Intravenous recombinant tissue-type plasminogen activator in patients with acute myocardial infarction: a report from the NHLBI thrombolysis in myocardial infarction trial*

DAVID O. WILLIAMS, M.D., JEFFREY BORER, M.D., EUGENE BRAUNWALD, M.D., JAMES H. CHESEBRO, M.D., LAWRENCE S. COHEN, M.D., JAMES DALEN, M.D., HAROLD T. DODGE, M.D., CHARLES K. FRANCIS, M.D., GENELLE KNATTERUD, PH.D., PHILLIP LUDBROOK, M.B., B.S., JOHN E. MARKIS, M.D., HILTRUD MUELLER, M.D., PATRICE DESVIGNE-NICKENS, M.D., EUGENE R. PASSAMANI, M.D., ERIC R. POWERS, M.D., A. KONETI RAO, M.D., ROBERT ROBERTS, M.D., ALLAN ROSS, M.D., THOMAS J. RYAN, M.D., BURTON E. SOBEL, M.D., MICHAEL WINNIFORD, M.D., BARRY ZARET, M.D. AND CO-INVESTIGATORS**

ABSTRACT The efficacy and safety of a 3 hr, 80 mg intravenous infusion of recombinant tissue-type plasminogen activator (rt-PA) were investigated in 47 patients with acute myocardial infarction. Coronary angiography, performed before the administration of rt-PA and for 90 min thereafter, demonstrated that 37 patients had total coronary occlusion before therapy. After 90 min of rt-PA (50 mg), reperfusion of the infarct-related artery was observed in 25 patients (68%). Continuous infusions of heparin for anticoagulation were administered for 8 to 10 days. Of 36 patients who underwent follow-up coronary cineangiography, 21 had initially presented with total occlusion and had experienced reperfusion at 90 min. Sustained perfusion of the infarct-related artery was observed in 14 (67%) of these 21 initially reperfused patients. Late angiography was performed in nine patients who initially demonstrated subtotal occlusion of the infarct-related artery; sustained perfusion was observed in eight (89%). Significant bleeding was observed in 15 patients (32%). A hematoma at the site of the acute catheterization accounted for most instances of significant bleeding (11/15, 73%). Administration of rt-PA resulted in a significant decline in fibrinogen and plasminogen while amounts of fibrin(ogen) degradation products rose. In no patient, however, did fibrinogen levels decline to less than 140 mg/dl. Thus, rt-PA, administered as a brief 80 mg intravenous infusion, is capable of restoring blood flow in a high proportion of patients with acute myocardial infarction due to total coronary obstruction. Declines in plasma fibrinogen and plasminogen are observed. If combined with heparin anticoagulation and invasive vascular procedures, significant bleeding is a common complication. Despite anticoagulation with heparin after rt-PA, reocclusion of the reperfused infarct-related artery occurs in one-third of patients.


A SUBSTANTIAL BODY of evidence indicates that coronary thrombosis contributes to the development of acute myocardial infarction (AMI) and that the administration of thrombolytic agents to patients with AMI can reestablish antegrade blood flow in a totally occluded coronary artery.1 While some trials have indicated that both the intracoronary and intravenous administration of the thrombolytic agent streptokinase can improve short-term survival and left ventricular function after AMI,2-4 others have failed to confirm these salutary effects.5-7 Differences in study design, sample size, and in concomitant therapy have been implicated as reasons for disparate results.8

Conventional intravenous thrombolytic therapy is not free from potentially serious side effects. A bleeding diathesis occurs after systemic administration of
thrombolytic agents such as streptokinase or urinokinese because of the formation in plasma of plasminogen. Consumption of α2-antiplasmin is followed by increased circulating plasmin with subsequent proteolysis of numerous plasma proteins required for normal hemostasis. However, certain recently discovered plasminogen activators appear to be more specific for plasminogen when bound to fibrin.9-11 The theoretical advantage of fibrin specific activation is that systemic lytic states may be avoided, thus reducing the potential for serious bleeding. One of these activators, recombinant tissue-type plasminogen activator (rt-PA), has been isolated and produced by recombinant DNA techniques.12

To determine whether thrombolytic therapy favorably affects outcome in patients with AMI, the National Heart, Lung, and Blood Institute established a multicenter trial, the Thrombolysis in Myocardial Infarction Trial (TIMI). Selecting the optimal thrombolytic agent to be compared against placebo was an early objective of this trial. Although substantial data are available regarding the use of streptokinase in AMI, only one investigation had previously assessed the ability of intravenous rt-PA to recanalize patients with AMI.13 Rt-PA was administered in varying doses (0.25 to 0.75 mg/kg) for varying durations (30 to 120 min). A dose of 0.75 mg/kg administered over 120 min to 15 patients resulted in the highest repertusion rate (87%). Modest declines in fibrinogen concentration were observed at 90 min after rt-PA therapy; reocclusion was observed in 20% of patients within 30 min after cessation of the rt-PA infusion.

