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Platelet Glycoprotein IIb/IIIa Receptor Antagonists

Current Concepts and Future Directions

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Contents

Abstract

Platelets play a key role in the development of thrombosis. Glycoprotein (GP) IIb/IIIa antagonists are a new class of potent drugs that profoundly inhibit platelet function by blocking the key receptor involved in platelet aggregation.

Several antiplatelet agents with varying characteristics have emerged in the past few years and have been evaluated in a variety of potential clinical settings. Clinical trials have established the effectiveness of these drugs in conditions where thrombosis plays a major contributing role such as unstable angina pectoris, myocardial infarction, and high-risk coronary intervention. Despite their po-

tent antiplatelet effects, GP IIb/IIIa antagonists appear to be remarkably well tolerated, provided that the concomitant use of other anticoagulants such as heparin is managed carefully. Ongoing and future studies will further refine the role of GP IIb/IIIa antagonists, explore new applications, and further test their safety and cost effectiveness in the short and long term.

Platelets play an integral role in the cascade of thrombus formation that follows vascular injury. However, the pathological activation of thrombotic mechanisms can result in ischaemic vascular injury[1-3] (fig. 1). Endothelial damage and overt plaque rupture can result in the exposure of substances that promote platelet adhesion, activation, aggregation, and subsequent thrombus formation. If a thrombus completely occludes a coronary vessel, an acute myocardial infarction (MI) can develop. A nonobstructive thrombus can result in symptoms of unstable angina pectoris or a non-Q wave MI.

Recently, a new group of potent antiplatelet agents have been developed which inhibit platelet aggregation and subsequent thrombus formation by blocking glycoprotein (GP) IIb/IIIa receptors on the surface of platelets (fig. 2). This article briefly reviews key aspects of platelet physiology in relation to GP IIb/IIIa and describes the major compounds currently available, as well as recent relevant clinical trials. It also discusses potential complications related to the use of these drugs, and highlights areas of controversy and potential future directions for their use.

1. Platelets and GP IIb/IIIa Receptors

Platelets are small discoid non-nucleated fragments that circulate in the blood. Because of higher shear forces, they tend to be positioned close to the blood vessel wall interface. When circulating platelets encounter a damaged vessel they adhere to the exposed adhesive glycoproteins, such as GP Ib and Ia/IIa[4] (fig. 3).

Following adhesion, various agonists, including thrombin, collagen, thromboxane A2, serotonin, adrenaline (epinephrine) and adenosine diphosphate (ADP) combine with specific receptors on the platelet's surface to induce platelet activation.[5] These agonist-receptor interactions are coupled through G proteins to generate secondary messengers which, in turn, induce structural and morphological changes in the platelets and result in the release of platelet granules.[6,7]

During platelet activation, a key receptor on the surface of the platelet, the GP IIb/IIIa receptor, also becomes activated. Although many agonists have the potential to activate platelets, the final common pathway of platelet aggregation proceeds via GP IIb/IIIa[8] (fig. 3).

The GP IIb/IIIa receptor is a member of a family of adhesive receptors (integrins) composed of α and β transmembrane proteins[9] (fig. 4). GP IIb/IIIa itself is composed of α_{IIb} and β_3 units and is specific for platelets. There are an estimated 50 000 to 80 000 GP IIb/IIIa receptors on the surface of each platelet.[10] Platelet activation results in a change in the shape of the receptor, which greatly increases its normal low affinity for its natural ligands, specifically, fibrinogen and von Willebrand

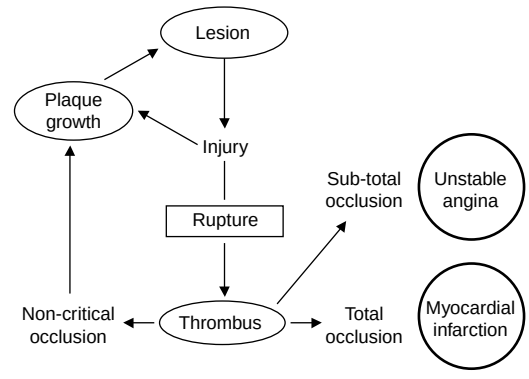

Fig. 1. The progression from stable atherosclerotic disease to acute coronary syndromes. Thrombus forms at the site of plaque rupture; it can be occlusive (acute myocardial infarction), subtotally occlusive (unstable angina pectoris), or noncritically occlusive (plaque growth).

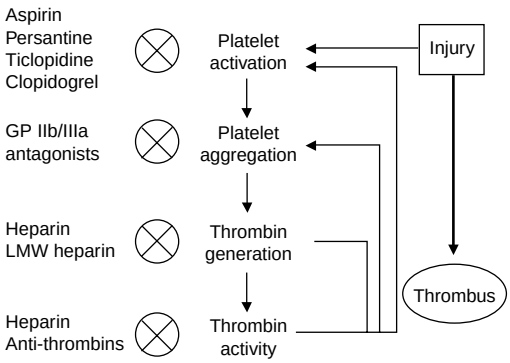

Fig. 2. The progression from vessel wall injury to thrombus formation. Four major steps are targeted by current therapeutic agents: platelet activation, platelet aggregation, thrombin generation and thrombin activity. **LMW** = low molecular weight.

factor.[11,12] In addition to activation of surface receptors, internal stores of GP IIb/IIIa are mobilised to join the existing surface receptors and further increase the overall surface expression of GP IIb/IIIa.

Fibrinogen is a dimeric molecule of 3 chains: α, β, and γ.[13] It contains 2 arginine-glycine-aspartic acid (RGD) sequences on each α chain. It also contains a 6-amino acid sequence of lysine-glutamic acid-alanine-glycine-aspartic acid-valene (KQAGDV) on the carboxyl terminal of the γ chain.[14-16] Electron microscopic examination of isolated GP IIb/IIIa receptors reveals that 85% of the receptor is bound specifically to the γ chain of fibrinogen, while the remaining 15% is presumably bound to α chain RGD sequences at a variety of positions in the molecule.[17] The relationship between RGD and KQAGDV sequences, and the possible role of other, as yet unidentified receptors, is still not fully understood.

Von Willebrand factor is a multimeric molecule that plays a much more important role than fibrinogen in mechanical shear-induced platelet aggregation.[18] By being able to bind to more than one GP IIb/IIIa receptor, fibrinogen and von Willebrand factor act to crosslink platelets, creating an arborising network of activated platelets at the injury site as platelet aggregation proceeds (fig. 5). Because an activated platelet membrane is an important cofactor in the generation of thrombosis, the end result of the adhesion/activation/aggregation process is a concentration of activated platelet membrane at the injury site. This allows coagulation to proceed, but confines the coagulation process to the injured surface.[2]

2. Types of GP IIb/IIIa Receptor Antagonists

Two general types of GP IIb/IIIa receptor antagonists are available: noncompetitive (monoclonal antibodies) and competitive (peptides, peptidomimetics).

