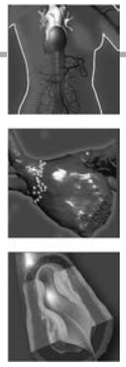

Glycoprotein IIb/IIIa inhibitors during percutaneous coronary interventions

Intravenous glycoprotein IIb/IIIa inhibitors are widely used during percutaneous coronary interventions (PCIs). There are three commercially available pharmacological agents: abciximab, eptifibatide and tirofiban. This article presents the evidence indicating their use in connection with PCI, and focuses on the differences between the three regimens, as well as on their use in special clinical conditions. The documentation for their use in high-risk PCI (in other words, for acute coronary syndromes and complex coronary anatomy), and in primary PCI for ST-elevation myocardial infarction will be scrutinized, as well as the use of intracoronary administration. Furthermore, the role of glycoprotein IIb/IIIa inhibitors as opposed to, or in combination with, thienopyridines and thrombin inhibitors will be analyzed, as will their use in diabetics, in patients with renal insufficiency and when performing PCI in vein grafts. Finally, the possible effects of glycoprotein IIb/IIIa inhibitors on restenosis and inflammation, as well as dosing and bleeding issues will be discussed.

KEYWORDS: abciximab ■ eptifibatide ■ glycoprotein IIb/IIIa inhibitor ■ myocardial infarction ■ percutaneous coronary intervention ■ tirofiban

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Percutaneous coronary intervention, coronary thrombosis & development of glycoprotein IIb/IIIa inhibitors

Percutaneous coronary intervention (PCI) was introduced as balloon dilatation by Grüntzig in 1977 – a revolution with respect to revascularization of coronary artery disease. However, it soon became evident that the intracoronary trauma and tissue injury, and the resulting exposure of subendothelial tissue, was very thrombogenic. Antithrombotic regimens based on platelet inhibition by aspirin in combination with anticoagulation by heparin were therefore established early [1]. Despite these agents, thrombotic complications remained substantial hazards, especially when performing PCI in high-risk patients with complicated coronary artery disease or with increased thrombus burden, such as those with acute coronary syndromes [2,3]. Thus, there was a need for more effective antithrombotic agents.

■ Abciximab

Upon platelet activation, the glycoprotein (GP) IIb/IIIa receptor is activated and exposed on the platelet surface. It binds to fibrinogen and the von Willebrand factor and is thus essential for and, in a sense, constitutes the final common pathway of platelet aggregation [4,5]. A murine–human chimeric fragment of a monoclonal antibody against the GP IIb/IIIa receptor, c7E3 Fab (abciximab) was the first GP IIb/IIIa inhibitor to be developed and brought forward for clinical use [6,7]. Abciximab has a high molecular weight of more than 47,000 Da, a high affinity to the GP IIb/IIIa receptor and a relatively short plasma half-life (20–30 min). Its high affinity is responsible for the slow recovery of platelet function, taking days after administration. With more than 80% of the receptors occupied minutes after a bolus administration, approximately 30% receptor occupancy is observed after 8 days and 10% is observed 15 days after drug discontinuation [8]. In addition to the binding to the platelet GP IIb/IIIa receptor, this molecule demonstrates affinity to the CD11b/18($a_m\beta_2$ or MAC 1) receptor [9], inhibiting inflammatory leukocyte–platelet interaction and $a_v\beta_3$ (vitronectin) receptors [10], with possible beneficial effects on endothelial dysfunction and restenosis after PCI.

■ Eptifibatide & tirofiban

Abciximab carries some potential drawbacks. Its use is associated with an increased risk of bleeding, and the tight binding and long-standing inhibition of platelet aggregation make this difficult to manage. Furthermore, as a fragment of a foreign antibody, it is potentially allergenic, causing thrombocytopenia in a number of patients severe enough to mandate platelet count monitoring and, in some cases, platelet substitution is necessary to prevent bleeding.

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Lastly, as previously mentioned, it is not very selective. These properties served as an impetus for developing more selective drugs with shorter half-lives.

The amino acid sequence that accounts for the binding of the GP IIb/IIIa receptor to fibrinogen is constituted of arginine, glycine and aspartic acid. The small molecules developed to block this sequence should theoretically be very selective for the binding of the GP IIb/IIIa receptor to fibrinogen (in other words, the target when aiming at blocking aggregation), the final common pathway of platelet activation. Two molecules, the cyclic heptapeptide eptifibatide (Integrilin™, Millennium Pharmaceuticals, Inc., MA, USA) and the nonpeptide tirofiban (Aggrastat®, Iroko Pharmaceuticals, PA, USA) were thus developed and introduced for clinical use.

Eptifibatide is a synthetic heptapeptide with low molecular weight (less than 1000 Da) that is modeled on a compound isolated from the venom of the pygmy rattlesnake [11]. It is reversibly bound to the β_3 subunit of the GP IIb/IIIa receptor, causing a platelet inhibition correlated to the plasma level of the drug. Eptifibatide is excreted through the kidneys with a plasma half-life of approximately 2–3 h.

Tirofiban is a tyrosine derivative nonpeptide that has a structure modeled on a compound isolated from saw-scaled viper venom [12]. It has similarities to the amino acid sequence of fibrinogen, making it possible to bind to the GP IIb/IIIa receptor. Its affinity is between those of abciximab and eptifibatide and it has a plasma half-life of between 1.5 and 2 h. Tirofiban is excreted through the kidneys (60–70%) and metabolized through the biliary system (30–40%).

Role of GP IIb/IIIa receptor antagonists in high-risk PCI

Both the American College of Cardiology and the European Society of Cardiology recommend the use of GP IIb/IIIa inhibitors in patients undergoing PCI for different indications (Table 1) [13–18].

GP IIb/IIIa inhibitors in connection with PCI for patients without ongoing ST-elevation MI

■ Abciximab

The first of a number of pivotal studies (Table 2) that broke the ground for current GP IIb/IIIa receptor antagonist regimens was the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) study, which demonstrated that the addition of GP IIb/IIIa inhibition by abciximab, compared with heparin and aspirin only, reduced thrombotic complications associated with high-risk PCI [19]. It was also evident that a bolus at the time of PCI was not enough, but that the therapy had to be prolonged with a postprocedural infusion. A drawback was the increased rate of bleeding that, according to *post hoc* analysis, was related to greater age, female sex and lower weight [20]. From this, it was hypothesized that the excess in bleedings was attributed to the concomitant use of non-weight-adjusted unfractionated heparin as an adjunctive anticoagulant regimen.