Based on these initial observations, rt-PA appeared to be a potential activator for use in the TIMI trial. To be selected as the agent of choice, however, additional important questions needed to be addressed. First, would the effects of rt-PA be similar when administered as a single, fixed dosage regimen to a larger cohort of patients derived from multiple clinical sites with data analyzed by central laboratories? Second, could the incidence of reocclusion be decreased if the rt-PA infusion was prolonged and continuous anticoagulation with heparin was added? Third, would a greater dose of rt-PA have more pronounced effects on fibrinogenolysis? To address these questions, TIMI investigators performed an open-label trial of intravenous rt-PA. rt-PA was administered as a 3 hr infusion, 40 mg for the first hour and 20 mg for each of the 2 subsequent hours, to 47 patients with AMI. The results of this trial, reported herein, formed the basis for selecting this dosage regimen of rt-PA in a subsequent blinded, direct comparison of the safety and efficacy of intravenous rt-PA vs that of intravenous streptokinase.14

**Methods**

**Study population.** To be eligible for recruitment, patients had to satisfy the following inclusion criteria: (1) age less than 76 years, (2) chest pain characteristic of myocardial ischemia for at least 30 min, (3) electrocardiographic ST segment elevation of at least 0.1 mV in at least two leads reflecting a single myocardial region (Q waves were not a contraindication), (4) elapsed time from onset of ischemic pain to recruitment less than 7 hr, and (5) angiographically documented obstruction (greater than 50% diameter reduction) of the coronary artery supplying the infarct zone. Patients were excluded for the following reasons: (1) shock despite vasopressor therapy, (2) agitation or lethargy such that informed consent could not be obtained, (3) child-bearing potential, (4) past or present bleeding disorder or significant gastrointestinal bleeding, (5) anticoagulation therapy, (6) left bundle branch block, (7) prostatic heart valve, (8) dilated cardiomyopathy, (9) other serious advanced illnesses, such as cancer, (10) uncontrolled hypertension (diastolic pressure greater than 120 mm Hg), (11) significant surgical procedure within last 2 weeks, (12) previous participation in this trial, (13) prolonged cardiopulmonary resuscitation within the last 2 weeks, (14) psychological or physical inability to participate, (15) cerebral vascular accident within the last 6 months, (16) previous coronary artery bypass surgery, or (17) severe trauma within the last 6 months.

**Study design.** After obtaining informed consent, patients meeting all eligibility criteria were taken to the cardiac catheterization laboratory. An intravenous bolus of heparin (100 units/kg USP) was administered after access to the systemic venous and arterial circulations was obtained. Left ventricular and systemic arterial pressures were recorded. Contrast left ventriculography was performed in the right anterior oblique projection. The coronary arterial system remote from the infarct zone was visualized first, followed by coronary cineangiographic examination of the vessel supplying the infarct zone. Angiographic projections were standardized among clinical sites. Patients not demonstrating significant obstruction (less than 50% reduction in luminal diameter) of the coronary artery supplying the infarct zone did not receive rt-PA. For those patients with significant obstruction 200 μg nitroglycerin was injected selectively into the infarct-related artery. If obstruction persisted, rt-PA was infused intravenously at a dosage of 40 mg/hr for 1 hr followed by 20 mg/hr for 2 hr (total dose 80 mg over 3 hr). Coronary cineangiography of the infarct-related artery was repeated at 10, 20, 30, 45, 60, 75, and 90 min after the initiation of intravenous rt-PA. Immediately before the infusion of rt-PA and after 90 min of therapy (50 mg rt-PA) orthogonal coronary cineangiograms of the infarct-related artery were obtained to permit quantitative analysis of the degree of narrowing of the coronary artery. One hour after the initiation of rt-PA therapy, a continuous infusion of heparin was begun at a dose of 1000 units/hr.

After the 90 min coronary cineangiogram, patients were transported to the coronary care unit. Indwelling vascular sheaths were secured for removal the following day when the dose of heparin was adjusted such that partial thromboplastin time values approximated twice control. Intravenous heparin infusion was continued for 8 to 10 days, until repeat cardiac catheterization with contrast left ventriculography and coronary cineangiography was performed. After this catheterization, patients received aspirin and dipyridamole orally. If patients demonstrated recurrent ischemia or infarction after rt-PA therapy, revascularization was performed if clinically warranted.

