb/IIIa binding and thus interfere with platelet cross-linking and platelet-derived thrombus formation (Fig. 1). Due to this mechanism of action, GPIs are very effective in inhibiting platelets and 3 parenteral GPIs with different pharmacologic features have been approved for clinical use: abciximab, eptifibatide, and tirofiban (Table 1).

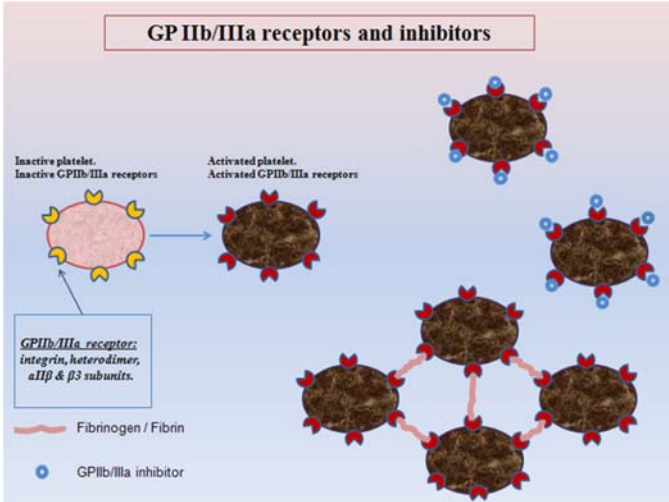


Figure 1. Schematic representation of glycoprotein IIb/IIIa receptors and inhibitors.

Table 1. Pharmacologic properties of Glycoprotein IIb/IIIa inhibitors (GPIs)

	Abciximab	Eptifibatide	Tirofiban
Molecule	Fab 7E3	Synthetic peptide	Non-peptide mimetic
Binding	Non competitive	Competitive	Competitive
Half-life	Plasma: 10-15 h Biologic: 12 - 24 h	Plasma: 2-2.5 h Biologic = plasma	Plasma: 2-2.5 h Biologic = plasma
PCI dosing	<b>Bolus:</b> 0.25 mg/kg <b>Infusion:</b> 0.125 µg/kg/min (12h) Max: 10 µg/min	<b>Bolus:</b> 180 µg/kg (10 min) + 180 µg/kg <b>Infusion:</b> 2 µg/kg/min (24-48 h)	<b>Bolus:</b> 25 µg/kg <b>Infusion:</b> 0.15 µg/kg/min (18h)
Renal adjustment	No	<b>Bolus:</b> 180 µg/kg <b>Infusion:</b> 1 µg/kg/min (24 to 48 h)	<b>Bolus:</b> 12.5 µg/kg <b>Infusion:</b> 0.075 µg/kg/min (18h)

GPIs became widely accepted into the standard of care for PCI during the 90's, especially in the setting of acute coronary syndromes (ACS), as a strategy to reduce ischemic complications with a notable clinical benefit.<sup>1-4</sup> Although rates of short-term ischemic complications were as high as 10-13% in patients receiving only aspirin and intra-procedural heparin during PCI, the addition of GPIs reduced that risk by as much as 50% and long-term mortality by nearly 20%.<sup>3, 5</sup> However, since platelet inhibition is particularly intense with GPIs, their use is linked to increased rates of bleeding.<sup>6, 7</sup> Such events are associated with prolonged hospital stay, increased costs, can unfavorably impact mortality and should be prevented, that is why the use of GPIs has not always been broad but cautious and somehow limited.<sup>8, 9</sup>

Improvements in interventional tools (such as minimally thrombogenic thinner-strut stent designs) and pharmacotherapy (such as early administration of P<sub>2</sub>Y<sub>12</sub> receptor antagonists to patients with ACS and/or those undergoing PCI and introduction of the more potent P<sub>2</sub>Y<sub>12</sub> inhibitors, prasugrel and ticagrelor) have remarkably enhanced the safety and efficacy of PCI.<sup>10-13</sup> Thus, progressively the balance of benefit versus risk with GPIs changed and their diminished role is reflected in current PCI guidelines.<sup>14</sup> An overview of the gradual changes in GPI use over time, as affected by advances of interventional pharmacotherapy and until reaching their current role is attempted in this paper.

### **The era before clopidogrel**

Before the era of pretreatment with clopidogrel loading doses, the safety and efficacy of GPIs was tested in several clinical studies that included patients with both ACS and stable coronary artery disease (CAD). EPIC was the landmark trial that demonstrated the efficacy of GPIs in the PCI setting.<sup>1</sup> In this study, high-risk patients undergoing balloon angioplasty were randomized to abciximab bolus and infusion, abciximab bolus alone or placebo. No significant benefit with abciximab bolus alone was observed while the group treated with abciximab bolus and infusion had a 35% lower rate of death, myocardial infarction (MI), or unplanned urgent revascularization at 30 days compared with the placebo group. Major bleeding complications occurred in a very high proportion of patients treated with abciximab.<sup>1</sup> EPILOG was another landmark trial that was conducted in patients undergoing balloon angioplasty who were at a lower risk than the patients in EPIC.<sup>2</sup> In EPILOG, abciximab was given with weight-adjusted infusions and was combined with lower doses of weight-adjusted heparin. This study showed a significant reduction in the incidence of death or MI in patients treated with abciximab with acceptable bleeding rates.<sup>2</sup> Similar results were reported in the EPISTENT trial, which was the first randomized trial to examine the use of a GPI (abciximab) among patients undergoing stent implantation.<sup>3</sup> The ESPRIT trial conducted in patients undergoing coronary stenting using eptifibatide was terminated early because of the superior efficacy of eptifibatide. Major bleeding was rare but occurred more frequently in eptifibatide-treated patients compared with placebo-treated patients.<sup>4, 15</sup> Having the support of these trials, GPIs became a cornerstone in the treatment of patients undergoing PCI because of their ability to improve short- and long-term outcomes, mostly by reducing the occurrence of peri-procedural MI.