This led to the design of the following Evaluation of PTCA to Improve Long-Term Outcomes by c7E3 GP IIb/IIIa Receptor Blockade (EPILOG) study in which abciximab in combination with a weight-adjusted heparin, in a lower dose than previously used, was compared with either heparin alone or the combination of abciximab with the hitherto used standard dose of heparin [21]. The positive effects from the EPIC study of abciximab compared with heparin only were confirmed. Furthermore, this study demonstrated that with a weight-adjusted and lower dose of heparin, the bleeding rate was no longer increased compared with the heparin-only group. However, it is worth noting that in the EPILOG study, as well as in all subsequent studies with abciximab, the postbolus abciximab infusion dose was, as with heparin, weight-adjusted, as opposed to the fixed infusion dose used in the EPIC study.

A further development was the use of abciximab as a pretreatment for 20–24 h before a PCI for unstable angina (UA). In the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial, this was demonstrated to reduce the combined end point of death, myocardial infarction (MI) and urgent revascularization at both 30 days and 6 months after the intervention compared with placebo [22], an effect observed only among patients with elevated troponin T levels [23].

In all three of the aforementioned studies, usage of stents was either discouraged or established as an exclusion criterion. To bring therapy up to modern standards of PCI, the Evaluation of IIb/IIIa Platelet Inhibitor for Stenting (EPISTENT) study was conducted in which patients were randomly assigned to either stenting with placebo, stenting with abciximab or balloon dilatation with abciximab alone [24]. The stent plus abciximab group was shown to be superior to the other groups, but an interesting aspect of this study was that even balloon dilatation with abciximab was safer than stenting with placebo.

Table 1. Extracts of the American and European guidelines for the use of glycoprotein inhibitors in patients undergoing percutaneous coronary interventions.

American College of Cardiology/American Heart Association Guidelines			European Society of Cardiology Guidelines		
	Class of recommendation	*Level of evidence*		*Class of recommendation*	*Level of evidence*
For patients with STEMI (ACC/AHA 2009 and ESC 2008)					
During primary PCI:					
– Administration of abciximab	IIa	A		IIa	A
– Administration of tirofiban	IIa	B		IIb	B
– Administration of eptifibatide	IIa	B		IIb	C
Before PCI:					
– Administration of GP IIb/IIIa inhibitors	IIb	B		–	–
For patients with NSTEMI/UA (ACC/AHA 2007 and ESC 2007)					
During PCI:					
Administer an intravenous GP IIb/IIIa inhibitor providing it is not started before diagnostic angiography for troponin-positive and other high-risk patients	I	A	In high-risk patients not pretreated with GP IIb/IIIa inhibitors and proceeding to PCI, abciximab should be administered directly after angiography	I	A
It is reasonable to omit administration of an intravenous GP IIb/IIIa antagonists if bivalirudin was administered ≤6 h earlier.	IIa	B	In patients pretreated with eptifibatide or tirofiban before coronary angiography, the same medicine should be maintained during and after the procedure	IIa	B
			The use of eptifibatide or tirofiban in the above mentioned patients' group is less established	IIa	B
For patients undergoing PCI (ACC/AHA 2007 and ESC 2005)					
In patients with UA/NSTEMI undergoing PCI without clopidogrel administration, a GP IIb/IIIa inhibitor (abciximab, eptifibatide or tirofiban) should be administered	I	A	Due to stable coronary artery disease, GP IIb/IIIa inhibitors should be administered in patients with complex lesions, threatening/actual vessel closure, visible thrombus and no/slow reflow	IIa	C
In patients with UA/NSTEMI undergoing PCI with clopidogrel administration, it is reasonable to administer a GP IIb/IIIa inhibitor (abciximab, eptifibatide or tirofiban)	IIa	B			
In patients undergoing elective PCI with stent placement, it is reasonable to administer a GP IIb/IIIa inhibitor (abciximab, eptifibatide or tirofiban)	IIa	B			

Classes of recommendations (ACC/AHA/ESC): Class I: evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful and effective; Class II: conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment; Class IIa: weight of evidence/opinion is in favor of usefulness/efficacy; Class IIb: usefulness/efficacy is less well established by evidence/opinion; Class III: conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.
Levels of evidence (ACC/AHA/ESC): Level of evidence A: data derived from multiple randomized clinical trials or meta-analyses; Level of evidence B: data derived from a single randomized clinical trial or large non-randomized studies; Level of evidence C: consensus of opinion of the experts and/or small studies, retrospective studies and registries.
ACC: American College of Cardiology; AHA: American Heart Association; ESC: European Society of Cardiology; GP: Glycoprotein; NSTEMI: Non-ST-elevation myocardial infarction; PCI: Percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; UA: Unstable angina.

Table 2. Studies comparing different glycoprotein IIb/IIIa inhibitors with placebo in patients undergoing percutaneous coronary interventions due to non-ST-elevation myocardial infarction, unstable angina or stable angina.

Study	Drug	Type of patients	Patients (n)	Enrolment period	Routine use of stents	Primary end point	Results (drug vs placebo)	p-value	Ref.
EPIC	Abciximab	Evolving MI or high-risk PCI	2099	Up to 1994	No	Death/MI/unplanned stent, revascularization or IABP (30 days)	12.8 vs 8.3% (11.4% in the only bolus arm)	0.008 (dolus + infusion vs placebo), 0.43 (bolus vs placebo)	[19]
EPILOG	Abciximab	Urgent or elective PCI without MI	2792	1995	No	Death/MI/unplanned revascularization (30 days)	5.2 vs 11.7% (5.4% in the high-dose heparin arm)	<0.001 for both abciximab groups	[21]
CAPTURE	Abciximab	Refractory angina	1265	1993–1995	No	Death/MI/reintervention (30 days)	15.9 vs 11.3%	0.012	[22]
EPISTENT	Abciximab	Stable angina, UA and NSTEMI	2399	1996–1997	67% (two of three study arms received stents)	Death/MI/urgent unplanned revascularization (30 days)	5.3 vs 10.8% (6.9% in the balloon + drug group)	<0.001 (stent + placebo vs stent + abciximamab), 0.007 (stent + placebo vs balloon + abciximab)	[24]
ISAR-REACT	Abciximab	Low-risk (excluded MI, diabetes and visible thrombus)	2159	2002–2003	Yes	Death/MI/TVR (30 days)	4.2 vs 4.0%	0.82	[26]
ISAR-REACT 2	Abciximab	NSTEMI or UA	2022	2003–2005	Yes	Death/MI/TVR (12 months)	23.3 vs 28%	0.012	[27]
PURSUIT	Eptifibatide	NSTEMI or UA	10,948 (1228 PCI treated)	1995–1997	50%	Death or MI (30 days)	14.2 vs 15.7%	0.04	[29]
ESPRIT	Eptifibatide	Stable angina (49%) and ACS (51%)	2064	1999–2000	Yes	Death/MI/TVR/bail out GP inhibitors (at 48 h)	6.6 vs 10.5%	0.0015	[30]
EARLY-ACS	Eptifibatide	NSTEMI or UA	9492 (5453 PCI treated)	2005–2008	Yes	Death/MI/urgent revascularization/ thrombotic complication during PCI (at 96 h)	9.3 vs 10%	0.23	[31]
RESTORE	Tirofiban	UA or MI (6% STEMI)	2212	1995	No	Death/MI/reintervention/bail out stenting (at 30 days)	10.3 vs 12.2%	0.16	[32]

