Relative Importance of Thrombin Compared With Plasmin-Mediated Platelet Activation in Response to Plasminogen Activation With Streptokinase

Kenneth J. Winters, MD; Samuel A. Santoro, MD, PhD; Joseph P. Miletich, MD, PhD; and Paul R. Eisenberg, MD, MPH

Background. Platelet activation occurs in vivo during pharmacologic thrombolysis and may contribute to recurrent thrombosis. Plasmin does not directly activate platelets except at high concentrations; thus, the mechanisms for platelet activation during thrombolysis remain undefined. Increases in thrombin activity also occur in patients treated with fibrinolytic agents and may contribute to activation of platelets. We have shown that one mechanism for increased thrombin activity is activation of the coagulation system by plasmin.

Methods and Results. In the present study we sought to determine whether activation of platelets in response to pharmacologic activation of plasminogen in plasma is due primarily to plasmin or mediated by increased thrombin activity. Platelet-rich citrated plasma (PRP) was recalcified and incubated with 1,000 IU/ml of streptokinase or 1.0 caseinolytic units/ml of plasmin. Concentrations of fibrinopeptide A, a marker of thrombin activity, increased markedly over 10 minutes in plasma incubated with streptokinase or plasmin, but not in PRP incubated without plasminogen activator. Platelet activation characterized by the secretion of 14C-serotonin occurred within 2–4 minutes after thrombin activity increased. In stirred recalcified PRP, platelet aggregation was accelerated from 3.6±0.5 to 2.5±0.3 minutes (p<0.01) when incubated with 1,000 IU/ml of streptokinase. Leupeptin and aprotinin, inhibitors of plasmin activity, markedly attenuated platelet activation in response to pharmacologic activation of plasminogen. However, inhibition of thrombin with heparin, hirudin, or D-Phe-D-Pro-L-Arg-chloromethylketone was more effective in inhibiting the acceleration of platelet activation induced by plasminogen activation, despite the elaboration of plasmin activity.

Conclusions. Activation of platelets during coronary thrombolysis may be due in part to increased procoagulant activity induced by plasminogen activation as well as other factors that promote platelet activation in vivo. (Circulation 1991;84:1552–1560)

Recurrent coronary thrombosis or failure of clot lysis occurs in 20–30% of patients treated for acute myocardial infarction with pharmacologic thrombolysis.1–3 In experimental preparations, inhibition of thrombin activity4–7 or platelet function8–10 has been shown to reduce the incidence of rethrombosis. In patients with acute myocardial infarction treated with tissue-type plasminogen activator (t-PA) or streptokinase (SK), the rate of sustained coronary artery patency is higher in those treated with heparin, with or without aspirin.11–13 Because there is evidence of both increased thrombin activity and platelet activation during thrombolysis, it is not clear whether plasmin has direct platelet-activating effects or whether platelet activation is secondary to activation of the coagulation system.14–19 Although high concentrations of plasmin have been shown to activate washed platelets,20 we have shown that activation of plasminogen with pharmacologic concentrations of SK or t-PA in citrated plasma does not induce platelet activation.21 However, the extent to which these observations

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reflect responses to thrombolysis in vivo is limited because the use of purified systems or anticoagulated plasma precludes activation of the coagulation system. We have shown that SK and t-PA induce marked thrombin activity in nonanticoagulated whole blood or recalcified citrated plasma and that this is attributable to plasmin-mediated activation of the coagulation system. Thus, increases in thrombin activity induced by plasminogen activation may be one of the mechanisms for platelet activation in patients treated with SK or t-PA. Accordingly, the present study was designed to characterize in a nonanticoagulated plasma system the extent to which activation of platelets in response to activation of plasminogen is due to the direct effects of plasmin as opposed to increases in thrombin activity.

**Methods**

**Materials**

All reagents were of analytic quality. Aprotinin, e-aminocaproic acid, imipramine, and hirudin were obtained from Sigma (St. Louis, Mo.). Heparin sodium was purchased from Elkins-Sinn (Cherry Hill, N.J.). PPACK (d-Phe-d-Pro-L-Arg-chloromethylketone), a synthetic thrombin inhibitor, was obtained from Calbiochem (La Jolla, Calif.) and SK and plasmin from Kabi-Vitrum, Inc. (Kabikinase, Alameda, Calif.).