### **The clopidogrel era**

With the advent of P<sub>2</sub>Y<sub>12</sub> inhibitors it was suggested that GPIs may no longer benefit patients if they had been

pretreated with high-dose clopidogrel, particularly those with stable CAD or in the absence of elevated cardiac enzymes. The ISAR-REACT trial showed that among low- to intermediate-risk patients undergoing elective PCI and pretreated for at least 2 hours with a 600-mg loading dose of clopidogrel, no benefit of abciximab therapy was found, compared with placebo, regarding the incidence of death, MI, and urgent target-vessel revascularization at 30 days.<sup>16</sup> The findings were similar in the ISAR-SWEET trial, a dedicated randomized trial to evaluate glycoprotein IIb/IIIa blockade in patients with diabetes scheduled for elective PCI.<sup>17</sup> Overall, these two studies suggest that GPIs offer no clinical benefit in low- to intermediate-risk patients scheduled for PCI, including diabetics, in case of sufficient pretreatment with clopidogrel.<sup>16, 17</sup> The ISAR-REACT 2 trial assessed the incremental benefit of GPIs for patients with ACS pretreated with a high loading dose of 600mg clopidogrel at least 2 hours before PCI. Included patients were randomized to either abciximab or placebo in the catheterization laboratory at the time of PCI. Abciximab reduced the incidence of the primary end point of death, MI, or target-vessel revascularization at 30 days, but the benefit of abciximab treatment was limited only to those patients who presented with elevated troponin.<sup>18</sup> Overall, these findings suggest that with high clopidogrel dosing regimens, GPIs should be reserved only for high-risk patients with ACS and elevated cardiac biomarkers and also that these agents could be particularly useful in patients with substantial thrombus burden, high-risk anatomy, or intra-procedural complications in order to reduce ischemic complications of PCI.<sup>7, 18</sup>

### **Timing of GPIs administration in ACS**

Two different timing strategies for the administration of GPIs have been used in relevant randomized trials: before angiography (upstream treatment) or in the cardiac catheterization laboratory in patients about to undergo PCI (provisional or downstream treatment). These two strategies were compared in the EARLY-ACS trial, which randomized 9492 invasively managed patients with non ST-segment elevation ACS (NSTEMI-ACS) to either routine upstream eptifibatide or placebo infusion and provisional eptifibatide after coronary angiography. No differences were found between the groups in the primary ischemic composite end point, while patients in the early eptifibatide group had significantly higher rates of bleeding and transfusion.<sup>7</sup> These findings do not support the routine use of upstream GPIs compared with ad hoc GPIs in patients with NSTEMI-ACS undergoing PCI.

The use of GPIs, in particular abciximab, in STEMI patients undergoing primary PCI is supported by a meta-analysis of 11 randomized trials that involved a total of 27115 patients. In this meta-analysis, the administration of

abciximab was associated with a significant reduction in the rate of re-infarction, as well as mortality rates, at 30 days.<sup>19</sup> However, most of the studies included in this meta-analysis were conducted in patients who had not been pretreated with clopidogrel. In the BRAVE 3 study, 800 patients with acute STEMI, all of whom were treated with clopidogrel 600 mg, were randomly assigned to receive either upstream abciximab or placebo. Abciximab was not associated with a reduction in the primary end point, infarct size, or ischemic end points at 30 days, which argued against the routine use of upstream abciximab in clopidogrel-pretreated patients undergoing primary PCI.<sup>20</sup> Apart from abciximab, small-molecule GPIs are also commonly used in clinical practice for STEMI, without evidence so far that would support their upstream use.<sup>21</sup>

Strategies of facilitated PCI for STEMI have been developed based on the principle that time to reperfusion is a critical determinant of outcome. In the FINESSE trial, 2452 patients with STEMI who presented within 6 hours after symptom onset were randomized to receive PCI facilitated with early abciximab and half-dose reteplase (combination facilitated), PCI with early abciximab alone (abciximab facilitated) or primary PCI with abciximab at the time of the procedure. The primary end point (composite of death from all causes, ventricular fibrillation occurring more than 48 hours after randomization, cardiogenic shock, and congestive heart failure during the first 90 days after randomization) occurred in 9.8%, 10.5%, and 10.7% of the patients in the combination-facilitated, abciximab-facilitated and primary PCI groups, respectively ( $p = 0.55$ ) without significant differences in mortality. These results did not support the use of a facilitated pharmacologic strategy for reperfusion, with either abciximab alone or abciximab plus reduced-dose reteplase, in anticipation of urgent PCI for patients who present early with STEMI.<sup>22</sup>

### **The advent of bivalirudin and how it interferes with GPI use**

Bivalirudin has been studied as an alternative to heparin for patients undergoing PCI with stable CAD,<sup>23, 24</sup> NSTEMI-ACS,<sup>25, 26</sup> and STEMI.<sup>27-29</sup> These studies found that bivalirudin reduced bleeding complications when compared with regimens of heparin plus a GPI by as much as 40%. However, many of these trials also found small numerical increases in ischemic events with bivalirudin and increases in acute stent thrombosis, particularly in patients with STEMI.<sup>27, 29</sup>

