Intravenous Recombinant Tissue-Type Plasminogen Activator in Patients With Unstable Angina Pectoris

Results of a Placebo-Controlled, Randomized Trial

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Because thrombus formation may contribute to coronary obstruction in patients with unstable angina pectoris, we performed a pilot investigation to determine whether thrombolytic therapy can relieve coronary narrowing in this acute ischemic syndrome. Sixty-seven patients with rest angina and angiographic evidence of coronary stenosis were randomly assigned to receive either low-dose intravenous recombinant tissue-type plasminogen activator (rt-PA) (0.75 mg/kg over 1 hour), high-dose intravenous rt-PA (0.75 mg/kg over 1 hour; total dose, 100 mg over 6 hours), or intravenous placebo followed by repeat coronary angiography at 24–48 hours to assess change in the severity of coronary narrowing. Each patient also received oral aspirin and intravenous heparin. Mean values of coronary stenosis severity (percent of diameter reduction) declined to a similar extent in each group: placebo, 75±14% to 72±14% (p=0.07); low-dose rt-PA, 75±16% to 71±18% (p=0.03), and high-dose rt-PA, 82±11% to 77±17% (p=0.18), with only the low-dose rt-PA group achieving statistical significance. Resolution of intracoronary filling defects, increase in antegrade flow grade, or both also occurred equally among the three groups. There was considerable variation in individual patient response. Between 29% and 50% of patients within each group demonstrated a decrease in stenosis severity, whereas 50% to 57% noted either improvement in antegrade flow or resolution of intracoronary thrombus. There was no difference in incidence of major bleeding events among the three groups. Thus, a combination of intravenous t-PA, aspirin, and heparin can reduce the severity of coronary stenosis in patients with unstable angina, but the treatment effect is mild in magnitude, varies among individual patients, and is not clearly superior to that achieved by the combination of aspirin and heparin alone. (Circulation 1990;82:376–383)

Unstable angina pectoris is a common manifestation of coronary artery disease and is associated with a greater risk of myocardial infarction and death than stable angina pectoris.1 Angiographic studies have demonstrated that a substantial proportion of patients with unstable angina have fixed atherosclerotic disease in association with thrombus that contributes to severe coronary obstruction.2–8 Recently, the presence of intracoronary thrombus has been correlated with a greater frequency of adverse cardiac events.9 Accordingly, anticoagulation and antiplatelet therapy have become established as standard for patients with unstable angina pectoris.10–12 Thrombolytic therapy, theoretically a more potent means of reducing thrombotic obstruction, has not been thoroughly evaluated, although results of preliminary trials appear encouraging.8,13–16 Recombinant tissue-type plasminogen activator (rt-PA) has been demonstrated to be particularly efficacious in augmenting coronary blood flow in patients with thrombotic coronary occlusion resulting in acute myocardial infarction.17–19 Thus, the purpose of this investigation was to evaluate the ability of intravenous rt-PA to relieve the severity of coronary obstruction and the extent of intracoronary thrombus in patients with unstable angina pectoris.
Clinically Eligible Patients Undergoing Coronary Angiography

Angiographic Criteria Satisfied

Randomization

*low* dose *high* dose
rt-PA rt-PA

placebo

Intravenous Heparin

End Point Coronary Angiography

**Figure 1.** Study design.

**Methods**

**Patient Selection**

Patients were eligible for entry into the trial if they met the inclusion criteria of rest pain of coronary origin associated with ischemic electrocardiographic changes, diagnostic coronary angiography (within 7 days after onset of rest angina) demonstrating an identifiable culprit lesion characterized by 80% or greater luminal narrowing (visual assessment) or intraluminal thrombosis, age of 75 years or less, and ability and willingness to provide written informed consent. Patients were excluded if they met any of the exclusion criteria of documented myocardial infarction in the preceding 2 weeks; symptomatic valvular, congenital, or cardiomyopathic heart disease; systemic blood pressure of 180/110 mm Hg or more by two separate measurements or history of poorly controlled chronic hypertension; or contraindications to thrombolytic therapy, including recent surgery, trauma, bleeding episodes, or known cerebrovascular disease or intracranial neoplasm. Sixty-seven patients who satisfied these eligibility requirements were enrolled in the study.