2.1 Monoclonal Antibodies

The first GP IIb/IIIa antagonists developed were murine monoclonal antibodies. These agents proved extremely effective in preventing thrombosis in experimental animal models,[19-21] but were significantly immunogenic.

The structure of the antibody was then modified to reduce the immunogenic nature of the murine compound. The murine constant domain was replaced with the corresponding human sequence, producing a chimeric compound, and the Fab fragments taken to create c7E3 Fab or abciximab.

Administered intravenously, circulating abciximab has a plasma half-life of less than 10 min-

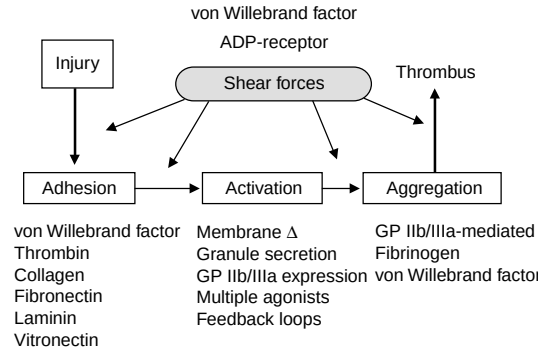

Fig. 3. The 3 major steps of platelet activity during thrombus formation: adhesion, activation, and aggregation.

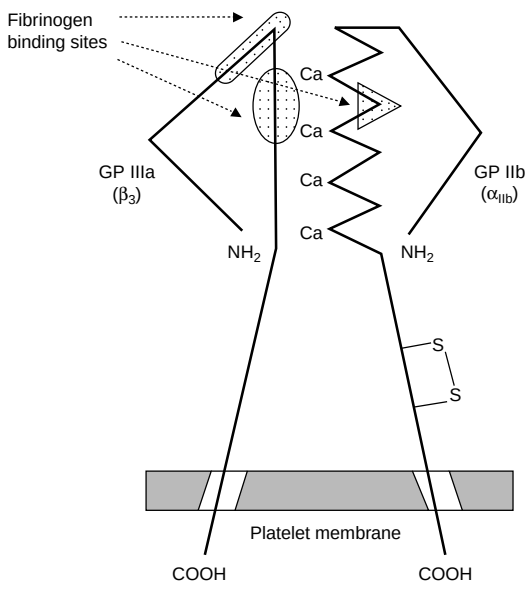

Fig. 4. Structure of the GP IIb/IIIa receptor.

utes;[22] however, after administration, abciximab is very avidly bound to platelets. This results in a prolonged biological effect because platelet-bound abciximab remains attached to the platelets.

Receptor blockade assays have shown that maximal blockade occurs 30 minutes after a bolus dose of abciximab. Twelve hours after drug infusion the median extent of the receptor blockade drops to approximately 68%. Partial recovery from platelet blockade occurs gradually after cessation of abciximab therapy, with a residual blockade of 29% at 8 days and 13% at 15 days.[23] Thus, platelet to platelet transfer of the antibody must occur, since inhibition extends beyond the lifetime of an individual platelet.

2.2 Peptides and Peptidomimetics

Another approach to GP IIb/IIIa blockade involves the use of compounds that mimic the RGD sequences on fibrinogen.[24,25] A variety of peptides (eptifibatide) and peptidomimetic compounds (tirofiban, lamifiban) have been developed. Eptifibatide and tirofiban have recently been approved for clinical use by the Food and Drug Administration (FDA) in the United States.

Peptide GP IIb/IIIa antagonists contain either the RGD sequence itself, or a similar sequence, such as lysine-glysine-aspartic acid (KGD). Cyclic forms of the peptides are more resistant to degradation than linear peptides, but still have significantly short half-lives because they are broken down in the body.[26] Another factor contributing to their relatively short half-life is renal excretion.

The nonpeptide, or peptidomimetic, antagonists are designed to have a spatial and charge conformation which closely resembles that of the RGD binding sequence. Yet other GP IIb/IIIa antagonists (xemilofiban, orbofiban, sibrafiban) are prodrugs of peptidomimetic compounds and can be given orally. These oral compounds significantly extend the potential duration of potent antiplatelet inhibition.

Because peptide and peptidomimetic compounds are competitive GP IIb/IIIa antagonists, therapeutic efficacy is dependent on maintaining plasma concentrations high enough to compete successfully with fibrinogen for GP IIb/IIIa receptor binding.

2.3 Possible Role of the Vitronectin Receptor

Competitive inhibitors are generally specific for the GP IIb/IIIa receptor. This is in contrast to the noncompetitive antibody compound abciximab, which binds not only to the GP IIb/IIIa receptor but also to other integrins such as the vitronectin receptor ($\alpha_v\beta_3$). This receptor is present on many cell types, particularly vascular endothelial cells. Blocking the vitronectin receptor may be important because it has a regulatory role in the processes of cell adhesion, migration, and proliferation; it also is upregulated under conditions of rapid vascular growth, such as occurs with angiogenesis.

Thus, inhibitors of $\alpha_v\beta_3$-induced neointimal cell proliferation might have a role in the prevention of restenosis. However, to date, the GP IIb/IIIa antagonists have not been shown to reduce restenosis, except perhaps in the very special setting of patients with diabetes mellitus undergoing stent im-

