Clinical Perspectives

Platelet glycoprotein IIB/IIIa receptor antagonists

An asset for treatment of unstable coronary syndromes and coronary intervention

Introduction

Platelet aggregation, at the site of an atherosclerotic plaque in the coronary arteries has been recognized as a crucial step in the pathogenesis of unstable angina and myocardial infarction. As part of current medical therapy in patients with unstable angina, evolving myocardial infarction and in patients undergoing coronary intervention, platelet aggregation is inhibited partly by administration of aspirin or ticlopidin[1,2]. In addition, heparin is administered in order to reduce thrombin activity. In spite of such combined anti-platelet and anticoagulant therapy, between 6% and 15% of patients with unstable angina progress to myocardial infarction or death within the first month[3,4]. Similarly, myocardial damage as assessed by peri-procedural enzyme elevation has been reported in 4%–14% of patients undergoing PTCA[5–11]. Follow-up studies indicate that larger, but also smaller peri-procedural enzyme elevations are associated with impaired long-term outcome[12–14].

Major progress has been made by development of platelet glycoprotein IIb/IIIa receptor blockers, which block the final common pathway of platelet aggregation, the fibrinogen receptor on the thrombocytes[15]. In this review, the clinical value of treatment with platelet glycoprotein IIb/IIIa receptor blockers is assessed, based on data from medium size and large clinical trials in different groups of patients with unstable angina, evolving myocardial infarction and patients undergoing coronary intervention (Table 1).

Different medical treatments of unstable angina

Medical treatment of patients with unstable angina and suspected myocardial infarction without ST segment elevation includes aspirin and heparin in addition to beta-blockers[16], nitrates and in some patients calcium antagonists. Recent studies have assessed the value of different platelet glycoprotein IIb/IIIa receptor blockers administered in addition to established medical therapy (Tables 2 and 3).

The PARAGON study enrolled 2282 patients who received placebo or low dose lamifiban (1 µg. min\(^{-1}\)) or high dose lamifiban (5 µg. min\(^{-1}\))[17]. Patients receiving lamifiban were further randomized to receive either heparin or heparin placebo. At the 30 day follow-up no significant difference was apparent among the different treatment groups. Yet, in retrospect, the lowest event rate (death and myocardial infarction) was observed in patients receiving low dose lamifiban with heparin (10·3%) in comparison with placebo (11·7%). In fact, this difference was similar to the difference observed later in the PRISM and PURSUIT studies. At the 6 month follow-up, patients receiving low dose lamifiban with heparin had a 30% relative reduction in death or myocardial infarction. This difference persisted at the 1 year follow-up. No good explanation has been offered for the increased difference between the placebo and low dose lamifiban groups between the 1 and 6 month follow-up. It is likely that this was a chance result. Patients receiving high dose lamifiban with heparin had event rates similar to the control group, while bleeding rates in this group were increased.

Tirofiban was investigated in the PRISM and PRISM+ studies[18]. PRISM enrolled 3232 patients with angina at rest within 24 h before inclusion and either ECG changes indicating ischaemia or a history of coronary artery disease[19]. All patients received aspirin and either heparin or tirofiban, 6 µg. kg\(^{-1}\). min\(^{-1}\) for 30 min followed by 0·15 µg. kg\(^{-1}\). min\(^{-1}\) for 48 h. At 48 h a significant reduction in death, myocardial infarction or refractory ischaemia was observed. The reduction in death and myocardial infarction was still apparent at 30 days, although no longer statistically significant, showing an 18% reduction, from 7·1% for placebo to 5·8% for tirofiban-treated patients (\(P=0·11\)).

The PRISM+ study enrolled patients at somewhat higher risk: all had symptoms of unstable angina with concomitant ‘ischaemic’ ECG changes within 12 h prior to enrolment[20]. Three treatment arms were compared. Tirofiban in the same dose as in PRISM without
heparin, was discontinued because of an increased mortality rate in the first 345 patients. At the time of the primary end-point (7 days) patients receiving tirofiban with heparin had a lower rate of death, myocardial infarction and refractory ischaemia (12.9%) when compared to the heparin group (17.9%).

