Role of Heparin in Coronary Thrombolysis*

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Although the benefits of coronary thrombolysis are well established, the optimal therapeutic strategy for ensuring rapid and sustained coronary artery patency remains controversial. The available data suggest that the success of coronary thrombolysis depends not only on the induction of clot lysis, but also on the extent to which procoagulant activity that promotes recurrent thrombosis is inhibited. Procoagulant activity increases almost immediately in patients treated with fibrinolytic agents, and persistent increases in thrombin activity have been associated with recurrent coronary thrombosis. Heparin administered intravenously appears to markedly attenuate the thrombin activity associated with thrombolysis and, in patients treated with tissue plasminogen activator (t-PA), prevents early recurrent coronary thrombosis. The results of clinical trials of coronary thrombolysis indicate that conjunctive treatment of patients with heparin improves survival compared with treatment with fibrinolytic agents alone. Although recent clinical trials in which patients were treated with streptokinase suggested that 12,500 units of heparin administered subcutaneously twice daily decreases mortality, this dosage regimen does not induce therapeutic levels of anticoagulation within the first 24 h in most patients. The failure to achieve early therapeutic anticoagulation may account for the lack of mortality benefit in trials in which patients given t-PA were treated with conjunctive subcutaneous heparin therapy. Thus, the available experimental and clinical data suggest that intravenous heparin should be given to patients treated with fibrinolytic agents for acute myocardial infarction.

It is now well established that treatment of patients with acute myocardial infarction with fibrinolytic agents reduces mortality. The benefits of coronary thrombolysis depend on the rapidity with which coronary recanalization is achieved and the maintenance of coronary patency. Despite considerable clinical data, controversy remains regarding the optimal treatment regimens for achieving these goals. The results of two recent clinical trials suggest that the higher rate of early coronary recanalization achieved with tissue plasminogen activator (t-PA [alteplase]) compared with streptokinase may not be associated with a greater reduction in mortality.1,2 However, the failure of these trials to include conjunctive treatment with intravenous heparin has been cited as a major flaw in study design because coronary patency rates with t-PA (alteplase) are decreased in patients not given conjunctive intravenous heparin.3-5 Thus, the potential mortality benefit of treatment with t-PA (alteplase) compared with streptokinase may be compromised if patients are not given early conjunctive therapy with intravenous heparin.6 Because of the continued controversy, another large clinical trial (Global Utilization of Streptokinase and rt-PA for Occluded Coronary Arteries [GUSTO]) has been initiated to compare mortality in patients treated with t-PA (alteplase), streptokinase, or both and conjunctive intravenous heparin or with streptokinase and subcutaneous heparin.

Although additional clinical data may clarify the role of specific treatment regimens, there is already sufficient evidence to support the role of anticoagulation with heparin in patients treated with coronary thrombolysis. The available data indicate that the success of coronary thrombolysis depends on a favorable balance between fibrinolytic activity and factors that promote recurrent thrombosis. Inhibition of such procoagulant factors by heparin, and perhaps even more effectively by newer anticoagulant agents, potentiates the effects of thrombolysis in experimental models, and appears to be the basis of the benefit of conjunctive heparin therapy observed in clinical trials.

**Clinical Evidence That Procoagulant Activity Increases During Thrombolysis**

Despite induction of intense fibrinolytic activity during coronary thrombolysis, recurrent coronary thrombosis often occurs. Even during administration of the fibrinolytic agent, episodes of transient reperfusion followed by reocclusion often precede sustained coronary reperfusion.7 Thus, the apparent failure to achieve sustained reperfusion may reflect the early or almost immediate recurrence of thrombosis. The factors responsible for the recurrent thrombosis during coronary thrombolysis likely include the procoagulant activity of the residual thrombus8,9 or that induced by exposure of procoagulant factors in subendothelium of the underlying injured arterial wall10,11 or by activation of the fibrinolytic system.12,13 Although the specific mechanisms have not been defined, results of several clinical studies indicate that the persistence of increased thrombin activity in patients given fibrinolytic agents correlates with failure of therapy.

