

Antithrombotic Effects of Abciximab

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The observation that platelet-platelet interaction and thrombosis are ultimately regulated by the glycoprotein (GP) IIb/IIIa receptor complex, triggered the development of agents capable of interfering with this platelet receptor complex. Several large clinical trials have demonstrated the effectiveness of this class of agents. The first of these agents to show beneficial effects after coronary interventions was the mouse/human chimeric Fab fragment antibody c7E3 (abciximab; ReoPro). This study analyzes whether the addition of heparin to the GP IIb/IIIa antagonist abciximab would enhance the antithrombotic effect. Blood drawn directly from patients on aspirin who underwent interventional procedures perfused an ex vivo perfusion chamber containing a severely injured arterial wall at local rheologic conditions of a mildly stenosed coronary artery. Blood was perfused directly from patients at baseline and following

administration of heparin, abciximab, or both. The antithrombotic effects of the 3 treatments were assessed by reduction of the thrombus formation on the perfused specimens. Thrombus formation at baseline was not significantly modified by the administration of heparin ($13,897 \pm 1,316$ vs $11,917 \pm 1,519 \mu\text{m}^2$). Abciximab produced a 58% reduction in thrombus formation ($11,631 \pm 861$ vs $4,925 \pm 585 \mu\text{m}^2$; $p < 0.001$). The addition of heparin to abciximab did not further reduce thrombus area versus abciximab alone ($5,651 \pm 581$ vs $4,925 \pm 585 \mu\text{m}^2$). Thus, our data show that abciximab dramatically decreases mural thrombus formation and that combining heparin with abciximab did not add any additional antithrombotic effect to abciximab alone.

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(Am J Cardiol 2000;85:1167-1172)

Several agents capable of interfering with the glycoprotein (GP) IIb/IIIa receptor complex have been developed and clinically tested. The effectiveness of the first of these agents, abciximab, in preventing ischemic complications in unstable angina and after coronary interventions has been demonstrated in several clinical trials.¹ The effects of the GP IIb/IIIa antagonists are mediated by interfering with the binding of fibrinogen to the exposed GP IIb/IIIa receptors, blocking platelet-platelet interactions and thrombus formation. In addition, GP IIb/IIIa antagonists may also interfere with the exposure of procoagulant phospholipids by the platelets and thus inhibit thrombin

generation.^{2,3} Thus, abciximab may have an anticoagulant as well as antiplatelet effect. Based on these observations, this study was designed to assess whether the addition of the anticoagulant heparin would enhance the antithrombotic effect of abciximab in a well-characterized perfusion system. The study was performed using an ex vivo perfusion chamber, mimicking the in vivo local rheologic conditions that develop in a mildly stenosed coronary artery with deep vascular injury. In this perfusion system, thrombus formation is triggered by exposing medial components of the arterial wall to flowing blood.⁴⁻⁶ Blood from patients with an acute coronary syndrome who underwent percutaneous coronary interventions was allowed to circulate directly from the patient through the perfusion system.⁷ Antithrombotic activity was assessed by morphometric analysis of the thrombus formed when using blood from patients before and after receiving abciximab.

METHODS

Patient population: Twenty-three patients with unstable angina, who were judged eligible for coronary intervention after diagnostic angiography, were recruited for the study. The Institutional Review Board approved the study, and all enrolled patients gave voluntary written informed consent. All procedures were performed at the Cardiac Catheterization Laboratory, Zena and Michael A. Wiener Cardiovascular Institute at Mount Sinai Hospital, New York. Inclusion criteria were the presence of an acute coronary syndrome or an angiographically high-risk lesion (defined in the following). Only patients with native coronary artery lesions of $\geq 70\%$ diameter stenosis were included. Exclusion criteria included restenotic

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Conflict of interest statement: Dr. Barry S. Collier is an inventor of abciximab. In accordance with federal law and the patent policy of Research Foundation of the State University of New York, Dr. Collier shares in the royalty payments made to the Foundation for the sale of abciximab. Dr. Collier contributed to the scientific design and review of the experiments but did not participate in the collection of any of the clinical data or in their statistical analysis.

