Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase*

Clinical findings through hospital discharge

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ABSTRACT Intravenous administration of 80 mg of recombinant tissue plasminogen activator (rt-PA, 40, 20, and 20 mg in successive hours) and streptokinase (SK, 1.5 million units over 1 hr) was compared in a double-blind, randomized trial in 290 patients with evolving acute myocardial infarction. These patients entered the trial within 7 hr of the onset of symptoms and underwent baseline coronary arteriography before thrombolytic therapy was instituted. Ninety minutes after the start of thrombolytic therapy, occluded infarct-related arteries had opened in 62% of 113 patients in the rt-PA and 31% of 119 patients in the SK group (p<.001). Twice as many occluded infarct-related arteries opened after rt-PA compared with SK at the time of each of seven angiograms obtained during the first 90 min after commencing thrombolytic therapy. Regardless of the time from onset of symptoms to treatment, more arteries were opened after rt-PA than SK. The reduction in circulating fibrinogen and plasminogen and the increase in circulating fibrin split products at 3 and 24 hr were significantly less in patients treated with rt-PA than in those treated with SK (p<.001). The occurrence of bleeding events, administration of blood transfusions, and reocclusion of the infarct-related artery was comparable in the two groups. Thus, in patients with acute myocardial infarction, rt-PA elicited reperfusion in twice as many occluded infarct-related arteries as compared with SK at each of seven serial observations during the first 90 min after onset of treatment.


CORONARY ARTERIOGRAPHY and bypass operations early after onset of acute myocardial infarction demonstrate complete thrombotic coronary occlusion in approximately 80% of patients with prolonged chest pain and ST segment elevation.1,2 Acute myocardial infarction causes more than a half million deaths and results in over 700,000 hospitalizations each year in the United States alone.3 Thrombolytic therapy results in recanalization of totally occluded arteries in 25% to 75% of patients, depending on the drug, dosage, and route of administration.3-11 Early reperfusion is necessary for salvage of myocardium12,13 and reduction of mortality.14 Salvage of myocardium can be achieved in a high proportion of patients treated within 1 to 2 hr.12,13 Several relatively fibrin-specific thrombolytic agents are being developed.15-18 Tissue-type plasminogen activator is a human protein with a circulating half-life of several minutes that is available in large quantities for pharmacologic use through recombinant technology.15,16

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The National Heart, Lung, and Blood Institute established the TIMI Study Group in 1983. The group includes 13 clinical sites, a data coordinating center, and core laboratories for angiographic, radionuclear, electrocardiographic, coagulation, and pathologic studies. The results of two TIMI open-label studies, preliminary results from TIMI Phase I, and two European studies of similar design but without pretreatment angiography have been published.9–11,19–21 This report presents the core laboratory angiographic and central review of clinical results for TIMI Phase I. The thrombolytic efficacy and side effects of intravenous recombinant tissue-type plasminogen activator (rt-PA) were compared with those of intravenous streptokinase (SK) in patients with acute transmural myocardial infarction and occlusion of the infarct-related artery documented at pretreatment coronary arteriography.

Methods

Patients were assigned randomly to rt-PA or SK from August 20, 1984, to February 5, 1985, when the National Heart, Lung, and Blood Institute stopped Phase I on the recommendation of the TIMI Policy Advisory and Data Monitoring Board because of substantial statistically significant differences in recanalization rates between treatment groups.19

Patient selection. Eligible patients had at least 30 min of chest pain considered to be caused by myocardial ischemia and ST segment elevation (0.1 mV) in at least two contiguous electrocardiographic leads. Patients were excluded for any of the following reasons: lack of informed consent, more than 7 hr time elapsed since the onset of chest pain, age above 75 years, uncontrolled hypertension (>200/120 mm Hg), shock (systolic pressure <80 mm Hg), unresponsiveness to volume expansion and intravenous vasopressors, cerebrovascular event or severe trauma within 6 months, hemorrhagic diathesis or active hemorrhage, recent treatment with streptokinase or streptococcal infection, left bundle branch block, prior cardiac surgery, prolonged cardiopulmonary resuscitation or major surgical procedure within 2 weeks, dilated cardiomyopathy, oral anticoagulant therapy, psychological or physical inability to participate, childbearing potential, or known advanced illness.