Table 1  List of available platelet glycoprotein IIb/IIIa receptor blockers

<table>
<thead>
<tr>
<th>Agent</th>
<th>Form type</th>
<th>Company</th>
<th>Trials</th>
<th>Stage of development</th>
</tr>
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<tbody>
<tr>
<td>Abciximab</td>
<td>intravenous antibody</td>
<td>Centocor, Eli Lilly</td>
<td>PTCA, MI, UAP</td>
<td>FDA approved 1994, PTCA</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>intravenous peptide</td>
<td>Cor Therapeutics, Schering-Plough</td>
<td>PTCA, MI, UAP</td>
<td>FDA approved 1998, unstable angina and PTCA</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>intravenous small molecule</td>
<td>Merck</td>
<td>PTCA, unstable angina</td>
<td>FDA approved 1998, unstable angina phase II/III</td>
</tr>
<tr>
<td>Lamifiban</td>
<td>intravenous small molecule</td>
<td>Hoffman LaRoche</td>
<td>PTCA, unstable angina</td>
<td>phase II</td>
</tr>
<tr>
<td>Fradafiban</td>
<td>intravenous nonpeptide, small molecule</td>
<td>Karl Thomae, Boehringer Ingelheim</td>
<td>PTCA</td>
<td>phase II</td>
</tr>
<tr>
<td>Xemilofiban</td>
<td>oral nonpeptide</td>
<td>Searle</td>
<td>PTCA, unstable angina</td>
<td>phase III</td>
</tr>
<tr>
<td>Sibrafiban</td>
<td>oral peptido-mimetic</td>
<td>Hoffman LaRoche, Genentech</td>
<td>acute coronary syndromes</td>
<td>phase III</td>
</tr>
<tr>
<td>Lefradafiban</td>
<td>oral pro-drug of fradafiban</td>
<td>Karl Thomae, Boehringer Ingelheim</td>
<td>PTCA, unstable angina</td>
<td>phase II</td>
</tr>
</tbody>
</table>

MI=myocardial infarction; UAP=unstable angina pectoris; PTCA=percutaneous transluminal coronary angioplasty; FDA=Food and Drug Administration.

Table 2  Trial characteristics

<table>
<thead>
<tr>
<th>Trial</th>
<th>Disease</th>
<th>n</th>
<th>Drug</th>
<th>ASA</th>
<th>Heparin</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>PRISM</td>
<td>UAP</td>
<td>3231</td>
<td>tirofiban</td>
<td>+</td>
<td>or tirofiban</td>
<td>Rx</td>
</tr>
<tr>
<td>PARAGON</td>
<td>UAP</td>
<td>2282</td>
<td>lamifiban</td>
<td>+</td>
<td>or placebo</td>
<td>Rx</td>
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<tr>
<td>PURSUIT</td>
<td>UAP</td>
<td>10948</td>
<td>eptifibatide</td>
<td>+</td>
<td>at investigator</td>
<td>Rx</td>
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<tr>
<td>PRISM+</td>
<td>UAP/non Q</td>
<td>1915</td>
<td>tirofiban</td>
<td>+</td>
<td>+ (#)</td>
<td>Rx</td>
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<td>CAPTURE</td>
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<td>+</td>
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<tr>
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<td>High risk PTCA</td>
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<td>+</td>
<td>PTCA</td>
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<td>Elective PTCA</td>
<td>2792</td>
<td>abciximab</td>
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<td>+</td>
<td>PTCA</td>
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<td>Elective PTCA</td>
<td>4010</td>
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<td>+</td>
<td>PTCA</td>
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<tr>
<td>RESTORE</td>
<td>Elective PTCA</td>
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<td>tirofiban</td>
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<td>+</td>
<td>PTCA</td>
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<td>+</td>
<td>+</td>
<td>Stent</td>
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<td>+</td>
<td>Stent</td>
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<td>+</td>
<td>Stent</td>
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<td>Stent</td>
<td>2399</td>
<td>abciximab</td>
<td>+</td>
<td>+</td>
<td>Stent</td>
</tr>
<tr>
<td>EPIC-MI**</td>
<td>Infarction</td>
<td>64</td>
<td>abciximab</td>
<td>+</td>
<td>+</td>
<td>PTCA</td>
</tr>
<tr>
<td>RAPPORT</td>
<td>Infarction</td>
<td>483</td>
<td>abciximab</td>
<td>+</td>
<td>+</td>
<td>PTCA</td>
</tr>
<tr>
<td>INTEGRILIN AMI</td>
<td>Infarction</td>
<td>171</td>
<td>eptifibatide</td>
<td>+</td>
<td>–</td>
<td>Streptokinase</td>
</tr>
<tr>
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<td>eptifibatide</td>
<td>+</td>
<td>+</td>
<td>Alteplase</td>
</tr>
<tr>
<td>TIMI 14A</td>
<td>Infarction</td>
<td>446</td>
<td>abciximab</td>
<td>+</td>
<td>+</td>
<td>Alteplase</td>
</tr>
<tr>
<td>SPEED</td>
<td>Infarction</td>
<td>130</td>
<td>abciximab</td>
<td>+</td>
<td>+</td>
<td>Reteplase</td>
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</tbody>
</table>