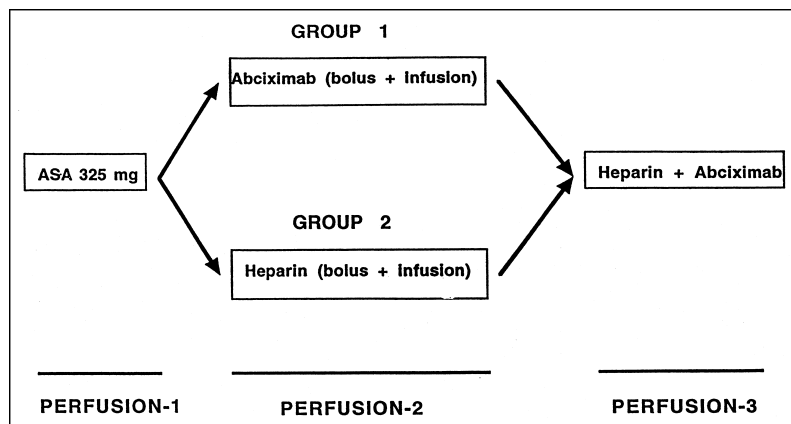


FIGURE 1. Scheme of the study design. All patients enrolled in the study had the first perfusion study (Perfusion-1) under basal conditions. Thereafter, group 1 had the second perfusion study (Perfusion-2) performed 10 minutes after receiving abciximab. Group 2 had the perfusion-2 study performed 10 minutes after receiving heparin. The third perfusion study (Perfusion-3) was performed when both groups of patients received both therapies.

lesions, thrombocytopenia ($<130,000$ platelets/ μL), bleeding disorder, or a history of stroke.

Definitions: The definition of acute coronary syndromes included postinfarction, refractory, new, or increased angina (Braunwald classes II or III, B or C)⁸ within 2 weeks. Angiographically, high-risk lesions were defined as complex or types B or C lesions according to the American Heart Association/American College of Cardiology classification.⁹ Lesion complexity was assessed according to the Ambrose criteria and characterized by irregular borders, overhanging edges, and with or without proximal or distal intracoronary filling defects.¹⁰

Study design (Figure 1): All patients enrolled in the study received 325 mg of aspirin. An 8Fr introducer sheath was placed into the femoral artery and a bolus of 1,000 IU of heparin was given to flush the sheath. This dose did not have any effect on the activated partial thromboplastin time (aPTT). Blood was then obtained for the first perfusion study (PS-1) to assess blood thrombogenicity under baseline conditions in the ex vivo perfusion chamber. Thereafter, all patients received abciximab (0.25 mg/kg bolus given intravenously over 5 minutes followed by an intravenous infusion of 10 $\mu\text{g}/\text{min}$ for 12 hours) and heparin (70 IU/kg bolus plus 15 IU/kg/h infusion to maintain aPTT of 60 to 80 seconds). Patients were randomized into 2 groups (Figure 1): group 1 received abciximab before heparin administration, and group 2 received heparin before abciximab. A second perfusion study (PS-2) was performed 10 minutes after the initial medication was given, but before administering the second medication. The patients then underwent the scheduled coronary intervention. A third perfusion study (PS-3) was performed 6 hours after the coronary intervention while patients were on abciximab and intravenous heparin infusion.

Revascularization procedures: Percutaneous coronary interventions consisted of ≥ 1 of the following: transluminal coronary angioplasty (balloon-to-artery

ratio 1.0 to 1.1), rotational coronary atherectomy, directional coronary atherectomy, transluminal extraction catheterization, or intracoronary stent implantation. All stents were deployed with high-pressure balloons (balloon-to-artery ratio 1.0) without intravascular ultrasound guidance. Procedural success was defined as $\leq 30\%$ residual diameter stenosis and absence of dissection or major complications (death, infarction, need for bypass surgery). The preprocedural heparin infusion was discontinued ≥ 1 hour before coronary intervention. Heparin was administered during the procedure as repeated boluses to maintain the target activated clotting time of >300 seconds.