Data from the ACUITY trial that included 13819 patients with NSTEMI-ACS randomized to heparin plus a GPI, bivalirudin monotherapy or bivalirudin plus a GPI, revealed that ischemic outcomes were similar across all three regimens, but bivalirudin monotherapy was

associated with less major bleeding.<sup>25</sup> In the HORIZONS-AMI trial, bivalirudin monotherapy was compared with heparin plus GPI in 3602 patients with STEMI undergoing primary PCI. The composite end point of major adverse cardiovascular events (death, re-infarction, target vessel revascularization and stroke) occurred at nearly identical rates by 30 days in the 2 treatment arms: 5.4% with bivalirudin versus 5.5% with heparin plus a GPI, while bivalirudin was associated with a 40% reduction in major bleeding and a 34% reduction in 30-day mortality. These reductions in bleeding and mortality were found despite a significant increase in the risk of acute stent thrombosis with bivalirudin, however overall stent thrombosis rates did not differ in the two study groups at 30 days.<sup>27</sup> Due to these two landmark trials, bivalirudin has been regarded in recent years as a mainstay of anticoagulation in ACS patients undergoing PCI, offering significant benefits in terms of reduced bleeding events and thus supplanted heparin plus GPI during PCI for many patients.

Over time, the need for routine GPIs for PCI has become less evident. Two studies showed that upstream GPI use to treat NSTEMI-ACS increased the risk of bleeding without reducing ischemic events.<sup>7, 30</sup> Novel potent P<sub>2</sub>Y<sub>12</sub> antagonists have also decreased the need for additional GPI use. This change of practice is reflected in current guidelines that recommend that GPIs should be reserved as bail-out therapy for thrombotic complications.<sup>14</sup> As a result, there has been a need to reassess the efficacy of bivalirudin when compared with heparin, by conducting studies in which GPIs are used only on a provisional basis in both treatment groups. Following the publication of data derived from such studies, controversies have emerged regarding the potential of bivalirudin to prevent thrombotic complications and its superior safety when compared with heparin alone with provisional GPI use.

In accordance with the HORIZONS-AMI findings, the recently published EUROMAX trial data in patients with STEMI undergoing primary PCI showed that bivalirudin, compared with heparin with or without a GPI, significantly reduced the incidence of major bleeding, transfusions, and thrombocytopenia. Yet, in contrast with the HORIZONS-AMI, overall cardiovascular mortality did not differ significantly. Acute stent thrombosis was still significantly higher with bivalirudin regardless of prolonged infusions or the use of novel P<sub>2</sub>Y<sub>12</sub> inhibitors, whereas stent thrombosis rates at 30 days did not differ significantly between treatment arms.<sup>29</sup>

Furthermore, according to current practices, the British single center HEAT-PPCI trial randomized 1812 patients with STEMI to receive bivalirudin or heparin.<sup>31</sup> GPIs were used infrequently with bivalirudin (13%) and heparin (15%). In contrast with prior trials, there was no difference

in bleeding and bivalirudin increased the composite end point of death, stroke, re-infarction, or unplanned target lesion revascularization (8.7% vs 5.7%,  $p=0.01$ ) and stent thrombosis (3.4% vs 0.9%,  $p=0.001$ ).<sup>31</sup>

The BRIGHT multi-center trial which was published most recently was more supportive for the use of bivalirudin.<sup>32</sup> The trial was performed in 82 centers in China and randomized 2194 patients with acute MI undergoing PCI into 1 of 3 open-label treatment groups: bivalirudin and provisional GPIs, heparin and provisional GPIs or heparin and routine GPIs. The primary end point was a net adverse clinical end point (a composite of death, re-infarction, ischemia-driven revascularization, stroke or any bleeding event). Patients treated with bivalirudin and provisional GPIs had lower rates of this net composite end point (8.8%) than patients treated with either heparin and provisional GPIs (13.2%) or heparin and routine GPIs (17%). The difference between the groups was almost entirely driven by the difference in bleeding. There were no differences in ischemic events, including stent thrombosis. Of note, the strongest evidence supporting the use of bivalirudin in patients with STEMI has been the significant mortality reduction with bivalirudin seen in the HORIZONS-AMI trial. This finding was not replicated in BRIGHT, where there was no signal of mortality reduction with no difference between the bivalirudin–provisional GPI and the heparin–provisional GPI treatment groups.<sup>32</sup>

The results of HEAT-PPCI and BRIGHT are discordant but could be explained by the fundamental differences between the two trials. Firstly, the studies enrolled different populations since HEAT-PPCI only included patients with STEMI undergoing primary PCI, and BRIGHT randomized patients with both STEMI and NSTEMI-ACS undergoing emergency PCI. Secondly, the two trials significantly differed regarding the anticoagulation treatment. In the HEAT-PPCI trial, anticoagulation was initiated before arrival at the catheterization laboratory, whereas in the BRIGHT trial, anticoagulation was not administered until patients arrived in the catheterization laboratory. The doses of heparin to which bivalirudin and provisional GPIs were compared (70 IU/Kg in HEAT-PPCI vs 100 IU/Kg in BRIGHT) and the management of bivalirudin following PCI (stopped at the end of PCI in HEAT-PPCI with increased stent thrombosis vs continued for at least 30 minutes or more in BRIGHT without increased stent thrombosis) also differed. Finally, the majority of patients in HEAT-PPCI received novel potent platelet P<sub>2</sub>Y<sub>12</sub> inhibitors, whereas these agents were not available in BRIGHT.