UAP=unstable angina pectoris; Rx=medical therapy; PTCA=percutaneous transluminal coronary angioplasty; ASA=aspirin.
# a third group of patients received tirofiban without heparin.
* subgroup of stented patients.
** subgroup of patients with myocardial infarction at enrolment.
*** study ongoing.
myocardial infarction at the 30 day follow-up were 8·7% for tirofiban-treated patients and 11·9% for heparin-treated patients (\(P=0·03\)).

The largest trial in patients with unstable angina was PURSUIT\(^{[21,22]}\). 10 948 patients were randomized to receive an eptifibatide bolus (180 \(\mu\) g.k g\(^{-1}\)) followed by an infusion (1·3 or 2·0 \(\mu\) g.k g\(^{-1}\). min\(^{-1}\)) vs placebo. All groups received aspirin and heparin. The low dose group was discontinued since at interim analysis the high dose group appeared safe to continue. The primary end-point was a reduction in death or myocardial infarction, as assessed by the clinical event committee, at the 30 day follow-up which was reduced from 15·7% in placebo-treated patients to 14·2% in the eptifibatide group (\(P=0·04\)).

The results of these studies are remarkably similar, showing a modest reduction in death or myocardial infarction, ranging from 1·4 to 3·0 at 30 days per 100 patients treated. Yet a few differences between the trials should be appreciated. First, patient enrolment criteria in these trials were different (Table 2), as were the definitions for myocardial infarction. In particular, a rise of creatine kinase or creatine kinase MB exceeding twice the upper limit of normal was required to define an infarct in the PARAGON, PRISM and PRISM+ studies, while any creatine kinase MB above the upper limit of normal was labelled as an infarct by the PURSUIT clinical event committee. In fact, the investigators in PURSUIT called fewer infarcts. Using the investigator clinical approach a reduction in the primary end-point from 10·0% to 8·0% was reported by eptifibatide, at a rate similar to the other studies.

A further difference is the proportion of patients undergoing coronary intervention. In particular the larger treatment effect in the PRISM+ study may be due in part to the fact that all patients were scheduled to undergo coronary angiography after approximately 48 h and a third of the patients subsequently underwent coronary intervention while receiving the study drug. In contrast, approximately 15% of patients in PURSUIT underwent PTCA while receiving study drug and very few patients in PRISM. Since treatment with a platelet glycoprotein IIb/IIIa receptor blocker in patients undergoing PTCA reduces periprocedural infarction (see below) the favourable outcome in the PRISM+ study, and to a lesser extent in PURSUIT, reflects a combined effect of medical treatment and protection in patients undergoing early coronary intervention.