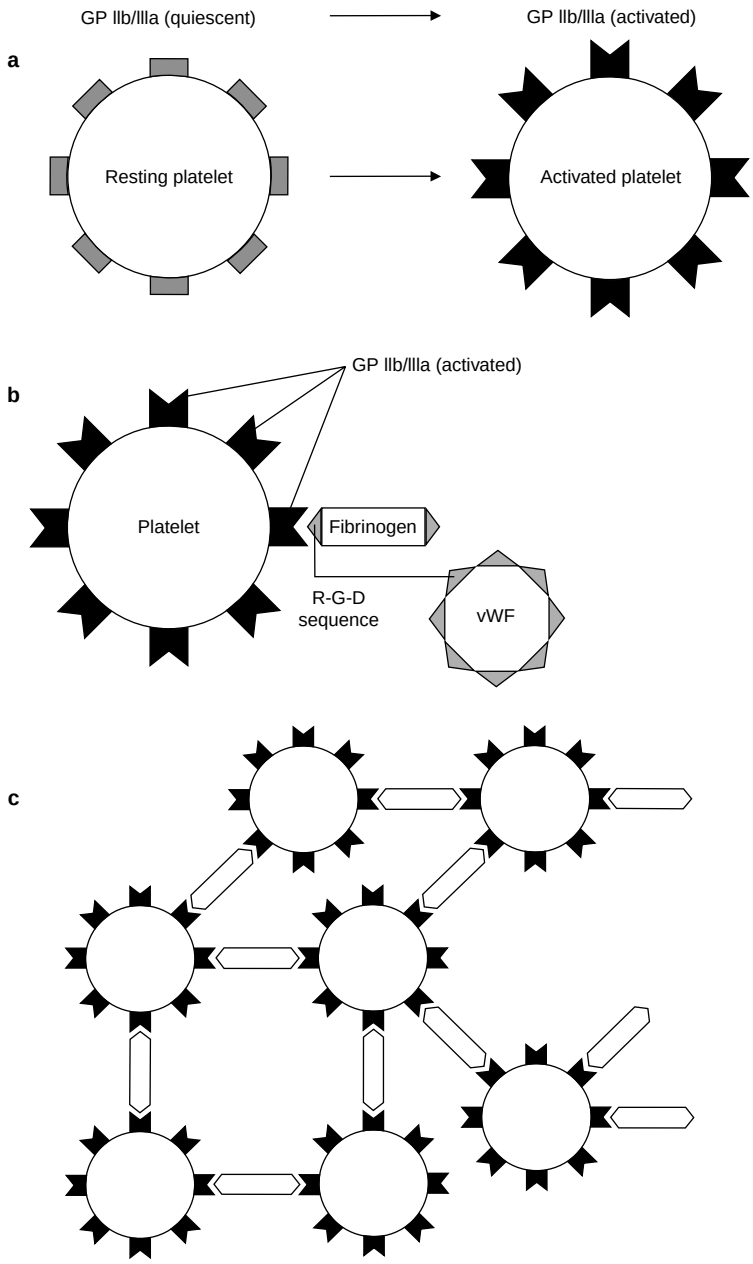

Fig. 5. The role of GP IIb/IIIa in platelet aggregation. Quiescent platelets are activated, and expose the activated GP IIb/IIIa receptor (**a**). The natural ligands for the GP IIb/IIIa receptor are fibrinogen and von Willebrand factor (vWF) (**b**). Fibrinogen (which is dimeric) and vWF (which is multimeric) can crosslink platelets, creating a growing mass of aggregated, activated platelets (**c**).

plantation. The role of $\alpha_v\beta_3$ in other long term events is theoretically intriguing, but as yet unproven. Whether differences in the specificity of the GP IIb/IIIa antagonists translate into differ-

ences in clinical efficacy is not yet known, and awaits head-to-head trials of the agents.

3. Clinical Trials of Intravenous Agents

Tables I and II list major recent clinical trials of GP IIb/IIIa antagonists.

3.1 Interventional Cardiology

3.1.1 Abciximab

EPIC

EPIC, (for the full names of clinical trials referred to in this article, see Glossary of trial acronyms) the first major clinical trial utilising a GP IIb/IIIa antagonist, involved high-risk patients undergoing angioplasty or directional atherectomy.[27,28] Patients were randomised to placebo, a bolus dose of abciximab, or a bolus plus a 12-hour infusion of abciximab.

The composite rate of adverse events (death, MI or urgent revascularisation) was significantly reduced with abciximab at 30 days (8.3% with bolus/infusion *vs* 12.8% with placebo; p = 0.008), and at 6 months (27% with bolus/infusion *vs* 35.1% with placebo; p = 0.001). At 3 years, this clinical benefit was maintained (composite event rate 41.1% with bolus/infusion *vs* 47.2% with placebo; p = 0.009).[29] Moreover, in the highest risk subgroup of patients (those with unstable angina pectoris or acute MI at 3 years, there was a dramatic improve-

Glossary: Clinical trials and their acronyms

ADMIRAL	Abciximab with PTCA and stent in acute myocardial infarction
APLAUD	AntiPLAtelet Useful Dose
BRAVO	Blockade of the GP IIb/IIIa Receptor to Avoid Vascular Occlusion
CAPTURE	c743 Fab Antiplatelet Therapy in Unstable Refractory Angina
EPIC	Evaluation of GPIIb/IIIa platelet receptor antagonist 7E3 in Preventing Ischemic Complications
EPILOG	Evaluation in PTCA to Improve Long-term Outcome with abciximab GPIIb/IIIa blockage
EPISTENT	Evaluation of Platelet GPIIb/IIIa Inhibitor for Stenting
ERASER	Evaluation of ReoPro and Stenting to Eliminate Restenosis
EXCITE	Evaluation of Xemilofiban in Controlling Thrombotic Events
GRAPE	Glycoprotein Receptor Antagonist Patency Evaluation
GUSTO-IV-AMI	Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries-IV Acute Myocardial Infarction
IMPACT-II	Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II
IMPACT-AMI	Integrelin to Manage Platelet Aggregation to Prevent Coronary Thrombosis in Acute Myocardial Infarction
OPUS	Ofofiban in Patients with Unstable coronary Syndromes
ORBIT	Oral Glycoprotein IIb/IIIa Receptor Blockage to Inhibit Thrombosis
PARADIGM	Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction
PARAGON	Platelet GPIIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organisation Network
PRISM	Platelet Receptor Inhibition in Ischemic Syndrome Management
PRISM-PLUS	Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms
PURSUIT	Platelet GPIIb/IIIa in Unstable angina Receptor Suppression Using Integrilin Therapy
RAPPORT	ReoPro and Primary PTCA Organization and Randomized Trial
RESTORE	Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis
SOAR	Safety of Orbofiban in Acute Coronary Research
SPEED	Strategies for Patency Enhancement in the Emergency Department
SYMPHONY	Sibrafiban Versus Aspirin to Yield Maximum Protection from Ischaemic Heart Events Post Acute Coronary Syndromes
TAMI	Thrombolysis and Angioplasty in Myocardial Infarction
TIMI	Thrombolysis in Myocardial Infarction

GP = glycoprotein; **PTCA** = percutaneous transluminal coronary angioplasty.

Table I. Reported clinical trials with the GP IIb/IIIa antagonists[a]

	Clinical setting		
Agent	Percutaneous intervention	Unstable angina pectoris	Acute myocardial infarction
Abciximab (ReoPro®)	EPIC PROLOG EPILOG RAPPORT ERASER EPISTENT CAPTURE ADMIRAL	RAPPORT CAPTURE	TAMI-8[b] GRAPE RAPPORT
Eptifibatide (Integrilin®)	IMPACT-II	PURSUIT	IMPACT-AMI
Tirofiban (Aggrastat®)	RESTORE	PRISM PRISM-PLUS	
Lamifiban		Canadian Lamifiban Study PARAGON-A	PARADIGM

a See Glossary for the full names of the clinical trials cited in this table.

b TAMI-8 utilised a murine antibody, not the chimeric antibody.

ment in the incidence of death (5.1 *vs* 12.7% with placebo), MI (6.9 versus 14.7% with placebo), revascularisation (34 versus 41.1% with placebo) and composite events (39.2 versus 51% with placebo).

EPILOG

The EPILOG study evaluated the efficacy of abciximab therapy in a broader population including low-to-medium risk patients undergoing percutaneous coronary intervention.[30] This study also evaluated the use of more controlled doses of heparin and early sheath removal to reduce the risk of bleeding. Patients were randomised to 3 groups: abciximab with standard dose heparin (100 U/kg), abciximab with low dose heparin (70 U/kg), or placebo with standard dose heparin.