**Preparation of Platelet-Rich Plasma**

Blood was obtained from healthy volunteers who gave written informed consent and who were not taking medications known to interfere with platelet function. Antecubital venipuncture was performed with a 19-gauge needle after application of a tourniquet. Whole blood was anticoagulated with 1/10 volume of 3.8% (wt/vol) trisodium citrate, pH 7.4. Citrated platelet-rich plasma (PRP) was isolated after centrifugation of anticoagulated whole blood at 150g for 15 minutes. Autologous platelet-poor plasma (PPP) was prepared by centrifuging citrated PRP at 150g for 10 minutes. To ensure that results were not specific to a single donor, only findings in experiments repeated in two or more donors are reported.

**Platelet 14C-Serotonin Release**

Activation of platelets in plasma during incubation with plasminogen activators was characterized by the secretion of 14C-serotonin (14C-hydroxytryptophan) from platelets. 14C-serotonin was obtained from Amersham (Arlington Heights, Ill.) and had a specific activity of 0.01 μCi/μl. After adjusting the platelet count to 200,000/μl with autologous PPP, PRP was incubated with 14C-serotonin (0.7 μCi/ml PRP) for 60 minutes at room temperature. Imipramine was then added to the PRP to a final concentration of 4 μM to prevent reuptake of serotonin. Spontaneous leakage of 14C-serotonin during the time course of experiments was less than 10%. Secretion of 14C-serotonin during activation of plasminogen in recalcified PRP was determined by removal of 100-μl aliquots of PRP at the specified time points and incubation at 4°C with EDTA (10 mM final) and paraformaldehyde (0.9% vol/vol final) to inhibit further platelet uptake or release of serotonin. Platelets were then collected by high-speed microcentrifugation, the supernatant was removed and transferred to scintillation fluid (Universal Cocktail, ICN Radiochemicals, Irvine, Calif.), and the 14C activity was measured in a β counter (LKB-1209 Rackbeta, Bromma, Sweden).

**TABLE 1. Platelet Aggregation and Clotting in Recalcified Platelet-Rich Plasma Incubated With or Without 1,000 units/ml Streptokinase and Thrombin Inhibitors**

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Concentration</th>
<th>n</th>
<th>Condition</th>
<th>Platelet aggregation</th>
<th>Clotting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>0.3 units/ml</td>
<td>1</td>
<td>-SK</td>
<td>5.8</td>
<td>&gt;7.0</td>
</tr>
<tr>
<td>Heparin</td>
<td>1.0 units/ml</td>
<td>1</td>
<td>-SK</td>
<td>&gt;7.0</td>
<td>&gt;7.0</td>
</tr>
<tr>
<td>Heparin</td>
<td>0.3 units/ml</td>
<td>4</td>
<td>+SK</td>
<td>5.0</td>
<td>&gt;7.0</td>
</tr>
<tr>
<td>Heparin</td>
<td>0.5 units/ml</td>
<td>2</td>
<td>+SK</td>
<td>5.8</td>
<td>&gt;7.0</td>
</tr>
<tr>
<td>Heparin</td>
<td>1.0 units/ml</td>
<td>3</td>
<td>+SK</td>
<td>&gt;7.0</td>
<td>&gt;7.0</td>
</tr>
<tr>
<td>Hirudin</td>
<td>1.0 μM/ml</td>
<td>1</td>
<td>-SK</td>
<td>4.8</td>
<td>5.4</td>
</tr>
<tr>
<td>Hirudin</td>
<td>3.0 μM/ml</td>
<td>1</td>
<td>-SK</td>
<td>&gt;8.0</td>
<td>&gt;8.0</td>
</tr>
<tr>
<td>Hirudin</td>
<td>1.0 μM/ml</td>
<td>2</td>
<td>+SK</td>
<td>3.3</td>
<td>4.1</td>
</tr>
<tr>
<td>Hirudin</td>
<td>2.0 μM/ml</td>
<td>2</td>
<td>+SK</td>
<td>4.1</td>
<td>4.9</td>
</tr>
<tr>
<td>Hirudin</td>
<td>3.0 μM/ml</td>
<td>5</td>
<td>+SK</td>
<td>4.1</td>
<td>5.3</td>
</tr>
<tr>
<td>Hirudin</td>
<td>5.0 μM/ml</td>
<td>3</td>
<td>+SK</td>
<td>6.3</td>
<td>&gt;7.0</td>
</tr>
<tr>
<td>Hirudin</td>
<td>15.0 μM/ml</td>
<td>1</td>
<td>+SK</td>
<td>&gt;7.0</td>
<td>&gt;7.0</td>
</tr>
<tr>
<td>PPACK</td>
<td>1.0 μM</td>
<td>1</td>
<td>-SK</td>
<td>&gt;7.0</td>
<td>&gt;7.0</td>
</tr>
<tr>
<td>PPACK</td>
<td>3.0 μM</td>
<td>1</td>
<td>-SK</td>
<td>&gt;7.0</td>
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<td>&gt;7.0</td>
</tr>
</tbody>
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PPACK, d-Phe-d-Pro-L-Arg-chloromethylketone.
Percent of serotonin secretion was calculated after correction for dilutions as:

