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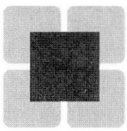

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The clinical role of platelet glycoprotein IIb/IIIa receptor inhibitors in ischemic heart disease

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SUMMARY The platelet glycoprotein (GP) IIb/IIIa receptor antagonists are powerful new antiplatelet drugs that show promise in reducing complications of coronary angioplasty and acute coronary syndromes.

KEY POINTS Platelets play a key role in the pathogenesis of ischemic heart disease. The platelet glycoprotein (GP) IIb/IIIa receptor binds fibrinogen and is the final common pathway leading to platelet aggregation. Compounds that inhibit the GP IIb/IIIa receptor have recently undergone extensive clinical evaluation. The Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial evaluated chimeric 7E3 Fab (c7E3), a monoclonal antibody to the GP IIb/IIIa receptor, in 2099 high-risk patients undergoing angioplasty. Patients treated with c7E3 had 35% fewer ischemic complications after angioplasty than did patients receiving placebo, although at the cost of increased bleeding. Patients with unstable angina or acute myocardial infarction or undergoing directional atherectomy derived particular benefit from c7E3 treatment. Treatment with c7E3 also reduced the 6-month rate of clinical restenosis and especially the number of repeat revascularizations. Several other peptide-based GP IIb/IIIa inhibitors have also been tested in pilot studies in patients with unstable angina and acute myocardial infarction, with positive results.

INDEX TERMS: PLATELET MEMBRANE GLYCOPROTEINS; MYOCARDIAL ISCHEMIA CLEVE CLIN J MED 1996; 63:181–189

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PLATELETS are implicated in the formation of rapidly progressing atherosclerotic lesions, and there is ample evidence of platelet activation and aggregation during acute myocardial infarction, unstable angina, and percutaneous coronary intervention.[1] Platelet glycoprotein (GP) IIb/IIIa receptor inhibitors, which are potent inhibitors of platelet aggregation, have expanded our antithrombotic options, and will likely make an important contribution to the fight against ischemic heart disease in the years to come. These drugs are likely to become the first "anti-integrins" in clinical use and graphically illustrate the power and effectiveness of a close cooperation between basic science and clinical research.

BLOCKING THE FINAL COMMON PATHWAY

Intensive research into the biology of platelet function has identified the GP IIb/IIIa receptor as the binding site for fibrino-

The glycoprotein IIb/IIIa receptor: structure and function

As many as 90 different pathways lead to platelet aggregation, and thromboxane A_2, serotonin, platelet-activating factor, adenosine diphosphate (ADP), epinephrine, thrombin, collagen, and physical factors such as shear stress all promote the process.

Aspirin, the most commonly used antiplatelet agent, inhibits platelet cyclo-oxygenase and thus prevents the production of thromboxane A_2, but leaves open all the other agonist pathways, notably thrombin and collagen, potentially allowing platelet aggregation to proceed.

Aspirin and the other antiplatelet agents available today, including ticlopidine, are all relatively weak platelet antagonists. In contrast, the GP IIb/IIIa receptor antagonists prevent platelet aggregation irrespective of the agonist pathway involved.

The GP IIb/IIIa complex is classified as a member of the integrin family of adhesion molecules because it "integrates" with a ligand (mainly fibrinogen). It has two subunits, the α (αIIb or IIb) subunit, and the β (IIIa) subunit (Figure). Each subunit has a single domain that spans the platelet membrane,[1] and both have tails that extend into the cytoplasm for signal transduction.The binding of fibrinogen to GP IIb/IIIa is the principal underlying mechanism for platelet aggregation.[2–5] However, other adhesive ligands also bind to GP IIb/IIIa, such as von Willebrand factor, fibronectin, and vitronectin.[2,6] All these ligands bear at least one of two specific peptide sequences, which GP IIb/IIIa recognizes: the arginine-glycine-aspartic acid (RGD) sequence and the lysine-glutamine-alanine-glycine-aspartic acid-valine (KQAGDV) sequence. The RDG sequence is present in fibrinogen, von Willebrand factor, and vitronectin[7]; the KQAGDV sequence is found only at the carboxy terminus of the γ-chain of fibrinogen.[8,9]

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gen and other adhesive proteins. This receptor mediates the final common pathway leading to platelet aggregation. The GP IIb/IIIa inhibitors, a new and diverse class of drugs, are designed to block the GP IIb/IIIa receptor and prevent platelet aggregation.