**Methods of data analysis.** Coronary cineangiograms were

---

Vol. 73, No. 2, February 1986

339
assessed by the radiographic core laboratory. Qualitative analysis of the coronary cineangiograms included classification of the degree of perfusion of the infarct-related artery. The following grading system was used: grade 0, no perfusion (absence of contrast beyond the point of occlusion); grade 1, penetration of the thrombus with minimal perfusion (contrast material passes beyond the area of obstruction but fails to opacify the distal coronary bed and is not cleared during the course of the cine run); grade 2, partial perfusion (the contrast material passes through the obstruction and opacifies the coronary bed distal to the obstruction and the rate of entry of contrast into the distal vessel and its clearance are slower than that of nonstenosed vessels); grade 3, complete perfusion (contrast material promptly enters the coronary artery distal to the obstruction and clears at a rate similar to that in nonstenosed coronary vessels).

Based on the grading system, total coronary occlusion was considered to be present when perfusion was grade 0 or grade 1. Reperfusion of a totally occluded coronary artery was defined as an improvement to grade 2 or grade 3. Additional quantitative analysis of the obstruction in the infarct-related artery included, when technically possible, measurement of percent diameter reduction with the use of a computerized edge-detection technique. Measurements were made before treatment, at 90 min, and during the second catheterization procedure. Left ventricular cineangiograms were also analyzed by the radiographic core laboratory. Projected cine images were traced and digitized. End-diastolic and end-systolic volumes were determined and ejection fraction was calculated.

Statistical design of the study and data collection and management and analysis of results were performed by the data coordinating center. rt-PA was supplied by Genentech Laboratories. rt-PA was packaged, labeled, and shipped to clinical centers by the drug distribution center. A coagulation core laboratory was established to assess the changes in plasma levels of fibrinogen, plasminogen, and fibrinogen degradation products. Blood samples for these measurements were collected before, immediately after, and 24 hr after the infusion of rt-PA. Because of the presence of heparin in the blood samples, fibrinogen levels were measured by the method of Martinez and Berry in citrated plasma prepared from blood collected into tubes containing 250 μl/ml of apotinin (Trasylo1, FBA Pharmaceuticals, New York). Plasma plasminogen activity was measured in citrated plasma by the method of Friberger and Knox with the use of a chromogenic substrate, S-2251 (Kabi Diagnostica, Stockholm, Sweden). The results are expressed as percent of activity in relation to that in pooled normal plasma taken as 100%. The levels of fibrinogen degradation products were measured in serum harvested from blood (2 ml) collected into tubes containing thrombin (20 NIH units), soybean trypsin inhibitor (3670 NF units), and protamine sulfate (50 μg, Eli Lilly Company, Indianapolis). The Thrombo-Welcotest method was employed using latex particles coated with antibodies against fibrinogen fragments D and E (Wellcome Diagnostics, Temple Hill, Dartford, England).

All deaths and episodes of significant bleeding were reviewed by a mortality and morbidity committee. Bleeding episodes were reviewed if they were associated with any of the following: (1) a reduction in heparin dosage, (2) a decline in hemoglobin of 3 g/dl, (3) transfusion of blood cells, clotting factors, or platelets, (4) intracranial or gastrointestinal bleeding, or (5) the administration of drugs to reverse thrombolytic or anticoagulant effects. After review, bleeding episodes were classified as major, minor, or not significant. Bleeding was judged to be major if hemoglobin declined more than 5 g/dl or if bleeding was intracranial. Bleeding episodes were considered to be minor if blood loss (1) was observed and hemoglobin declined more than 3 but less than 5 g/dl or (2) was unobserved and hemoglobin declined 4 g/dl or more. Less severe episodes of bleeding were classified as not significant.

Statistical methods. Statistical analysis of comparisons with respect to stenosis and coagulation were performed by paired t test. Comparison of proportions was done by Fisher’s exact test.

Results

Fifty-one eligible patients consented to participate in this trial. Four did not receive rt-PA because a catheterization lab was not available (n = 2) or less than a 50% stenosis was observed in the infarct-related artery (n = 2). Thus, 47 patients with AMI received intravenous rt-PA. Thirty-two of the patients were men. The age ranged from 34 to 74, with a mean age of 57 years. The infarct-related artery was the left anterior descending in 25 patients (53%), the right coronary in 20 patients (43%), and the left circumflex in two patients (4%). No patient had myocardial infarction attributed to left main coronary occlusion. Nineteen patients (40%) had single-vessel disease. The elapsed time from the onset of symptoms to the initiation of thrombolytic therapy ranged from 66 to 477, with the mean of 289 minutes. Left ventricular ejection fraction ranged from 21% to 79%; the value for the group was 47.6 ± 12.5% (mean ± SD).