Ex vivo perfusion chamber: The perfusion chamber used in this study has been extensively described else-

where.^{11,12} It consists of a cylindrical flow channel (1 mm diameter and 2.5 cm length) that allows the blood to flow over the thrombogenic substrate. All the perfusions were performed for a period of 5 minutes at a flow rate of 10 ml/min (calculated shear rate of 1,690/s; Reynolds number 60; average blood velocity 21.2 cm/s). The selected dynamic conditions modeled the local rheology to develop on mild to moderately stenotic coronary arteries. Our previous work demonstrated that these rheologic conditions resulted in consistent levels of platelet deposition.^{4,7} The experimental perfusion system was connected to the arterial sheath to allow the patient's blood to flow directly into the perfusion chamber.

To mimic the in vivo situation of severe arterial injury associated with coronary interventions, porcine aortic tunica media was used as the substrate to trigger thrombus formation. Segments of porcine tunica media were cut into segments (2.8×0.8 cm) and surgically prepared to expose the deeper components of the arterial wall as described.^{7,11,13}

During each perfusion study, blood was circulated directly from the patient arm's through 3 chambers connected in series. The input of the perfusion chamber system was connected to the intravenous sheath by polyethylene tubing. The output of the chamber was connected to a distal peristaltic pump (Master-Flex model 7013, Cole-Palmer Inc., Vernon Hills, Illinois) calibrated to maintain the selected blood flow. All the perfusions were performed at 37°C by placing the chambers in a water bath. Blood samples were taken before each perfusion for hematocrit, platelet count, fibrinogen levels, and clotting parameters.

The thrombi that formed on the exposed substrates were morphologically similar to those that formed on human arterial segments that contained lipid-rich plaques.^{2,11,13} Previous studies have indicated that murine antibody 7E3 does not react with porcine endothelial cell or porcine platelets (BS Collier and L Badimon, unpublished results).

Evaluation of platelet-thrombus formation: After perfusion, specimens were removed from the chamber and immediately fixed in 4% phosphate buffered paraformaldehyde. Specimens were transversely cut into 2- to 4-mm thick pieces and paraffin embedded. Histologic sections (5 μm) from each specimen were prepared and stained with Combined Mason-Elastin, which stains thrombus red.

Morphometric analysis of thrombus was conducted at 400-fold magnification by 2 independent observers blinded to the treatment assignments. Images were digitized with a Sony DKC-5000 camera using Adobe Photoshop 4.0 software on a PowerMacIntosh 8500 computer. Thrombus area on each section was measured by computerized planimetry using Image 1.6 software. The results of ≥ 3 sections were averaged to determine the thrombus area for each chamber, and then the results of the 3 chambers were averaged to measure the overall thrombus formation for each perfusion study.

Platelet aggregation and receptor occupancy studies: In vitro platelet aggregation in citrated platelet-rich plasma was measured as previously described¹² using adenosine diphosphate (ADP) (20 μM) as an agonist to initiate aggregation. Platelet aggregation, measured as the maximal aggregation response, was expressed as a percentage of the baseline.

Platelet membrane GP IIb/IIIa receptor complex occupancy was evaluated as described.¹⁴ In brief, citrated platelet-rich plasma prepared from blood obtained at the designated time-points was incubated with a known amount of iodine-125 abciximab. Unoccupied GP IIb/IIIa receptors can bind radioactive abciximab, whereas receptors blocked by unlabeled abciximab cannot bind the labeled antibody. The effect of the treatment on receptor occupancy is expressed as percentage occupancy versus the pretreatment value. An occupancy of $\geq 80\%$ is the therapeutic target level.