BRIGHT has been the third recently published trial after EUROMAX and HEAT-PPCI that has evaluated bivalirudin in patients with STEMI and has not been able

to replicate the mortality reduction seen in HORIZONS-AMI. Furthermore, in a recent meta-analysis where all of the trials in which bivalirudin has been compared with heparin were pooled (including BRIGHT), bivalirudin increased the risk of ischemic events, reduced the risk of bleeding but there was no relationship between the reduction in bleeding and death.<sup>33</sup> The reduction in bleeding observed with bivalirudin was most apparent when it was compared with a regimen that included both heparin and a GPI. Similar results were found in a network meta-analysis that compared multiple anticoagulants used in patients with STEMI.<sup>34</sup> In contrast, a pooled patient level analysis from the HORIZONS-AMI and EUROMAX studies found that primary PCI with bivalirudin improved 30-day net clinical outcomes, with significant reductions in cardiac mortality, major bleeding, transfusions and thrombocytopenia, despite increased acute stent thrombosis in comparison with heparin with or without GPI.<sup>35</sup> However the radial approach was used only in 21.3% of patients, prasugrel or ticagrelor only in 18.1% of patients, and GPI was used in 84.8% of the control group, numbers that are clearly aberrant from current interventional practice.<sup>35</sup> Finally, a meta-analysis (at study and not patient level) by Navarese et al was the largest in the ACS setting to evaluate the 30-day safety and efficacy of bivalirudin compared to heparin in conjunction with routine or provisional administration of a GPI.<sup>36</sup> This comprehensive analysis showed that bivalirudin treatment resulted in a significant reduction of major bleeding as compared with heparin with routinely administered GPI but not with provisionally administered GPI. However, it also showed that bivalirudin compared with heparin was associated with a significant increase in 30-day definite stent thrombosis, largely driven by a greater than 4-fold increase in acute stent thrombosis regardless of routine or provisional GPI use. Moreover it demonstrated that overall mortality or risk of MI did not differ significantly, but overall revascularization rates were significantly increased with bivalirudin compared with heparin. Finally, in concert with the overall analysis, the sensitivity analyses of STEMI patients showed a reduction of major bleeding compared with heparin plus routine (but not with provisional) GPI and increased MI rates mainly attributed to increased acute (but not subacute) stent thrombosis compared with heparin with or without GPI.<sup>36</sup>

In general, most recent data that followed the initial landmark trials in favor of bivalirudin (ACUITY and HORIZONS-AMI) cast some doubt about its ability to reduce bleeding if other bleeding prevention strategies are used (e.g. radial approach, heparin at 70-80 IU/kg instead of 100 IU/kg without GPI use and 50-60 IU/kg with GPI use, ACT monitoring during PCI, provisional and not



systematic use of GPIs with heparin). Such doubt, combined with an alarming signal for increased stent thrombosis with bivalirudin found among several relevant studies and without forgetting its increased cost, may have already decreased its use in favor of heparin with provisional GPI by many interventional cardiologists.

#### **The advent of novel P<sub>2</sub>Y<sub>12</sub> antagonists, prasugrel / ticagrelor**

In TRITON-TIMI 38 trial, prasugrel (an irreversible, but also fast-acting blocker of the P<sub>2</sub>Y<sub>12</sub> receptor) has been compared to the hitherto gold standard clopidogrel among ACS patients with known coronary anatomy who were clopidogrel-naïve and was associated with significantly reduced rates of ischemic events with respect to a combined primary endpoint (cardiovascular mortality, re-infarction and stroke), but not with an overall mortality advantage.<sup>13</sup> Prasugrel has been shown to be especially effective in diabetic patients, high-risk patients with recurrent thrombotic events and in reducing stent thrombosis.<sup>37</sup> The main side-effect is an increase in spontaneous major bleeding events (an absolute increase of 0.6%) compared to clopidogrel. It should be avoided in patients with prior stroke or transient ischemic attack, in patients older than 75 years and in underweight patients (< 60 kg) which are subgroups with particularly elevated bleeding risk if prasugrel is administered.<sup>13</sup>

In the PLATO trial, ticagrelor (a reversible and fast-acting ADP-receptor blocker) has been investigated among ACS patients (treated primarily invasively as well as primarily conservatively) and shown to be superior to clopidogrel with respect to the same as in TRITON-TIMI 38 combined primary endpoint (cardiovascular mortality, re-infarction and stroke).<sup>12</sup> Of note, ticagrelor has demonstrated a significant reduction of all-cause and cardiovascular mortality, which was also shown in a pre-specified subgroup analysis for diabetics and patients referred for coronary bypass surgery.<sup>38, 39</sup> Potential side-effects, besides an increase in spontaneous major bleeding events (an absolute increase of 0.6%), include dyspnea and bradycardia, both of which have been associated with the adenosine-like properties of the agent.

The two above mentioned trials demonstrated the superiority of those two agents among patients with ACS and supported their upgraded status over clopidogrel in the most recent revascularization guidelines.<sup>14</sup> Appropriate utilization of 3rd-generation P<sub>2</sub>Y<sub>12</sub> antagonists is expected to attenuate the incremental benefit of GPIs in ACS with lower risk of bleeding and thus their availability contributed to a further decrease of GPI use in ACS.