The trial was terminated prematurely because of excess benefit in the 2 abciximab groups compared with placebo. At the time the trial was stopped, 2792 patients had been enrolled. At 30 days, the combined incidence of death, MI, or urgent intervention was 11.7% in the standard-dose heparin (100 U/kg) plus placebo group, 5.4% in the standard-dose heparin (100 U/kg) plus abciximab group, and 5.2% in the low-dose heparin (70 U/kg) plus abciximab group ($p < 0.001$).

The relative decrease of 56% in adverse events in both low- and medium-risk patients amounted to almost twice the benefit shown in the previous EPIC study, which included only higher risk patients. At 6 months the incidence of the primary end point of death, MI, or any additional revascularisation was 25.8% with placebo, 22.3% with standard-dose heparin plus abciximab, and 22.8% with low-dose heparin plus abciximab ($p = 0.04$).

The incidence of bleeding complications was much lower than in the EPIC trial, and was not significantly different among the 3 groups. The incidence of major bleeding was 3.1% in the standard-dose heparin plus placebo group, 3.5% in the standard-dose heparin plus abciximab group, and 2% in the low-dose heparin plus abciximab group.

CAPTURE

The CAPTURE trial investigated the effects of abciximab treatment in patients with refractory unstable angina undergoing coronary intervention.[31] CAPTURE differed from the preceding trials in that pretreatment lasted for 18 to 24 hours prior to intervention, and only 1 hour (instead of 12 hours) of post-intervention therapy was given.

Like EPILOG, CAPTURE was also terminated prematurely, at the recommendation of the data and safety monitoring board, because of excess benefit in the active treatment group that exceeded prespecified criteria for stopping the trial. At 30 days there was a significant (29% relative) reduction of

Table II. Published major clinical trials of glycoprotein (GP) IIb/IIIa antagonists: clinical setting and 30-day results[a]

Study (no. of patients)	Clinical setting	Composite events measured at 30 days	Magnitude of effect of drug *vs* placebo (p value) at 30 days
Abciximab			
EPIC[27-29] (n = 2099)	High risk coronary angioplasty or atherectomy	Death, MI urgent revascularisation	8.3 *vs* 12.8% (p = 0.008)
EPILOG[30] (n = 2792)	Coronary intervention	Death, MI or urgent revascularisation	Standard dose: 5.4 *vs* 11.7% (p < 0.001) Low dose: 5.2 *vs* 11.7% (p < 0.001)
CAPTURE[31] (n = 1265)	Refractory unstable angina undergoing intervention	Death, MI or urgent revascularisation	11.3 *vs* 15.9% (p = 0.012)
EPISTENT[32,33] (n = 2399)	Stent-eligible coronary intervention	Death, MI or urgent revascularisation	5.3 *vs* 10.8% (p < 0.001)
RAPPORT[34] (n = 483)	Acute MI undergoing primary PTCA	Death, MI or any revascularisation	13.3 *vs* 16.1% (P=.32)
TIMI-14[35] (n = 681)	Acute MI (with SK or t-PA)	Endpoint of TIMI grade-3 flow at 90 minutes	72 *vs* 43% (with thrombolytic therapy)
GRAPE[36] (n = 60)	Acute MI	Angiographic TIMI flow grade (median time of 45 minutes)	40% TIMI grade 2/3 flow 18% TIMI grade 3 flow (no placebo control)
Murine antibody			
TAMI-8[37] (n = 70)	Acute MI (with t-PA)	Endpoint of presence of rest angina with ECG changes, reinfarction, the need for urgent revascularisation or revascularisation and death	13 *vs* 20%
Eptifibatide			
IMPACT-II[38] (n = 4010)	Coronary intervention	Death, MI, or urgent revascularisation	Low dose: 9.2% *vs* 11.4% (p = 0.062) High dose: 9.9% *vs* 11.4% (P=.22)
PURSUIT[39] (n = 10984)	Acute coronary syndromes	Death, MI	14.2 *vs* 15.7% (p = 0.04)
IMPACT-AMI[40] (n = 180)	Acute MI (with t-PA)	Endpoint of TIMI grade-3 flow at 90 minutes	66 *vs* 39% (p = 0.006)
Lamifiban			
Canadian Lamifiban Study[41] (n = 365)	Acute coronary syndromes	Death or MI	3.7 *vs* 8.1% (p = 0.07)
PARAGON-A[42] (n = 2282)	Acute coronary syndromes	Death or MI	Low dose: 10.6 *vs* 11.7% (p = 0.48) High dose: 12.0 *vs* 11.7% (p = 0.668)
PARADIGM[32] (n = 353)	Acute MI (with t-PA)	Reperfusion as assessed by continuous ECG at 90 minutes	80.1 *vs* 62.5% (p = 0.005)
Tirofiban			
PRISM[43] (n = 3232)	Acute coronary syndromes	Death, MI or recurrent ischaemia	15.9 *vs* 17.1% (p = 34)
PRISM-PLUS[44] (n = 1915)	Higher risk acute coronary syndromes	Death, MI or recurrent ischaemia	18.5 *vs* 22.3% (p = 0.03)
RESTORE[45] (n = 2141)	Unstable angina patients undergoing coronary intervention	Death, MI or any revascularisation	10.3 *vs* 12.2% (p = 0.160)

a For the full names of the clinical trials cited in this table, see the Glossary.

MI = myocardial infarction; **PTCA** = percutaneous coronary angioplasty; **t-PA** = tissue plasminogen activator (alteplase).

death, MI or urgent intervention with abciximab, (treatment group 11.3%, placebo group 15.9%, p = 0.012). At 6 months, however, there was no significant difference between the treatment group and the placebo group with respect to the composite rates of adverse events of death, MI, or any repeat

revascularisation (treatment group 30.8%, placebo group 31%).

RAPPORT

The RAPPORT trial examined the efficacy of abciximab in the setting of primary percutaneous transluminal coronary angioplasty (PTCA) for acute MI.[34] In this study, patients presenting within 12 hours of an acute MI and deemed to be candidates for primary angioplasty were randomised to receive either an abciximab bolus plus a 12-hour infusion (n = 241) or placebo (n = 242). Heparin was administered in all patients as a 100 U/kg bolus, with activated clotting times (ACTs) titrated to >300s, and could be continued for up to 48 hours after the procedure.

By intention-to-treat analysis, there were no significant differences between groups in the composite endpoint of death, reinfarction, or any total target vessel revascularisation at 30 days (13.3% with abciximab *vs* 16.1% with placebo; p = 0.32) or at 6 months, the preliminary endpoint of the study (28.2% with abciximab *vs* 28.1% with placebo; p = 0.97). However, when looking at the composite incidence of death, MI and urgent (rather than total) revascularisation, there was significant benefit with abciximab at 30 days (5.3 *vs* 11.2% with placebo; p = 0.03) and at 6 months (11.6 *vs* 17.8% with placebo; p = 0.05).