Thirty-eight patients (81%) had total occlusion of the infarct-related artery at the time of the initial angiogram (figure 1). After intracoronary nitroglycerin, one of these patients demonstrated reperfusion and thus 37 patients had total occlusion at the outset of rt-PA therapy. During the 90 min of angiographic observation, while rt-PA was being infused, 29 of these patients (78%) demonstrated reperfusion. Reperfusion was transient in four of these patients who developed reoclusion during the period of observation. Thus, at the final 90 min angiogram, reperfusion during rt-PA therapy was observed in 25 (68%) of the 37 patients who presented with total coronary occlusion. The degree of stenosis in the reperfused arteries ranged from 69% to 93% and averaged 84 ± 7%. The elapsed time from the initiation of rt-PA therapy to reperfusion ranged from 10 to 90 and averaged 40 ± 25 min, with a median time of 30 min.

If patients with total occlusion were alternatively defined as those with grade 0 perfusion, reperfusion rates were similar to those described above. Hence, of the 27 patients who exhibited grade 0 perfusion after receiving intracoronary nitroglycerin, 20 (74%) demonstrated reperfusion during the period of observation, with 18 (67%) remaining grade 2 or 3 at 90 min.

Ten patients demonstrated subtotal occlusion of the infarct-related coronary artery before rt-PA therapy. The degree of narrowing ranged from 84% to 99%,
PATIENTS WITH AMI TREATED WITH rt-PA

TOTAL OCCLUSION

YES

NO

IC NTG

1

37

10

ANY REPERFUSION

YES

NO

90 MIN STATUS

25

12

FIGURE 1. Initial angiographic results in patients with AMI treated with rt-PA.

with a mean of 89 ± 5%. Before therapy, perfusion was grade 2 in seven patients and grade 3 in three. At 90 min of rt-PA therapy, two patients with grade 2 perfusion advanced to grade 3. No patient who presented with grade 3 perfusion regressed to grade 2 or developed total occlusion. For the group of patients with subtotal occlusion, the mean value for percent stenosis at 90 min ranged from 65% to 94%, with a mean of 80 ± 9%, a value significantly less (p < .01) than that before rt-PA therapy.

Thirty-six patients underwent follow-up coronary cineangiography from 1 to 16 days (mean 9.5), after intravenous rt-PA therapy for AMI (figure 2). Eleven patients did not undergo a subsequent catheterization because of intercurrent coronary artery bypass surgery (n = 3), death (n = 4), patient refusal (n = 2), a bleeding complication (n = 1), or proximal left coronary dissection at the time of the initial procedure (n = 1 with uneventful hospital course). In 33 patients, the follow-up catheterization was done just before hospital discharge. In the other three, catheterization was done earlier (1 to 2 days after rt-PA therapy) because of recurrent ischemia. Of the 25 patients who had initially presented with total occlusion and experienced reperfusion at 90 min, 21 underwent follow-up angiography. The infarct-related artery demonstrated sustained perfusion in 14 or two-thirds of this subset. In 12 patients reperfusion was not demonstrated at 90 minutes. Six of these patients underwent follow-up angiography. Late reperfusion was observed in four or two thirds of those who were studied. Thus, although a high proportion of patients presenting with total occlusion demonstrated reperfusion during rt-PA infusion, one-third of the reperfused patients who were restudied developed reocclusion during the period of anticoagulation with heparin. Of patients who did not demonstrate reperfusion during the initial catheterization, two-thirds did so later.

Of the 10 patients who had subtotal occlusion before receiving rt-PA therapy, follow-up angiography was obtained in nine. Sustained perfusion of the infarct artery was observed in eight or 89%. Each patient demonstrated grade 3 perfusion upon late catheterization. The degree of narrowing of the infarct-related artery was 73 ± 10%, a value significantly different than that observed at 90 min.

Paired (initial and follow-up) contrast left ventriculograms were available in 24 patients. The mean difference between the ejection fractions on the initial and follow-up ventriculograms was 0.0 ± 10.8%.