**Study Design**

The study design is summarized in Figure 1. Patients scheduled for diagnostic cardiac catheterization were evaluated with a baseline survey before their procedure. Those who met clinical eligibility criteria and subsequently demonstrated luminal narrowing of more than 80% diameter reduction or an intracoronary filling defect suggesting thrombus in what was considered the coronary artery most likely to be responsible for the acute syndrome were requested to enroll in the trial. The judgment as to which coronary artery was the culprit was based on analysis and review of each patient’s electrocardiogram, left ventriculogram, and coronary angiogram. After informed consent was obtained, subjects were randomized to one of four groups: 1) low-dose rt-PA, 2) high-dose rt-PA, 3) low-dose placebo, or 4) high-dose placebo.

The low-dose rt-PA group received a total dose of 0.75 mg/kg over 1 hour with a 5-mg aliquot given as an initial bolus. The total dose in this group could not exceed 60 mg (all patients weighing more than 80 kg received a 60-mg dose). The high-dose rt-PA group received a total dose of 100 mg intravenously over 6 hours. During the first 60 minutes, 0.75 mg/kg was administered, 5 mg of which was given as an initial bolus. The maximal first hour dose was 60 mg, and the remaining dose was given as a steady infusion during the next 5 hours. Sham infusions of sterile water were given to high- and low-dose placebo groups to maintain the blinding.

Randomization was performed and treatment was initiated within 2 hours of catheterization. All patients received a bolus of intravenous heparin at the time of the diagnostic catheterization and were treated with a constant heparin infusion until the time of the follow-up angiogram to maintain activated partial thromboplastin time values at 1.5–2.0-fold the control value. Preangiogram antianginal medications were continued until the end of the study period. In addition, each patient received 325 mg aspirin orally each day. Intravascular sheaths were secured in place until repeat angiography of the angina-related artery was performed 12–48 hours after enrollment, when the study was considered completed.

This investigation was designed as a pilot trial with an aim of detecting major efficacious or hazardous effects. A sample size of 60–70 patients, with approximately 20 assigned to each treatment group (combining the two placebo subgroups into a single treatment group), was considered sufficient for this purpose. The sample size, however, was considerably underpowered to permit a comparison of smaller, although potentially clinically meaningful, differences among the three groups.

The protocol was completed in four clinical centers after the procurement of local institutional review board approval. Randomization was performed at the time of baseline catheterization and accomplished locally by opening in sequence consecutively numbered sealed envelopes, beginning with envelope 1. Study subjects and investigators were blinded as to treatment assignment during the entire phase of patient recruitment, film analysis, and data entry. Coronary cineangiograms were read by core laboratory readers, who were blinded to treatment assignment.

**Data Evaluation**

The primary end point of the study was the percent change in luminal diameter reduction of the angina-producing lesion from baseline to repeat coronary angiography. Quantitative assessment of paired angiograms was performed by a blinded reviewer at the core laboratory. Images suitable for analysis were selected from the best orthogonal projections in which the targeted coronary artery was fully opacified and the segment with the stenosis was not overlapped by an adjacent artery. Whenever possible, the catheter-
ter to be used as a reference and the stenosis were examined in the central portion of the radiographic field to minimize pincushion distortion. Once selected, two comparable frames per lesion from the pretreatment and posttreatment cineangiograms were magnified and digitized for quantitative processing with a previously validated algorithm that provides values for both diameter and area reductions (ADAC DPS-4100C, Digital Imaging Processing Unit, Sunnyvale, Calif.).

In addition to the quantitative end points, qualitative angiographic analysis assessed three additional indexes of success: 1) achievement of at least a 5% decrease in percent diameter reduction, 2) resolved or smaller intraluminal thrombus, and 3) improved coronary perfusion. Thrombus was considered to be present when there was definite evidence of intracoronary filling defects or lucencies. Coronary perfusion was assessed according to the Thrombolysis in Myocardial Infarction (TIMI) trial grading system.

Patients were also monitored for clinical end points, including incidence of rest angina; increase in antianginal medications; emergency coronary angioplasty, bypass surgery, or intra-aortic balloon pump placement; and myocardial infarction. Adverse effects, particularly hemorrhagic complications, were recorded and classified according to severity.