ERASER

The ERASER trial sought to determine whether abciximab was of value in preventing intimal hyperplasia after stenting.[46] 225 patients were randomised to receive either placebo, a bolus plus a 12-hour infusion of abciximab, or a bolus plus a 24-hour infusion of abciximab. The primary endpoint was the percentage volume obstruction, as measured by intravascular ultrasound, at 6-month follow-up catheterisation, which was performed in 152 patients (68%).

At 6 months the mean percentage volume obstruction was 32.4% in the placebo group, 37.7% in the 12-hour abciximab group, and 34.2% in the 24-hour abciximab group (not significant). Similarly, the composite incidence of death, MI, and target vessel revascularisation at 6 months was 25.4% in the placebo group, 20.3% in the 12-hour abciximab group, and 22.7% in the 24-hour abciximab group. Thus, treatment with abciximab did not result in a significant decrease in intimal hyperplasia after intracoronary stent placement.

EPISTENT

The EPISTENT trial evaluated the use of an GP IIb/IIIa antagonist in the setting of elective coronary stenting in a broad patient population, with the only exclusion criteria being interventions performed in the setting of an acute MI.[32] A total of 2399 patients were randomised to one of 3 treatment groups: stenting with abciximab, angioplasty with abciximab, and stenting alone (plus placebo). In the stent-only arm, heparin was given as a 100 U/kg bolus, and ACTs were adjusted to between 300 and 350 seconds. In the 2 abciximab arms, low dose heparin was given as a 70 U/kg bolus, and ACTs were titrated to >200 seconds.

The incidence of the primary composite end point (death, MI, or urgent revascularisation) was significantly decreased at 30 days in the abciximab groups (5.3% with stenting, p < 0.001; angioplasty 6.9%, p < 0.007) compared to the stent-only group (10.8%). The incidence of death or large MI at 30 days [Q-wave MI or creatine kinase (CK)/CK-MB elevation >5x control] was also significantly reduced with abciximab: the incidence was 3.0% in the stent plus abciximab group (p < 0.001), 4.7% in the PTCA plus abciximab group (p = 0.01), and 7.8% in the stent only group. At 30 days, major bleeding complications were noted in 1.5% of the stent plus abciximab group, 1.4% of the angioplasty plus abciximab group, and 2.2% of the stent alone group.

At 6 months, the combined incidence of death, MI or total revascularisation was 13.0% in the stent plus abciximab group, 20.5% in the PTCA plus abciximab group and 18.3% in the stent alone group (p < 0.001 stent alone *vs* stent plus abciximab). The respective 6-month combined rates for death, MI, or urgent revascularisation were 6.4, 9.2, and 12.1% (p < 0.001), and for death or MI were 5.6, 7.8 and 11.4% (p < 0.001). The rate of clinically-driven target vessel revascularisation was 8.7% in

the stent plus abciximab group, 15.4% in the PTCA plus abciximab group, and 10.6% in the stent-only group ($p < 0.005$ stent plus abciximab *vs* PTCA plus abciximab).[33]

Patients with diabetes undergoing stenting with adjunctive abciximab had a highly significant reduction in target vessel revascularisation: 8.1% (a rate similar to that of non-diabetics) in the stent plus abciximab group, versus 18.4% in the PTCA plus abciximab group, and 16.6% in the stent alone group ($p = 0.02$).[33]

Recent longer term follow-up results have shown a significant mortality benefit associated with the adjunctive use of abciximab. The 1-year mortality was 2.4% in the stent alone group, and 1.0% in the stent plus abciximab group ($p = 0.037$).

ADMIRAL

The ADMIRAL study was a randomised, placebo-controlled trial of abciximab in patients treated with primary interventional therapy for acute MI.[47] Patients presenting within 12 hours of the onset of symptoms were randomised to abciximab (n = 149) or placebo (n = 150) prior to intervention. All patients were treated with aspirin, heparin and ticlopidine. Patients with cardiogenic shock were excluded from the study. Stents were utilised in approximately 85% of patients; approximately 30% of patients received ≥2 stents. Study drug therapy was initiated prior to arrival in the catheterisation laboratory in approximately 25% of patients. Angiography was repeated 24 hours after the interventional procedure.

The 30-day primary composite clinical endpoint (death, MI, and ischaemia-driven target vessel revascularisation) was significantly reduced in the abciximab group (10.7 *vs* 20% with placebo). Compared with the placebo group, abciximab patients had a significantly higher incidence of TIMI grade III flow prior to intervention (21 *vs* 10.3%) and at 24 hours following the procedure (85.6 *vs* 78.4%). Major bleeding was slightly, but not significantly, higher in the abciximab group (4.0 *vs* 2.6% with placebo). Minor bleeding was more frequent with abciximab.

3.1.2 Eptifibatide and Tirofiban

Trials investigating other GP IIb/IIIa antagonists in the setting of coronary interventions include IMPACT-II (with a cyclic K-G-D heptapeptide), and RESTORE (with a peptidomimetic compound).

IMPACT-II

IMPACT-II tested 2 dosages of eptifibatide (integrelin) in the setting of elective, urgent, or emergent coronary intervention: a 135 μg/kg bolus followed by either a 0.5 or a 0.75 μg/kg/min infusion for 20 to 24 hours.[38] On an intention-to-treat basis, there was no significant difference between eptifibatide and placebo at 30 days with regard to the composite endpoint of death, MI or urgent revascularisation, although there was a trend in favour of active treatment. However, when analysed according to treatment received, there was a significant difference favouring the 0.5 μg/kg/min infusion group with regard to the same composite end point (9.1% in the lower dose group *vs* 10% in the higher dose group *vs* 11.6% for placebo).

In retrospect, because of an error in assessing the degree of inhibition relating to the use of citrated plasma, the dose of eptifibatide was probably significantly underestimated in IMPACT-II. It remains unclear as to why the lower dose group should be slightly, but not significantly, better than the so-called high-dose group. The differences between the 2 treatment regimens are relatively minor, and both doses used in IMPACT II are significantly lower compared with the doses of eptifibatide subsequently used in PURSUIT (section 3.2.1).

RESTORE

The RESTORE study was a placebo-controlled trial of adjunctive tirofiban in higher risk patients (with unstable angina pectoris) undergoing percutaneous intervention.[45] There was a significant difference favouring tirofiban in the composite incidence of death, MI and total revascularisation at 7 days (7.6 *vs* 10.4%; $p = 0.022$), but this difference was not maintained at 30 days (10.3 *vs* 12.2%; $p = 0.16$).

However, when an endpoint of urgent revascularisation rather than total revascularisation was utilised in determining composite end points (similar to the primary endpoint of EPIC, EPILOG, and EPISTENT), the difference was more substantial, although still not quite significant (8% with tirofiban *vs* 10.5% with placebo, p = 0.052).

3.2 Acute Coronary Syndromes

Several studies have examined the efficacy of GP IIb/IIIa-targeted therapy in the setting of acute coronary syndromes, including PURSUIT (eptifibatide), PRISM and PRISM-PLUS (tirofiban), and the Canadian Lamifiban and PARAGON studies (lamifiban).