Several agents in clinical trials

Several GP IIb/IIIa inhibitors are currently being evaluated in clinical trials (*Table 1*). Of these, chimeric 7E3 Fab (c7E3), a monoclonal antibody against the GP IIb/IIIa receptor, has undergone the most extensive evaluation, notably in the large-scale Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial (discussed below).[2,3] The lysine-glycine-aspartic acid (KGD) peptide Integrelin, the peptide derivative lamifiban (previously called Ro 44-9883), and the nonpeptide tirofiban (previously called MK-383) are all undergoing phase II or III trials. Approximately eight to 10 more agents are expected to reach clinical trial evaluation over the next few years.

POSITIVE RESULTS IN PRELIMINARY CLINICAL STUDIES

The clinical utility of c7E3 was first evaluated in percutaneous transluminal coronary angioplasty (PTCA) because platelet activation and aggrega-

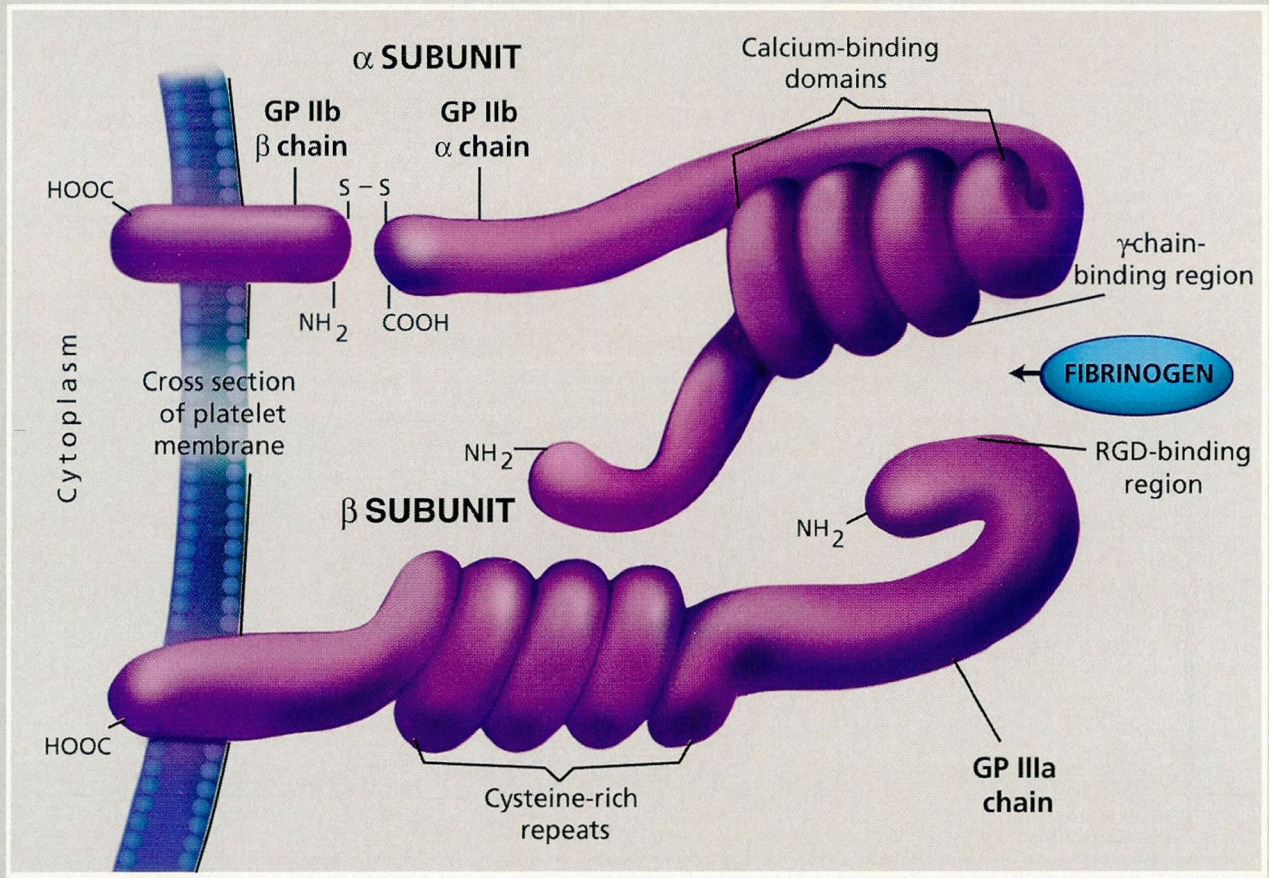

FIGURE. Schematic diagram of the detailed structure of the glycoprotein IIb/IIIa receptor, illustrating how it binds to fibrinogen, other adhesive ligands, or to GP IIb/IIIa receptor inhibitors.

tion are known to occur during this procedure.[4,5] The shearing or tearing effect of PTCA causes platelets to aggregate immediately at the site of vessel injury, which can predispose to abrupt vessel closure—a well-recognized complication of PTCA. In three studies, involving more than 4500 patients,[6–8] vessels abruptly closed during PTCA in 7% to 8% of patients, of whom 20% to 40% suffered myocardial infarctions, 20% to 40% required emergency bypass surgery, and 5% to 8% died.