ACS: Acute coronary syndrome; GP: Glycoprotein; IABP: Intra-aortic balloon pump; MI: Myocardial infarction; NSTEMI: Non-ST-elevation myocardial infarction; PCI: Percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; TVR: Target vessel revascularization; UA: Unstable angina.

Another analysis from the EPISTENT study revealed that pretreatment with ticlopidine, compared with institution of ticlopidine after PCI, significantly improved the outcome [25]. It was also demonstrated that when this pretreatment was taken into account, abciximab no longer had any significant effect on the combined primary end point of the study.

The same effect was observed in the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) study in which abciximab failed to demonstrate any further positive effects than pretreatment with thienopyridines in a low-risk population [26]. However, the subsequent ISAR-REACT 2 study showed beneficial effects of abciximab in high-risk patients with non-ST-elevation MI (NSTEMI) or UA despite preprocedural loading with clopidogrel [27]. Furthermore, as in the CAPTURE study, a subgroup analysis demonstrated that all benefits were found in the group with troponin elevation.

■ Eptifibatide & tirofiban

For the small molecules eptifibatide and tirofiban, the evidence of positive effects has been far less convincing. Both eptifibatide and tirofiban have been tested in large-scale clinical trials evaluating their effectiveness as adjunctive treatment in patients with acute coronary syndromes, among whom only a fraction had undergone PCI. Only a few investigations were designed to study patients specifically undergoing PCI.

The Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis (IMPACT)-II study failed to demonstrate any positive effect of either of the two different dosing regimens of eptifibatide compared with placebo in patients undergoing elective, urgent or emergency PCI [28]. However, a subanalysis from the large Platelet IIb/IIIa in Unstable Angina Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, in which 1228 out of a total of 10,949 patients with acute coronary syndrome underwent PCI within 72 h of randomization, suggested a benefit of high-dose eptifibatide regarding the composite end point of death and nonfatal reinfarction within 30 days [29].

In the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial, investigating a population without MI within 24 h and with planned stenting, the eptifibatide dose was increased even more to two bolus doses plus infusion [30]. Patients administered eptifibatide had fewer events at 48 h compared with patients given placebo, an effect that was presented in all subgroups of the study population and remained evident even 30 days after randomization.

The recent Early Glycoprotien IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndromes (EARLY-ACS) study was a large-scale trial that randomized 9492 patients with acute coronary syndrome with NSTEMI or UA and with intended intervention with either early treatment with eptifibatide instituted before coronary angiography or a matching placebo infusion with provisional use of eptifibatide during and after a subsequent PCI [31]. Overall, this study failed to prove the superiority of early institution of eptifibatide compared with provisional use at the time of intervention. However, among patients who underwent PCI (~50% of the study population), data suggest that pretreatment with eptifibatide may reduce the composite end point of death and MI within 30 days compared with provisional use.

The Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trial conducted to explore the effects of tirofiban in patients undergoing PCI without ongoing STEMI did not show any positive effects regarding clinical outcomes [32]. Results of the Early or Late Intervention in Unstable Angina (ELISA)-2 study pointed in a similar direction, as tirofiban failed to reduce enzymatic infarct size in patients undergoing PCI for non-ST-elevation acute coronary syndrome and who were pretreated with aspirin and clopidogrel [33].

■ Oral inhibitors

With the recognition of the central role of platelets and platelet activation for thrombotic complications during and after PCI and the positive and promising results of blocking the important GP IIb/IIIa receptors by intravenous antagonists, it was natural to search for compounds that could be orally active and thus applicable for long-term use. After abciximab and then the small molecules eptifibatide and tirofiban, the oral GP IIb/IIIa inhibitors such as lotrafiban, orbofiban, roxifiban, sibrafiban and xemilofiban constitute a third group of compounds. Oral inhibitors have been tested in several large randomized studies [34,35]. Although platelet inhibition has been achieved to the targeted degree, the overall results have been neutral or even negative, with an increase in mortality among those treated with these inhibitors. At present, these compounds have no place in the therapeutic arsenal.

GP IIb/IIIa inhibitors in patients with ST-segment elevation myocardial infarction

It has long been recognized that patients with acute coronary syndromes have more platelet activation than those with stable coronary disease. Furthermore, platelet activity appears to be more enhanced in periods of instability than during more quiescent phases [36]. In patients with ongoing MI, this activation may be even more pronounced, as detected by shortened bleeding times in these patients compared with those with UA [37]. Thus, platelet inhibition may have different results in patients with ongoing STEMI than in patients included in the previosuly cited trials, that is, mainly patients undergoing high-risk PCI owing to acute coronary syndrome without ongoing STEMI or those with complex coronary anatomy.

Abciximab was the first regimen tested in patients undergoing primary PCI for STEMI. In the ReoPro® and Primary PTCA Organization and Randomized Trial (RAPPORT) study [38], abciximab was associated with improved outcomes in patients undergoing primary PCI without routine stent implantation compared with placebo. These results were repeated in the Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term follow-up (ADMIRAL) and Abciximab and Carbostent Evaluation (ACE) studies with the routine use of stents (Table 3) [39,40].

The Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) study was the largest trial testing abciximab versus placebo in patients undergoing primary PCI [41]. It was a 2 × 2 factorial design study with randomization between balloon angioplasty alone versus stenting and between abciximab and no abciximab. The results were negative since the primary end point did not differ between the patients who were administered abciximab or placebo.

Thus, the findings of the aforementioned trials were somewhat divergent. However, a meta-analysis by de Luca *et al.* comprising 27,115 patients from 11 studies, including the CADILLAC study, demonstrated that abciximab reduced both 30-day and long-term mortality compared with control treatment in association with primary PCI for STEMI [42]. In a more recent meta-analysis, this benefit from treatment with GP inhibitors was observed in patients with high-risk characteristics but not among low-risk patients, which may provide an explanation for the diverging results [43].