Significant bleeding was the most common complication; 21 bleeding episodes were observed in 15 of the 47 patients (32%, table 1). Bleeding was classified as major in seven patients and minor in eight. The catheterization site was the most common source of bleeding and was the primary bleeding site in 11 of 15 patients and in five of the seven patients in whom bleeding was considered major. The other primary bleeding sites were gastrointestinal (n = 2), other vascular puncture (n = 1), and unknown (n = 1). Ten patients required blood transfusions; three patients received one and seven two or more units of blood. Eight of these 10 patients had bleeding at the site of the initial catheterization, one had gastrointestinal bleeding, and in one the site of bleeding was undetectable. Transfusions were administered from 1 to 8 days after rt-PA therapy, with an average elapsed time from rt-PA to transfusion of 3 days. One patient required surgical
intervention to control hemorrhage from a brachial artery.

Twelve patients noted nausea and vomiting within 24 hr of receiving rt-PA. No patients experienced urticaria, fever, chills, seizures, or an anaphylactic reaction within 24 hr.

Twenty patients developed recurrent ischemic pain. In seven of these patients (15% of treated patients), ischemic pain was associated with clinical evidence of reinfarction. Reinfarction occurred 1 day after entry in two patients, at 2 days in two, on day 7 in one, and on day 8 in two. Five of these seven patients had initially presented with total occlusion of the infarct-related artery and had demonstrated reperfusion at 90 min of rt-PA therapy. Hence, the prevalence of reinfarction among patients presenting with total occlusion who demonstrated reperfusion was 20% (5/25). Reinfarction occurred in one patient who presented with a subtotal occlusion and in one who presented with total occlusion and failed to reperfuse at 90 min. Coronary cineangiography was performed in three patients at the time of reinfarction; reocclusion of the infarct-related artery was noted in each.

Six patients underwent coronary bypass surgery. Three of these patients presented with total occlusion and demonstrated reperfusion at 90 min, two initially had total occlusion with no reperfusion at 90 min, and one entered the study with subtotal occlusion. Six patients underwent coronary angioplasty, two of whom also required bypass surgery. Four of the six presented with total occlusion and reperfused, one failed to reperfuse, and one presented with subtotal occlusion.

Six patients (13%) died during hospitalization (table 2). Each of these patients presented with total occlusion. Reperfusion at 90 min was noted in two of these patients. Death occurred from 0 to 17 days after therapy.

Determinations of fibrinogen, fibrin(ogen) degradation product, and plasminogen concentrations before, immediately after, and 24 hr after rt-PA therapy are displayed in table 3. Before therapy, the mean values were normal. At 5 min after therapy, a significant

TABLE 1
Episodes of bleeding after rt-PA, cardiac catheterization, and anticoagulation with heparin

<table>
<thead>
<tr>
<th>Site of bleeding</th>
<th>Total episodes of bleeding</th>
<th>Primary site of bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheterization</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Other vascular puncture</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>15</td>
</tr>
</tbody>
</table>

FIGURE 2. Angiographic results in rt-PA-treated patients undergoing both initial and follow-up coronary angiography. IRA = infarct-related artery.
THERAPY AND PREVENTION—CORONARY THROMBOLYSIS

TABLE 2
In-hospital deaths after intravenous rt-PA

<table>
<thead>
<tr>
<th>Patient ID No.</th>
<th>Days from treatment to death</th>
<th>Cause of death</th>
<th>Mechanism(s) of death</th>
<th>CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td>027073</td>
<td>3</td>
<td>QMI</td>
<td>Pump failure and arrhythmia</td>
<td>No</td>
</tr>
<tr>
<td>047121</td>
<td>0</td>
<td>QMI</td>
<td>Ventricular rupture</td>
<td>No</td>
</tr>
<tr>
<td>047252</td>
<td>0</td>
<td>NMI</td>
<td>Pump failure</td>
<td>No</td>
</tr>
<tr>
<td>067075</td>
<td>1</td>
<td>QMI</td>
<td>Pump failure and arrhythmia</td>
<td>No</td>
</tr>
<tr>
<td>097110</td>
<td>17</td>
<td>QMI</td>
<td>Pump failure</td>
<td>Yes</td>
</tr>
<tr>
<td>097136</td>
<td>2</td>
<td>QMI</td>
<td>Perioperative complications</td>
<td>Yes</td>
</tr>
</tbody>
</table>

QMI = qualifying myocardial infarction; NMI = new myocardial infarction; CABG = coronary artery bypass surgery.

