Sequential Combination Thrombolytic Therapy for Acute Myocardial Infarction: Results of the Pro-Urokinase and t-PA Enhancement of Thrombolysis (PATENT) Trial

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Objectives. The present study was designed to test the efficacy and safety of a sequential combination of recombinant tissue-type plasminogen activator (rt-PA) and pro-urokinase in patients with acute myocardial infarction.

Background. Efforts continue to identify a thrombolytic regimen that induces rapid, complete, and sustained coronary artery patency in acute myocardial infarction. The two endogenous plasminogen activators rt-PA and pro-urokinase have been shown experimentally to induce fibrinolysis by sequential and complementary mechanisms. As a result, certain combinations of these activators have been found to be synergistic in vitro and in vivo.

Methods. In a multicenter observational study with core facilities for angiographic and laboratory analysis, 101 patients with acute myocardial infarction were enrolled and given a low dose bolus of rt-PA (5 to 10 mg) followed by a 90-min infusion of pro-urokinase (40 mg/h). All patients received intravenous heparin and oral aspirin. Coronary angiography was performed in all patients at 90 min.

Results. Angiography at 90 min showed the infarct-related artery to be patent (Thrombolysis in Myocardial Infarction [TIMI] grade 2 or 3 flow) in 77% of patients, and 60% achieved TIMI grade 3 flow. At one center, angiography was repeated at 24 h to detect a possible reocclusion. All 28 patients with a patent infarct-related artery at 90 min had patency at 24 h (82% achieved TIMI grade 3 flow). Treatment was well tolerated, with bleeding complications essentially confined to arterial puncture site hematomas. There was only one in-hospital death.

Conclusions. A sequential combination of low dose rt-PA and reduced-dose pro-urokinase produced a high TIMI 3 patency rate, was well tolerated, and was associated with a low reocclusion rate.

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the principal function of rt-PA is to initiate fibrinolysis to overcome the relative resistance of intact fibrin to pro-urokinase. The primary end point was 90-min infarct-related artery patency. At one of the participating centers, reocclusion at 24 h was also evaluated.

**Methods**

**Centers.** This study was conducted by investigators from eight institutions (see Appendix). The coordinating center was the Deaconess Hospital in Boston, Massachusetts.

**Inclusion criteria.** Patients were eligible for inclusion in the study if they were between 21 and 75 years of age and had chest pain characteristic of myocardial ischemia for \( \geq 30 \) min with ST segment elevation \( \geq 0.1 \) mV (1 mm) in at least two limb leads or \( \geq 0.2 \) mV (2 mm) in at least two precordial leads. The elapsed time from onset of ischemic pain to start of therapy was required to be \( \leq 6 \) h.

**Exclusion criteria.** The exclusion criteria were previous coronary artery bypass surgery, recent \(<6\) months) percutaneous transluminal coronary angioplasty, cardiogenic shock despite vasopressor therapy; severe uncontrolled hypertension, defined as supine systolic blood pressure \( > 180 \) mm Hg and supine diastolic blood pressure \( > 110 \) mm Hg; left bundle branch block; prosthetic heart valve; dilated cardiomyopathy or severe left ventricular dysfunction, or both; history of cerebrovascular accident or severe head trauma within the last 6 months; major surgery within the previous 2 months; known bleeding disorder; active peptic ulcer; internal bleeding; history of genitourinary or gastrointestinal bleeding within the previous year; women of child-bearing potential; severe type I diabetes or hemorrhagic retinopathy, or both; oral anticoagulant therapy; other serious advanced illnesses such as cancer; psychological or physical inability to participate in the study; aspirin sensitivity; administration of any investigational drug or procedure within the previous month; or inability to undergo a coronary angiographic procedure. The protocol was approved by each hospital's institutional review board, and all patients provided written informed consent before entry into the study.

**Treatment schedule.** All patients received premedication with heparin sulfate, 5,000 IU intravenously, and aspirin, 160 mg chewed and swallowed. An intravenous heparin drug was administered simultaneously with the thrombolytic therapy and was continued for 24 to 72 h and adjusted to maintain the upper limit of the normal range.

The decision to administer a beta-adrenergic blocking agent or nitroglycerin, or both, before or during thrombolytic therapy was based on clinical judgment. Aspirin was continued daily. All concomitant medications used from hospital entry to patient discharge were recorded on the appropriate Case Report Form provided to each center.