To try to reduce this rate of complications, Ellis et al[9] gave a 0.25-mg/kg bolus of nonchimeric 7E3 to patients undergoing angioplasty; this dose blocked 90% of the platelet fibrinogen receptors and reduced platelet aggregation to less than 10% (in response to 20 μmol ADP). Of note, very high template bleeding times occurred during receptor blockade, leading to concern about increased risk of bleeding. However, Bernardi and colleagues[10] later demonstrated that prolonged bleeding times did not correlate with bleeding events. The antiplatelet effects diminished over time after the bolus dose, but there still was some receptor blockade at 24 hours.

In a subsequent study, Tcheng and colleagues[11] addressed whether platelet function could be suppressed longer. Fifty-six patients undergoing PTCA received the same bolus dose of c7E3 as in the previous study, followed by an infusion at a very low,

TABLE 1
GLYCOPROTEIN IIb/IIIa INHIBITORS RECENTLY EVALUATED IN CLINICAL TRIALS

Agent	Type	Manufacturer
Chimeric 7E3 Fab (c7E3)	Monoclonal antibody	Centocor, Malvern PA
MK-852	Cyclic RGD peptide	Merck & Co., West Point PA
Integrelin	Cyclic KGD peptide	COR Therapeutics, South San Francisco CA
Lamifiban	Peptide derivative	Hoffman-La Roche, Basel Switzerland
Tirofiban	Nonpeptide	Merck & Co., West Point PA
Xemlofiban	Orally active agent	Searle, Skokie IL