#### **Meta-analyses & large registries assessing GPIs in ACS**

Several meta-analyses and large observational studies tried to answer the question of what are the benefits and risks when GPIs are used in patients with ACS. In a meta-

analysis of more than 30000 patients with ACS (24% of whom underwent PCI), Boersma et al found that treatment with GPIs led to a 9% reduction in the relative risk of death or MI with a concurrent 1% absolute increase in major bleeding.<sup>9</sup> More recently, Sethi et al performed a meta-analysis of randomized trials of GPI use in patients undergoing primary PCI.<sup>40</sup> In this study of more than 7000 patients, GPI use was associated with a 25% reduction in mortality. Meta-regression suggested that the benefits of GPIs were confined to patients at highest risk of mortality.<sup>40</sup> Finally, Winchester et al performed a meta-analysis of GPI use in ACS and PCI on the basis of trials performed in the contemporary era of stents and dual antiplatelet therapy.<sup>41</sup> Among ACS patients, GPI use was associated with a significant reduction in nonfatal MI and an increase in minor bleeding but no differences in mortality or major bleeding.<sup>41</sup> Thus, although there are numerous differences in patient populations, timing of drug administration and concomitant medical therapy, most studies have tended to demonstrate that GPI use in ACS and PCI (particularly in the highest risk patients) leads to modest benefits in terms of ischemic complications with a concomitant increase in bleeding.

Most recently Safley et al reported the results of an observational study examining the efficacy and safety of GPI in the contemporary interventional management of patients with ACS.<sup>42</sup> They performed a retrospective analysis of data obtained from the National Cardiovascular Data Registry of more than 970,000 patients undergoing PCI for an ACS between 2009 and 2011. About one-third of these patients received GPIs, and the association between GPI use and in-hospital mortality and major bleeding was assessed with three different methods of statistical adjustment that all resulted in very similar hazard ratios for the mortality and bleeding endpoints. Thus, GPI use was associated with reduced mortality (relative risk 0.72 to 0.90) and increased major bleeding (relative risk 1.53 to 1.93). GPIs reduced mortality in patients receiving heparin, but not those treated with bivalirudin. Despite being the most recent relevant publication, this study is reflective of practices between 2009 and 2011 which differ from current ones, since only 5-7% of patients in this cohort had radial artery access and only 11-12% of patients received third-generation P<sub>2</sub>Y<sub>12</sub> inhibitors, while results were not reported for these important subgroups. However, after rigorous data analysis, the authors validly concluded that in the modern PCI era there may still be a role for judicious use of GPI.<sup>42</sup>

#### **Current use of GPIs for PCI**

##### **1. Stable Coronary Artery Disease (CAD)**

Recent trials did not demonstrate additional benefit from GPIs after a clopidogrel loading dose of 600 mg.<sup>16, 43,</sup>

<sup>44</sup> Anecdotal experience, however, suggests that GPIs may be beneficial in bail-out situations (intra-procedural thrombus formation, slow flow, threatened vessel closure). The REPLACE-2 trial demonstrated that outcome with bivalirudin and provisional GPI is similar to that of heparin plus planned GPI during PCI for stable CAD.<sup>23</sup> Subsequently, ISAR-REACT 3, performed in patients pre-treated with clopidogrel, showed similar net clinical outcomes to bivalirudin and heparin, but heparin dosage was higher (140 U/kg) than recommended, leading to an excess in major bleeding in patients mostly undergoing procedures via femoral access. In view of the primary endpoint results and a trend towards a lower risk of MI, anticoagulation with heparin with an i.v. bolus of 70 – 100 U/kg remains the standard anticoagulant treatment for elective PCI. Among PCI patients with negative biomarkers, bivalirudin reduced bleeding without affecting mortality and might therefore be considered for use in patients at high risk for bleeding.<sup>45</sup>

Based on the fact that recent trials could not demonstrate any additional benefit of GPIs after a clopidogrel loading dose of 600 mg, they should only be used in bail-out situations or at the discretion of the operator when PCI is performed in complex lesions.<sup>14</sup>

## 2. *Non-ST Elevation ACS*

In the era before dual antiplatelet therapy, trials of adequately dosed GPIs in patients undergoing balloon angioplasty and coronary stenting demonstrated a lower incidence of composite ischemic events in favor of GPIs in combination with heparin, than with heparin alone, primarily through a reduction in MI.<sup>9</sup> In the ISAR-REACT 2 trial, this benefit was maintained despite clopidogrel pretreatment with a loading dose of 600 mg in patients with non-STEMI (13.1% vs 18.3%,  $p=0.02$ ), but not in those with unstable angina (4.6% vs 4.6%,  $p=0.98$ ).<sup>18</sup>

The ACUITY trial compared a regimen of bivalirudin alone (with bail-out GPI in 7.4%) against heparin plus GPI and found a significant benefit of bivalirudin alone with respect to the primary 30-day composite endpoint of ischemic and bleeding complications (10.1% vs. 11.7%;  $p=0.02$ ), driven by a reduction in major bleeding complications (3.0% vs 5.7%, respectively;  $p=0.001$ ) without a significant increase in ischemic complications (7.8% vs 7.3%,  $p=0.32$ ).<sup>25</sup> This benefit of bivalirudin was found regardless of downstream or upstream GPI use and was maintained during 1-year follow-up.<sup>46</sup>