3.2.1 Eptifibatide

PURSUIT

The PURSUIT study evaluated the role of GP IIb/IIIa inhibition with eptifibatide in the empiric management of patients with non–ST-segment elevation acute coronary syndromes.[39] Entry criteria included chest pain (≥10min) within the previous 24 hours and either ischemic ECG changes or any CK-MB elevation above the upper limit of the normal value evaluated. A total of 10 948 patients at 726 hospitals in 27 countries (North America, Western Europe, Eastern Europe and Latin America) were randomised (between November 1995 and January 1997) to receive placebo, eptifibatide as a 180 μg/kg bolus plus 1.3 μg/kg/min infusion, or eptifibatide as a 180 μg/kg bolus plus 2.0 μg/kg/min infusion. As prespecified in the study protocol, the 180/1.3μg arm was discontinued after an interim analysis showed that the safety profile of the higher dose regimen was comparable with that of the lower dose. North America had the largest enrollment (40.5%), followed by Western Europe (39.0%); contributions from Eastern Europe and Latin America were smaller (16.3 and 4.2%, repectively). Study drug infusions were administered until hospital discharge or initiation of coronary artery bypass surgery, up to a maximum of 72 hours; if percutaneous intervention was performed near the end of 72 hours, infusions could be continued for an additional 24 hours, up to 96 hours. All patients received aspirin, and heparin was recommended but not mandated. Decisions about the use of invasive procedures and their timing were at the discretion of the investigator.

The primary endpoint (death or MI at 30 days) occurred significantly less often in the eptifibatide group (14.2 *vs* 15.7%; p = 0.042). The benefit was established within 72 hours (median duration of study drug infusion) and was sustained out to 30 days. The investigator-determined event rates (10.0% with placebo *vs* 8.0% with eptifibatide; p = 0.001) were somewhat lower, but also showed a significant benefit with eptifibatide. At 6 months, the composite end-point rate determined by investigators was reduced from 13.6% in the placebo group to 12.1% in patients who had received eptifibatide (p = 0.021).

3.2.2 Tirofiban

PRISM

The PRISM study randomised patients with unstable angina pectoris (ischaemic symptoms and evidence of coronary artery disease) to receive either heparin or tirofiban for 48 hours; all patients also received aspirin.[43] At 48 hours (the primary endpoint of the trial) there was a significant reduction with tirofiban relative to heparin in composite events of death, MI, or refractory ischaemia (3.8 *vs* 5.6%; p = 0.01).

However, there was no significant intergroup difference in the composite endpoint at 7 days (10.3% with tirofiban *vs* 11.2% with heparin; p = 0.33) or 30 days (15.9 *vs* 17.1%; p = 0.34). Nevertheless, the mortality rate was significantly lower at 30 days in the tirofiban group (2.3 *vs* 3.6%; p = 0.02).

PRISM-PLUS

PRISM-PLUS studied a slightly higher-risk group of patients with unstable angina pectoris and ischaemic ECG changes who were randomised to receive heparin alone, tirofiban alone, or heparin plus tirofiban.[44] The tirofiban-alone arm was dropped because of excess of mortality at 7 days (4.6 *vs* 1.1% with heparin alone). Unlike in the

PRISM study, if coronary intervention was needed, the tirofiban infusion was continued during and after the intervention.

At 7 days there was a significant reduction in the composite endpoint of death, MI, or refractory ischaemia (12.9% with tirofiban plus heparin *vs* 17.9% with heparin alone; p = 0.004). This benefit favouring tirofiban in the incidence of composite endpoint event was maintained at 30 days (18.5% with tirofiban plus heparin *vs* 22.3% with heparin alone, p = 0.03) and at 6 months (27.7% with tirofiban plus heparin *vs* 32.1% with heparin alone, p = 0.02).

3.2.3 Lamifiban

Canadian Lamifiban Study

The Canadian Lamifiban Study randomised 365 patients with unstable angina pectoris to several intravenous doses of lamifiban (1, 2, 4, or 5 μg/min) or placebo, administered for 72 to 120 hours.[41] Outcome events were measured during the infusion period and at 30 days.

During the infusion period the composite incidence of death, MI or urgent revascularisation was 8.1% in the placebo group and 3.3% in the combined lamifiban groups (p = 0.04). At 30 days the incidence of death or MI was 8.1% with placebo and 3.7% in the lamifiban groups (p = 0.07). The 2 highest doses of lamifiban had a 2.5% incidence of death or MI (p = 0.03).

PARAGON-A

The PARAGON-A study randomised 2282 patients with unstable angina pectoris and ischaemic ECG changes to receive low-dose lamifiban (with and without heparin), high-dose lamifiban (with and without heparin) or heparin alone.[42]

At 30 days there was no significant benefit of lamifiban with regard to the combined incidence of death or MI (11.7% with heparin alone, 10.6% with low dose lamifiban, and 12.0% with high-dose lamifiban). However, at 6 months, there was a significantly lower incidence of death/MI in the low-dose lamifiban group (13.7 *vs* 16.4% with high-dose lamifiban, compared with 17.9% with heparin alone) and in death (5.2% with low dose lamifiban *vs* 6.8% with high dose lamifiban and 6.6% with heparin alone). This effect on mortality was sustained at 1 year in the low-dose lamifiban group (7.3% with low dose lamifiban, 8.9% with high-dose lamifiban, and 8.7% with heparin alone).

Although this study supports the use of this class of compounds in unstable angina pectoris, the lack of acute benefit remains a puzzling observation, as does the long term benefit in the low-dose but not the high-dose lamifiban group.

3.3 Acute Myocardial Infarction

3.3.1 M7E3 Fab

TAMI-8

The TAMI-8 pilot study was the first trial to investigate the use of GP IIb/IIIa antagonists (using a murine monoclonal antibody fragment; m7E3 Fab) with thrombolytic therapy in patients with acute MI.[37] Although this study was not primarily designed to examine the efficacy of combination therapy, it did show a decrease (from 20 to 9.5%) in the frequency of ischaemia in patients treated with the combination of alteplase (tissue plasminogen activator; tPA) plus high-dose m7E3 Fab, compared with alteplase alone.

3.3.2 Eptifibatide

IMPACT-AMI

The IMPACT-AMI study documented a significant benefit with respect to the incidence and rate of reperfusion in response to a combination of escalating doses of eptifibatide and thrombolytic agents.[40] At 90 minutes, 66% of the highest eptifibatide dose groups achieved TIMI grade 3 flow (versus 39% with placebo) accompanied by a decrease in the median reperfusion time, as reflected by ST-segment recovery time (65 minutes, compared with 116 minutes with placebo).

3.3.3 Abciximab

GRAPE

In the GRAPE pilot study, 60 patients with acute MI were treated with abciximab in the emergency room (along with aspirin and heparin) and brought to the catheterisation laboratory to evaluate the pa-

tency of the infarct-related artery.[36] The median time between abciximab administration and angiography was 45 minutes. At angiography, 40% of patients had TIMI grade 2 or 3 flow, and 18% had TIMI grade 3 flow.