TABLE 2
30-DAY OUTCOMES IN THE EPIC* TRIAL

Event	Number of patients (%)			*P* value for dose response
	Placebo (n = 696)	c7E3 Fab bolus (n = 695)	c7E3 Fab bolus plus infusion (n = 708)	
Death	12 (1.7)	9 (1.3)	12 (1.7)	.96
Nonfatal myocardial infarction	60 (8.6)	43 (6.2)	37 (5.2)	.013
Q-wave	16 (2.3)	7 (1.0)	6 (0.8)	.02
Large non-Q-wave	28 (4.0)	19 (2.7)	21 (3.0)	.265
Small non-Q-wave	16 (2.3)	17 (2.4)	10 (1.4)	.239
Emergency percutaneous transluminal coronary angioplasty	31 (4.5)	25 (3.6)	6 (0.8)	< .001
Emergency coronary artery bypass grafting	25 (3.6)	16 (2.3)	17 (2.4)	.17
Stent placement	4 (0.6)	12 (1.7)	4 (0.6)	.98
Balloon pump insertion	1 (0.1)	1 (0.1)	1 (0.1)	.99
Composite endpoint (includes all of the above)	89 (12.8)	79 (11.4)	59 (8.3)	.009†

*EPIC, Evaluation of c7E3 for the Prevention of Ischemic Complications; adapted with permission from the EPIC investigators, reference 2
†$P = .003$ for overall test trend, $P = .43$ for placebo vs bolus only, and $P = .008$ for placebo vs bolus plus infusion

fixed (not weight-adjusted) rate—10 μg/minute for 12 hours. This regimen extended the time of complete GP IIb/IIIa receptor blockade, reducing platelet aggregation to less than 20% of normal and keeping the bleeding time elevated during the time of the infusion. Platelet function gradually returned to normal over the 48 to 72 hours after the infusion was stopped.

THE EPIC TRIAL: CONCLUSIVE RESULTS IN HIGH-RISK PATIENTS

These pilot trials provided the background for the EPIC trial,[2,3] the first large-scale, randomized trial to show a clinically meaningful reduction in adverse events after coronary intervention. Ellis and colleagues[12] had previously demonstrated that patients with unstable angina, acute myocardial infarction, or recent myocardial infarction (within 7 days) are at increased risk for abrupt vessel closure after PTCA—as high as 10% to 12%, compared with 6% in all patients. The EPIC trial therefore included only patients at high risk: those with acute myocardial infarction, unstable angina, or angiographic features associated with an increased risk of abrupt vessel closure.

In this double-blind, randomized trial, 2099 patients from 56 US sites received one of three treatments before and during PTCA: a c7E3 bolus (given at least 10 minutes before the procedure) followed by a continuous c7E3 infusion at 10 μg/minute for 12 hours, a c7E3 bolus followed by a placebo infu-

sion, or a placebo bolus and a placebo infusion. All patients also received aspirin before the procedure and enough heparin during it to keep the activated clotting time between 300 and 350 seconds. The trial's primary endpoint was a composite of events that included death, myocardial infarction, emergency bypass surgery, and emergency angioplasty. Emergency stenting was also included as a surrogate for emergency bypass surgery, and intra-aortic balloon counterpulsation was included as a marker for recurrent ischemia. However, very few patients who experienced one of these last two endpoints did not also experience one of the other endpoints. The study was completed in November 1992.

Significant short-term benefit

The trial demonstrated a graded effect of c7E3 on the composite endpoint: the bolus dose was better than placebo, and the bolus and infusion was better yet. At 30 days the adverse event rate was 12.8% in the placebo group, 11.4% in the bolus-alone group (11% less), and 8.3% in the bolus-plus-infusion group (35% less, $P = .009$; *Table 2*).

The death rates in the three groups did not differ by intention-to-treat analysis. However, two of the deaths in the bolus-plus-infusion group occurred in patients who died after they were randomized but before they ever received the study drug. Nonfatal myocardial infarction was significantly reduced: the rate was 8.6% in the placebo group and 5.2% in the bolus-plus-infusion group ($P = .013$). The need for urgent intervention was also reduced: the rate was 8.8% in the placebo group and 4.0% in the bolus-plus-infusion group ($P < .001$).

In the placebo group, when abrupt closure necessitating repeat urgent angioplasty occurred, it tended to happen in the first few hours after intervention. The bolus of c7E3 delayed these adverse events, although the absolute benefit was relatively trivial. Only the bolus and 12-hour infusion both delayed the onset of these adverse events and markedly reduced their frequency (*Figure 1*).