In the first 10 patients, rt-PA (alteplase, Genentech) was administered as a single 10-mg intravenous bolus injection over 1 min. This was followed immediately by an infusion of nonglycosylated recombinant pro-urokinase from *Escherichia coli* (Farmitalia Carlo Erba) at a rate of 40 mg/h for 90 min (60 mg total dose). This regimen was based on experimental studies indicating synergy by a sequential combination of rt-PA and pro-urokinase (6,7) and preliminary clinical observations with combination thrombolytic therapy (8-10,12). Two of the first 10 patients had a major bleeding complication. After review of the results in these 10 patients, 9 of whom were found to have Thrombolysis in Myocardial Infarction (TIMI) grade 3 patency, it was decided to reduce the rt-PA bolus dose from 10 to 5 mg to improve fibrin specificity because the patency end point \((\geq 75\%)\) had been exceeded. The remaining 91 patients all received a 5-mg bolus of rt-PA followed by the same pro-urokinase infusion regimen (40 mg/h over 90 min). All deviations from the protocol were recorded and were included in the evaluation of the efficacy and safety of the combination therapy. Results are presented on an intention-to-treat basis.

**Laboratory analysis.** Hemostatic assays were performed by an independent core laboratory (directed by J. Loscalzo, Brigham and Women's Hospital, now Whitaker Cardiovascular Institute, Boston University School of Medicine). Blood was collected in citrate (9:1 by volume) or in citrate and aprotinin (Trasylol®. Miles Inc., final concentration 200 kal-likrein international units (KIU)/ml) or in aprotinin alone. The samples were centrifuged within 1 h and stored at \(-20^\circ\)C. The following assays were performed on samples collected onto aprotinin: fibrinogen level determined by sodium sulfate precipitation (13) and fibrin(ogen) degradation products. In the first 28 patients, fibrinogen degradation products in serum were measured by tanned red cell hemagglutination (14); in the remaining 73 patients, fibrinogen degradation products were measured in plasma by latex agglutination (American Bioproducts). Plasminogen and alpha2-antiplasmin were determined on samples collected without aprotinin using a chromogenic substrate, S2251 (Kabi Pharmacia) (15). Blood samples were obtained before treatment and 3, 6, 12, 18 and 24 h after the start of the thrombolytic therapy and shipped to the central laboratory on dry ice.

**Coronary angiography.** Coronary angiography was performed at 90 min in all patients. In a subgroup of 28 patients with a patent infarct-related artery at 90 min, angiography was repeated at 24 h. Perfusion status was determined independently in blinded manner by three reviewers from a central radiographic committee according to the TIMI grading system. Patency was defined as TIMI grade 2 or 3 flow in the infarct-related artery. Coronary artery disease was defined as either \( \geq 60\% \) reduction of the internal diameter of one of the major epicardial arteries or \( \geq 50\% \) reduction of the internal diameter of the left main coronary artery. The extent of coronary artery disease (single, double, triple, left main), residual thrombus, and presence of ulcerated lesions was recorded.

**Review/safety committee.** A central safety-monitoring committee monitored efficacy (patency) and safety (adverse experiences, bleeding complications) data. Bleeding complications were classified as major (hemoglobin decrease \( \geq 5 \) g/dl or requiring transfusion), minor (hemoglobin decrease 3 to 5 g/dl).
Table 1. Clinical Characteristics of 101 Study Patients

<table>
<thead>
<tr>
<th>No. of Pts</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to treatment (h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>2–4</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>&gt;4</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2.9 ± 1.4</td>
<td>0.8–6.9</td>
</tr>
<tr>
<td>Infarct-related artery</td>
<td>LAD</td>
<td>LCx</td>
</tr>
<tr>
<td>Pts = patients.</td>
<td></td>
<td></td>
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</tbody>
</table>

or not significant. The relation of bleeding episodes to invasive procedures was recorded.

Statistical methods. Results are presented as mean value ± SD for continuous variables and as a percent of the total cohort for categoric variables. Plasminogen and alpha2-antiplasmin levels are reported as mean change over time from the baseline value. Point estimates are reported with the 95% confidence interval (CI).