However, it is important to keep in mind that these studies were conducted during a time when the standard treatment for patients with STEMI was quite different from what it is today. Thus, pretreatment with high-dose clopidogrel (300–600 mg) was not routinely used when these studies were conducted.

The only study testing abciximab administration in patients scheduled for primary PCI in the modern era is the Bavarian Reperfusion Alternatives Evaluation (BRAVE)-3 study [44]. In this study, all patients were pretreated with

Table 3. Studies comparing different glycoprotein IIb/IIIa inhibitors with placebo in patients undergoing primary percutaneous coronary intervention owing to ST-elevation myocardial infarction.

Study	Drug	Patients (n)	Pretreatment with thienopyridines	Routine use of stents	Primary end point	Results (drug vs placebo)	p-value	Ref.
RAPPORT	Abciximab	483	No	No	Death/MI/urgent TVR (30 days)	5.8 vs 11.2%	0.03	[38]
ADMIRAL	Abciximab	300	No	Yes	Death/MI/urgent TVR (30 days)	6.0 vs 14.6%	0.01	[39]
ACE	Abciximab	400	No	Yes	Death/MI/urgent TVR (1 year)	23 vs 36%	0.004	[40]
CADILLAC	Abciximab	2082	No	50% (in two of four arms)	Death/MI/urgent TVR/stroke (6 months)	16.5 vs 20.0% if no stent; 10.2 vs 11.5% if stent	NS NS	[41]
BRAVE 3	Abciximab	800	Yes	Yes	Infarct size before discharge	15.7 ± 17.2% vs 16.6 ± 18.6%	0.47	[44]
ON-TIME 2	Tirofiban	984	Yes	Yes	Residual ST segment deviation before and 1 h after PCI	10.9 ± 9.2 mm vs 12.1 ± 9.4 mm (before); 3.6 ± 4.6 mm vs 4.8 ± 6.3 mm (1 h after PCI)	0.028 (before), 0.003 (after PCI)	[45]

MI: Myocardial infarction; NS: Not significant; PCI: Percutaneous coronary intervention; TVR: Target vessel revascularization.

acetylsalicylic acid 500 mg and clopidogrel 600 mg. The primary end point was infarct size measured with SPECT before hospital discharge. The results did not differ between the two groups, nor did clinical outcomes. However, the study was not powered for such an analysis.

The largest randomized trial including a small GP IIb/IIIa receptor inhibitor during primary PCI was the Ongoing Tirofiban in Myocardial Infarction Evaluation (ON-TIME)-2 trial, where patients were randomized between early prehospital high-dose tirofiban or placebo [45]. The study demonstrated that tirofiban reduced the extent of residual ST-segment deviation both before and 1 h after the procedure. However, this improved outcome was not related to a significant improvement in thrombolysis in myocardial infarction (TIMI) flow or myocardial blush grade after PCI. Although this study was not powered to identify clinical differences, there was a significant reduction of the composite clinical end point of death, recurrent MI, urgent target vessel revascularization and 'bail out' use of tirofiban 30 days after inclusion. This difference was due to a reduction in the bail out tirofiban administration, while there was no difference in the clinical composite of death, nonfatal reinfarction or target vessel revascularization.

Facilitated primary PCI

It is understood that myocardial necrosis during MI is correlated with the duration of occlusion of the infarct-related artery. The concept of early GP IIb/IIIa inhibitor administration in patients with ST-elevation (in the ambulance, the emergency department or the first contact hospital without on-site PCI facilities) was therefore a natural step. The Glycoprotein Receptor Antagonist Patency Evaluation (GRAPE) study demonstrated that patients receiving early abciximab before primary PCI had preprocedural vessel patency in the same magnitude as had been achieved after streptokinase in earlier studies [46]. That early administration of a GP IIb/IIIa receptor inhibitors can improve patency and flow in an infarct-related coronary artery has since been demonstrated in a number of studies.

A meta-analysis from Montalescot *et al.* summarizing the results of six small studies (three with abciximab and three with tirofiban) that enrolled a total of 931 STEMI patients concluded, however, that although patients pretreated with GP IIb/IIIa inhibitors have a greater possibility to present at the catheterization laboratory with an open culprit artery (TIMI 2 or 3), this did not result in a proven clinical benefit [47]. In another partially overlapping meta-analysis with 602 patients who received abciximab in six studies, it was also demonstrated that early abciximab, rather than late, resulted in an improved rate of TIMI 3 flow after the procedure and improved ST-resolution but, again, with no demonstrable clinical benefits [48]. Two trials, the Time to Integrilin Therapy in Acute Myocardial Infarction (TITAN)-TIMI 34 and the Integrilin in Acute Myocardial Infarction (INTAMI), randomized 343 and 102 patients, respectively, between early preprocedural eptifibatide or optional peri- or post-procedural institution of eptifibatide [49,50]. In both studies, coronary flow measures were better before the primary PCI after early eptifibatide, but no differences in clinical end points were observed.

The Facilitated Intervention with Enh anced Reperfusion Speed to Stop Events (FINESSE) trial is the only large-scale trial testing the hypothesis of facilitated PCI [51]. In this study, 2452 patients were randomly assigned with a 1:1:1 ratio between prehospital combination treatment with reteplase (two 5 IU boluses separated by 30 min) and abciximab or abciximab alone or primary PCI with abciximab administration just before the procedure. All patients received abciximab infusion for 12 h. None of the facilitated treatments appeared to be better than primary PCI with periprocedural abciximab administration. The small benefit of the combination treatment of thrombolysis with GP IIb/IIIa inhibition in terms of TIMI flow before PCI was counterbalanced by the increased number of bleeding complications [51].

Comparison between different GP IIb/IIIa inhibitors

As is evident from above, the positive effects of GP IIb/IIIa inhibitors are far better documented for abciximab than for eptifibatide or tirofiban. However, from this, it cannot been deduced that the positive effects of abciximab are superior to that of the other two compounds. Although there is a great need for comparative trials to establish the efficacy of one compound towards the others, only a few comparative studies have been conducted. For patients without ongoing STEMI, the only randomized trial addressing this issue is the Do Tirofiban and ReoPro Give Similar Efficacy Trial (TARGET), which failed

to demonstrate the noninferiority of tirofiban compared with abciximab with regard to the composite end point of death, MI and urgent target vessel revascularization [52].