The more recent ISAR-REACT 4 trial in PCI patients with non ST-segment elevation MI did not find a significant benefit of heparin with abciximab compared with bivalirudin alone. The primary endpoint of death, re-infarction, urgent target vessel revascularization, or major bleeding within 30 days occurred in 10.9% of patients in

the heparin plus abciximab group, as opposed to 11% in the bivalirudin group ( $p=0.94$ ). However, heparin plus abciximab was associated with significantly more major bleeding than bivalirudin (4.6% vs 2.6%,  $p=0.02$ ).<sup>26</sup>

Consistent with ACUITY and ISAR-REACT 4, the EARLY-ACS trial did not confirm a benefit in death or MI at 30 days from routine early versus provisional late eptifibatide, while routine early eptifibatide was associated with a higher bleeding risk (TIMI major hemorrhage 2.6% vs 1.8%, respectively,  $p=0.02$ ).<sup>7</sup> In TRITON-TIMI 38, 7414 patients (54.5% of the total study population) received GPIs and, in terms of reducing the risk of cardiovascular death, MI or stroke, a consistent advantage was observed from prasugrel when compared with clopidogrel, irrespective of the use of GPIs. The risk of TIMI major or minor bleeding was not significantly different with either prasugrel or clopidogrel, regardless of whether or not patients were treated with GPIs.<sup>47</sup> Overall, there is no evidence for an additional benefit of routine upstream use of a GPI in NSTEMI-ACS patients scheduled for coronary angiography and the recent guidelines recommend downstream GPI use in the catheterization laboratory for bail-out situations.<sup>14</sup>

The use of bivalirudin preserves the option for bail-out glycoprotein IIb/IIIa inhibition.<sup>26</sup> However, in lower-risk patients pre-treated with clopidogrel, bivalirudin does not appear to offer an advantage over heparin.<sup>24</sup> It should be reemphasized that most of the evidence in support of bivalirudin is derived from trials in which the comparator was heparin plus GPIs, a combination that is no longer routinely applied.

Ticagrelor (in all NSTEMI-ACS patients) and prasugrel (in high-risk patients referred for PCI after the coronary anatomy is known) are now recommended over clopidogrel based on the above mentioned data from PLATO and TRITON-TIMI 38 studies. Whether there is only residual benefit of GPIs with the increasing use of new antiplatelet agents, such as prasugrel or ticagrelor in NSTEMI-ACS, is under discussion but has not been addressed so far in a specific randomized controlled trial.

## 3. *STEMI*

Several trials, performed before the use of pre-loading with clopidogrel and mostly using abciximab, documented clinical benefits from GPIs as adjunct to primary PCI performed with heparin.<sup>48-51</sup> Of note, a significant 1-year survival benefit was demonstrated in a meta-analysis of abciximab.<sup>19</sup> With respect to the use of GPIs in acute STEMI patients referred for primary PCI, the best data exist for use of abciximab (0.25 mg/kg IV bolus followed by infusion of 0.125 µg/kg/min up to a maximum of 10 µg/min for 12 h) in combination with heparin.<sup>14, 21</sup> A meta-analysis by Gurm et al evaluated for differences in clinical

outcome between small-molecule GPIs and abciximab in patients with STEMI undergoing primary PCI.<sup>52</sup> Five randomized trials (n=2138 patients) comparing tirofiban or eptifibatide with abciximab as an adjunctive therapy to primary PCI were included. There were no differences in 30-day mortality, re-infarction or major bleeding between the two adjunctive strategies.<sup>52</sup> Thus, and according to the most recent guidelines for STEMI management and revascularization, abciximab, eptifibatide or tirofiban can be used in primary PCI for STEMI.<sup>14,21</sup>

Similar to NSTEMI-ACS, the upstream use of GPIs is not recommended in the present guidelines, because the only prospective randomized trial investigating the pre- vs in-cath lab use of abciximab (FINESSE trial) was negative with respect to hard clinical endpoints.<sup>22</sup> In contrast, based upon meta-analyses, registries, large post hoc analyses and the OnTIME II trial, it has been possible to demonstrate a benefit of early use of abciximab, particularly in patients that contacted rapidly the health care system (diagnosed and treated less than 3 hours from the onset of pain).<sup>53-57</sup> This is why upstream use of GPIs has regained a weak recommendation (IIB) in the last STEMI guidelines.<sup>21</sup>

Although GPIs are approved for intravenous use, several studies have assessed the efficacy of intracoronary administration in patients with STEMI undergoing primary PCI. A meta-analysis of small-sample studies suggests a benefit of intracoronary use of GPIs.<sup>58</sup> In the INFUSE-AMI trial, intracoronary abciximab delivered through a specialized drug-delivery catheter reduced infarct size compared with no abciximab in 452 patients with large, anterior STEMI undergoing primary PCI.<sup>59</sup> However, this finding was not supported by the large AIDA-STEMI trial. In this trial, a total of 2065 patients with STEMI undergoing primary PCI were randomly assigned to an intracoronary or intravenous abciximab bolus during the PCI procedure, followed by an intravenous infusion. No difference was found between groups in the primary end point of all-cause mortality, recurrent MI, or new congestive heart failure at 90 days, nor were there any significant differences in the secondary end points of early ST-segment resolution, TIMI flow grade, or enzymatic infarct size.<sup>60</sup>