\[
\text{14C-serotonin secretion (\%)} = \frac{\text{sample supernatant (cpm)} - \text{baseline supernatant (cpm)} \times 100}{\text{total platelet (cpm)}}
\]

**Assay of Platelet Activation and Clotting in Recalciﬁed PRP**

Activation of platelets and clotting of PRP in response to plasminogen activation were characterized with a dual-channel platelet aggregometer (Payton Scientific Inc., Buffalo, N.Y.). Incubations with PRP were performed in a ﬁnal volume of 1 ml, and the amount of added reagents was 12% (vol/vol) or less. 14C-serotonin–labeled citrated PRP was incubated in an aggregometer cuvette at 900 rpm at either 32°C or 37°C for 3–5 minutes to obtain a stable baseline tracing. At the start of each incubation a premixed aliquot of CaCl₂ (ﬁnal concentration 25 mM) and 1,000 IU of SK were added to the cuvette, and light transmission was monitored continuously with a strip chart, while samples were removed for determination of 14C-serotonin release. Inhibitors of thrombin or plasmin were also added simultaneously with SK. In control incubations normal saline was substituted for SK. In other experiments plasmin (1 CU/ml) was substituted for SK. Platelet aggregation and subsequent clotting of the sample typically occurred in three detectable stages: a decrease in light transmission corresponding to a change in platelet shape, an increase in light transmission indicative of platelet aggregation, and finally an abrupt drop in light transmission caused by the formation of a visible fibrin clot (Figure 1). The interval from time zero to the nadir of shape change was measured as the time to onset of platelet activation and aggregation. This event was followed by platelet aggregation and progressive 14C-serotonin release. The interval from time zero to the abrupt drop in light transmission corresponding to fibrin clot formation was measured as the time to sample clotting.

Additional studies were performed in which 4 ml of citrated PRP was incubated with SK or plasmin in the presence or absence of 0.5 units/ml of heparin sodium after addition of CaCl₂ (25 mM ﬁnal concentration). These incubations were at 37°C in polypropylene tubes without stirring. The secretion of 14C-serotonin was measured as described, and thrombin activity was characterized by the change in the plasma concentration of ﬁbrinopeptide A (FPA).

**Assay of Procoagulant Activity With a Two-Stage Procedure**

Procoagulant activity induced by activation of plasminogen with SK, in the presence or absence of platelets, was characterized with a two-stage procedure. In the ﬁrst stage, citrated PRP or PPP was prewarmed to 37°C in a polypropylene tube. SK was added simultaneously with CaCl₂ to yield ﬁnal concentrations of 1,000 IU/ml and 25 mM, respectively. The mixture was incubated at 37°C for 5 minutes, and a 100-µl aliquot of the ﬁrst-stage mixture was added to 100 µl of citrated PPP in a ﬁbroimeter with sufﬁcient CaCl₂ to maintain the ﬁnal concentration of Ca²⁺ at 25 mM along with 100 µl of a 1:10 dilution of rabbit brain cephalin stock in 0.15 M NaCl, pH 7.4. The second-stage mixture was incubated in a ﬁbroimeter (Becton-Dickenson, Cockeyesville, Md.), and the clotting time was measured. The two-stage procedure was designed to minimize the anticoagulant effects of ﬁbrinogen degradation products due to activation of plasminogen in the ﬁrst-stage plasma. This procedure also allowed comparison of procoagulant activity in response to plasminogen activation with SK in PRP compared with PPP.