A decline (-29 ± 16%) was observed in fibrinogen and plasminogen (-59 ± 18%) concentrations while fibrinogen degradation products rose. In no patient did the fibrinogen levels decline to less than 140 mg/dl. At 24 hr after intravenous rt-PA, values of fibrinogen and plasminogen increased, but were still significantly different from baseline values. At 24 hr, the concentration of fibrinogen degradation products was not different than that at baseline.

Discussion

The objective of this trial was to assess the efficacy and safety of a new thrombolytic activator, rt-PA, administered as a 3 hr, 80 mg continuous infusion. Although rt-PA was given intravenously, each patient underwent cardiac catheterization, including coronary cineangiography, before and during the rt-PA infusion. Coronary cineangiographic examinations provided: (1) confirmation of significant obstructive coronary artery disease and identification of the infarct-related artery, (2) a determination of whether the infarct-related artery was either totally or subtotaly occluded, and (3) an objective and accurate means of determining reperfusion.

The primary end point in this investigation was reperfusion of the infarct-related artery in patients who presented with total occlusion. It should be noted that the 90 min end point reflects the results of 50 mg of rt-PA therapy. The rt-PA infusion was continued beyond the primary angiographic end point for an additional 90 min in the hope that this would reduce the likelihood of subsequent reocclusion. Additional measures used to maintain patency of the reperfused infarct-related artery included anticoagulation with intravenous heparin for 8 to 10 days, and then oral aspirin and dipyridamole.

Patients recruited for this trial were mostly men of middle age. The infarct-related artery was usually either the right or the left anterior descending coronary artery. The inclusion requirement of electrocardiographic ST segment elevation may have created a bias against patients with myocardial infarction due to left circumflex disease. Slightly less than half the patients had single-vessel disease. Even though a complete cardiac catheterization was performed before therapy, most patients received rt-PA in less than 5 hr from the onset of symptoms.

Since a prior report suggested that coronary vasoconstrictor responsive to nitroglycerin may be responsible for coronary occlusion in patients with AMI, each patient received intracoronary nitroglycerin followed by repeat coronary cineangiography before receiving rt-PA. Reperfusion after intracoronary nitroglycerin was rare (3%), suggesting that intracoronary nitroglycerin has little value in relieving coronary occlusion in patients with AMI.

Intravenous infusion of rt-PA, administered as a uniform fixed dosage, restored coronary blood flow in a high proportion of patients with AMI. Thus, of 37 patients with total coronary occlusion, 78% experienced reperfusion during the 90 min observation period. Reperfusion was transient in four patients; hence, sustained reperfusion at the 90 min end point was observed in 68% of those patients presenting with total occlusion. Furthermore, in the majority of patients, reperfusion occurred less than 45 min from the initi-
ation of intravenous rt-PA therapy. These observations may be compared with those of Collen et al. In their study, several dosages and infusion rates of rt-PA were assessed. Their reported reperfusion rate of 75% for a dosage of 0.5 mg/kg of rt-PA over 30 to 60 min is similar to that reported in the present investigation. Moreover, the reperfusion rates in both intravenous rt-PA trials exceed those of 31% to 52% observed in angiographically monitored trials of intravenous streptokinase. In fact, the incidence of reperfusion among rt-PA–treated patients is more similar to that of 60% to 79% reported with intracoronary streptokinase.

A decrease in the severity of coronary obstruction during the infusion of rt-PA was also observed in patients presenting with subtotal occlusion of the infarct-related artery. Thus, the extent of coronary narrowing declined significantly from 89 ± 5% to 79 ± 9% during rt-PA therapy. Moreover, improvement was also observed in the degree of distal coronary perfusion.

Follow-up angiographic data, available in 77% of initially treated patients, indicated that one-third of patients who initially experienced reperfusion developed reocclusion. The clinical course of patients who developed reocclusion supports the concept that early restoration of blood flow in the infarct-related artery results in myocardial salvage. Hence, five of the six patients who developed reocclusion experienced recurrence of ischemic pain. Two of these patients underwent either emergency coronary angioplasty or bypass surgery; the three remaining patients demonstrated infarctation.

The 33% reocclusion rate observed after intravenous rt-PA in this trial exceeds that reported after intravenous (10% to 24%) or intracoronary (17%) streptokinase. Since intravenous streptokinase causes a prolonged systemic “lytic state” associated with depletion of clotting factors and reduction in blood viscosity, coronary reocclusion may be less common after streptokinase than after agents demonstrating fibrin specificity. Results of the randomized phase I TIMI trial, which compared rt-PA and streptokinase, will address this issue. On the other hand, factors unrelated to characteristics of thrombolytic agents, such as the severity of the underlying atherosclerotic coronary stenosis, may be of greater importance in contributing to reocclusion.