Results

Study patients. A total of 101 patients (86 men, 15 women) met inclusion criteria and were enrolled in the study between November 4, 1991 and November 16, 1993. Two centers (Carolinas Medical Center and University of Washington) supplied 71 of the patients. The mean age of patients enrolled was 57 ± 9 years (range 31 to 79). The average time from onset of pain to the administration of thrombolytic therapy was 2.9 ± 1.4 h (range 0.8 to 6.9). Treatment was started within 2 h after the onset of chest pain in 31 patients, within 2 to 4 h in 49 patients and after 4 h in 21 patients (Table 1).

All patients experienced a myocardial infarction documented by electrocardiographic changes and transient elevations of serum enzyme activities. One patient was retrospectively determined to have been inappropriately enrolled because he exceeded the age entry criteria. This patient was included in the evaluation of safety and efficacy.

Angiography. Posttreatment angiography was performed for all patients at a mean time of 93 ± 17 min. The infarct-related artery was the left anterior descending coronary artery in 42% of patients, the left circumflex coronary artery in 16% and the right coronary artery in 42%. Two patients were found to have essentially normal arteries (Table 1).

In the entire group of 101 patients, a TIMI 2 or 3 patency rate of 77% (95% CI 69% to 85%) and a TIMI grade 3 patency rate of 60% (95% CI 50% to 69%) were obtained. A subgroup of 28 patients from one of the participating centers (Seattle) with a patent infarct-related artery at 90 min underwent repeat catheterization at 24 h. None of these patients had undergone any intervening procedure. In all of these patients, the infarct-related artery remained patent at 24 h, and in 23 (82%) TIMI grade 3 flow was found (Table 2).

Percutaneous transluminal coronary angioplasty was performed in 53 patients and was successful in 51. Thirty patients underwent angioplasty within 24 h; in 18 this procedure constituted "rescue" angioplasty. Coronary artery bypass surgery was performed during the hospital period for the index myocardial infarction in 11 patients. Bypass surgery was performed within 24 h in 1 patient (failed lysis) and after 48 h in the remaining 10 patients. Nitrates were administered in 98 patients, heparin in 97 and beta-blockers in 7. All patients received aspirin.

Hematologic effects. Hematologic data are presented for the entire group of 101 patients. The mean values at 3 h, as a percent of their baseline values for fibrinogen, plasminogen and alpha2-antiplasmin were 50%, 33% and 22%, respectively. The mean of the maximal fibrinogen degradation products value, which also occurred at 3 h, was 28.6 ± 32.3 μg/ml (Table 3).

For the entire group, the mean hemoglobin and hematocrit at baseline were 15.2 ± 1.4 g% and 44.1 ± 3.8%, respectively. These values decreased to 12.1 ± 1.0 g% and 35.6 ± 4.6% at 24 h, respectively, and were similar at discharge. The mean activated partial thromboplastin time was 91 ± 45 s at 12 h and 62 ± 38 s at 24 h.

Bleeding complications and other adverse reactions. Of the 101 patients, 10 had a major bleeding episode requiring transfusion; 9 of these 10 patients had a groin hematoma at the catheterization site. Hematemesis occurred in one patient. There were 26 minor bleeding episodes that were also confined to the catheterization sites (Table 4).

There were no cerebrovascular accidents. Of the 101 patients, 1 died in hospital of cardiogenic shock occurring on day 5.

The most frequently reported clinical events were dysrhythmias or disturbances of conduction. One patient experienced transient hypotension during infusion of pro-urokinase, and in no patient was pro-urokinase infusion interrupted because of an adverse clinical event. No allergic or anaphylactoid reactions were noted.

Table 2. Patient Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI grade at 90 min</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>TIMI grade at 24 h</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>1</td>
</tr>
</tbody>
</table>

Pts = patients; TIMI = Thrombolysis in Myocardial Infarction.
Combination coronary thrombolysis