The double effect of platelet glycoprotein IIb/IIIa receptor blockers to prevent progression to myocardial infarction in patients with unstable angina and to avoid myocardial infarction at the time of coronary intervention was first shown in the CAPTURE study (Fig. 1), in which almost all patients underwent PTCA after 24 h treatment with abciximab or placebo. A similar pattern has now been described in PRISM+ and in a subgroup of patients in the PURSUIT study. In view of the consistent findings in these studies, treatment with a platelet glycoprotein IIb/IIIa receptor blocker will soon become standard in patients with unstable angina.

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### Table 3 Death and infarction at 30 days and 6 months

<table>
<thead>
<tr>
<th>Trial</th>
<th>30 days</th>
<th></th>
<th>6 months</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Drug</td>
<td>Placebo</td>
<td>(P) value</td>
<td>Drug</td>
</tr>
<tr>
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<td>5·8</td>
<td>7·1</td>
<td>0·11</td>
<td>na</td>
</tr>
<tr>
<td>PARAGON</td>
<td>10·3</td>
<td>11·7</td>
<td>0·48</td>
<td>12·6</td>
</tr>
<tr>
<td>PURSUIT</td>
<td>14·2</td>
<td>15·7</td>
<td>0·04</td>
<td>17·7</td>
</tr>
<tr>
<td>PRISM+</td>
<td>8·7</td>
<td>11·9</td>
<td>0·03</td>
<td>12·3</td>
</tr>
<tr>
<td>CAPTURE</td>
<td>4·8</td>
<td>9</td>
<td>0·003</td>
<td>9</td>
</tr>
<tr>
<td>EPIC</td>
<td>6·6</td>
<td>9·6</td>
<td>&lt;0·05</td>
<td>9·4</td>
</tr>
<tr>
<td>EPILOG</td>
<td>3·8</td>
<td>9·1</td>
<td>&lt;0·001</td>
<td>6·1</td>
</tr>
<tr>
<td>IMPACT-II</td>
<td>7·1</td>
<td>8·4</td>
<td>ns</td>
<td>10·3</td>
</tr>
<tr>
<td>RESTORE</td>
<td>5</td>
<td>6·4</td>
<td>ns</td>
<td>7·8</td>
</tr>
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<td>na</td>
<td>8·1</td>
<td>15</td>
</tr>
<tr>
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<td>5·5</td>
<td>10·5</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>EPILOG*</td>
<td>better,</td>
<td>na</td>
<td>0·001</td>
<td>na</td>
</tr>
<tr>
<td>EPI-STENT</td>
<td>3·0</td>
<td>7·8</td>
<td>&lt;0·001</td>
<td>na</td>
</tr>
<tr>
<td>EPIC-MI**</td>
<td>4·5</td>
<td>26·1</td>
<td>0·058</td>
<td>4·5</td>
</tr>
<tr>
<td>RAPPORT</td>
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<td>5·8</td>
<td>0·38</td>
<td>6·9</td>
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<tr>
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<td>7·7</td>
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<td>na</td>
<td>na</td>
</tr>
<tr>
<td>TIMI 14</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>SPEED</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
</tbody>
</table>

\(\text{ns}=\text{not significant}; \text{na}=\text{not available}.\)

\(*=\text{patients with stent}; **=\text{EPIC, myocardial infarction at enrolment}.\)
Medical treatment during coronary intervention

All studies with platelet glycoprotein IIb/IIIa receptor blockers in patients undergoing coronary intervention consistently show a reduction of death (which is infrequent) and myocardial infarction at the 30 day follow-up and beyond\(^{23-27}\). In three studies with abciximab, a 50% reduction of death and myocardial infarction at 30 days was reported\(^{28-36}\). The magnitude of the benefit in the studies varies, reflecting differences in patient selection, differences in definition of myocardial infarction and possibly differences in the efficacy among various treatment regimens. In particular, the smaller effect observed in the IMPACT-II\(^{37,38}\) study with eptifibatide when compared to the CAPTURE, EPIC and EP ILOG studies with abciximab may be explained by the lesser degree of platelet inhibition as achieved by the rather low dose of eptifibatide used in IMPACT-II.