Increases in the plasma concentration of fibrinopeptide A (FPA), a marker of thrombin activity, have been documented in patients given t-PA or streptokinase.
for acute myocardial infarction. Fibrinopeptide A is a small peptide cleaved by thrombin from fibrinogen when fibrin is formed. Fibrinopeptide A has a half-life in plasma of 3 to 5 min. Thus, elevations of the concentration of this peptide in plasma reflect ongoing thrombin activity. In patients given streptokinase without conjunctive heparin, plasma concentrations of FPA were found to increase in those in whom reperfusion did not occur and in those in whom reocclusion followed initial reperfusion. In the group with recurrent thrombosis, plasma concentrations of FPA remained elevated despite intravenous administration of heparin. Similar results were reported by Rapold et al in patients given t-PA for acute myocardial infarction. Persistent elevations of FPA, despite intravenous heparin, in patients treated with t-PA were also associated with recurrent coronary thrombosis in that study. These results indicate that thrombin activity increases during coronary thrombolysis in patients who are not treated with concurrent intravenous heparin, and that the extent of persistent thrombin activity appears to be an important determinant of the failure of therapy.

Conjunctive administration of heparin appears to attenuate increases in thrombin activity, judging from studies showing less marked elevations in concentrations of FPA in plasma of patients given t-PA or streptokinase after an intravenous bolus of 5,000 units of heparin compared with results in patients given these agents without intravenous heparin. The increased levels of FPA observed in patients treated with t-PA or streptokinase but not given heparin initially decrease promptly after patients are given a bolus of intravenous heparin. The prompt response to heparin is consistent with the increases in FPA being due to activity of thrombin at intravascular sites.

Recently, Gulba et al characterized plasma concentrations of thrombin-antithrombin III complexes, another marker of procoagulant activity, in patients treated with coronary thrombolysis. As opposed to plasma concentrations of FPA, which reflect thrombin activity, concentrations of thrombin-antithrombin III complexes reflect elaboration of thrombin and the quantity of thrombin inhibited by antithrombin III. The results of the study by Gulba et al are similar to those of earlier studies of FPA: in patients treated with urokinase or t-PA, thrombin-antithrombin III complex levels increase in those in whom reperfusion is not achieved and in those who suffer reocclusion.

The results of clinical studies characterizing procoagulant activity during coronary thrombolysis have consistently demonstrated that increases in thrombin activity occur in patients given fibrinolytic agents. Persistent increases in thrombin activity are associated with failure of thrombolysis to induce sustained reperfusion. Administration of intravenous heparin appears to markedly attenuate the thrombin activity induced, but judging from the data of Owen et al, in which FPA elevations were documented despite heparin, it is likely that ongoing thrombin activity may occur at sites relatively protected from inhibition by heparin-antithrombin III. Thus, coronary thrombolysis is a dynamic process in which there is a balance between procoagulant activity, which promotes recurrent thrombosis, and fibrinolytic activity, which induces clot lysis.

**Potential Mechanisms for Increased Procoagulant Activity during Thrombolysis and Implications for the Efficacy of Heparin**

Although the results of clinical studies indicate that procoagulant activity increases in patients treated with fibrinolytic agents, the mechanisms responsible are not well defined. In patients treated with t-PA or streptokinase, plasma concentrations of FPA increase almost immediately on infusion of the fibrinolytic agent. Such increases are markedly attenuated, but not eliminated, by administration of intravenous heparin. Recent experimental studies suggest that pharmacologic activation of plasminogen may induce plasmin-mediated activation of the coagulation system. Incubation of nonanticoagulated blood with pharmacologic concentrations of streptokinase or t-PA induces marked thrombin activity, judging from the rapid increase in the concentration of FPA. Heparin is effective in inhibiting the procoagulant activity induced by plasmin, but concentrations higher than those typically achieved during intravenous therapy are required. The amount of thrombin activity induced appears to be directly related to the extent of free plasmin activity, so that agents, such as streptokinase, that induce extensive plasmin activity are associated with more marked procoagulant effects compared with fibrin-specific agents, such as t-PA, which induce less activation of plasminogen in plasma. In addition, plasmin induces activation of factor V, a cofactor that, when activated, increases the activity of the factor Xa/Va complex, which induces the formation of thrombin (Fig 1).