A committee blinded to study treatment independently adjudicated all adverse events and reviewed all cases of possible myocardial infarction. There was initial concern that any beneficial effect of c7E3 in reducing myocardial infarction rates would mainly reflect suppression of small cardiac enzyme elevations resulting from angioplasty rather than reduction of large Q-wave myocardial infarctions. This concern proved unfounded.

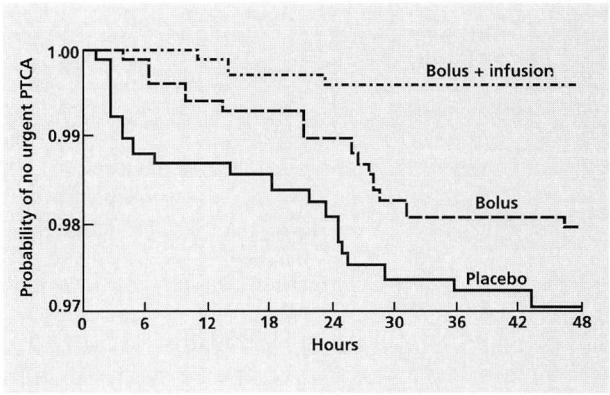

FIGURE 1. Kaplan-Meier plot of freedom from repeat percutaneous transluminal coronary angioplasty in the first 48 hours after c7E3 Fab administration in the EPIC trial. From the EPIC investigators, reference 2.

The reduction in Q-wave myocardial infarctions was significant, as was the reduction in large non-Q-wave myocardial infarctions, and these decreases accounted for most of the effect of c7E3 on myocardial infarction rates.

Specific patient subgroups appeared to derive particular benefit from the c7E3 bolus plus infusion. Patients with unstable angina who received the bolus and infusion had significantly lower rates of death and myocardial infarction, a trend toward fewer repeat interventions, and a 70% reduction in the composite endpoint.[13] Another subgroup deriving significant benefit was patients with acute myocardial infarction.[14]

Yet a third subgroup that benefited more were patients undergoing directional atherectomy—10% of the patients in the EPIC trial. Recent studies[15,16] showed that such patients have a higher incidence of non-Q-wave myocardial infarction after angioplasty than do those undergoing balloon angioplasty. However, the bolus and infusion of c7E3 nearly abolished this excess risk and provided strong evidence that platelet thrombi are involved in the pathogenesis of this complication.[17]

Bleeding events a problem

Bleeding was a major problem in the EPIC trial. Because the potency of GP IIb/IIIa inhibition was not known before the study, large doses of heparin and aspirin were given concurrently, resulting in rates of bleeding complications similar to those that occurred during the initial thrombolytic trials 10 years ago. Although the transfusion rate was twice

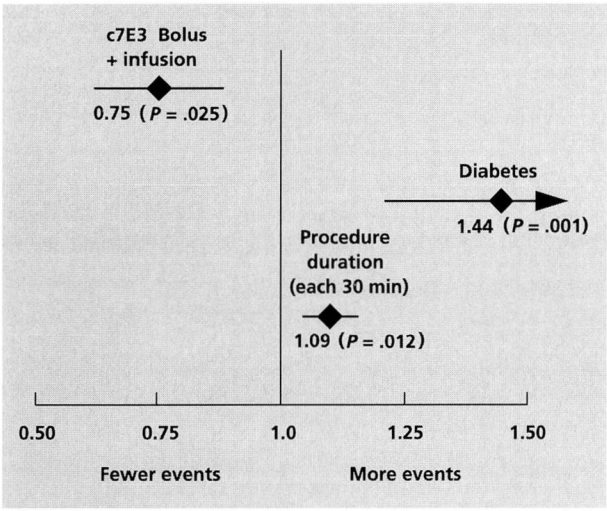

FIGURE 2. Independent predictors of 6-month outcome in the EPIC trial, by multivariate analysis, using the composite endpoint of death, myocardial infarction and repeat revascularization. Odds ratios (with 95% confidence intervals) are shown.

as high in the bolus-plus-infusion group as in the placebo group (15% vs 7%), there was little difference between the bolus and bolus-plus-infusion groups (13% vs 15%). Of interest, 3% of patients in the placebo group received a platelet transfusion, because the study was double-blinded and the site investigators did not know the treatment assignment of any patient with a bleeding episode.