Treatment with abciximab or other platelet glycoprotein IIb/IIIa receptor blockers should be recommended for all patients undergoing PTCA, including those treated with direct atherectomy\(^{39}\) and those receiving stents\(^{40}\). In fact platelet glycoprotein IIb/IIIa receptor blockers and stents have different complementary effects: the former improve procedural outcome by reducing thrombotic complications, such as myocardial infarction, and the latter by treating mechanical complications (large dissections) and reduction of restenosis\(^{41,42}\). There is no evidence from randomized trials on bail out use of abciximab in coronary intervention, although widely used\(^{43}\).

PTCA in patients with unstable angina

Many patients with unstable angina admitted to a hospital will subsequently undergo coronary intervention or coronary bypass surgery. In some hospitals early coronary intervention may be offered to a majority of these patients although the superiority of such an approach has not been established by randomized trials. In fact, a systematic strategy of early intervention was not superior to a strategy of watchful waiting in the TIMI IIIb study\(^{44-46}\). In recent studies in patients with unstable angina, intervention rates at 30 days with either PTCA or surgery were as high as 38% in PURSUIT and 54% in PRISM+. Major differences in intervention rates were observed among different regions in the world participating in PURSUIT. For example, percutaneous coronary intervention and bypass surgery were performed in 8% and 7% of patients, respectively, in eastern Europe, 25% and 14% in western Europe, compared to as many as 35% and 21% in North America.

If early coronary intervention is considered in patients with unstable angina or evolving myocardial infarction, current available data indicate that such patients will particularly benefit from treatment with a platelet IIb/IIIa receptor blocker\(^{47}\) both before and during the interventional procedure, in addition to aspirin, heparin, beta-blockers and nitrates. Troponin T levels can help to define a high risk subgroup likely to benefit most from the addition of platelet glycoprotein IIb/IIIa receptor blockers to standard therapy\(^{48,49}\).

Direct PTCA in patients with evolving myocardial infarction

Patients with evolving myocardial infarction usually have a completely occluded coronary artery. Treatment with a platelet glycoprotein IIb/IIIa receptor blocker in this setting may result in opening of the artery through clot resolution\(^{50}\). Gold and co-workers observed opening of an occluded coronary artery in seven (54%) out of 13 patients undergoing angiography and treatment with abciximab in the early phase of myocardial infarction. These observations are supported by the GRAPE study in the Netherlands which documented a patent coronary artery in 24 (40%) out of 60 patients undergoing coronary angiography and treatment with abciximab in the early phase of myocardial infarction. In studies without pre-treatment with a platelet glycoprotein IIb/IIIa receptor blocker, approximately 20% patent coronary arteries are reported\(^{52,53}\). In the RAPPORT trial, TIMI flow rates 2 or 3 prior to angioplasty were higher (34.1%) in patients receiving abciximab compared to 25.5% in the placebo group, although this difference was not statistically significant\(^{54,55}\). The combined primary end-point at 6 months of death, re-infarction and urgent revascularization was reduced in the RAPPORT study from 17.8% in the placebo group to 11.6% in the abciximab group \((P=0.062)\). For those receiving study treatment and PTCA the reduction was from 12.0% to 4.6% \((P=0.005)\).

The total body of randomized data in patients undergoing direct PTCA for myocardial infarction is limited. However, the findings are consistent with those reported in PTCA for stable or unstable angina as summarized above, and support the use of the platelet glycoprotein IIb/IIIa receptor blockers in this setting.
Platelet glycoprotein IIb/IIIa receptor blockers and thrombolytic therapy

Early animal experiments\textsuperscript{[56,57]} reported enhanced thrombolytic activity when recombinant tissue type plasminogen activator was concomitant with platelet glycoprotein IIb/IIIa receptor blockers. However, it remains uncertain whether this will translate into an improved clinical treatment regimen.