These observations suggest that plasmin-mediated activation of the coagulation system may account for the rapid increases in thrombin activity observed in patients given fibrinolytic agents. These procoagulant effects of pharmacologic thrombolysis appear to be attenuated by high therapeutic concentrations of heparin, providing a theoretic basis for initiation of intravenous heparin before administration of the fibrinolytic agent. In addition to plasmin-mediated effects on procoagulant activity, recent data suggest that other mechanisms for recurrent thrombosis are likely in patients treated with coronary thrombolysis.
The procoagulant properties of the residual thrombus and high-grade stenosis that are present after coronary thrombolysis are potent stimuli for recurrent thrombosis. Although several factors appear to contribute to the procoagulant properties of the residual arterial thrombus, the activity of thrombin bound to fibrin may be the most important.9,25,26 Thrombin bound to fibrin retains its catalytic activity, and therefore will induce fibrin deposition and platelet activation.27 In addition, thrombin activates factors V and VIII, cofactors that, when activated, promote activation of the coagulation system (Fig 1).28 Because the thrombin activity associated with a thrombus appears to induce relatively little fibrin formation,9,9 it is likely that the secondary activation of factors V and VIII and the activation of platelets are the predominant mechanisms by which clot-associated thrombin activity induces recurrent thrombosis.

Thrombin bound to fibrin appears to be relatively protected from the inhibitory effects of heparin-antithrombin III.9,23 In contrast, agents that inhibit the thrombin active site directly, such as D-phe-pro-arg-chloromethylketone, are equally effective in inhibiting fibrin-bound and free thrombin.9 In nonhuman primates, this inhibitor prevents platelet and fibrin deposition on Dacron vascular grafts in a model of arterial thrombosis.29 Recombinant hirudin, another potent thrombin inhibitor, has been shown to prevent platelet-rich arterial thrombosis in response to deep arterial wall injury and to prevent recurrent thrombosis in a canine model of coronary thrombolysis.10,30 In the thrombolysis preparation, hirudin also significantly accelerated the rate of clot lysis compared with that which occurred with conjunctive treatment with heparin or aspirin.30

Although the results of recent experimental studies suggest that potent thrombin-specific inhibitors may be more active than heparin in preventing recurrent thrombosis after coronary thrombolysis, heparin is likely to be of clinical value. As opposed to thrombin-specific inhibitors, heparin-antithrombin III has inhibitory effects on factors other than thrombin, including IXa, Xa, and XIa. Thus, adequate concentrations of heparin may attenuate activation of the coagulation system.
system by inhibiting the activity of factors other than thrombin. In addition, the relative lack of efficacy of heparin in experimental models may reflect properties specific to the manner in which thrombosis is induced in the model. In most instances, the experimental preparations are designed to induce extensive arterial wall injury in which fresh thrombus containing relatively large quantities of thrombin is formed. In contrast, coronary thrombosis in response to atherosclerotic plaque rupture may be associated with less thrombin activity, while the role of other procoagulants, such as tissue factor, may be more important. Nonetheless, the results of these studies have been of considerable value in emphasizing the importance of persistent thrombin activity as a determinant of recurrent thrombosis after coronary thrombolysis.