The synergistic effects of a GP IIb/IIIa antagonist and fibrinolytic therapy were further explored in the TIMI-14 and SPEED trials.

TIMI-14

In the TIMI-14 trial, 681 patients with an acute MI were randomised to receive standard front loaded alteplase (100mg), low dose alteplase (20, 35, or 50mg) plus abciximab, low dose streptokinase (500 000 to 1 500 000U) plus abciximab, or abciximab alone.[35] TIMI grade 3 flow at 90 minutes was achieved in 57% of patients with standard alteplase alone, 32% of patients in the abciximab group alone, and 34 to 46% in the low-dose streptokinase plus abciximab groups (doses of streptokinase between 500 000 U and 1.25 MU). Patients in the low-dose alteplase plus abciximab group had increasing degrees of TIMI grade 3 flow with increasing doses and duration of alteplase therapy, up to a 76% incidence of TIMI grade 3 flow with 50mg of alteplase (infused over 60 minutes) plus abciximab.

This dose was then further tested in conjunction with low-dose or very-low-dose heparin, and yielded TIMI grade 3 flow in 72% of patients at 60 minutes and 77% of patients at 90 minutes.

Major bleeding rates were not significantly increased in the low-dose alteplase plus abciximab groups. The rates of major haemorrhage were 6% with alteplase alone, 3% with abciximab alone, 10% with streptokinase plus abciximab, 7% with 50mg alteplase, abciximab and low-dose heparin, and 1% with 50mg alteplase, abciximab, and very low dose heparin. Excessive bleeding and excess mortality were noted with the highest dose of streptokinase (1 500 000U) plus abciximab, and this arm was discontinued after 5 patients were treated.

SPEED

Similar to TIMI-14, SPEED was a dose escalation trial of the combination of reteplase (r-PA) and abciximab in patients with acute MI within 6 hours of symptom onset.[48] All patients received a full-dose abciximab bolus and infusion and were randomised in a 4 : 1 ratio to receive either reteplase (5U, 7.5U, 10U, 2.5 + 5U, or 5 + 5U) plus abciximab or abciximab alone. The patients also received aspirin and low-dose heparin (60 U/kg) and underwent angiography 60 to 90 minutes after starting therapy. Angioplasty, if necessary, was encouraged.

At 60 minutes, the percentage of patients with TIMI grade 3 flow was 28% with abciximab alone, 53% with reteplase 5U plus abciximab, 46% with reteplase 7.5U plus abciximab, 44% with reteplase 10U plus abciximab, 48% with reteplase 5U + 2.5U plus abciximab, and 63% with reteplase 5U + 5U plus abciximab.

Thus, GP IIb/IIIa antagonists combined with low-dose thrombolytics may prove to be at least as good, if not better, than standard-dose thrombolytic therapy in achieving reperfusion, and may be accompanied by a lower risk of bleeding if employed with very-low-dose heparin therapy.[49] Larger clinical trials such as GUSTO-IV AMI are ongoing, and will help to define whether combination therapy may emerge as the treatment of choice.

4. Oral GP IIb/IIIa Antagonists

Another class of drugs that might theoretically expand the potential application of GP IIb/IIIa-targeted therapy is the oral GP IIb/IIIa antagonists. These drugs are capable of achieving prolonged periods of profound platelet inhibition, comparable to the degree achieved with the intravenous compounds.[50] Preliminary safety studies (ORBIT, SOAR, TIMI 12, APLAUD) have suggested that the oral agents can be administered without causing a prohibitive increase in major bleeding complications for up to 3 months.[51-53] However, their performance in clinical trials has been disappointing.

Currently, a number of compounds are undergoing investigation, including sibrafiban (SYMPHONY I and II) and lotrafiban (BRAVO). Recently, further work on RPR-109891 (TIMI-15)

was suspended, largely due to cost-of-manufacture and dose-response issues, not safety concerns. The OPUS-TIMI 16 trial (orbofiban) was terminated prematurely because of safety concerns, primarily a significant increase in early 30-day mortality in one of the dosage arms.[54]

The recently reported EXCITE trial examined the use of xemilofiban in 7232 patients undergoing coronary intervention who were randomised to placebo, xemilofiban 10mg 3 times day or xemilofiban 20mg 3 times daily.[55] Therapy was started 30 to 90 minutes prior to intervention and continued through 6 months afterward. Xemilofiban therapy did not result in any significant decrease in composite events of death, MI, or urgent revascularisation at 30 days or 6 months, and there was a non-significant trend toward higher mortality in the lower-dose xemilofiban group. Further development of both xemilofiban and orbofiban was recently halted by Searle.

The recently-reported SYMPHONY trial showed no difference between sibrafiban and aspirin in 9233 patients with acute coronary syndromes. The composite end point of death, MI, or severe recurrent angina pectoris leading to revascularisation at 90 days was 9.8% with aspirin alone, 10.1% with low dose sibrafiban, and 10.0% with high dose sibrafiban. At present, there are no data to suggest that oral GP IIb/IIa antagonists are effective in improving long term outcomes or in secondary prevention. Additional data with other agents will be forthcoming, but whether these compounds will emerge as truly clinical useful remains unknown at present.

5. Potential Complications

5.1 Bleeding

Bleeding complications are a major concern associated with the use of GP IIb/IIIa antagonists. In the EPIC trial, the incidence of major bleeding, as defined by TIMI criteria, was 14% in the group that received a bolus plus infusion abciximab (with standard dose heparin). However, in subsequent recent studies with careful adjustment of heparin and early post-procedure sheath removal, there was a substantial decrease in the incidence of bleeding. For instance, in EPILOG the incidence of major bleeding was 3.5% in the 'standard dose' heparin (100 U/kg) plus abciximab, 2% in the low dose heparin (70 U/kg) plus abciximab group, and 3.1% in the standard dose heparin alone group. Other recent trials such as EPISTENT and IMPACT-II have reported major bleeding rates that are at least as low, if not lower, than that of heparin alone.[46]

Current recommendations designed to decrease bleeding complications with abciximab include reducing the dose of heparin to 70 U/kg, targeting procedural ACTs to between 200 and 250 seconds, early sheath removal, avoidance of routine venous sheaths, meticulous groin care, and avoiding the use of post-procedure heparin.[56,57]

The availability of oral GP IIb/IIIa antagonists further complicates the therapeutic alternatives. With the oral agents, prolonged profound platelet inhibition is possible, thus significantly increasing the risk of bleeding, especially with the concomitant use of other anticoagulant and antiplatelet agents.

Recent data, however, suggest that there is no prohibitive increase in major bleeding complications when chronic therapy is administered for up to 3 months. Nevertheless, the ultimate tolerability of a higher frequency of minor and 'nuisance' bleeding as encountered with oral GP IIb/IIIa antagonists remain to be verified.[52,53] There is, as yet, no adequate understanding of exactly what degree of platelet inhibition is necessary or how to best monitor therapeutic efficacy over the long term, and much further research in this field will be necessary.