A pilot study with streptokinase and different dosages of eptifibatide in 181 patients showed an improvement in coronary patency (TIMI 2 or 3 flow) at 90 min coronary angiography (62% vs 79%), but the differences in patency were not very large and combination therapy was associated with increased bleeding rates\textsuperscript{[58]}. Similar improved patency rates were observed in patients receiving eptifibatide and recombinant tissue type plasminogen activator (rtPA) as well as in patients treated with abciximab and a low dose of rtPA in the TIMI 14 study\textsuperscript{[59–61]}. In the latter, TIMI 3 flow was achieved in 79% of 34 patients treated with full dose abciximab combined with 50 mg rtPA infused in 1 h, while a standard accelerated rtPA regime showed a 58% TIMI 3 flow in 146 patients \textit{(}P<0.001\text{)}. These initial results should be verified in larger patient series. Combination therapy with a thrombolytic agent and a platelet glycoprotein IIb/IIIa receptor blocker was associated with increased bleeding risk. It may be expected, or at least hoped, that further studies will allow development of an improved regimen for reperfusion therapy, through a combination of carefully chosen doses of thrombolytics and platelet glycoprotein IIb/IIIa receptor blockers.

Oral platelet glycoprotein IIb/IIIa receptor blockers

The platelet inhibitory effect of eptifibatide and tirofiban rapidly disappears after discontinuation of the intravenous infusions, while the effect of abciximab persists and gradually disappears during subsequent weeks\textsuperscript{[62–65]}. Whether this difference in pharmacology has an impact on clinical outcome remains to be established. However, investigators realize that healing of the vessel wall in patients with unstable angina and myocardial infarction takes several weeks. Accordingly, treatment with antiplatelet agents during such a period may be expected to be beneficial\textsuperscript{[66,67]}.

Oral platelet glycoprotein IIb/IIIa receptor blockers may provide such long-term (weeks, perhaps months) treatment for patients with unstable angina or following acute myocardial infarction, to prevent early re-thrombosis. Alternative platelet glycoprotein IIb/IIIa receptor blockers which act after oral administration are currently being investigated, and a few phase II studies have been reported.

Twice daily administration of sibrafiban resulted in consistent platelet inhibition, defined as inhibition in over 50% of ADP-induced platelet aggregation for more than 75% of the day. Major bleeding slightly increased, while muco-cutaneous bleeds were reported in one third of patients on the highest dose of sibrafiban\textsuperscript{[68,69]}.

Xemilofiban is a non-peptide pro-drug that inhibits platelet aggregation for more than 8 h after a single oral dose\textsuperscript{[70,71]}.

In the first larger trial with abxicimab a high rate of major bleeding complications (14%) was observed in patients receiving abxicimab with concomitant aspirin and heparin\textsuperscript{[76]}. Subsequent studies have shown that this bleeding excess is due to the combined therapy with heparin and may be avoided through reduction of the latter. With such modification in the EPilogue study, no excess of bleeding was observed in patients receiving abxicimab with low dose heparin (70 U . kg\textsuperscript{-1}, a maximal dose of 7000 U and additional bolus dosing to maintain an activated clotting time (ACT) of over 200 s\textsuperscript{[77,78]}), while the efficacy to avoid thrombotic complications remained intact. In studies with abxicimab the rate of stroke was not increased (Table 4).

However, in the PRISM, PRISM+ and PURSUIT studies, bleeding rates were higher in patients receiving the respective platelet glycoprotein IIb/IIIa receptor blockers. Again, this may have been related to the amount of heparin administered. In spite of the higher bleeding rates in PURSUIT, no excess intracranial haemorrhage or stroke was observed. In fact, intracranial haemorrhages were very rare, while embolic strokes were more common: 0.9% in the placebo group and 0.7% in the eptifibatide group. This difference was not statistically significant\textsuperscript{[79]}.