The number of intracerebral hemorrhages did not differ significantly among the groups: two in the placebo group, one in the bolus group, and three in the bolus-and-infusion group (although one of the latter patients never received the study drug). This finding contrasts with the experience with thrombolytics, and more recently in the GUSTO-IIa trial of hirudin vs heparin for acute coronary syndromes, in which intracerebral bleeding did pose a significant problem.[18]

However, nearly three times as many c7E3-treated patients had episodes of bleeding at the femoral vascular access site as did placebo-treated patients. More c7E3-treated patients also had episodes of gastrointestinal bleeding, and in a graded pattern: 11 in the bolus-plus-infusion group, five in the bolus group, and none in the placebo group. Retroperitoneal bleeding accounted for most of the difference in bleeding episodes between the bolus-alone and bolus-plus-infusion groups: 12 patients had retroperitoneal hemorrhages in the bolus-plus-infusion group, vs three each in the bolus group and the placebo group. The complication of retroperitoneal bleeding will require particular vigilance in the future as infusions of GP IIb/IIIa inhibitors are used more commonly.

Most bleeding episodes occurred in patients with low body weight, the chief determinant of bleeding in a multivariate model.[19] Patients who weighed more than 90 kg had essentially no significant increase in bleeding, patients of intermediate weight had only a slight increase, but patients weighing less than 77 kg (the lowest weight tertile) had a large increase. The reason may be that all patients in the study received essentially the same heparin dose during the procedure, regardless of body weight (12 000 to 14 000 units). Therefore, the patients weighing the least were exposed to very high doses of heparin per kilogram of body weight—in addition to potent GP IIb/IIIa inhibition. Further, the infusion of c7E3 was not weight-adjusted.

Long-term restenosis rates reduced

The EPIC investigators followed up the 1825 patients who had a successful initial procedure. At 6 months (the period in which restenosis is likely to develop), fewer patients in the bolus-plus-infusion group had experienced adverse events (death, myocardial infarction, elective bypass surgery, or elective angioplasty) than did patients in the other groups, a composite event rate of 26.9%, compared with 35% in the placebo group (23% lower; P = .001) and 32% in the bolus-only group (*Table 3*). The baseline demographic and angiographic characteristics of the patients followed up long-term did not differ among the study groups.

The investigators also focused on how many patients needed repeat procedures to the same vessels that were originally revascularized: 26% fewer in the bolus-plus-infusion group than in the placebo group (16.5% vs 22.3%, P = .007).

In multivariate regression analysis, the bolus-plus-infusion regimen of c7E3 was an independent determinant of clinical restenosis, resulting in a 23% reduction of events at 6 months (*Figure 2*). Patients with diabetes mellitus had higher restenosis rates—a finding consistent with several other studies.[20–22] The duration of the procedure also predicted clinical restenosis, an effect thought to be related to more-complex lesion morphology.[23] Each additional 30 minutes in procedure time translated into a 1.1 times higher risk of clinical restenosis.