Use of coronary angioplasty subsequent to thrombolytic therapy to further relieve coronary obstruction needs to be considered and will be evaluated in forthcoming phases of the TIMI trial.

In contrast to patients with totally occluded infarct-related arteries, patients who presented with subtotal occlusion rarely experienced subsequent closure. Thus, of nine such patients who underwent follow-up angiography, only one demonstrated total occlusion. Moreover, distal perfusion was additionally improved in those patients with impaired perfusion within 90 min.

For the most part, the intravenous infusion of rt-PA was well tolerated. No reactions indicating hypersensitivity were noted. The nausea and vomiting that did occur could have been due to rt-PA, the AMI, or to concomitant therapy such as the opiates that are employed for analgesia.

After treatment with rt-PA, significant decreases were noted in plasma levels of fibrinogen (−29%) and plasminogen (−59%) that were associated with an increase in fibrinogen degradation products. These findings indicate that, at the dosage used, rt-PA induced some degree of systemic fibrinogenolysis. The magnitude of this effect, however, appears to be less than that reported with streptokinase.

Bleeding was the most common complication in this trial; most of the episodes of bleeding were classified as major and required blood transfusion. However, it must be noted that each patient was fully anticoagulated with heparin immediately before and after the administration of rt-PA and each patient underwent an invasive vascular procedure immediately before the administration of rt-PA. In all but two instances of major bleeding, the primary source of bleeding was at the vascular entry site used for the catheterization procedure. Thus, a significant proportion of patients who receive rt-PA and heparin may demonstrate bleeding if cardiac catheterization is performed. Since serious episodes of bleeding at sites other than that of catheterization were infrequent (two in 47 patients), and since the observed declines in fibrinogen were not extreme in magnitude, if rt-PA were administered alone and without initial catheterization, one would expect that instances of major bleeding would be infrequent.

Recurrent myocardial infarction was observed in 15% (7/47) of the patients in this trial. With the exception of two patients, reinfarction occurred among patients who initially presented with total occlusion and demonstrated reperfusion at 90 min. The occurrence of reinfarction was distributed over the week after the qualifying AMI. Of patients who might have been expected to benefit the most from thrombolytic therapy, i.e., those with total occlusion and early reperfusion, the incidence of subsequent reinfarction was 20%. Initial angiographic examinations indicated that reinfarction was highly predictive of reocclusion of the
infarct-related artery. Thus, although a brief intravenous infusion of rt-PA is capable of promoting reperfusion in a high proportion of patients with AMI and total coronary obstruction, for some patients, efforts in addition to anticoagulation with heparin will be required to sustain this salutary effect.

We acknowledge the assistance of Christine Abatiello in the preparation of this manuscript.

Appendix
Clinical centers
Baylor College of Medicine, Houston, Principal Investigator: Robert Roberts, M.D.; Co-investigators: Phyllis Bienvenue, R.N., I. Kenneth Inouye, M.D., Jerry C. Luck, M.D., Alfredo Montero, M.D., Craig Pratt, M.D., Albert Raizner, M.D., Mary Kay VanderMolen, R.N., Mario S. Verani, M.D., James B. Young, M.D.

Boston University Medical Center, Boston, Principal Investigator: Thomas J. Ryan, M.D.; Co-investigators: Carl S. Apstein, M.D., David P. Faxon, M.D., Alice K. Jacobs, M.D., Mirle A. Kellett, M.D., Carolyn H. McCabe, R.N., Timothy A. Sanborn, M.D., James R. Wilentz, M.D.

Brown University, Providence, RI, Principal Investigator: David O. Williams, M.D.; Co-investigators: Robert J. Capone, M.D., Thomas M. Drew, M.D., Diane L. Hardink, R.N., John MCB. Hodgson, M.D., Gregory Macina, M.D., Raymond S. Riley, M.D., Nicholas A. Ruocco, M.D., Harvey J. White, M.D.

Columbia University, New York, Principal Investigator: Eric Powers, M.D.; Co-investigators: Andrew Berke, M.D., Edith Escala, R.N., Kenneth D. Friedman, M.D., Lynne Johnson, M.D., Mark Krischenbaum, M.D., John Owne, M.D., Allen B. Nichols, M.D., Dennis S. Reinson, M.D., Allan Schwartz, M.D., Rita Watson, M.D.

Cornell Medical Center, New York, Principal Investigator: Jeffrey S. Borer, M.D.; Co-investigators: David H. Miller, M.D., Theodore L. Schreiber, M.D., Denise A. Silvasi, R.N.