A combination regimen of low dose bolus rt-PA followed by an infusion of pro-urokinase produced a 90-min TIMI 2 or 3 patency of 77% (95% CI 69% to 85%), a value similar to the Activator for Occluded Arteries (GUSTO) trial (16). The TIMI 81% induced by 100 mg of accelerated rt-PA and the 73% induced by a combination of rt-PA and streptokinase in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) trial (16). The TIMI grade 3 patency rate of 60% (95% CI 50% to 69%) achieved in the present study compared favorably with the 54% for accelerated rt-PA in GUSTO. The other treatment arms of GUSTO gave much lower TIMI 3 patency rates: 29% for streptokinase and 38% for rt-PA plus streptokinase (16). In the Pro-Urokinase in Myocardial Infarction (PRIMI) trial (17), the 90-min TIMI 2 or 3 patency rate was 71.2% (95% CI 65% to 78%). The TIMI 3 patency rate was not given in that study. However, a pro-urokinase infusion of 60 to 80 mg over 90 min was recently reported to produce a TIMI grade 3 patency rate of 52% (18). Restoration of normal flow (TIMI grade 3) is critical because it has been associated with lower rates of reocclusion, recurrent ischemia and mortality (19). The relatively high TIMI 3 patency rate combined with a low reocclusion rate may help explain the low (1%) in-hospital mortality rate observed in the present study, which is also supported by the findings of Weaver et al. (18), who reported that 1 of 128 patients treated with 60 to 80 mg pro-urokinase died in hospital.

Secondary end points of the present trial were fibrin specificity and safety. In view of the high efficacy (90% TIMI 3 patency) associated with two major bleeding complications in the first 10 patients, it was elected to reduce the rt-PA bolus from 10 to 5 mg. This had no significant effect on the hemostatic measures, but major bleeding complications were thereafter confined to eight catheter site hematomas. The alterations in hemostatic variables in the present study were similar to those reported for rt-PA monotherapy (20) but were considerably less than those with pro-urokinase monotherapy in the PRIMI trial, which induced a major (86%) reduction in fibrinogen and corresponding increase in fibrinogen degradation product levels (144 μg/ml) as a result of the systemic conversion of pro-urokinase to urokinase that occurs at a dose of 80 mg in 1 h (17). Moreover, the nonglycosylated recombinant pro-urokinase from E. coli that was used in the PRIMI trial and in the present study is somewhat less stable in plasma than the glycosylated native form, being more readily converted to urokinase (21). Nevertheless, the hemorrhagic complications encountered in the present study were modest and related principally to bleeding at the arterial puncture site; therefore, such complications would not be expected in patients not subjected to posttreatment coronary angiography.

In the 28 patients who underwent follow-up angiography after successful restoration of patency at 90 min, all had a patent infarct-related artery at 24 h, and 82% achieved TIMI grade 3 flow. None of these patients had undergone angio-plasty. This finding is consistent with other reports of exceptionally low reocclusion rates after thrombolysis with pro-urokinase. Among patients not subjected to interventions in the PRIMI study, a rethrombosis rate of 0.9% (1 of 108) was reported (17). Similarly, Weaver and co-workers (18) found a reocclusion rate of 1.4% (1 of 70) 24 h after successful thrombolysis with pro-urokinase. This contrasts with the 10% to 20% rate of reocclusions reported in the early studies with rt-PA (22) and the 5.9% (11 of 185) observed with rt-PA in GUSTO (16). Reocclusion has been attributed largely to residual thrombus and underlying plaque thrombogenicity as well as thrombophilia secondary to the thrombolytic agent. The low rate of reocclusion reported for pro-urokinase may be related to the finding that it is not associated with thrombin or platelet activation (18), in contrast to rt-PA and streptokinase (23–26). Moreover, pro-urokinase in blood has been shown to become tightly associated with platelets, a phenomenon that has also been postulated to contribute to its low reocclusion rate (27).

**Table 3. Hemostologic Variables (mean ± SD) in 101 Study Patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>3 h</th>
<th>6 h</th>
<th>12 h</th>
<th>18 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen (mg/ml)</td>
<td>355 ± 153</td>
<td>178 ± 96</td>
<td>183 ± 103</td>
<td>206 ± 109</td>
<td>253 ± 95</td>
<td>276 ± 112</td>
</tr>
<tr>
<td>FDP (μg/ml)</td>
<td>1.7 ± 5.4</td>
<td>28.6 ± 32.3</td>
<td>17.3 ± 26.0</td>
<td>6.1 ± 12.8</td>
<td>7.4 ± 16.4</td>
<td>2.9 ± 12.2</td>
</tr>
<tr>
<td>PGN (%)</td>
<td>100</td>
<td>32.9 ± 124</td>
<td>38.4 ± 13.8</td>
<td>45.8 ± 13.9</td>
<td>49.9 ± 12.2</td>
<td>55.1 ± 12.5</td>
</tr>
<tr>
<td>AP (%)</td>
<td>100</td>
<td>21.9 ± 18.1</td>
<td>36.6 ± 17.2</td>
<td>53.5 ± 20.8</td>
<td>68.3 ± 19.6</td>
<td>78.9 ± 22.7</td>
</tr>
</tbody>
</table>

AP = alpha-antiplasmin; FDP = fibrin degradation products; PGN = plasminogen.