Statistical analysis: The design of the study allows each patient's pretreatment value to serve as his/her own control. Data are presented as mean $\pm$ SEM unless stated. Thrombus areas are expressed as square micrometers. The statistical significance of differences between the normal and treated groups was determined using analysis of variance for repeated measures. Differences were considered significant if the p value was <0.05 , using Statview 512+ software (Brain Power, Inc.).

RESULTS

Study population: Four of a total of 23 patients who underwent coronary interventions during the study period were excluded. Two patients were excluded because the aPTT at the time of PS-1 was >60 seconds. One patient was excluded because the heparin and abciximab treatments were discontinued immediately after the coronary procedure due to local bleeding at the femoral artery puncture site; and the fourth patient was excluded because the intervention was considered unsuccessful due to inability to cross the lesion with the guidewire.

Three patients underwent balloon angioplasty alone (2 in group 1, 1 in group 2); 2 underwent rotational coronary atherectomy plus stent placement (both in group 2); 6 patients underwent rotational atherectomy (5 in group 1 and 1 in group 2); 5 underwent stent placement alone (3 in group 1, 2 in group 2); 1 underwent directional atherectomy alone (group 2); 1 underwent directional atherectomy plus stent placement (group 2); and 1 underwent transluminal extraction catheterization combined with balloon angioplasty (group 2). All patients who underwent stent placement (5 in group 1 and 3 in group 2) received 250 mg of ticlopidine after PS-2 was completed, but before coronary interventions.

There were no significant differences between the 2 groups of patients with respect to their clinical and angiographic characteristics. Hematocrit, platelet count, activated clotting time (ACT), and aPTT during the baseline studies were also similar in both groups.

Evaluation of thrombus formation: Results of the perfusion studies for groups 1 and 2 are shown in Figure 2. At baseline there was no significant difference in thrombus area between groups 1 and 2 ($11,631 \pm 861$ vs $13,987 \pm 1,316 \mu\text{m}^2$, respectively).

Data obtained from group 1 indicated that the treatment with abciximab alone reduced thrombus formation by 58% ($4,924 \pm 585$; $p < 0.01$ vs baseline). Furthermore, the addition of heparin to abciximab did not produce a further reduction in thrombus area versus abciximab alone ($5,651 \pm 581$ vs $4,924 \pm 585 \mu\text{m}^2$, respectively). The data in group 2 showed that thrombus formation was not inhibited by the administration of heparin alone ($13,897 \pm 1,316$ vs $11,917 \pm 1,519 \mu\text{m}^2$). The addition of abciximab to heparin significantly reduced thrombus formation ($6,038 \pm 1,519$ vs $11,917 \pm 1,519 \mu\text{m}^2$; $p < 0.001$).

Results on platelet aggregation, receptor occupancy, and anticoagulation: The effects of the treatments on platelet aggregation in response to 20 μM ADP are presented in Figure 3. Heparin did not inhibit platelet aggregation ($98 \pm 2\%$ of the baseline), whereas abciximab, either alone or in combination with heparin, significantly inhibited platelet aggregation ($12 \pm 6\%$ and $25 \pm 5\%$, respectively; $p < 0.001$ vs baseline for both values). Comparison of platelet aggregation with abciximab treatment alone versus combined therapy with heparin and abciximab demonstrated that abciximab alone produced a greater reduction of platelet aggregation than the combined therapy ($p < 0.05$).

The results of the GP IIb/IIIa receptor occupancy studies are presented in Figure 4. The average receptor occupancy in group 1 after abciximab treatment alone was $84 \pm 6\%$. When abciximab and heparin were administered, the average receptor occupancy was $75 \pm 4\%$, which was not significantly less than that obtained with abciximab alone. Receptor occupancy values after abciximab administration, either alone or in combination with heparin, were significantly higher compared with either baseline or heparin treatment ($p < 0.001$). The administration of heparin alone did not have any effect on receptor occupancy compared with baseline ($4 \pm 3\%$ vs 0% , respectively).