Statistical Analysis

Baseline clinical and angiographic characteristics were compared among the three treatment groups using analysis of variance for continuous variables and exact tests for discrete variables. The percent reduction in stenosis in the angina-producing artery was analyzed with the Wilcoxon signed-rank test. Differences between groups in incidence of negative clinical outcomes and number of bleeding episodes were determined with exact tests for contingency tables. Differences were considered statistically significant at probability values of less than 0.05.

Results

Baseline Clinical Characteristics

Sixty-seven patients entered the trial with 23 assigned to receive low-dose t-PA, 22 to receive high-dose t-PA, and 22 to receive placebo (Table 1). Most patients were middle-aged men who were receiving more than one antianginal agent. Aspirin had been administered to 30% (20 of 67), whereas 7% (five of 67) were receiving heparin anticoagulation at time of study entry. There was considerable variability in the duration of time from the occurrence of rest pain to study (range, 0.5–10.4 days; average, 3.4±2.4 days).

Baseline Coronary Angiographic Characteristics

The coronary artery responsible for the unstable angina syndrome was considered to be the left anterior descending in 29 patients, the right coronary artery in 22, the left circumflex in 11, and the left intermediate branch in four (Table 2 and Figure 2). Quantitative analysis was possible in all but four patients. In almost all patients, severe coronary narrowing of the culpable coronary artery was observed. Patients with apparently less severe narrowing (i.e., those with less than 60% diameter reduction) represented those with suspected thrombus in the absence of obvious severe narrowing or instances where investigator visual assessment at the time of baseline angiography suggested more severe narrowing than was confirmed by subsequent quantitative analysis. Twenty-two patients (34%) had either intracoronary thrombus or impaired flow; 16 patients (25%) demonstrated intracoronary filling defects suggesting...
TABLE 2. Findings at Baseline and Follow-Up Coronary Angiogram

<table>
<thead>
<tr>
<th>Lesion severity</th>
<th>Placebo (n=22)</th>
<th>Low-dose rt-PA (n=23)*</th>
<th>High-dose rt-PA (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter reduction (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>76±14</td>
<td>75±16</td>
<td>79±12</td>
</tr>
<tr>
<td>After</td>
<td>72±14</td>
<td>71±18</td>
<td>73±19</td>
</tr>
<tr>
<td>Area reduction (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>92±9</td>
<td>92±10</td>
<td>94±8</td>
</tr>
<tr>
<td>After</td>
<td>90±11</td>
<td>89±13</td>
<td>90±13</td>
</tr>
<tr>
<td>Definite thrombus (n) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>6/22 (27)</td>
<td>6/21 (29)</td>
<td>4/21 (19)</td>
</tr>
<tr>
<td>After</td>
<td>2/21 (9.1)</td>
<td>1/22 (4.8)</td>
<td>1/21 (4.8)</td>
</tr>
<tr>
<td>Impaired antegrade flow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;TIMI grade 2) (n) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>2/22 (9.1)</td>
<td>4/21 (19)</td>
<td>4/21 (19)</td>
</tr>
<tr>
<td>After</td>
<td>1/22 (4.5)</td>
<td>4/21 (19)</td>
<td>2/21 (9.5)</td>
</tr>
<tr>
<td>Either thrombus or impaired flow (n) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>7/22 (32)</td>
<td>9/21 (43)</td>
<td>6/21 (29)</td>
</tr>
<tr>
<td>After</td>
<td>3/22 (14)</td>
<td>5/21 (24)</td>
<td>3/21 (14)</td>
</tr>
</tbody>
</table>

rt-PA, recombinant tissue-type plasminogen activator; Before, After, before treatment (baseline values) and after treatment (values at follow-up coronary angiogram), respectively; TIMI, Thrombolysis in Myocardial Infarction trial.

*Twenty-one paired angiograms available for analysis.

Values are given as mean±1 SD.

thrombus, and 10 (16%) had impaired antegrade coronary flow of radiographic contrast.

No significant differences in the distribution of these baseline coronary angiographic findings qualitative variables were detected among the groups (Table 2). Thus, for the cohort investigated, severe coronary stenosis was usually present, although definite thrombus or impaired antegrade blood flow was angiographically evident in only one third of patients.