5.2 Thrombocytopenia

Another major concern with the overall family of GP IIb/IIIa antagonists is thrombocytopenia. Mechanistically this is probably related to newly exposed Ligand-Induced Binding Sites (LIBS) and rapid clearance of the drug/platelet complex. The incidence of thrombocytopenia varies somewhat among the different agents but is probably present

to some degree with all of them. It usually responds promptly to platelet transfusion, at least as documented in the clinical experience with abciximab over the last 3 to 4 years.

One clinical scenario where thrombocytopenia may be of more concern is following re-treatment with abciximab. Empirical observations have suggested that with retreatment with abciximab clinical efficacy is not compromised and anaphylaxis is not a major issue, but thrombocytopenia may be somewhat more likely than a first time administration.[58] Furthermore, thrombocytopenia, if it occurs after retreatment, may be somewhat more profound and may respond somewhat less rapidly to platelet transfusion.

The oral agents also carry a risk of thrombocytopenia. Moreover, since these drugs are administered over longer periods of time, thrombocytopenia may not appear immediately (as with intravenous compounds), and may not become manifest for 1 to 2 weeks after starting therapy. This suggests that some form of monitoring may be warranted. Fortunately, with most of the agents recently under investigation (xemilofiban, orbofiban, sibrafiban, lotrifiban) the incidence of thrombocytopenia appears low, and the problem appears to resolve after discontinuing therapy.

6. Future Directions

A recent meta-analysis by Kong et al.[59] has painstakingly documented the benefits of GP IIb/IIIa antagonist therapy across a broad range of clinical applications. The challenge we face is how to move forward from the world of clinical trials to future clinical applications.

6.1 Which Agent to Use?

The number of available GP IIb/IIIa antagonists is growing (3 intravenous agents are currently available in the US) and the choice of the 'appropriate' agent is becoming increasingly difficult. Although all GP IIb/IIIa antagonists share a similar basic mechanism of action, there is considerable variation in their pharmacodynamic and pharmacokinetic activity, their binding characteristics and receptor specificity, not to mention differences in cost.

As yet, there have been no head-to-head trials of these compounds, although the forthcoming TARGET trial will directly compare tirofiban and abciximab in patients undergoing coronary stent implantation. In all likelihood, their penetration into the marketplace will be dictated by individual experience, rather than direct comparative trials. Although the latter approach would be preferred, the expense of large-scale trials and the already existing uncertainty about how these agents ought to be integrated into already complicated management algorithms would make such trials difficult (although not impossible) in the near future, particularly in patients with acute coronary syndromes.

As previously mentioned, considerable controversy exists about what constitutes an 'adequate' degree of platelet inhibition and an 'adequate' duration of therapy. Formal GP IIb/IIIa antagonist-induced platelet aggregation studies do not lend themselves well to bedside use. There are, however, a number of bedside devices which appear to provide a reliable assessment of the degree of platelet inhibition, and which may prove very useful in fine-tuning antiplatelet therapy.[60-65]

6.2 Aspirin Resistance

In recent years we have learned that aspirin alone does not provide enough platelet inhibition for prevention of thrombotic vascular pathologies; thienopyridines (such as ticlopidine and clopidogrel) yield additional benefit when added to aspirin, and GP IIb/IIIa antagonists appear to provide even more of an added benefit. There is a subgroup of patients who, despite taking aspirin therapy, show little or no inhibition of platelet function.

This aspirin resistance is a major concern, and a major potential risk factor; this subgroup may be an ideal target population that could benefit the most from additional forms of antiplatelet therapy. There are also a significant number of patients who go on to have additional events despite aspirin therapy. Are these aspirin failures? We do not yet know,

but if we have learned anything, we have learned that we have the tools, when necessary, to go beyond aspirin.

6.3 Other Possible Indications

To date, most of the clinical studies with the GP IIb/IIIa antagonists have been conducted in patients with coronary artery disease. The role that this new form of therapy may play in treating other vascular pathologies, such as cerebrovascular disease, peripheral vascular disease and acute pulmonary embolism, remains to be defined. Moreover, the potential role for these new forms of therapy as adjuncts to other procedures that require inhibition of platelet function (such as operations involving cardiopulmonary bypass) is still unclear.

6.4 Risk Stratification and Cost Effectiveness

Two final important issues are risk stratification and cost effectiveness. In fact, these issues are 2 facets of the same problem. Given the added expense of GP IIb/IIIa antagonists, how can we utilise them in a cost-effective manner? Despite their wide potential benefits, we are unlikely to be able to use them in all patients. Therefore, the question arises 'In whom should we use them?'. Hospital administrators frequently ask 'How much will it cost to use this new therapy?'. A more appropriate question might in fact be 'How much will it cost not to use it?'.

Risk stratification plays a key role in identifying patients at heightened risk for adverse events, in whom (from the outset) costly but effective forms of therapy may be more cost effective because they can prevent complications which may be even more expensive. This point is illustrated by the troponin-T data from the CAPTURE trial.[66] Patients in CAPTURE who presented with elevated (>0.2 μg/L) levels of troponin-T had substantial benefit with GP IIb/IIIa antagonist therapy with respect to death or recurrent MI at 6 months (combined incidence 9.5% with abciximab *vs* 26.3% without abciximab; $p = 0.005$). Patients who did not have elevated troponin-T levels showed a trend, but no significant benefit, in the 6-month composite endpoint (8.3% with abciximab *vs* 9.7% without abciximab). Risk stratification thus can be applied to identify patients who may benefit the most from GP IIb/IIIa antagonist therapy.

6.5 The Future

What does the future hold? Simply stated, a lot of promise, but a lot of uncertainty as well. The adjunctive role of intravenous GP IIb/IIIa antagonists in interventional therapy is well established. The combination of GP IIb/IIIa antagonists and fibrinolytic therapy for acute MI looks very promising, but will require additional large-scale studies before such a combination could be considered as standard therapy.

The role of GP IIb/IIIa antagonists in the treatment of acute coronary syndromes remains in evolution at present, and the issues of how GP IIb/IIIa antagonists will be incorporated into the rapidly evolving management algorithms for these patients remains somewhat controversial. These agents do not appear to be the final and definitive therapy, but will probably be a very useful adjunct in medium-to-high risk patients and patients destined to undergo coronary intervention.

The role (if any) of oral GP IIb/IIIa antagonists awaits the availability of more than dose-ranging and safety data. The initial large-scale data from EXCITE, OPUS and SYMPHONY are not encouraging, but additional large ongoing trials will help resolve some of the uncertainties.

Finally, the future application of this potent form of therapy in peripheral vascular disease and in cerebrovascular disease is unknown. In the case of the oral agents, their role in secondary prevention of recurrent vascular events (probably most effectively in conjunction with plaque stabilisation and risk-factor modification) is promising, but will need a lot more study.

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