**Clinical Evidence of the Importance of Conjunctive Heparin Therapy with Coronary Thrombolysis**

Three recent trials have shown that coronary artery patency rates are significantly increased in patients who are given conjunctive intravenous heparin therapy with t-PA (alteplase) compared with patients given t-PA either with no conjunctive therapy or with aspirin alone.\(^4\) Bleich et al\(^9\) found that coronary artery patency was 71% in patients given heparin (n = 42) at 57 h compared with only 43% in patients not given heparin (n = 41) (Fig 2). In this trial, patients in the control group were not given aspirin. In the Heparin-Aspirin Reperfusion Trial, patients were randomly assigned to intravenous heparin, titrated to maintain the activated partial thromboplastin time at 1.5 to 2.0 times control, or aspirin (80 mg/d) (Fig 2).\(^3\) Coronary artery patency was assessed at a mean of 18 h after the onset of treatment. In patients treated with heparin (n = 106), patency was 82%, compared with 52% in those who received only aspirin (n = 99). The results of the European Cooperative Study Group trial comparing treatment with conjunctive intravenous heparin and aspirin to treatment with aspirin alone are consistent with the results of these earlier trials; coronary artery patency was demonstrated in 83% of patients given heparin and aspirin, compared with 75% of those treated with aspirin alone (Fig 2).\(^5\) Unfortunately, the sample sizes of these trials are inadequate to allow assessment of whether there is a mortality benefit associated with the higher rate of patency in patients given conjunctive intravenous heparin treatment with t-PA. Nonetheless, an analysis of pooled data from trials with fibrinolytic agents suggests that early mortality is decreased in patients who are given conjunctive heparin treatment with coronary thrombolysis.\(^6\)

The value of conjunctive intravenous heparin therapy in patients treated with streptokinase, urokinase, or anisoylated plasminogen streptokinase activator complex (APSAC) has not been established by randomized clinical trials. Nonetheless, there is clinical evidence that streptokinase and urokinase induce marked procoagulant activity, judging from the elevations in plasma concentrations of FPA and thrombin-antithrombin III complexes.\(^15,31\) Heparin appears to attenuate markedly, although not completely prevent,\(^2\) the thrombin activity induced by streptokinase.\(^9\) However, the marked decreases in the concentration of clottable fibrinogen in patients treated with streptokinase or urokinase and the inhibitory effects of fibrinogen degradation products on fibrin polymerization and platelet aggregation may attenuate recurrent thrombosis, particularly early after administration of the agent.\(^33-38\)

Although comparative studies including conjunctive intravenous heparin are lacking, several trials have compared mortality in patients treated with coronary thrombolysis with or without high-dose subcutaneous heparin (12,500 units given twice daily) started at various intervals after administration of the fibrinolytic agent. In the Studio sulla Calcioparina nell'Angina e nella Thrombosi Ventricolare nell'Infarto (SCATI) trial,\(^39\) patients were given either a 2,000-unit intravenous bolus of heparin followed by 12,500 units subcutaneously every 12 h or no anticoagulant therapy. In a nonrandomized subset of SCATI patients given streptokinase within 6 h of the onset of symptoms, mortality was lower in the patients treated with heparin than in those not treated with an anticoagulant (4.5% compared with 8.8%).\(^36\) There was also a trend toward decreased mortality in the Second International Study of Infarct Survival (ISIS-2) in patients randomly assigned to treatment with streptokinase with or without aspirin, in whom treatment with heparin was "planned at entry."\(^37\) In ISIS-2, however, the decision whether to treat with heparin and the mode of heparin administration (ie, subcutaneous or intravenous) was made in a nonrandomized manner by the treating physician. A trend toward lower mortality in patients randomly assigned to treatment with streptokinase and high-dose subcutaneous heparin (7.2%), compared with that in patients given streptokinase alone (9.2%), was also noted in the Gruppo Italiano per lo Studio della Sopravvenza nell'Infarto miocardico (GISSI)-II/International Study Group trial.\(^5\) This finding may have been due to chance alone, because a difference in mortality existed between these two groups before heparin was initiated. Preliminary results of the Third International Study of Infarct Survival (ISIS-3) apparently indicate a mortality benefit (5 lives saved per 1,000 patients) with treatment with high-dose subcutaneous heparin started 4 h after administration of t-PA (duteplase), APSAC, or streptokinase.\(^36\)