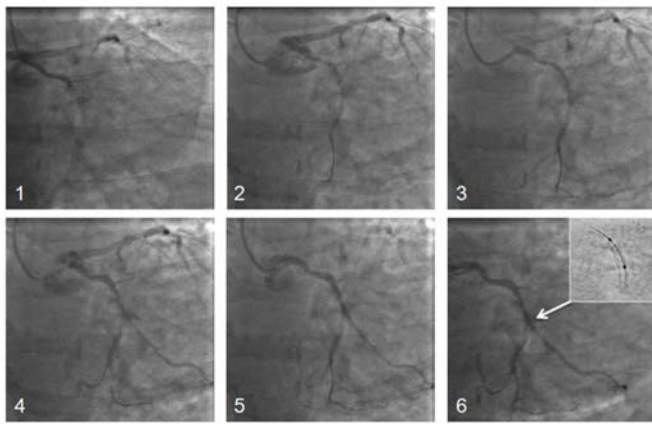
Based on the HORIZON-AMI study, bivalirudin monotherapy has been shown to be a better alternative compared to heparin plus GPI in patients with acute STEMI referred for primary PCI. Ischemic events were similar between both study arms, but severe bleeding complications were significantly reduced under bivalirudin.<sup>27</sup> As a consequence, short- and long-term mortality was statistically reduced, which cannot be explained by the reduction of bleeding alone, but was the main trigger for a strong guideline recommendation of

bivalirudin in this indication.<sup>14,28</sup> However, as analyzed above, this mortality benefit was not replicated in studies and meta-analyses that followed, while the advantages of bivalirudin regarding bleeding complications prevention seems to fade when the comparator is heparin with provisional and not routine GPI use and furthermore if most current practices with other bleeding prevention strategies are applied during PCI.<sup>29,31-33,36,61</sup> This is why in the latest revascularization guidelines, heparin plus planned or provisional GPI holds a class I recommendation, while bivalirudin holds a class IIa recommendation for primary PCI.<sup>14</sup> As for patients with stable CAD or NSTEMI-ACS undergoing PCI, current guidelines strongly recommend the use of GPIs during primary PCI for STEMI for bail-out or evidence of thrombotic complication or no-reflow.<sup>14</sup> An example of GPI use for bail-out in a primary PCI procedure for STEMI due to subacute stent thrombosis with massive thrombus burden is shown in Figures 2 and 3.

Prasugrel and ticagrelor have replaced clopidogrel as the first choice therapy in STEMI.<sup>14,21</sup> Clopidogrel, but not prasugrel and ticagrelor, was used before in randomized studies of primary PCI for STEMI comparing bivalirudin to heparin with or without use of GPIs. However, like clopidogrel these agents also have delayed absorption in STEMI, and the type of P<sub>2</sub>Y<sub>12</sub> inhibitor used did not affect the relative safety or efficacy profile of bivalirudin vs heparin with or without GPIs in the EUROMAX trial.<sup>29,62</sup>

With the new fast-acting and highly effective antiplatelet drugs such as prasugrel or ticagrelor a strategy of early use of GPIs seems less promising, although this has not been adequately investigated up to now. However, as recently shown, the early use of prasugrel or ticagrelor might not sufficiently inhibit platelet activity at the time when primary PCI is actually performed.<sup>62</sup> Accordingly, primary PCI outcomes might be improved by appropriately administered IV antiplatelet therapy with GPIs as shown in the FABOLOUS PRO study. This study has shown that with prasugrel administration, the inhibition of platelet aggregation is suboptimal for at least 2 hours in STEMI patients, but when given in association with a bolus only of tirofiban (25 µg/kg in 3 minutes), sufficient inhibition of platelet aggregation is obtained without residual variability after treatment, which makes a post-bolus tirofiban infusion unnecessary.<sup>63</sup>

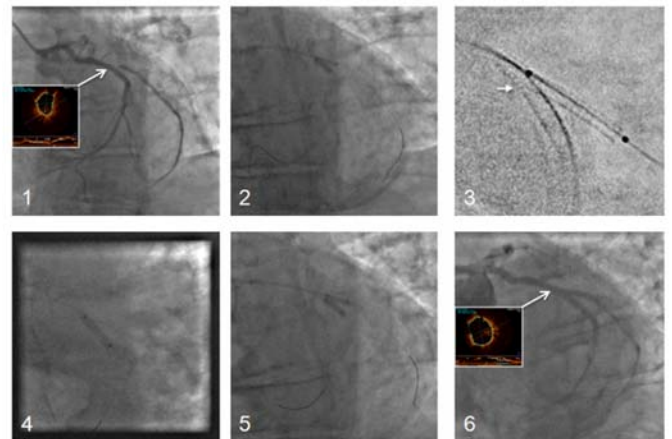
Cangrelor, which is expected to be available soon for clinical use, is an IV, potent, rapidly acting P<sub>2</sub>Y<sub>12</sub> receptor inhibitor that has been evaluated in several phase III studies involving over 25,000 patients undergoing PCI for stable CAD or ACS and might prove to be a game changer.