Platelet glycoprotein IIb/IIIa receptor blockers and bleeding risk

In a study of patients undergoing PTCA, lefradafiban in appropriate dosage resulted in blockade of over 80% of fibrinogen (platelet glycoprotein IIb/IIIa) receptors on the thrombocyte. Bleeding of mucous membranes and gums were seen, but no serious bleeding complications occurred. The half life of 12 h enables effective triple day dosage.

Further studies of these and similar drugs in different clinical settings are ongoing to address whether prolonged administration will help to reduce the incidence of coronary events, without an excessive risk for bleeding complications. Monitoring the effect of platelet glycoprotein IIb/IIIa receptor blockade may be required for optimal safety and efficacy during long-term treatment\textsuperscript{[74,75]}.

The measures to be taken, if a significant bleeding occurs, differ in the various groups of platelet glycoprotein IIb/IIIa receptor blockers. In all cases, the platelet glycoprotein IIb/IIIa receptor blocker should be stopped, as well as heparin and any other anticoagulant. Patients receiving abxicimab can effectively be treated with an infusion of thrombocytes. When abxicimab is administered in the recommended dosages, almost all drug is bound to platelets and the concentration of circulating abxicimab is very low. Thus, the receptors on fresh platelets which are being administered will not be blocked and will remain available to induce platelet aggregation. Over time, some exchange of abxicimab will occur from 'old' to 'fresh' platelets, but the overall level of platelet inhibition will decrease after administration of fresh platelets.

The small molecule platelet glycoprotein IIb/IIIa receptor blockers which have been developed for intravenous administration (lamifiban, tirofiban, eptifibatide) are rapidly cleared from the body with a half life of a few hours. Thus, in patients developing major bleeding complications it suffices to discontinue drug administration and wait for the compound to clear (Table 5). During drug administration, plasma concentrations of these competitive antagonists to the platelet glycoprotein IIb/IIIa receptors are high. Accordingly it is not useful to administer platelets to counteract the drug effect in these patients.

The oral compounds, which are currently under clinical investigation, have been selected for their long half-life. These are also competitive antagonists which require a relatively high plasma concentration. In patients developing bleeding complications while being treated with oral platelet glycoprotein IIb/IIIa receptor blockers, it may be necessary to take measures which will help to remove the compound from the body, including gastric emptying, forced diuresis, and possibly ultra filtration. Treatment with fresh platelets will not be useful in the presence of high concentrations of platelet receptor blockers.

**Thrombocytopenia**

Reversible thrombocytopenia has been reported in patients receiving platelet glycoprotein IIb/IIIa receptor blockers. The rate of such complications is low, varying from 0·5% of 744 patients described in a single centre registry\cite{80,81} to 1·6% in the CAPTURE population (platelets below 50 000 10⁹ \(1^{-1}\)). A rapid increase in thrombocytes is noted after cessation of the drug. A thrombocyte measurement after 12 h of intravenous platelet glycoprotein IIb/IIIa receptor blocker is advised to detect thrombocytopenia early.

**Antibodies to the monoclonal antibody abxicimab**

The early IgG murine monoclonal antibody, 7E3, consisted of a Fc and Fab fragment targeted against the glycoprotein IIb/IIIa receptor\cite{82}. The Fc fragment, in particular, is expected to give a human antimurine response (HAMA) and subsequently remove the IgG bound platelets. The monoclonal antibody currently in use, abxicimab, is a human/chimeric version of the earlier antibody, of which the Fc portion has been removed before administration. The binding capacities of the 7E3 Fab fragment, however, remain intact, while antibody formation is minimized\cite{83–85}. Preliminary data are being gathered on re-administration in the R3 Reopro Readministration Registry\cite{86}. In 92 prospectively evaluated patients no increase in thrombocytopenia was seen (2·2% <50 000 10⁹ \(1^{-1}\)) and no allergic reaction was observed. Clinical consequences of antibody formation seem limited, although data on re-administration are scarce.