A few studies have compared the different GP IIb/IIIa inhibitors in the setting of primary PCI for STEMI, all using the surrogate of different levels of ST-resolution on ECG as primary end points, but with somewhat different aims and hypotheses. In the Facilitated Angioplasty with Tirofiban or Abciximab (FATA) trial, tirofiban did not prove to be equivalent to abciximab [53] while in the Multicentre Evaluation of Single High-dose Bolus Tirofiban versus Abciximab with Sirolimus-eluting Stent or Bare-metal Stent in Acute Myocardial Infarction (MULTISTRATEGY) trial [54], a 2 × 2 factorial design study comparing the effect of high-dose tirofiban and a sirolimus-eluting stent with abciximab and a bare-metal stent, tirofiban was proven to be noninferior to abciximab. In the Eptifbatide versus Abciximab in Primary PCI for Acute ST Elevation Myocardial Infarction (EVA AMI) trial, eptifibatide was demonstrated to be superior to abciximab concerning the primary end point of ST segment resolution 1 h after the intervention. However, in none of these studies has there been any differences in the clinical events between the different groups [55]. A meta-analysis of all randomized trials between abciximab and low-molecule GP IIb/IIIa inhibitors (tirofiban or eptifibatide) in patients treated for STEMI showed that abciximab was not superior in any of the parameters measured (TIMI 3 flow after PCI: 89.8 vs 89.1%; p = 0.72, ST-segment resolution: 67.8 vs 68.2%; p = 0.66, 30-day mortality: 2.2 vs 2%; p = 0.66, bleeding complications: 1.3 vs 1.9%; p = 0.27) [56].

Abciximab and eptifibatide have been compared in a number of nonrandomized retrospective trials, either with consecutive patients series [57–59] or after switching from abciximab to eptifibatide [60–62]. The findings of these studies are divergent and no firm conclusions can be drawn regarding any possible differences in effect between the three available GP IIb/IIIa inhibitors. In a large registry study using data from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), Åkerblom *et al.* confirmed the hypothesis that eptifibatide is not inferior to abciximab in patients undergoing primary PCI [63].

Intracoronary administration of GP IIb/IIIa inhibitors

The concept of intracoronary administration of a bolus dose of GP inhibitors was raised recently [64]. This concept is attractive for abciximab, owing to its relatively short plasma half-life. The intracoronary administration leads to a greater drug concentration in the infarct-related artery, which can be especially high in totally or partially occluded vessels. This may lead to a greater affinity to the platelets responsible for the occlusion and distal embolization during PCI.

In one trial, intracoronary abciximab administration was associated with reduced infarct size, compared with patients treated with standard intravenous abciximab during primary procedures [65]. The intracoronary administration of eptifibatide or tirofiban has not been tested in randomized trials, but the limited data from nonrandomized trials indicate that these compounds may also have more beneficial effects after intracoronary than intravenous administration [66,67].

Dosages

Since the early EPILOG study, abciximab has been administered in doses that have not been changed (Table 4). Data suggest that the abciximab dose may have to be more individualized

Table 4. Different dose regimens used in trials with abciximab, eptifibatide and tirofiban.

Drug	Trial	Dosage	Ref.
Abciximab	EPIC	0.25 mg/kg bolus plus 10 µg/kg/min infusion	[19]
	EPILOG, CAPTURE, EPISTENT, ISAR-REACT, ISAR-REACT 2, TARGET, MULTISTRATEGY, ISAR-SWEET, DANTE and ERASER	0.25 mg/kg bolus plus 0.125 µg/kg/min infusion	[21,22,24, 26,27,52,54, 80,82,83]
Eptifibatide	IMPACT II	135 µg/kg bolus dose plus infusion 0.5 µg/kg/min (low-dose) and 135 µg/kg bolus dose plus 0.75 µg/kg/min (high-dose)	[28]
	PURSUIT	180 µg/kg bolus plus 2 µg/kg/min infusion (low-dose) and 180 µg/kg bolus plus 1.3 µg/kg/min infusion (high-dose)	[29]
	ESPRIT and EVA-AMI	180 µg/kg bolus × 2 plus 2 µg/kg/min infusion	[30,35]
Tirofiban	RESTORE, ELISA 2 and TARGET	10 µg/kg bolus followed by 0.15 µg/kg/min infusion for 12 h	[32,33,52]
	ON-TIME 2, FATA and MULTISTRATEGY	25 µg/kg bolus followed by 0.15 µg/kg/min infusion for 12 h	[45,53,54]

than what is commonly anticipated, and that observed platelet aggregation may vary considerably between patients [68]. This may be especially important among STEMI patients. An interesting feature is that it has been more difficult to prove the effects of abciximab among STEMI patients than among patients without STEMI.

By contrast to abciximab, both eptifibatide and tirofiban doses have been escalated as an evolution of these therapies. Thus, there has been a gradual increase of the eptifibatide dose from the IMPACT-2 trial to the PURSUIT trial and finally the ESPRIT trial, which established the dose regimen that has been followed thereafter (Table 4). In addition, for tirofiban there has been a gradual increase in dosage over time (Table 4).

It must be emphasized that current doses of all GP IIb/IIIa inhibitors have been derived from studies carried out in other patient categories than those in which these therapies are practiced today. This is especially true for the use during primary PCI for STEMI. In one study, patients with STEMI were randomized to abciximab (0.25 mg/kg bolus followed by 0.125 µg/kg/min infusion for 12 h), normal-dose tirofiban (10 µg/kg bolus followed by 0.15 µg/kg/min infusion for 12 h), high-dose tirofiban (25 µg/kg bolus followed by 0.15 µg/kg/min infusion for 12 h) or no GP IIb/IIIa inhibitor [69]. Platelet aggregation, measured after ADP stimulation, was individually variable and suboptimal in all groups, especially in the periprocedural phase. Only in the high-dose tirofiban group was platelet aggregation inhibited to more than 80%. The results are well in line with what is known about increased platelet activity during ongoing MI and highlight the fact that the current regimen for GP IIb/IIIa inhibition in this condition is not well defined.

Thus, the actual optimal dose with respect to the underlying patient and disease characteristics is not well defined and warrants further attention.

Bleeding

The favorable effect of reducing thrombotic complications with GP IIb/IIIa inhibitors may, however, lead to an unfavorable increase in the risk of bleeding complications. In the EPIC trial, major bleeding occurred in 14% of abciximab-treated patients compared with 7% in the placebo group [19]. These high figures in both groups indicate that factors other than GP IIb/IIIa receptor blockade may have influenced the bleeding rates. A *post hoc* analysis indicated that the use of non-weight-adjusted heparin may have influenced the results [20]. Furthermore, vascular sheaths were kept in place for at least 6 h after the procedures.