Thus, the results of several large clinical trials
suggest that treatment with high-dose subcutaneous heparin may decrease mortality in patients treated with t-PA. These results are not consistent with the data indicating that the rate of coronary artery patency is significantly decreased in patients treated with t-PA without conjunctive intravenous heparin.\(^5\) One interpretation of this discrepancy is that early coronary artery patency is not the primary determinant of mortality in patients treated with fibrinolytic agents for myocardial infarction. This view is inconsistent with the data indicating that the greatest mortality reduction in patients with myocardial infarction treated with fibrinolytic agents occurs in those treated within the first hour of symptoms,\(^6\) and that the benefit of thrombolysis decreases in patients treated more than 4 h after symptom onset.\(^7,8\)

The importance of early patency is also supported by preliminary data from a recent trial documenting a higher 90-min patency rate in patients given t-PA than in those given APSAC,\(^9\) which was associated with improved survival in the t-PA group.\(^10\) Of note, all patients in this study were treated with conjunctive intravenous heparin. Although other mechanisms may contribute to the reduction of mortality in patients given fibrinolytic agents for acute myocardial infarction, considerable clinical and experimental evidence suggests that early and sustained recanalization of the infarct-related artery is essential for maximal benefit to occur.

**Clinical Pharmacology of Conjunctive Heparin Therapy**

An important consideration in interpreting the results of recent clinical trials with regard to the role of conjunctive heparin therapy is the marked differences in the extent and rapidity of anticoagulation achieved with intravenous compared with subcutaneous heparin. Intravenous administration of heparin initiated with a 5,000-unit intravenous bolus followed by a continuous infusion of approximately 30,000 units over 24 h results in therapeutic heparin levels in most patients within the first 24 h.\(^11,12\) In contrast, Turpie et al\(^13\) reported that heparin levels are not in the therapeutic range during the first 24 h in patients with acute myocardial infarction who are treated with...
12,500 units of subcutaneous heparin twice a day. Thus, even high doses of subcutaneous heparin given conjunctively with fibrinolytic agents are unlikely to induce sufficient therapeutic levels of anticoagulant activity within the first 24 h.

In patients treated with t-PA, the results of the cited clinical and experimental studies indicate that adequate anticoagulation with intravenous heparin is essential during the first 24 h after administration of t-PA if procoagulant activity is to be inhibited and maximal rates of coronary patency are to be achieved. It has been argued that conjunctive anticoagulation with heparin may be less important when patients are given streptokinase, because the extensive fibrinogen degradation induced may have sufficient anticoagulant effects to prevent recurrent thrombosis, but the results of the SCATI and GISSI-2/International Study Group trials suggest that survival is improved in patients treated with conjunctive high-dose subcutaneous heparin.

Whether early administration of intravenous heparin would be of additional benefit in patients treated with streptokinase has not been defined by prospective studies. However, the extent and duration of anticoagulant effects induced by streptokinase may be variable; therefore, it is reasonable to administer heparin intravenously as opposed to subcutaneously during the first 24 h in patients treated with streptokinase to ensure that therapeutic levels of anticoagulant activity are achieved and maintained.

The timing and duration of heparin administration have also been poorly defined by clinical studies, and thus are the subject of controversy. In the Third Thrombolysis and Angioplasty in Myocardial Infarction study (TAMI-III), patients treated with t-PA (alteplase) were randomly assigned to receive either an intravenous bolus of 10,000 units of heparin or no initial heparin. Angiography was performed to determine coronary artery patency, and all patients were then treated with a continuous infusion of intravenous heparin for at least 24 h. Coronary artery patency was documented on the initial angiogram (approximately 60 min after initiation of treatment) in 79% of the patients given t-PA and heparin, compared with 73% treated with t-PA alone, and was 79% in both groups on the 90-min angiogram (Fig 2). Although these data suggest that administration of heparin before t-PA does not increase the 90-min patency rate, they do not exclude more rapid recanalization in patients given conjunctive heparin, nor do they suggest that intravenous heparin is not necessary to ensure sustained patency. When these data are viewed in the context of more recent studies of the role of conjunctive heparin therapy in patients treated with t-PA, it appears that recurrent thrombosis after initial coronary artery recanalization is the most likely mechanism for the lower patency rates after 18 h documented in patients treated with t-PA without conjunctive heparin.