Harvard University, Boston, Principal Investigator: John E. Markis, M.D.; Co-investigators: James Alderman, M.D., Cynthia Brewer, R.N., Raymond G. McKay, M.D.

Mayo Foundation, Rochester, MN, Principal Investigator: James H. Chesebro, M.D.; Co-investigators: Dennis R. Bresnahan, M.D., Bernard J. Gersh, M.D., LaVon Hammes, R.N., Laurie Meyers, L.P.N., Fletcher A. Miller, M.D., Michael B. Mock, M.D., Hugh C. Smith, M.D.

Montefiore Medical Center, Albert Einstein College of Medicine, New York, Principal Investigator: Hiltrud S. Mueller, M.D.; Co-investigators: Anne Dyer, R.N., Garet Gordon, M.D., Mark A. Greenberg, M.D., Richard Grose, M.D., Richard Steingart, M.D.

University of Massachusetts, Worcester, MA, Principal Investigator: James E. Dalen, M.D.; Co-investigators: Joseph S. Alpert, M.D., Steven P. Ball, R.N., Joseph R. Benotti, M.D., Paul Doherty, M.D., Joel M. Gore, M.D., Ira S. Ockene, M.D., James F. Rippe, M.D., Bonnie H. Weiner, M.D.

University of Texas, Dallas, Principal Investigator: James Willerson, M.D.; Co-investigators: L. David Hillis, M.D., George Revtyak, M.D., Blair Toates, R.N., Michael Winniford, M.D.

Washington University, St. Louis, Principal Investigator: Philip A. Ludbrook, M.B., B.S.; Co-investigators: Allan S. Jaffe, M.D., Peter B. Kurnik, M.D., Nancy A. Ricciotti, R.N., M.S.N., Burton E. Sobel, M.D., James J. Spadaro, M.D., Allan J. Tiefenbrunn, M.D.

Yale University, New Haven, CT, Principal Investigator: Charles K. Francis, M.D.; Co-investigators: Henry S. Cabin, M.D., Lawrence S. Cohen, M.D., Caroline Piselli, R.N., Daniel Wohlgenernt, M.D.

Harvard University, Boston, Study Chairman: Eugene Braunwald, M.D.

Coordinating center
Maryland Medical Research Institute, Inc., Baltimore, Principal Investigator: Genell L. Knatterud, Ph.D.; Co-investigators: Paul L. Caner, Ph.D., Sandra Forman, M.D., Dorothy T. Harris, William F. Krol, Ph.D., Michael L. Terrin, M.D., M.P.H., Patricia C. Wilkins, B.S.

Radiographic core laboratory

Radionuclide core laboratory
Yale University, New Haven, CT, Principal Investigator: Barry Zaret, M.D.; Co-investigator: Frans Wackers, M.D.

Coagulation core laboratory
Temple University, Philadelphia, Principal Investigator: A. Koneti Rao, M.D.; Co-investigators: Robert W. Colman, M.D., Andrei Z. Budzynski, Ph.D.

Pathology core laboratory
National Institutes of Health Clinical Center, Bethesda, Principal Investigator: William C. Roberts, M.D.; Co-investigator: Deborah Barbour, M.D.

National Heart, Lung, and Blood Institute program office
National Institutes of Health, Bethesda, Principal Investigator: Eugene R. Passamani, M.D.; Co-investigators: Kent R. Bailey, Ph.D., Patrice M. Desvigne-Nickens, M.D., Thomas L. Robertson, M.D., Janet T. Wirtes, Ph.D.

Drug distribution center
Cooperative Studies Program, Clinical Research Pharmacy Coordinating Center, Albuquerque, Principal Investigator: Michael John Kovach, R.Ph.; Co-investigator: Clair M. Haaken son, R.Ph., M.S.

Mortality and morbidity classification committee
Chairperson: James Chesebro, M.D.; Members: Andrew Berke, M.D., Henry Cabin, M.D., Patrice Desvigne-Nickens, M.D., Joel Gore, M.D., David Hillis, M.D., Craig Pratt, M.D., Michael Terrin, M.D.

References
Intravenous recombinant tissue-type plasminogen activator in patients with acute myocardial infarction: a report from the NHLBI thrombolysis in myocardial infarction trial.

D O Williams, J Borer, E Braunwald, J H Chesebro, L S Cohen, J Dalen, H T Dodge, C K Francis, G Knatterud and P Ludbrook

_Circulation_. 1986;73:338-346
doi: 10.1161/01.CIR.73.2.338

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/73/2/338

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/