Later analyses have revealed that the dose risk:benefit ratios of heparin as used during PCI are different in combination with GP IIb/IIIa inhibitors than without [70]. Thus, individualizing heparin dosing by, for example, activated coagulation time (ACT) improves the safety of this combination of compounds. Aiming at ACT levels from 200 to 300 s appears to be optimal to achieve proper anticoagulant effects without increasing the risk of bleeding.

Most bleeding associated with the use of GP IIb/IIIa inhibitors in connection with PCI is related to vascular access sites [20]. Experience has accumulated that attention and precautions when puncturing vessels (i.e., avoiding puncture of posterior walls and at sites not possible to compress), as well as the early removal of vascular sheaths, reduces bleeding complications [71].

With attention to heparin dosing and careful attention to punction techniques, the rate of major bleeding has been recorded in the range of 2–3% in later studies. From these figures it must be presumed that learning to use these compounds includes patient selection and avoiding their use in patients with an anticipated increased risk of bleeding.

Importantly, the rate of intracerebral bleeding has been in the order of 0–0.2% in trials, far lower than that observed for thrombolytic agents in connection with reperfusion therapy for acute MI, and with no increase compared with control treatments in randomized trials [72].

There are no specific antidotes to any of the GP IIb/IIIa antagonists. If severe and threatening bleeding occurs, or if the patient is scheduled for an immediate surgery procedure, the recommended mode of action differs between the compounds. With the half-lives of 1–2 h of eptifibatide and tirofiban, stopping drug administration will, in a relatively short-time, restore hemostasis with respect to GP IIb/IIIa inhibition. Since the effects of eptifibatide and tirofiban are highly concentration-dependent, platelet infusion will have limited, if any, effect on the inhibition in addition to stopping the administration.

Conversely, abciximab has a short half-life in plasma, and soon after stopping the administration there will be no drug left in the plasma. However, the binding to the platelet receptors

is tight, which is why a prolonged inhibitory effect will be expected, as pointed out previously. Infusion of platelets will, in this case, restore platelet function, even if some redistribution of abciximab from the host's platelets to those that are newly infused will occur [8].

In the case of bleeding, attention has to be focused on the level of anticoagulation. If ACT is high, careful reversal of heparin therapy with protamine should be considered. Presumably, with precautions in the use of GP IIb/IIIa receptor inhibitors and actions previously mentioned, when bleeding occurs, the common practice of administrating a high dose of a thienopyridine prior to a scheduled PCI may represent a problem that is at least as big and potentially more difficult to solve than the use of GP IIb/IIIa inhibitors.

Thrombocytopenia

A special feature is the occurrence of thrombocytopenia developing with platelet counts of less than 100,000 platelets/µl in approximately 0.5–5.6% of patients given GP IIb/IIIa inhibitors [19,21,22,28,29,32]. Severe thrombocytopenia (<50,000 platelets/µl) is observed in less than or equal to 2% of treated patients and among them a proportion develops profound thrombocytopenia (<20,000/µl), a condition that constitutes a substantial risk of bleeding *per se*. Severe or profound thrombocytopenia is observed more often after abciximab than after eptifibatide or tirofiban. Abciximab also increases the rate of thrombocytopenia compared with what is observed after the use of unfractionated heparin alone, while this is not the case for neither eptifibatide nor tirofiban [72–74]. Furthermore, an analysis from the TARGET study revealed that repeated treatment (i.e., previous exposure to the drug before the study) with abciximab, but not with tirofiban, was associated with an increased risk of thrombocytopenia [74]. However, data are conflicting, as the abciximab readministration registry could not demonstrate an increased rate of thrombocytopenia after abciximab readministration [75].

The mechanisms behind thrombocytopenia are somewhat unclear but the phenomenon may be related to conformation changes of epitopes on the surface of the platelets and subsequent clearance of the platelets from the circulation [73]. Being an antibody, abciximab may provoke an immunological response. The relationship with an immunological activation is supported by the increase risk of thrombocytopenia at repeated abciximab treatment and the fact that 6–7% of patients develop antibodies against abciximab after a single administration. Antibody development against eptifibatide and tirofiban has not been demonstrated.

The occurrence of thrombocytopenia is associated with an increased risk profile and, furthermore, with subsequent increased rates of ischemic complications, bleedings, urgent revascularizations and death. If profound thrombocytopenia develops, the risk of bleeding is eminent, which motivates platelet infusion to restore the platelet levels.

The risk of severe and profound thrombocytopenia observed after abciximab administration mandates monitoring of platelet count within 24 h after the start of abciximab administration, while monitoring is not necessary in patients given eptifibatide or tirofiban.

Studies of GP IIb/IIIa inhibitors versus bivalirudin

Bivalirudin is a direct thrombin inhibitor that is used as an anticoagulation treatment during PCI. Bivalirudin has been compared with GP IIb/IIIa inhibitors in three large-scale randomized trials: Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2, Acute Catherization and Urgent Intervention Triage Strategy (ACUITY) and Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trials.

The REPLACE-2 trial was the first large-scale trial comparing bivalirudin plus provisional GP IIb/IIIa inhibition with heparin plus standard GP IIb/IIIa inhibition in patients undergoing elective or urgent PCI [76]. Only 7% of the bivalirudin group received GP IIb/IIIa inhibitors. The primary end points of the study were the composite of death, MI or repeat revascularization at 6 months and death at 12 months after enrolment. Results were similar in the two groups. In addition, bivalirudin plus provisional GP IIb/IIIa inhibition reached the prespecified noninferiority margin.

In the ACUITY trial, 13,819 patients with acute coronary syndrome without ST-segment elevation undergoing coronary intervention were randomized to one of the three following treatments: heparin plus a GP IIb/IIIa inhibitor; bivalirudin plus a GP IIb/IIIa inhibitor; or bivalirudin alone [77]. PCI was performed in 7789 patients constituting the population for evaluation of bivalirudin in PCI. End points for the study were the composite ischemia en point (death, MI or urgent revascularization for ischemia), major bleeding (not coronary

artery bypass graft [CABG]-related) and the net clinical end point (composite ischemia end point or major bleeding). The composite ischemia end point did not differ between the three groups. It is worth noting that the majority of those patients who received a GP IIb/IIIa receptor inhibitor received eptifibatide (double bolus plus infusion) and less than 20% of those allocated to GP IIb/IIIa inhibitors received abciximab (standard dose). Major bleedings were significantly fewer in the bivalirudin-only group (3.5%) compared with both the heparin plus GP IIb/IIIa inhibitor group (6.8%) and the bivalirudin plus GP IIb/IIIa inhibitor group (7.8%). This radical reduction in major bleeding affected the net clinical end point in favor of the bivalirudin-only group.