Protocol Compliance

Each randomized patient received an initial intravenous infusion of the assigned treatment. Treatment infusions were completed in 66 of 67 patients; the assigned infusion was not completed in one patient due to excessive bleeding at the catheterization site. Follow-up angiography was performed in 66 of 67 patients; the follow-up angiographic examination was not performed in one patient due to technical problems of arterial access.

Coronary Angiographic Outcome

For both placebo and rt-PA treatment groups, the mean values of coronary diameter and area reduction were lower at the time of follow-up coronary angiography (Tables 2 and 3 and Figure 2). Although values of lesion severity observed on the follow-up angiogram and changes in lesion severity were similar (p=NS) among the three treatment groups, the low-dose rt-PA group did demonstrate significant changes.

FIGURE 2. Scattergrams of individual values (●) of coronary arterial obstruction expressed as percent of diameter reduction before (pre) and after (post) administration of low-dose rt-PA, high-dose rt-PA, or placebo. ○, Group mean values.
(p=0.03) reduction in lesion severity when comparing entry and follow-up angiograms. Figure 2 demonstrates the considerable individual patient response observed in each group. Lesion severity declined in most patients studied, but this response was more consistent among patients receiving low-dose rt-PA.

A similar salutary effect was observed for the prevalence of thrombus and impairment of coronary blood flow grades. Thus, each treatment group demonstrated a lower incidence of thrombus and impaired flow after treatment as compared with baseline values. A qualitative lesion outcome score was developed to detect more subtle individual patient responses. When lesion response was categorized as improved, worse, or unchanged, more patients receiving either dose of rt-PA had improved responses compared with placebo-treated patients, although the difference in proportions did not reach statistical significance.

**Clinical Events**

During the time period from randomization to follow-up angiography, 10 patients experienced recurrent ischemic pain at rest (five receiving placebo, two receiving low-dose rt-PA, and three receiving high-dose rt-PA) (Table 4). Four patients had evidence of myocardial infarction (three receiving high-dose rt-PA and one receiving placebo). One patient (low-dose rt-PA group) underwent emergency coronary angioplasty. The occurrence of these events did not differ among the three treatment groups. No patients required emergency coronary bypass surgery or died.

Bleeding was reported in 29 patients (43%)—five patients in the placebo group and 12 in each of the rt-PA groups. Of 39 sites of bleeding, 29 were related to indwelling or recently removed arterial or venous sheaths that had been used to perform the baseline cardiac catheterization. There was a trend toward a greater prevalence of instrumentation-related bleeding in patients who received rt-PA, although the difference was not statistically significant.

Ten sites of spontaneous bleeding were noted among eight patients—one in the placebo group, four in the low-dose rt-PA group, and three in the high-dose rt-PA group. Bleeding was considered severe in

**Table 3. Changes in Angiographic Findings**

<table>
<thead>
<tr>
<th>Lesion severity</th>
<th>Placebo</th>
<th>Low-dose rt-PA</th>
<th>High-dose rt-PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter reduction (%)</td>
<td>4.5±10.8</td>
<td>4.6±8.5</td>
<td>6.0±13.7</td>
</tr>
<tr>
<td>Area reduction (%)</td>
<td>1.5±4.8</td>
<td>3.4±7.2</td>
<td>4.9±9.8</td>
</tr>
<tr>
<td>Lesion score (&gt;5% change) (n) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>6/21 (29)</td>
<td>10/20 (50)</td>
<td>10/20 (50)</td>
</tr>
<tr>
<td>Worse</td>
<td>3/21 (14)</td>
<td>3/20 (15)</td>
<td>3/20 (15)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>12/21 (57)</td>
<td>7/20 (35)</td>
<td>7/20 (35)</td>
</tr>
<tr>
<td>Resolution of thrombus (n) (%)</td>
<td>4/6 (67)</td>
<td>5/6 (83)</td>
<td>3/5 (60)</td>
</tr>
<tr>
<td>Improved antegrade flow (≥1 TIMI grade) (n) (%)</td>
<td>1/2 (50)</td>
<td>2/4 (50)</td>
<td>2/4 (50)</td>
</tr>
<tr>
<td>Either thrombus resolution or improved flow (n) (%)</td>
<td>4/7 (57)</td>
<td>5/9 (56)</td>
<td>3/6 (50)</td>
</tr>
</tbody>
</table>

rt-PA, recombinant tissue-type plasminogen activator; TIMI, Thrombolysis in Myocardial Infarction trial. Values are given as mean±1 SD.