**Conclusion**

More than 12 000 patients have been enrolled in large-scale trials in the setting of non-surgical percutaneous

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**Table 4 Risk of stroke with abxicimab — combined results of three large trials**

<table>
<thead>
<tr>
<th></th>
<th>EPIC Placebo</th>
<th>EPIC Drug</th>
<th>CAPTURE Placebo</th>
<th>CAPTURE Drug</th>
<th>EPILOG Placebo</th>
<th>EPILOG Drug</th>
<th>Total Placebo</th>
<th>Total Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>681</td>
<td>678</td>
<td>630</td>
<td>623</td>
<td>939</td>
<td>1853</td>
<td>2250</td>
<td>3154</td>
</tr>
<tr>
<td>Non-haemorrhagic</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Haemorrhagic</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
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<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Any stroke</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>7</td>
<td>9</td>
</tr>
</tbody>
</table>

All \(P\) values >0·45; Unknown=unknown aetiology.
intervention, and the efficacy and safety of platelet glycoprotein IIb/IIIa receptor blockers is beyond dispute. These drugs markedly reduced the incidence of thrombotic and ischaemic complications in patients with unstable angina and during PTCA. Trials presented here show benefit sustained to a follow-up period of 1 month and lasting effect up to 3 years, the majority meeting primary efficacy endpoints with statistical significance. Treatment with platelet glycoprotein IIb/IIIa receptor blockers is beneficial in all patients undergoing PTCA, both with and without stent implantation, provided the cost of treatment is acceptable. Primary PTCA for acute myocardial infarction should be performed under the protection of platelet glycoprotein IIb/IIIa receptor blockers, as other interventions.

In unstable angina treated with percutaneous intervention and platelet glycoprotein IIb/IIIa receptor blockers, a dual effect is seen, consisting of stabilization of the disease and prevention of myocardial infarction before intervention, and reduction of thrombotic events associated with the intervention. In patients with unstable angina and evolving myocardial infarction without ST segment elevation treated medically, a modest reduction of early events is observed. Treatment with platelet glycoprotein IIb/IIIa receptor blockers is warranted as are aspirin, heparin (avoid excessive dosing) and beta-blockers and nitrates.

Trials in acute myocardial infarction with platelet glycoprotein IIb/IIIa receptor blocker alone or in adjunct with thrombolysis or intervention are currently under way. Dosing regimens of platelet glycoprotein IIb/IIIa receptor blockers, as well as dosing of thrombolytics, need to be clarified and tested for safety and efficacy. Available phase two data show improvement of TIMI 3 flow when platelet glycoprotein IIb/IIIa receptor blockers are added to thrombolytics for treatment of acute infarction.

Trials with orally active platelet glycoprotein IIb/IIIa receptor blockers are conducted to establish their efficacy and safety. A future strategy might comprise three phases for platelet glycoprotein IIb/IIIa receptor blockers in the treatment of coronary disease. Initial treatment will include intravenous platelet glycoprotein IIb/IIIa receptor blockers with high levels of aggregation inhibition for patients during hospitalization for unstable angina, percutaneous intervention and perhaps infarction. Follow-up treatment can include oral agents providing inhibition of platelet aggregation in a healing phase in the first weeks or months after hospitalization, with either a high or medium level of inhibition of platelet aggregation. Third, secondary prevention with oral agents in a lower dosage may be appropriate.

The benefits for all platelet glycoprotein IIb/IIIa receptor blockers are offset by a bleeding risk in higher dosage groups. This bleeding is strongly related to the addition of high dose heparin. Careful titration of heparin during PTCA to activated clotting time over 200 s instead of earlier to levels above 300 s has been shown to lower bleeding risk to near placebo levels. For longer treatment with concomitant heparin, activated partial thromboplastin time should be at most twice normal. Bleeding risk for combination therapy with thrombolytic regimens need further investigation, while the safety and efficacy of oral agents is to be proven in phase III and IV trials.

The development of the new class of the platelet glycoprotein IIb/IIIa receptor blockers has been a breakthrough in antithrombotic therapy for patients with coronary artery disease.

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