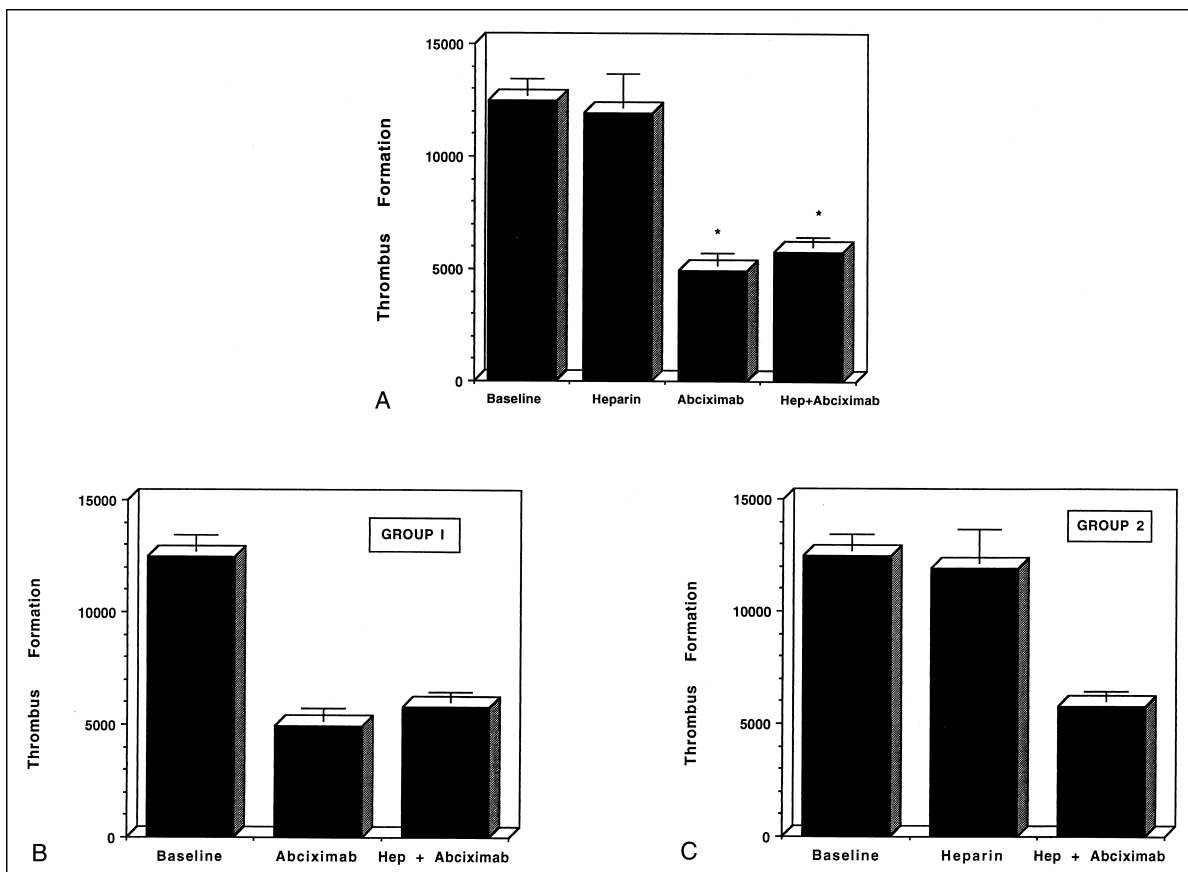


FIGURE 2. Effect of the different treatments on thrombus formation. (A) The composite data of all the patients involved in the study. (B) and (C) The results corresponding to groups 1 and 2, respectively. The results are expressed as square micrometers ($X \pm \text{SEM}$; * $p < 0.001$).