| Table 4. Major Clinical Events During Study Period by Treatment Group |
|-------------------------|---------|----------------|----------------|
|                          | Placebo | Low-dose rt-PA | High-dose rt-PA |
| Rest angina (n) (%)      | 5 (23)  | 2 (6.3)        | 3 (14)         |
| Myocardial infarction (n) (%) | 1 (4.5) | 0              | 3 (14)         |
| Emergency coronary angioplasty (n) (%) | 0     | 1 (4.5)        | 0              |
| Need for intra-aortic balloon counterpulsation (n) | 0 | 0            | 0              |
| Coronary artery bypass surgery (n) | 0 | 0            | 0              |
| Death (n)                | 0       | 0              | 0              |
| Total (n) (%)            | 6 (27)  | 3 (13)         | 6 (27)         |

rt-PA, recombinant tissue-type plasminogen activator.

| Table 5. Hemorrhagic Events During Study Period by Treatment Group |
|-------------------------|---------|----------------|----------------|
|                          | Placebo | Low-dose rt-PA | High-dose rt-PA |
| Sites of events          |         |                |                |
| Gastrointestinal         | 1       | 0              | 2              |
| Genitourinary            | 1       | 1              | 1              |
| Retroperitoneal          | 0       | 1              | 0              |
| Gingival                 | 0       | 2              | 1              |
| Groin (access site)      | 5       | 12             | 9              |
| Intracranial             | 0       | 0              | 0              |
| Total events             | 7       | 16             | 16             |
| Patients                 |         |                |                |
| With bleeding episode (n) | 5   | 12             | 12             |
| Requiring transfusion (n) | 2   | 4              | 3              |

rt-PA, recombinant tissue-type plasminogen activator.
two patients—one with catheterization site bleeding and one who experienced hematuria, retroperitoneal, and intraperitoneal bleeding. Both patients received low-dose rt-PA. No patient experienced intracerebral bleeding. Nine patients received blood transfusion—two receiving placebo, four receiving low-dose rt-PA, and three receiving high-dose rt-PA.

Discussion

Although unstable angina has been liberally defined to include patients with angina other than progressive and of new onset, most clinicians consider rest pain to be a key characteristic of this acute ischemic syndrome. Ischemic pain at rest or with minimal provocation suggests an exacerbation of coronary arterial narrowing sufficient to impair flow required for resting myocardial oxygen requirements. Substantial experimental, clinical, and pathological evidence suggest that transient reduction in coronary blood flow associated with rest angina can be ascribed to increased vascular tone, thrombus formation, or both.21–26 Angiographic observations in patients with unstable angina have demonstrated presence of intracoronary opacities indicative of thrombi in a substantial proportion in addition to unique anatomical lesion characteristics suggesting fissuring or ulceration.2–9,27 The likelihood of detecting coronary thrombus, however, appears to correlate with the elapsed time from the occurrence of rest pain to angiographic assessment.7,9

Based on the above considerations, the efficacies of both aspirin, as an antiplatelet agent, and heparin, as an anticoagulant, have been evaluated in patients with unstable angina.10–12 Recently, Theroux and colleagues compared the use of aspirin and heparin with the use of placebo in patients hospitalized with unstable angina pectoris and demonstrated that aspirin, heparin, or the combination substantially reduces the incidence of untoward cardiac events compared with the use of placebo.12

The present investigation was designed to determine whether patients with unstable angina pectoris treated with aspirin, heparin, and either rt-PA or placebo will experience a reduction in the severity of coronary obstruction in the artery considered responsible for the acute ischemic syndrome. Both a brief low-dose regimen of t-PA and a higher-dose, more sustained regimen were evaluated. A dose lower than that conventionally administered for the treatment of acute myocardial infarction was included because major morbid events are less common among patients with unstable angina compared with those with myocardial infarction and therapeutic interventions should correspondingly have lower potential likelihoods for untoward effects. Because thrombolytic therapy may cause fatal bleeding and the risk of such bleeding may be dose related, we evaluated a regimen that might be associated with a lower likelihood of spontaneous bleeding.