**Fibrinopeptide A**

Plasma concentrations of FPA, a 16-amino-acid peptide released by thrombin from ﬁbrinogen, were
Assay of Fibrinopeptide A (FPA)

The activity of FPA was assayed by radioimmunoassay with a commercially prepared polyclonal antiserum (Byk-Sangtek Diagnostica, Dietzenbach, FRG). Cross-reacting fibrinogen and fibrinogen degradation products were first removed by adsorption with bentonite. To exclude cross-reactivity of fibrinogen degradation products containing FPA, selected samples were also analyzed with an enzyme-linked immunoadsorbent assay (ELISA) based on monoclonal antibody specific for the carboxy terminus of FPA developed by Kudryk et al.

Assay of Plasmin and α2-Antiplasmin Activity

α2-Antiplasmin and plasmin activities were measured in plasma incubated with SK or plasmin. The activity of α2-antiplasmin was measured in an aliquot of plasma diluted 1:30 with 0.1 M Tris-HCl, pH 7.4, after incubation for 1 minute with human Glu-plasmin at a final concentration of 0.05 CU/ml. A chromogenic substrate for plasmin, S-2251 (Helena Laboratories, Beaumont, Tex.), was added and the rate of increase in absorbance at 405 nM at room temperature was measured with a ThermoMax Kinetic Plate Reader (Molecular Devices Inc., Menlo Park, Calif.) in a microtiter plate. Results were compared with α2-antiplasmin activity in serial dilutions of pooled citrate plasmin and expressed as a percentage of the control plasma. Plasmin activity was measured in aliquots of plasma after addition of S-2251 and expressed with respect to activity of purified human glu-plasmin in caseinolytic units (CU/ml). The lower limit of detectability of plasmin activity was 0.01 CU/ml.

Statistical Methods

Data are means ± SD. Differences between groups were analyzed by two-tailed unpaired t test.

Results

Platelet Activation and Thrombin Activity in Response to Streptokinase

The concentration of FPA increased markedly (p < 0.01) in recalcified platelet-rich citrated plasma incubated at 37°C, with either 1,000 IU/ml SK or 1.0 CU/ml plasmin, compared with that in recalcified PRP not incubated with SK or plasmin (Figures 2A and 3A). The increases in FPA were due to thrombin activity, judging from the lack of marked elevations in FPA in recalcified plasma incubated with SK or plasmin in the presence of 0.5 units/ml of heparin sodium (FPA < 100 nM). The marked elevations in FPA immunoreactivity were confirmed to be due to increases in its concentration with an ELISA assay based on a monoclonal antibody specific for the carboxy terminus of FPA.

Platelet activation characterized by secretion of 14C-serotonin was induced in unirrad recalcified citrated PRP incubated with SK and plasmin at 37°C over 15 minutes, but not in the absence of SK or plasmin during this time interval (Figures 2B and 3B). Increases in the concentration of FPA, indicative of increased thrombin activity, occurred consistently before platelet activation in PRP incubated with SK and with plasmin. For example, the concentration of FPA increased to 101 nM in recalcified PRP incubated with SK after 5 minutes as compared with 12 nM in recalcified PRP incubated under the same conditions without SK. Despite the increasing...
completely inhibited platelet activation despite induction of plasmin activity, which was 0.5 CU/ml in plasma incubated with SK, with or without heparin. The concentration of $\alpha_2$-antiplasmin was unmeasurable after 1 minute of incubation of recalcified PRP with SK. In plasma incubated with 1.0 CU/ml of plasmin, $\alpha_2$-antiplasmin activity was 42% of control pooled citrated plasma ($n=2$), and free plasmin activity could not be detected.

**Platelet Aggregation and Clotting of Platelet-Rich Plasma in Response to Streptokinase**

To characterize platelet activation and aggregation in response to plasminogen activation, recalcified PRP was incubated at 32°C in an aggregometer at 900 rpm. Platelet aggregation occurred in 3.6±0.5 minutes and was accelerated to 2.5±0.3 minutes ($p<0.01$) when recalcified PRP was incubated with 1,000 IU/ml of SK. Change in platelet shape indicated by a decrease in light transmission occurred first, followed by platelet aggregation and the formation of a visible fibrin clot (Figure 4A). Secretion of $^{14}$C-serotonin accompanied platelet aggregation (Figure 4B) and occurred earlier and was of greater magnitude in recalcified PRP incubated with SK than in recalcified PRP alone (Figure 5). Clotting could be differentiated from platelet aggregation and occurred approximately 1 minute later (at 4.2±0.6 minutes) without SK compared with 3.3±0.3 minutes with SK ($p<0.01$). Similar results were observed with an incubation temperature of 37°C; however, platelet activation and clotting occurred in less than 2 minutes in the presence of SK, precluding the possibility of obtaining samples in which to determine $^{14}$C-serotonin secretion.