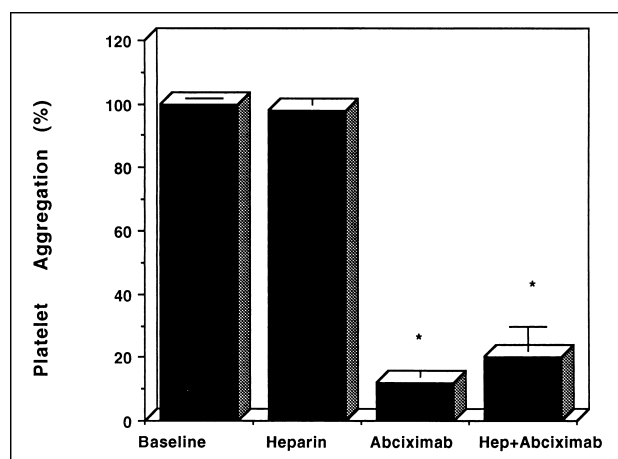


FIGURE 3. Results of in vitro platelet-rich plasma-platelet aggregation in response to 20-mM ADP. Results are expressed as percentage of the baseline values ($X \pm \text{SEM}$; * $p < 0.001$).

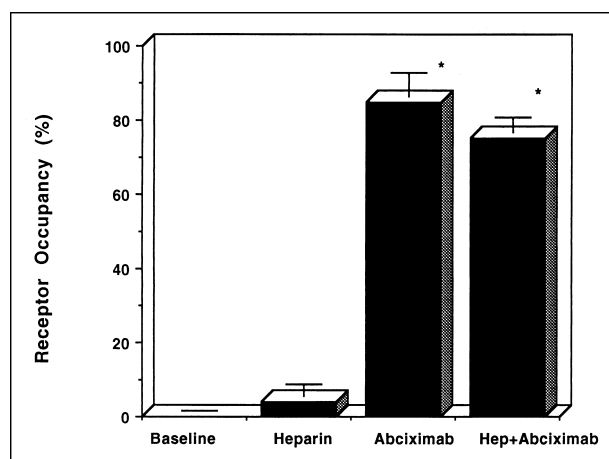


FIGURE 4. Effect of the treatments of GP IIb/IIIa receptor occupancy. Results are expressed as percentage of the baseline values ($X \pm \text{SEM}$; * $p < 0.001$).

The effects of the different therapies on aPTT values are presented in Figure 5. As expected, heparin administration significantly prolonged the aPTT (144 ± 22 seconds heparin vs 25 ± 1 second baseline group, respectively; $p < 0.001$), but abciximab did not (24 ± 1 second vs 25 ± 1 second, respectively). Combining abciximab and heparin did not result in a

greater prolongation of aPTT than that produced by heparin alone (112 ± 13 vs 144 ± 22 seconds; $p = \text{NS}$).

GP IIb/IIIa receptor occupancy correlated inversely with both the platelet aggregation ($r = 0.94$; $p < 0.0001$) and thrombus formation ($r = 0.57$; $p < 0.0001$). No correlation was observed between receptor occupancy and aPTT ($r = 0.01$; $p = 0.5524$).

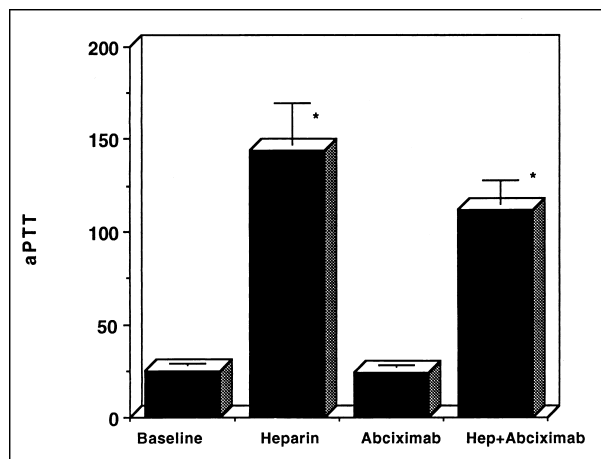


FIGURE 5. Results of the different treatments on aPTT values. The results are expressed in seconds ($\bar{X} \pm \text{SEM}$; * $p < 0.001$).