The recently conducted HORIZONS-AMI study compared bivalirudin with the combination of unfractionated heparin plus a GP IIb/IIIa inhibitor during primary PCI for STEMI [78]. In this study, 52% of the patients allocated to GP IIb/IIIa inhibitors received abciximab in standard dose and 45.6% received eptifibatide in double bolus plus infusion. The two primary end points of the study were major bleeding and the combined end point of major bleeding or major adverse cardiovascular events, including death, reinfarction, target vessel revascularization owing to ischemia and stroke within 30 days. Bivalirudin significantly reduced the net adverse clinical events from 12.1% in the heparin plus GP IIb/IIIa platelet inhibitor group to 9.2% (relative risk: 0.76, 95% CI: 0.63–0.92; $p = 0.005$). This beneficial effect of bivalirudin was mainly due to a significant reduction of major bleeding from 8.3 to 4.9% (relative risk: 0.60, 95% CI: 0.46–0.77; $p < 0.001$). However, bivalirudin was associated with an increase of acute (≤24 h from PCI) stent thrombosis (1.3 vs 0.3%; $p < 0.001$), but this unfavorable effect disappeared after 30 days (stent thrombosis: 2.5 vs 1.9%; $p = 0.30$). Bivalirudin-treated patients also had lower cardiac death rates at 30 days (1.8 vs 2.9%; $p = 0.03$) and lower all-cause death rates (2.1 vs 3.1%; $p = 0.047$) at 30 days postprocedure.

Pleiotropic actions of GP IIb/IIIa inhibitors

■ Effect on restenosis

The only GP IIb/IIIa inhibitor that theoretically should have any effect on restenosis after PCI is abciximab. This is due to the affinity of abciximab to the Mac-1 and vitronectin receptors, which have a direct effect on smooth muscle and endothelial cell activation, as well as an anti-inflammatory effect through the inhibition of platelet–monocyte binding.

Data suggesting an effect on restenosis, especially in diabetics, came from the EPISTENT study [79]. In 335 diabetic patients who received stents, it was found that there was a trend for reduced late loss after abciximab compared with after control treatment. These findings were confirmed by the Is Abciximab a Superior Way to Eliminate Elevated Thrombolic Risk in Diabetics (ISAR-SWEET) study, selectively investigating diabetic patients, in which the restenosis rate as well as the rate of target lesion revascularization was significantly lower in the abciximab group [80]. Further support was derived from a subgroup analysis of the 422 diabetic patients included in the ISAR-REACT trial, in which patients with planned stenting after preloading with clopidogrel 600 mg were included [81].

In the aforementioned studies, the data supporting effects on restenosis in diabetic patients were derived from evaluation by coronary angiographies. Following these observations, the randomized Diabetes Abciximab Stent Evaluation (DANTE) trial was designed with the primary aim of answering the question of the effect on restenosis by abciximab in diabetic patients undergoing coronary stenting [82]. The restenotic process was not only evaluated by coronary angiography but also by intravascular ultrasound, and neither parameters were influenced by treatment with abciximab. A limitation was that only 96 patients were included in the trial. Furthermore, the binary restenosis rate was unexpectedly low for a diabetic population.

Neither the ISAR-REACT nor the Evaluation of ReoPro® and Stenting to Eliminate Restenosis (ERASER) study could confirm any effect on restenosis in the general population [81,83].

GP IIb/IIIa inhibitors & inflammation

There is evidence that abciximab may have an anti-inflammatory effect. Neumann *et al.* demonstrated a reduced platelet–monocyte interaction in patients treated with abciximab compared with those treated with placebo [84]. This effect of abciximab on inflammatory response was then shown on a much larger scale in a subanalysis of the previously mentioned EPIC study [85]. Åstrom-Olsson *et al.* demonstrated a dissociation of the inflammatory response in patients treated with abciximab in the setting

of primary PCI [86]. There was an increase in the level of proinflammatory cytokines IL-6 and IL-8, metalloproteinase 9 and C-reactive protein, and a decrease in the levels of myeloperoxidase and malondialdehyde, while the levels of neutrophil gelatinase-associated lipocalin remained unaffected.

In another study, treatment with eptifibatide resulted in an increase in myeloperoxidase levels compared with bivalirudin treatment [87].

More answers about the anti-inflammatory effect of different GP IIb/IIIa inhibitors and bivalirudin will be drawn from the comparison of abciximab versus eptifibatide versus bivalirudin in patients treated with PCI for acute coronary syndromes (AEB study, European Clinical Trials Database number 2009–009039–32, [201]), where 180 patients (90 with STEMI and 90 with NSTEMI/UA) will be randomized between abciximab, eptifibatide and bivalirudin, and inflammatory parameters, as well as platelet activation, will be measured at different time points during and after the index procedure.

GP IIb/IIIa inhibitors in special clinical scenarios

■ Diabetes mellitus

Patients with diabetes carry a higher risk after PCI, after both balloon dilatation and stenting, than patients without diabetes [88]. This higher risk also implies a higher mortality. Although the risk after CABG is also increased in diabetics, the even worse outcome after PCI is a strong argument for choosing CABG instead of PCI for these patients, especially if they suffer from multivessel disease [89]. One explanation for the increased risk associated with PCI may be the known increase in platelet and coagulation activation among diabetics compared with nondiabetics [90]. Pooled data from the EPIC, EPILOG and EPISTENT studies, comprising 1462 patients with diabetes undergoing PCI, indicate that the use of abciximab in this patient group is especially beneficial [91]. Thus, 1-year mortality was reduced from 4.5 to 2.5% ($p = 0.031$) by abciximab in this patient group. Even in the era of drug-eluting stents, pooled retrospective data from a number of studies indicate beneficial effects of GP IIb/IIIa inhibitors among diabetics [92]. Data so far suggest that much of the increased risk that burdens diabetics in connection with PCI is neutralized by GP IIb/IIIa inhibitors. However, data from the ISAR-SWEET study indicate that at least in patients undergoing elective PCI, this beneficial effect of abciximab is no longer abundant if the patients are pretreated with a high dose of a thienopyridine (i.e., clopidogrel) [80].