**Table 4. Bleeding Complications**

<table>
<thead>
<tr>
<th>Type</th>
<th>No. of Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major (n = 10)</td>
<td></td>
</tr>
<tr>
<td>Puncture site bleeding</td>
<td>9</td>
</tr>
<tr>
<td>Hematoma</td>
<td>1</td>
</tr>
<tr>
<td>Minor (n = 26)</td>
<td></td>
</tr>
<tr>
<td>Puncture site bleeding</td>
<td>26</td>
</tr>
</tbody>
</table>

Pts = patients.

**Discussion**

**Angiographic and hemostatic outcomes.** The sequential combination regimen of low dose bolus rt-PA followed by an infusion of pro-urokinase produced a 90-min TIMI 2 or 3 patency of 77% (95% CI 69% to 85%), a value similar to the 81% induced by 100 mg of accelerated rt-PA and the 73% induced by a combination of rt-PA and streptokinase in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) trial (16). The TIMI grade 3 patency rate of 60% (95% CI 50% to 69%) achieved in the present study compared favorably with the 54% for accelerated rt-PA in GUSTO. The other treatment arms of GUSTO gave much lower TIMI 3 patency rates: 29% for streptokinase and 38% for rt-PA plus streptokinase (16). In the Pro-Urokinase in Myocardial Infarction (PRIMI) trial (17) of monotherapy with pro-urokinase (80 mg in 60 min), the 90-min TIMI 2 or 3 patency rate was 71.2% (95% CI 65% to 78%). The TIMI 3 patency rate was not given in that study. However, a pro-urokinase infusion of 60 to 80 mg over 90 min was recently reported to produce a TIMI grade 3 patency rate of 52% (18). Restoration of normal flow (TIMI grade 3) is critical because it has been associated with lower rates of reocclusion, recurrent ischemia and mortality (19). The relatively high TIMI 3 patency rate combined with a low reocclusion rate may help explain the low (1%) in-hospital mortality rate observed in the present study, which is also supported by the findings of Weaver et al. (18), who reported that 1 of 128 patients treated with 60 to 80 mg pro-urokinase died in hospital.

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was reversed (28). The mechanism underlying this sequence on which the present dosage regimen was based has been delineated in vitro and is related to the promotion by rt-PA of thrombolysis by pro-urokinase. In brief, fibrinolysis by pro-urokinase in plasma has a lag phase (29), reflecting the finding that pro-urokinase is relatively inactive against intact fibrin, in direct contrast to rt-PA (7). Pretreatment of fibrin with a small amount of plasmin attenuated the lag phase (30) by exposing new plasminogen binding sites on fibrin (31), which are required by pro-urokinase. These secondary plasminogen binding sites consist principally of carboxy terminal lysines on the E-domain of fibrin (7). Plasminogen bound to these sites is preferentially (>250-fold) activated by pro-urokinase, explaining its fibrin specificity (32). By contrast, rt-PA binds to and preferentially activates plasminogen bound to the primary plasminogen binding site on the D-domain of intact fibrin (33). The two activators, therefore, are sequential and complementary in their activation of the fibrin-bound plasminogens (6).

Subsequently, plasmin on the clot surface induces local activation of pro-urokinase to urokinase, which amplifies the fibrinolytic effect because urokinase is an unrestricted plasminogen activator capable of activating all fibrin-bound plasminogen (34). Therefore, synergy by combinations of rt-PA and pro-urokinase is limited to the early phase of fibrinolysis, before significant urokinase generation occurs.