**Response of Recalcified Platelet-Rich Plasma to Streptokinase in Presence of Plasmin Inhibitors**

Recalcified PRP was incubated with SK in the presence of leupeptin or aprotinin, protease inhibitors that inhibit plasmin but not thrombin. At a concentration of 2.2 $\mu$M for leupeptin or 1,000 KIU/ml for aprotinin, the accelerated platelet activation and $^{14}$C-serotonin secretion observed at 3 minutes with SK did not occur (Figure 6). The lysine binding site analogue, 8-aminocaproic acid, which inhibits plasmin binding to fibrin, did not prevent the acceleration of platelet activation with SK, as demonstrated by 33% secretion of $^{14}$C-serotonin at 3 minutes.

**Response of Recalcified Platelet-Rich Plasma to Skeptokinase in Presence of Thrombin Inhibitors**

To inhibit thrombin activity, recalcified PRP was incubated with 0.3 to 1.0 units/ml heparin, 1.0 to 5.0 U/ml hirudin, and 1.0 to 5.0 $\mu$M PPACK. In recalcified PRP incubated without SK, the lowest concentration of each of these inhibitors completely inhibited secretion of $^{14}$C-serotonin, platelet aggregation, and clotting for at least 5 minutes of incubation in the aggregometer. However, in plasma incubated with 1,000 IU/ml of SK,
1. Secretion of 14C-serotonin in recalcified platelet-rich plasma (PRP) incubated with or without 1,000 IU/ml streptokinase (SK). 14C-serotonin secretion was measured every minute for 5 minutes after addition of 25 mM CaCl2 (final concentration) to PRP simultaneously with (n=11) or without (n=10) SK. 14C-serotonin secretion from platelets was accelerated and was of greater magnitude in recalcified PRP incubated with SK.

minimum concentration of 0.3 units/ml of heparin, 5 units/ml of hirudin, or 3 μM of PPACK.

Procoagulant Response to Streptokinase in Presence or Absence of Platelets

Procoagulant activity induced in response to plasminogen activation with SK in PRP was compared with that in PPP in a two-stage clotting assay. In the first stage, either citrated PRP or PPP was recalcified with 25 mM CaCl2 and incubated with or without 1,000 IU/ml of SK for 5 minutes, and a 100-μl aliquot of the first-stage incubation mixture was added to citrated PPP along with sufficient CaCl2 to maintain the final concentration at 25 mM. The clotting time of the second stage, which directly relates to the thrombin activity induced by platelet activation, was measured with a fibrometer. The clotting time was significantly accelerated in the second-stage plasma with aliquots of first-stage plasma not incubated with SK (Figure 7) in both PRP and PPP (p<0.01). The clotting time of the second-stage plasma was significantly shorter in PRP incubated with SK in the first stage than in PPP incubated with SK. These results indicate that more thrombin activity is induced by SK in PRP than in PPP.

Discussion

We have shown that platelet activation induced by pharmacologic activation of plasminogen in plasma with SK is in part attributable to increases in thrombin activity induced by activation of the coagulation system by plasmin. The marked attenuation of SK-induced

higher concentrations of each of the inhibitors were required to inhibit platelet activation. As shown in Table 1, inhibition of platelet aggregation and secretion of 14C-serotonin for 5 minutes after SK required a
platelet activation when thrombin is inhibited by heparin suggests that plasmin at the concentrations achieved with lytic agents does not directly activate platelets, consistent with our previous observations in citrated plasma. Thus, increases in platelet activation observed in patients given SK for acute myocardial infarction are more likely to be mediated by increases in thrombin rather than in plasmin activity. Although mechanisms other than direct activation of the coagulation system by plasmin may be responsible for increases in thrombin activity that occur in patients treated with fibrinolytic agents, our data suggest that inhibition of thrombin may prevent platelet activation during thrombolysis. Our results are consistent with the observations of Fitzgerald et al in an experimental preparation that platelet activation is markedly attenuated during thrombolysis with conjunctive administration of argatroban, a potent synthetic thrombin inhibitor. The failure of heparin alone to inhibit platelet activation in response to SK in clinical trials may reflect its relative inefficiency in inhibiting thrombin, perhaps because thrombin bound to fibrin is less inhibitable by heparin-antithrombin III than thrombin in solution.