■ Patients with renal failure

Patients with renal failure have an increased risk of adverse outcomes including bleeding after PCI. The fact that the use of GP inhibitors is associated with an increased risk of bleeding raised concerns regarding their use in this particular population. The exclusion of patients with elevated serum creatinine from all randomized studies testing the effect of GP IIb/IIIa inhibitors led to a lack of evidence concerning their use in this high-risk population. Abciximab, eptifibatide and tirofiban have different characteristics that influence their administration in patients with renal failure. Abciximab is metabolized through the reticuloendothelial system and no dose adjustment is needed in patients with renal failure. Eptifibatide is almost totally excreted through the kidneys and a 50% dose reduction is recommended in patients with creatinine clearance less than 50 ml/min, while its use is contraindicated for patients under hemodialysis. Tirofiban is also partly excreted by the kidneys (60–70%) and a 50% dose reduction is recommended for patients with creatinine clearance less than 30 ml/min. However, tirofiban can be removed by hemodialysis.

There are no randomized studies testing the effect of GP blockers in patients with renal failure undergoing PCI. However, subgroup analyses from randomized trials, as well as nonrandomized registry data, point out the relative safety of GP inhibitors in this high-risk population [93–97]. Patients with renal failure have an increased risk of bleeding, but this risk does not seem to be severely increased by treatment with GP IIb/IIIa inhibitors. Abciximab may, for reasons previously highlighted, have an advantage for these patients. If the use of eptifibatide or tirofiban is considered, it is strongly recommended to perform a creatinine clearance calculation before administration, especially in the elderly and in women with borderline serum creatinine levels in order to use the right dose of GP inhibitor.

GP IIb/IIIa inhibitors in aorto–coronary bypass grafts PCI

Interventions in degenerated aorto–coronary bypass grafts are associated with a high risk for adverse outcomes and high complication rates [98,99]. Although the usefulness of GP IIb/IIIa inhibitors in patients undergoing graft PCI was not studied in randomized trials

addressing this specific issue, these patients were included in large-scale randomized trials in patients undergoing high-risk interventions. A pooled analysis of five randomized trials of intravenous GP inhibitor administration (three with abciximab and two with eptifibatide) demonstrated that PCI in vein grafts was followed by double mortality compared with if PCI was performed in a native vessel. However, there was no benefit of GP IIb/IIIa inhibitors among those treated in vein grafts [100]. On the contrary, placebo-treated patients tended to have better outcomes compared with those randomized to GP IIb/IIIa inhibitors.

Future perspective

The introduction of new antiplatelet and anticoagulant drugs for patients with coronary syndromes will change future indications for the use of GP IIb/IIIa inhibitors.

New and stronger platelet P2Y12 receptor blockers such as prasugrel and ticagrelor have already shown their clinical superiority compared with clopidogrel in patients with acute coronary syndromes [101,102]. Potent platelet inhibition by these drugs may reduce the need of GP IIb/IIIa inhibitor use. The protease-activated receptor 1 inhibitor SCH 530348 is now being tested in a large-scale randomized trial in high-risk patients with acute coronary syndromes, and possible positive findings will lead to changes of everyday practice in these patients [103].

The direct thrombin inhibitor bivalirudin is being increasingly used in patients undergoing PCI, mainly owing to the beneficial effect of reducing major bleeding complications. However, the use of the radial approach during PCI, which almost eliminates access site bleeding complications, may lead to a reappraisal of its use [104].

Owing to recent positive study results as well as the simplicity of their use, the wide use of thrombus aspiration devices in patients undergoing PCI may reduce the need of potent platelet inhibition provided by GP IIb/IIIa blockers[105].

Executive summary

- Platelet aggregation can be effectively inhibited by blocking the platelet glycoprotein (GP) IIb/IIIa receptors.
- There are three available GP IIb/IIIa inhibitors; abciximab (a chimeric fragment of a monoclonal antibody), eptifibatide (a heptapeptide) and tirofiban (a tyrosine derivative nonpeptide).
- GP IIb/IIIa inhibitors reduce the risk of clinically important thrombotic complications during and after high risk PCI (but without ongoing ST-elevation myocardial infarction [STEMI]).
- If patients are pretreated with thienopyridines, the beneficial effects are seen only in patients with elevated markers of myocardial injury (troponins), while no benefit can be demonstrated in patients without elevated markers.
- GPIIb/IIIa inhibitors also improve the outcome after primary percutaneous coronary intervention (PCI) for STEMI.
- Results are conflicting regarding the value of early administration of GP IIb/IIIa inhibitors (i.e. in the ambulance, the emergency department or the first-contact hospital without on-site PCI facilities) compared with periprocedural administration in primary PCI for STEMI.
- Although the beneficial effects of abciximab are better documented than the beneficial effects of eptifibatide and tirofiban, especially for patients without ongoing STEMI, the current body of knowledge does not speak in favor of any clinically important differences between the three compounds.
- Intracoronary administration may represent a promising strategy, especially in association with primary PCI for STEMI.
- The dosages that are currently used are not well defined with respect to demonstrating inhibitory effects of platelet aggregation.
- Bleeding may represent a problem that can be minimized by careful attention to vascular access sites and by using moderate dosages of adjunctive heparin guided by activated coagulation time.
- Thrombocytopenia occurs after abciximab administration and mandates monitoring of platelet counts during the first 24 h, while no excessive rates of thrombocytopenia have been observed after usage of eptifibatide or tirofiban.
- The thrombin inhibitor bivalirudin may represent an alternative to GP IIb/IIIa receptor antagonists.
- Effects of GP IIb/IIIa inhibitors on restenosis and inflammation are not sufficiently studied.
- GP IIb/IIIa inhibitors may be especially valuable in diabetic patients.
- In patients with renal failure, dose adjustments are needed for eptifibatide and tirofiban but not for abciximab.
- GP IIb/IIIa inhibitors have no beneficial effect during PCI for lesions in vein grafts.

The issue of responsiveness to the antiplatelet treatment is not adequately addressed in studies on GP IIb/IIIa inhibitors. An individualized treatment based on the results of bedside *in vitro* tests, with a different combination of orally and intravenously administered antiplatelet and anticoagulant agents may be the future in the treatment of patients undergoing PCI procedures.

Conclusion

Glycoprotein IIb/IIIa inhibitors are useful to prevent thrombotic complications in patients undergoing PCI. This is well demonstrated in patients with acute coronary syndromes and elevated markers of myocardial injury but without ongoing STEMI. For patients with STEMI undergoing primary PCI, data on the beneficial effects of these compounds are less robust. In low-risk patients, GP IIb/IIIa inhibitors have no beneficial effect if patients are treated with a thienopyridine before the PCI. Available data do not suggest any important differences between the three available compounds.

Bivalirudin, which is associated with a reduction of bleeding complications, represents a promising alternative to the use of GP inhibitors.

Specific issues, such as possible effect of GP IIb/IIIa inhibitors on restenosis or inflammation, are not fully resolved and need to be addressed in future studies. Furthermore, intracoronary administration may represent an interesting development in the setting of primary PCI.

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