TABLE 3
6-MONTH OUTCOMES IN THE EPIC* TRIAL

Event	Percent of patients			*P* value (placebo vs bolus plus infusion)
	Placebo (n = 696)	c7E3 Fab bolus (n = 695)	c7E3 Fab bolus plus infusion (n = 708)	
Death	3.4	2.6	3.0	.82
Myocardial infarction	10.5	8.0	6.9	.01
Coronary artery bypass grafting	11.0	9.7	9.4	.33
Percutaneous transluminal coronary angioplasty	20.8	19.8	14.3	.001
Composite endpoint (includes all of the above)	35.0	32.4	26.9	.001

*EPIC, Evaluation of c7E3 for the Prevention of Ischemic Complications; adapted with permission from the EPIC investigators, reference 3

OTHER STUDIES OF GP IIb/IIIa INHIBITORS

Coronary angioplasty in lower-risk patients

A recently-completed pilot study of Integrelin in coronary angioplasty, known as the Integrelin to Minimize Platelet Aggregation and Prevent Coronary Thrombosis (IMPACT-I) study, was open to all patients—not just high-risk patients.[24] In a double-blind fashion, 101 patients were randomly assigned to receive a bolus of Integrelin followed by either a 4- or 12-hour infusion, and 49 were assigned to receive placebo. Even though these patients were at lower risk than were the EPIC patients, there was a trend toward a reduction in endpoint events at 30 days, from 12.2% in the placebo group to 4.1% in the 12-hour infusion group (P=.13). The incidence of bleeding was similar in the placebo and Integrelin groups.

Two other large-scale trials of GP IIb/IIIa inhibitors in coronary intervention are currently in progress. The IMPACT-II trial is evaluating Integrelin in high vs low doses and has recently completed enrollment of more than 4000 patients. The Evaluation of PTCA to Improve Long-Term Outcome by c7E3 Glycoprotein Receptor Blockade (EPILOG) trial will compare regimens of c7E3 plus either heparin in a standard dose or heparin in a low dose during routine angioplasty. Planned enrollment is approximately 4800 patients.

Acute myocardial infarction

The Eighth Thrombolysis and Myocardial Infarction (TAMI-8) project[25] evaluated a regimen of tissue plasminogen activator (t-PA) followed by murine 7E3 Fab (m7E3) given in escalating doses at 3, 6, and 15 hours. At 24 hours, there was evidence of improved vessel patency and a trend towards fewer episodes of recurrent ischemia in the m7E3 groups. Overall, this pilot study's findings were promising and encouraged further studies of combined thrombolysis and GP IIb/IIIa inhibition.

The Integrelin to Minimize Platelet Aggregation and Prevent Coronary Thrombosis-Acute Myocardial Infarction (IMPACT-AMI) trial, currently underway, is examining adding Integrelin to t-PA in accelerated doses, heparin, and aspirin in a randomized, placebo-controlled study design. Preliminary results showed that the addition of Integrelin to the other agents profoundly inhibited platelet aggregation, but only in high doses, suggesting, as have other studies, that platelets are highly reactive in myocardial infarction.[26]

Unstable angina

Lamifiban treatment significantly reduced the 5- and 30-day rates of endpoint events (death, myocardial infarction, or urgent revascularization) in the largest completed trial to date of GP IIb/IIIa receptor inhibition in unstable angina.[27] This was a Canadian phase II trial in 360 patients. Of interest, the addition of heparin did not seem to add to the efficacy of lamifiban, but did increase the bleeding risk. However, there was a low incidence (2.9%) of major bleeding overall.

Integrelin was also recently tested in patients with unstable angina.[28] In a multicenter trial involv-

ing 17 centers and 89 patients, this agent decreased the number and duration of ischemic events detected by continuous ST-segment monitoring, principally in patients who received high doses. Other pilot studies also demonstrated positive results with c7E3[29] and with tirofiban.[30]

FUTURE CHALLENGES

Issues to be resolved include how to decrease bleeding complications, how platelet GP IIb/IIIa inhibitors interact with heparin, and how to use heparin concurrently to best advantage while minimizing the need for transfusion. More study is needed in low-risk patients undergoing coronary intervention, and the issue of cost-effectiveness will ultimately need to be addressed before these agents can enter widespread use. Finally, further investigation of orally active inhibitors is needed. Early studies have already been conducted with xemlofiban, a potent oral GP IIb/IIIa antagonist,[31,32] and this type of agent holds promise for a number of indications such as primary prevention in patients at high risk for acute myocardial infarction.

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