The effects of plasmin on platelet function have been controversial. Plasmin at concentrations in excess of 1 CU/ml has been shown to activate washed platelets. However, at a concentration of 1,000 IU/ml of SK, a concentration consistent with that achieved pharmacologically, plasmin activity did not exceed 0.5 CU/ml in our study. With a more fibrin-specific plasminogen activator, such as t-PA, even less plasmin activity is induced, yet platelet activation occurs in patients treated with t-PA for acute myocardial infarction. Platelet aggregation induced by subthreshold concentrations of platelet agonists has been shown to be enhanced when platelets are incubated with SK, an effect that appears to be due to plasminogen activation. However, the effects of plasmin on platelet aggregation in response to activation with various ago-

**FIGURE 6.** Bar graph showing secretion of 14C-serotonin at 3 minutes characterized in recalcified platelet-rich plasma (PRP) incubated in an aggregometer at 32°C with either 10 mM e-aminocaproic acid, 2.2 μM leupeptin, or 1,000 KIU/ml aprotinin with or without 1,000 IU/ml streptokinase (SK). Marked secretion of 14C-serotonin occurred in the preparation of recalcified PRP incubated with SK (no inhibitor) compared with secretion in recalcified PRP alone at 3 minutes (solid bar). The secretion of 14C-serotonin in response to SK was inhibited by leupeptin and aprotinin, but not e-aminocaproic acid.

**FIGURE 7.** Bar graphs of clotting times in the second stage of the two-stage assay for procoagulant activity when either platelet-poor plasma (PPP) or platelet-rich plasma (PRP) was incubated in the first stage with or without 1,000 IU/ml SK. The clotting time of recalcified citrated plasma was accelerated when an aliquot (0.1 ml) of recalcified PRP or PPP incubated in the first stage with streptokinase (SK) was added, consistent with increased thrombin activity induced by SK in the first stage. The clotting time of recalcified second-stage PPP was more rapid when SK was incubated with PRP compared with PPP.
nists may be mediated by the effects of plasmin-derived fibrinogen degradation products rather than direct effects of plasmin itself.\textsuperscript{34–37} In the absence of fibrinogen degradation products, activators such as t-PA at pharmacologic concentrations appear to have no direct effect on platelet activation.\textsuperscript{37}

Although the mechanism of plasmin-induced activation of the coagulation system has not been completely defined, the increase in procoagulant activity we observed in PRP compared with PPP with SK suggests that platelets potentiate the response. Platelets may increase procoagulant activity by providing membrane binding sites for the prothrombinase complex as well as other coagulation factors.\textsuperscript{39} In addition, they secrete activated factor V, a cofactor that markedly accelerates the rate of prothrombin activation by factor Xa.\textsuperscript{40,41} Thus, activation of platelets during thrombolysis may potentiate the procoagulant response to plasminogen activation.

Our data suggest that concomitant administration of a thrombin inhibitor during pharmacologic thrombolysis may attenuate platelet activation and potentially improve the success of therapy. Because thrombin binds to fibrin and remains active, elaboration of thrombin during thrombolysis may play a role in recurrent thrombosis.\textsuperscript{31,42,43} The increased frequency of sustained coronary patency in patients given heparin after administration of t-PA is consistent with the importance of persistent thrombin activity as a determinant of reocclusion.\textsuperscript{11,13} Because thrombin activation of platelets occurs even when platelets are inhibited with antagonists such as aspirin, inhibition of thrombin may be crucial during pharmacologic activation of plasminogen.\textsuperscript{44} In addition to increased procoagulant activity, platelet activation during coronary thrombolysis may be promoted by increases in shear stress,\textsuperscript{44,45} exposure of factors that promote platelet aggregation,\textsuperscript{46} and interaction of platelets with the endothelium.\textsuperscript{47} Thus, optimal inhibition of platelet activation during thrombolysis may require potent inhibition of platelet function. Ultimately, the extent to which a specific strategy to inhibit platelet activation during thrombolysis will reduce the incidence of rethrombosis will depend on the plasminogen activator used, the intensity of procoagulant effects induced, and the extent to which fibrinogen is degraded and fibrinogen degradation products, which inhibit platelet aggregation, are elaborated.

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**KEY WORDS** • thrombolysis • thrombin • streptokinase • platelet activation
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