In light of this mechanism, plasmin pretreatment of a clot induced by any activator should promote the effect of pro-urokinase. Indeed, urokinase has also been shown to promote clot lysis by pro-urokinase both in vitro (12) and in vivo (35,36). Recombinant tissue-type plasminogen activator was chosen as the "primer" for the present study for its fibrin specificity and because a bolus of rt-PA mimics the paradigm of endogenous fibrinolysis, which is initiated when rt-PA is released from the vessel wall at the site of a thrombus. Although the role of pro-urokinase in physiologic fibrinolysis has been questioned by studies of spontaneous lysis of platelet-poor plasma clots (37), endogenous pro-urokinase in plasma has been shown to mediate clot lysis of platelet-rich clots (38). Similarly, fibrinolysis by exogenous pro-urokinase was promoted by platelets, whereas that by rt-PA was inhibited (30). Because coronary thrombi tend to be platelet-rich, this property of pro-urokinase may make it additionally suitable for this indication.

**Study limitations.** Although our results are not inconsistent with a modest synergistic effect, the lack of monotherapy control groups precludes a definitive determination of synergy. Moreover, Weaver et al. (18) recently found that 60 mg of pro-urokinase over 90 min was similarly efficacious to 80 mg and further found that a "priming" dose of urokinase did not potentiate thrombolysis by the 60-mg dose. However, in that study, 20% of the pro-urokinase dose was given as a bolus, which may have resulted in sufficient systemic conversion to urokinase to alone serve the function of "priming" the clot.

**Conclusions.** A small bolus of rt-PA followed by an infusion of pro-urokinase induced a high rate of TIMI 3 patency at 90 min, was well tolerated and was associated with a low reocclusion rate and in-hospital mortality, consistent with that of another recently reported pro-urokinase study (18). The Pro-Urokinase and t-PA Enhancement of Thrombolysis (PATENT) trial findings, therefore, are promising and warrant further studies in which pro-urokinase used alone or in a sequential combination regimen is compared with the best current strategy for coronary thrombolysis.

We thank Dorinda George and Annemarie Ward for help in measuring the hemostatic variables and Joyce J. Lloyd for preparation of the manuscript.

**Appendix**

**Co-Investigators and Participating Institutions in the PATENT Trial**

**Coordinating center:** Deaconess Hospital, Boston, Massachusetts—Stuart Zarich, MD, Principal Investigator; James E. Muller, MD, Co-Investigator; Victor Gurewich, MD, Co-Investigator; Karen Manzo, RN, Research Nurse Coordinator; Christine Byrnes, Project Coordinator. **Clinical centers:** Cardiology Group of Memphis, Memphis, Tennessee—Steven Himmelstein, MD, Principal Investigator; Barbara Hamilton, RN, Research Nurse Coordinator. Carolinas Heart Institute, Charlotte, North Carolina—Glen J. Kowalchuk, MD, Principal Investigator; Susan Lingebach, RN, Research Nurse Coordinator. Fort Wayne Cardiology, Fort Wayne, Texas—Stephen Brown, MD, Principal Investigator; Judy Richmond, RN, MSN, Research Nurse Coordinator. New England Medical Center, Boston, Massachusetts—Deeb N. Salem, MD, Principal Investigator; Regina Miele, RN, Research Nurse Coordinator. San Diego Cardiovascular Center, San Diego, California—Brian E. Jaski, MD, Principal Investigator; Beth Penny, RN, Research Nurse Coordinator. Texas Cardiology Consultants, Dallas, Texas—Samuel DeMaio, MD, Principal Investigator; Florence Rothenberg, MD, Research Coordinator. University of Washington (MITI), Seattle, Washington—W. Douglas Weaver, MD, Principal Investigator; Jenny Martin, RN, Research Nurse Coordinator. Coagulation core laboratory: Brigham and Women's Hospital, Boston, Massachusetts—Joseph Loscalzo, MD, Laboratory Director; Dorinda George, Laboratory Supervisor. Angiography core laboratory: Deaconess Hospital, Boston, Massachusetts—Philip Fitzpatrick, MD; Samuel Shroobros, MD; Michael Sassower, MD. Safety committee: Brigham and Women's Hospital, Boston, Massachusetts—Samuel Z. Goldhaber, MD, Chairman; Marc Pfeffer, MD, PhD. Deaconess Hospital, Boston, Massachusetts—David Leeman, MD. Medical College of Virginia, Richmond, Virginia—W. Hans Carter, Jr., PhD. New England Medical Center, Boston, Massachusetts—Michael S. Pessin, MD.

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