Recent results of a trial reported by the National Heart Foundation of Australia Coronary Thrombolysis Group suggest that continuation of intravenous heparin for more than 24 h after treatment with t-PA (alteplase) may not improve coronary patency rates at 7 to 10 days. In this trial, patients treated with t-PA were randomly assigned after 24 h of intravenous heparin administration to receive either intravenous heparin for 7 to 10 days (n = 99) or aspirin, 300 mg/d, plus dipyridamole, 300 mg/d (n = 103). Coronary artery patency at 7 to 10 days was 81% in the heparin-treated group and 80% in those treated with the antiplatelet regimen (Fig 2). There also were no significant differences in the extent of coronary artery narrowing between the groups. Thus, prolonged administration of heparin does not appear to improve long-term coronary artery patency in patients treated with t-PA.

### Safety of Conjunctive Heparin Therapy

The results of the GISSI-II/International Study Group trial comparing t-PA (alteplase) and streptokinase with or without administration of high-dose subcutaneous heparin indicate that the incidence of bleeding complications is increased with conjunctive heparin therapy. However, the overall risk of major bleeding, defined as the requirement for transfusion of 2 or more units of blood, was only 1.0% with heparin compared with 0.5% in patients not given subcutaneous heparin. The risk of stroke was not increased by treatment with heparin.

In a recent analysis of the hemorrhagic event rate in the Thrombolysis in Myocardial Infarction Phase II trial (TIMI-II), in which all patients were given t-PA (alteplase), aspirin, and conjunctive intravenous heparin, the incidence of major bleeding in patients who did not undergo invasive procedures was found to be only 3.0%. The definition of major bleeding in this trial was based on a decrease in hemoglobin concentration of 50 g/L, and patients who had suffered an intracranial hemorrhage or cardiac tamponade were considered to have a major bleed. In patients who were assigned to a management strategy that included early coronary angiography and percutaneous coronary angioplasty, when indicated, or who underwent angiography for clinical indications, the frequency of bleeding was approximately 7.0%. Major and minor bleeding were associated with the extent of fibrinogen degradation, peak t-PA levels, thrombocytopenia, excessive prolongation (>90 s) of the activated partial thromboplastin time (aPTT), female gender, weight of less than 70 kg, and physical signs of cardiac decompensation. With respect to variables related to intravenous heparin therapy, prolongation of aPTT to more
Table 1—Recommendations for the Use of Conjunctive Heparin Therapy in Patients Given Fibrinolytic Agents for Myocardial Infarction

<table>
<thead>
<tr>
<th>Fibrinolytic Agent</th>
<th>Heparin Dosage</th>
<th>Duration of Therapy</th>
</tr>
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<tbody>
<tr>
<td>t-PA</td>
<td>5,000-U intravenous bolus before t-PA, followed by a 1,000-U/h continuous infusion titrated to maintain the aPTT at 1.5 to 2.0 times control</td>
<td>Intravenous heparin for 48 to 72 h followed by 325 mg of aspirin daily</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>5,000-U intravenous bolus before streptokinase, followed by a 1,000-U/h continuous infusion titrated to maintain the aPTT at 1.5 to 2.0 times control</td>
<td>Intravenous heparin for 48 to 72 h followed by 325 mg of aspirin daily</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>12,500 U of subcutaneous heparin started as soon as possible after initiation of the streptokinase infusion and repeated every 12 h*</td>
<td>Subcutaneous heparin for 48 to 72 h followed by 325 mg of aspirin daily</td>
</tr>
</tbody>
</table>

*This regimen is unlikely to induce therapeutic anticoagulation during the first 24 h of treatment, but has been shown to decrease mortality when used with streptokinase in patients with myocardial infarction.

than 90 s was associated with a 71% excess risk of major bleeding. In addition, the investigators noted that platelet counts decreased progressively over the first 4 to 5 days; this decrease was apparently attributable to administration of heparin. Thrombocytopenia (platelet count <150×10^9/L) occurred in approximately 12% of patients and was associated with an increased risk of bleeding.