DISCUSSION

Our study demonstrates that blockade of the platelet membrane GP IIb/IIIa receptor complex at the dose currently used in clinical practice significantly reduces mural thrombus formation on severely damaged arterial walls when exposed to human arterial blood. The conditions used in our study, severe arterial injury and high shear rate, were selected to mimic the clinical scenario occurring in mildly stenosed coronary arteries after plaque disruption. Our data indicate that abciximab dramatically decreases thrombus formation and that adding heparin, at the doses currently used for coronary interventions, with the GP IIb/IIIa receptor antagonist did not further reduce mural thrombus compared with abciximab alone. Moreover, the administration of heparin alone did not have any effect on mural thrombus formation despite its marked anticoagulant effect.

This study again shows that drugs that decrease the incidence of total occlusion can differ in their ability to decrease mural thrombus formation. Heparin, aspirin, or both, decrease clinical acute occlusion.^{15,16} Heparin or aspirin mildly decrease in vivo mural thrombus formation over 2 hours on deeply injured carotid arteries, and both prevent short-term in vivo acute occlusion.¹⁷ Abciximab is another example of an antithrombotic therapy that decreases clinical acute occlusion more than heparin plus aspirin,^{9,10,12} and in this study it also markedly decreased mural thrombus formation, whereas heparin plus aspirin did not (compared with aspirin alone). Thus, prevention of total occlusion is a less sensitive measure of antithrombotic potency and does not predict the extent of mural thrombus formation. However, superiority of reducing mural thrombus formation appears to predict superior clinical outcome of reducing clinical acute occlusion.

Our data are of particular interest in view of the results from the Evaluation of c7E3 Fab in the Prevention of Ischemic Complications (EPIC), Evaluation in PTCA to Improve Long-term Outcome with abciximab GPIIb/IIIa Blockade (EPILOG), and Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT)

studies. In EPIC, abciximab was given in conjunction with a 10,000 to 12,000 U recommended bolus dose of heparin that resulted in prolongation of the ACT to 300 to 350 seconds. The clinical benefit of abciximab treatment in reducing ischemic complications in EPIC was offset by a significant increase in major bleeding. A careful analysis of the results of EPIC indicated an association between the risk of bleeding and the weight-adjusted heparin dose. This suggested that a reduction of the heparin dose might decrease the hemorrhagic risk without decreasing the efficacy of the therapy. As a result, in EPILOG and EPISTENT, a lower bolus of heparin was recommended (70 IU/kg/min) and lower target ACTs were considered acceptable (>200 seconds). The results of these trials supported the hypothesis developed from the analysis of EPIC because the efficacy of abciximab treatment was as great or greater than in EPIC, whereas the risk of major hemorrhage was dramatically decreased and, in fact, did not differ from the control group.

At present, it is unclear what dose, if any, of heparin should be combined with abciximab to optimize the safety and efficacy of the treatment. Because the current heparin dose does not increase major bleeding, decreasing the dose further is unlikely to significantly decrease the risk of major bleeding, but may decrease the risk of minor bleeding associated with percutaneous coronary interventions. It is doubtful that reducing the heparin dose to that used in the coronary care unit (55 to 75 seconds) would either decrease or increase the efficacy of abciximab in preventing ischemic complications, because heparin could be beneficial, by virtue of its anticoagulant effects, or detrimental by virtue of its platelet proaggregatory effects.

Although our data raise the possibility that it might be possible to perform coronary interventions with abciximab and achieve maximal antithrombotic potential without the concomitant use of heparin, we would urge caution because of the demonstrated value of heparin in avoiding clot formation on intervention catheters and in regions of stasis, and because of uncertainty in extrapolating the data obtained with our ex vivo model to patients undergoing percutaneous interventions. However, these observations could have significant clinical implication for those patients with heparin-induced thrombocytopenia.

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