A second important study design feature was that each patient, including placebo-treated patients, received continuous intravenous heparin anticoagulation and oral aspirin during the study period. Thus, the placebo-treated group did receive active therapy. We observed a significant reduction of severity of coronary obstruction as assessed by measurements of both coronary diameter and area reduction in patients treated with low-dose rt-PA. In addition, there was a decrease in the prevalence of intracoronary thrombi and an improvement in coronary blood flow. Changes of similar magnitude were observed in the placebo-treated and the rt-PA–treated groups, although these changes did not achieve statistical significance for patients receiving placebo or high-dose rt-PA. Because some patients, however, in the placebo and high-dose rt-PA groups did demonstrate improvement in the various angiographic indexes and the absolute extent of change was similar to that of the low-dose rt-PA–treated patients, it appears that full heparin anticoagulation and aspirin therapy alone can be considered active therapy in reducing the severity of coronary obstruction for certain patients with unstable angina pectoris.

The magnitude of stenosis reduction observed in this study was not large. The change in percent diameter reduction averaged about 5%. In addition, not all patients with impaired flow or presence of intracoronary thrombus demonstrated a therapeutic effect. The most likely explanation for these observations was that not all patients may have had intracoronary thrombus at time of trial entry and that of those who did, thrombus may have been present sufficiently long enough to become resistant to thrombolytic therapy. The elapsed time from rest pain to angiography in this trial averaged 3 days, and only one third of patients had angiographic evidence of thrombus. Had patients undergone angiography within hours of the occurrence of rest pain, it is possible that our results might have demonstrated a greater effect of thrombolytic therapy.

Another possible explanation for the small magnitude of the observed response is that in these patients, coronary obstruction was more attributable to progression of atherosclerotic narrowing than to thrombus formation. Individual variation in the proportionality of thrombus to fixed atherosclerotic disease would also explain the wide range of observed individual patient responses (Figure 2).

The effects of intravenous rt-PA on angiographic indexes of coronary disease severity have been assessed previously in patients with unstable angina pectoris. Gold et al administered 1.75 mg/kg over 12 hours to 24 patients who presented with rest pain and abnormal electrocardiograms.13 Compared with placebo-treated patients, rt-PA–treated patients demonstrated a lower incidence of intracoronary thrombus on subsequent coronary angiography. Two separate trials assessing change in coronary stenosis severity after administration of intravenous rt-PA have yielded conflicting results. deZwaan et al noted a coronary diameter stenosis decrease from 65±22% to 51±19% in 20 patients who received 100 mg rt-PA
intravenously over 3 hours. Nicklas et al, however, observed a change in coronary stenosis from 82±7% at baseline to 73±10% at 24 hours, a difference that failed to achieve statistical significance.

Improvement in clinical outcome has been demonstrated after administration of intravenous rt-PA in patients with unstable angina pectoris. Gold et al observed fewer instances of recurrent rest pain in patients treated with intravenous rt-PA compared with those treated with placebo.

Bleeding was not infrequent in this trial, particularly in patients receiving rt-PA. Most instances of bleeding, however, were related to the presence of indwelling vascular sheaths or recent vascular punctures. Of importance, the incidence of spontaneous bleeding was relatively low and distributed among both rt-PA- and placebo-treated groups.

In conclusion, this study demonstrated that intravenous rt-PA combined with heparin and aspirin can reduce the severity of coronary narrowing in patients with rest angina. The treatment effect is mild in magnitude and varies considerably among patients. Using an angiographic end point, clear superiority of adding rt-PA to heparin and aspirin was not evident. This finding does not exclude, however, the possibility that rt-PA may enhance clinical outcome in patients with unstable angina. Larger trials addressing this issue are in progress.

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Appendix

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The University of Michigan, Ann Arbor. Principal Investigator: G.B. John Mancini, MD; Coinvestigators: Mark J. McGillem, BS, Ibraim M.F. Pinto, MD, and Paula Williamson, BS.

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**KEY WORDS** • thrombolytic therapy • coronary artery disease • heparin • aspirin • clinical trials
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