Comparison of these data with the results of the GISSI-II/International Study Group trial suggests that conjunctive treatment with heparin and aspirin is associated with a relatively low overall rate of major bleeding, but a higher rate than occurs in patients not treated with heparin. There is no published evidence that treatment with heparin increases the rate of intracranial bleeding: in the TIMI-II trial the rate was 0.5% in patients treated with 100 mg of t-PA (alteplase), compared with 0.4% for the same dose of t-PA in the GISSI-II/International Study Group trial and 0.3% for streptokinase. Not surprisingly, administration of intravenous heparin appears to be associated with a higher rate of major bleeding than was observed with subcutaneous administration of heparin in the GISSI-II/International Study Group trial, but in the absence of invasive procedures the overall risk of major bleeding is low (3%). Bleeding risk may be minimized by titrating the dose of heparin to maintain the aPTT at less than 90 s, by considering discontinuation of heparin in patients who develop thrombocytopenia, and by using weight-adjusted dosing for t-PA.

Recommendations

The available data suggest that increased procoagulant activity in patients treated with fibrinolytic agents is an important determinant of recurrent thrombosis. Results of clinical trials indicate that mortality is lower in patients treated with coronary thrombolysis when conjunctive heparin therapy is given. These data strongly support a role for heparin therapy in conjunction with coronary thrombolysis, a recommendation consistent with the guidelines recently published by the American College of Cardiology and the American Heart Association Task Force. In patients treated with t-PA, the results of recent clinical trials indicate that heparin should be given intravenously, initiated with a bolus of 5,000 units either before or within 90 min of initiation of the t-PA infusion, followed by an infusion of 1,000 units/h titrated to maintain the aPTT at 1.5 to 2 times control (Table 1). To avoid the tendency to underanticoagulate patients who are being treated with intravenous heparin, a standardized dosing regimen has been developed (Table 2). In patients with deep venous thrombosis, use of this dosing protocol increased the percentage of patients in whom the aPTT was in the therapeutic range after 24 h compared with a historical control group. Conjunctive heparin should be continued for at least 3 to 4 days, although treatment for 24 h may be sufficient in patients thought to be at a higher risk for bleeding. Although subcutaneous high-dose heparin has been shown to decrease mortality in patients treated with streptokinase, the possibility that intravenous administration of heparin would be of greater benefit has not been addressed. Because

Table 2—Standardized Protocol for Dosing of Intravenous Heparin*

<table>
<thead>
<tr>
<th>aPTT, s†</th>
<th>Dose Adjustment‡</th>
<th>Repeat aPTT</th>
</tr>
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<tbody>
<tr>
<td>&lt;50</td>
<td>5,000-U bolus, increase infusion by 2,880 U/24 h</td>
<td>6 h</td>
</tr>
<tr>
<td>50-59</td>
<td>Increase infusion by 2,880 U/24 h</td>
<td>6 h</td>
</tr>
<tr>
<td>60-85</td>
<td>Therapeutic range, no change in infusion rate</td>
<td>Next morning</td>
</tr>
<tr>
<td>86-95</td>
<td>High therapeutic range, decrease infusion by 1,920 U/24 h</td>
<td>Next morning</td>
</tr>
<tr>
<td>96-120</td>
<td>Stop infusion for 30 min, decrease infusion by 1,920 U/24 h</td>
<td>6 h</td>
</tr>
<tr>
<td>&gt;120</td>
<td>Stop infusion for 60 min, decrease infusion by 3,840 U/24 h</td>
<td>6 h</td>
</tr>
</tbody>
</table>

*Adapted from reference 48.
†Normal aPTT range is 27-35 s (Dade-Actin FS reagent).
‡Dosing protocol is based on an initial intravenous bolus of 5,000 U, followed by a continuous infusion of 31,000 U/24 h. The first aPTT should be obtained 6 h after the bolus of heparin.

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intravenous administration of heparin is more likely to provide therapeutic levels of anticoagulant activity in the first 24 h, compared with subcutaneous administration of the drug, and because there is no reason to suspect that the factors that promote recurrent thrombosis differ in patients treated with streptokinase, heparin should be given intravenously to these patients as well.

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