**Figure 2.** A case example of GPI use for bail-out due to heavy thrombus (procedure 1): **1.** Acute MI due to subacute stent thrombosis in a dominant circumflex artery (LCx) just proximal to the first obtuse marginal branch (OM<sub>1</sub>). Five days earlier the 58-year-old male patient had been hospitalized because of NSTEMI-ACS, pretreated with aspirin and clopidogrel 600 mg loading dose and treated with PCI under bivalirudin with implantation of two stents to treat a sub-occlusive (95-99%) lesion of the LCx at the level of the OM<sub>1</sub>. Two stents were implanted in the initial PCI: the first 3x15 mm was implanted directly in LCx (jailing the OM<sub>1</sub> ostium) and a second 3x9 mm was added with minimal overlap just distally (because of edge-dissection and slow-flow after implanting the first), to terminate a PCI procedure without application of any bifurcation technique. **2-5.** The patient was treated with multiple manual thrombectomy runs (10) that did not retrieve much of the massive thrombus which gradually “melted” during a long procedure after the administration of abciximab intracoronary bolus and infusion. **6.** Final result: TIMI III flow was restored despite some residual thrombus at the bifurcation. No balloon dilation or stent implantation was performed. A stent visualization enhancement technique (StentViz) showed that the stents were well expanded, but with somehow irregular borders at the most proximal part. Abciximab infusion was continued for 12 hours, the patient was switched from clopidogrel to prasugrel, remained under therapeutic anticoagulation with enoxaparin and a new procedure under optical coherence tomography (OCT) guidance was scheduled 8 days later in order to address the issues at the LCx- OM<sub>1</sub> bifurcation (continued in Figure 3).

In the CHAMPION-PHOENIX trial, which included stable patients as well as NSTEMI-ACS and STEMI patients, cangrelor (bolus 30 mg/kg, infusion 4 mg/kg/min) compared to clopidogrel (loading dose of 300 mg or 600 mg) reduced the rate of ischemic events, including stent thrombosis, without a significant increase in severe bleeding.<sup>64, 65</sup> A pooled analysis of patient-level data from the 3 major cangrelor trials (CHAMPION-PCI, CHAMPION-PLATFORM, and CHAMPION-PHOENIX) confirmed the lower rates of PCI peri-procedural thrombotic complications (3.8% for cangrelor vs 4.7% for clopidogrel,  $p=0.0007$ ) and of stent thrombosis (0.5% vs 0.8%, respectively,  $p=0.0008$ ) with no difference in major bleeding.<sup>64</sup> These early benefits were maintained at 30 days with consistency across all patient subgroups. There was no correlation between treatment effect and clinical presentation and there was a significant lower incidence of Q-wave MI in favor of cangrelor. Altogether, cangrelor

seems to be a good therapeutic option in P<sub>2</sub>Y<sub>12</sub> inhibitor-naïve patients undergoing PCI, although data showed no effect on mortality and benefits that are mainly derived from preventing intra-procedural stent thrombosis.<sup>64</sup> In general, cangrelor, with its fast on/off effect (half-life 3 min), seems superior to clopidogrel when preloading is not possible, promises rapid and sufficient inhibition of platelets among patients with STEMI treated with primary PCI, but it has so far not been compared against prasugrel, ticagrelor, or GPIs. Conceptually, however, it is expected to further challenge the GPI role in STEMI treatment.



**Figure 3.** A case example of GPI use for bail-out (continued, procedure 2): **1.** No more angiographic evidence of thrombus but severe stenosis remains at the OM<sub>1</sub> ostium, which is jailed by the LCx stent. By OCT examination, it becomes evident that the LCx stent part proximal to the OM<sub>1</sub> ostium has irregular contour and is underexpanded & undersized (mean diameter 2.56 mm and stent area 5.25 mm<sup>2</sup> for a 3 mm stent in an artery with a proximal reference diameter of 3.5 mm). **2.** After gaining guidewire access to the OM<sub>1</sub>, a kissing balloon inflation at the LCx-OM<sub>1</sub> bifurcation is performed with 3x12 mm and 2.5x12 mm non-compliant balloons respectively. **3.** A 2.5x19 mm stent is implanted at the ostial-proximal OM<sub>1</sub> lesion with minimal protrusion into the LCx. **4.** A 3.5x15 mm non-compliant balloon inflation in the LCx, in front of the OM<sub>1</sub> ostium, creates a mini-crush to the protruding part of the OM<sub>1</sub> stent. **5.** Final kissing at the LCx-OM<sub>1</sub> bifurcation with 2 non-compliant balloons, a 3x12 mm (LCx) and a 2.5x12 mm (OM<sub>1</sub>). **6.** Optimal final angiographic result. At OCT control the initially irregular, underexpanded and undersized proximal stent part is now corrected and well apposed with increased mean diameter (from 2.56 mm to 3.57 mm) and increased lumen and stent area (from 5.25 mm<sup>2</sup> to 10.16 mm<sup>2</sup>).

## Conclusion

GPIs provide superior protection against ischemic events in patients undergoing PCI for all indications and are particularly useful and strongly recommended in bail-out situations and patients at high risk for ischemic events (Table 2). However, bleeding is undoubtedly increased with GPIs and alternative approaches exist. Bivalirudin is not less effective and holds a safety advantage over heparin and routine GPI, but in recently published studies it does not hold a clear safety advantage over heparin with provisional GPI use, especially when other bleeding prevention measures are taken, such as radial approach and



not very high heparin doses combined with ACT monitoring. It is not wise to derive a universal recommendation concerning the use of GPIs on the basis of the data. Rather, it would appear prudent to reserve GPI use for patients who are at high risk of early ischemic complications and for already heparin treated patients. On the other hand, in patients for whom the short-term risk of major bleeding is predominant, avoidance of GPIs and preference for bivalirudin over heparin, unless faced with extreme thrombotic risk, would be reasonable.

**Table 2.** Situations where use of glycoprotein IIb/IIIa inhibitors is advocated or should be considered.

Heavy thrombotic burden	Slow flow / no-reflow
Intra-procedural thrombus formation	Threatened vessel closure
No preloading with P <sub>2</sub> Y <sub>12</sub> antagonists	Complex lesions/High risk patients

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