Procedures. Eligible patients were given lidocaine, a bolus of 1 to 1.5 mg/kg followed by an infusion at 2 to 4 mg/min (continued for a minimum of 24 hr), and were taken to the cardiac catheterization laboratory where they were given intravenous heparin (5000 USP U) after placement of an arterial sheath and acquisition of baseline coagulation laboratory studies. Left ventriculography was performed in the right anterior oblique projection. Coronary arteriography was then performed with the sequence of right and left coronary arteries determined from the electrocardiogram and left ventriculogram. Repeat arteriography of the infarct-related artery was performed after administration of intracoronary nitroglycerin (200 μg). Patients with less than a 50% reduction in the luminal diameter of the infarct-related artery after intracoronary nitroglycerin were not given thrombolytic therapy. Repeated opacification of the infarct-related artery was performed 10, 20, 30, 45, 60, 75, and 90 min after the onset of the intravenous infusion of the assigned thrombolytic agent. Just before and 90 min after commencement of the infusion of the thrombolytic agent, orthogonal arteriographic views of the infarct-related artery were obtained for quantitative analysis of the coronary lesion. Repeat left ventriculography and coronary arteriography of the infarct-related artery were performed (in the same views as in the initial studies) before hospital discharge at a mean of 10 days after admission (range 5 to 25 days).

Restoration of arterial patency was evaluated at each clinical site and at the central radiographic laboratory in a blinded fashion with respect to treatment assignment and according to rigorous predetermined definitions of reperfusion (table 1). Grade 0 or 1 signified a closed artery, and grade 2 or 3 an open artery with complete perfusion within at least three cardiac cycles. In the preliminary communication the angiographic assessments from each individual center were utilized19; core radiographic laboratory assessments are reported in this article. The core laboratory assessment involved a consensus reading by three coronary arteriographers who were blinded to clinical features of patients and treatment assessment. Ninety-seven percent of the gradings of the open or closed status of the artery by clinical sites were in agreement with those in the core laboratory. Determination of the baseline severity of coronary artery disease was assessed at the core laboratory by visual assessment of the reduction in luminal diameter (percent stenosis) of each coronary artery and its major branches. Quantitative angiography of the infarct-related artery was used to assess the reduction in luminal diameter (percent stenosis) and minimum diameter (in mm) of the infarct-related artery at baseline before therapy, at 90 min after commencing thrombolytic therapy, and at hospital discharge, by use of methods described previously.22–24

The left ventricular ejection fraction was determined from the ventriculogram by the area-length method of Dodge et al.25 Regional endocardial wall motion will be reported elsewhere.26

Coronary care. Coronary care was provided within usual practice and explicit TIMI protocol guidelines. Intravenous infusion of heparin was begun 3 hr after the initial bolus at 1000 USP U per hour and adjusted thereafter to maintain the activated partial thromboplastin time between 1.5 and 2 times the upper limit of normal. Heparin was continued in the absence of serious hemorrhage until 8 to 10 days after the onset of therapy when the predischarge catheterization was performed. Care of the arterial puncture site included removal of the arterial sheath 24 to 48 hr after placement and during a reduction of the dose of heparin.

Table 1

<table>
<thead>
<tr>
<th>Definition</th>
<th>TIMI Phase I</th>
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<tbody>
<tr>
<td>Grade 0 (no perfusion)</td>
<td>There is no antegrade flow beyond the point of occlusion.</td>
</tr>
<tr>
<td>Grade 1 (penetration without perfusion)</td>
<td>The contrast material passes beyond the area of obstruction but &quot;hangs up&quot; and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence.</td>
</tr>
<tr>
<td>Grade 2 (partial perfusion)</td>
<td>The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel — e.g., the opposite coronary artery or the coronary bed proximal to the obstruction.</td>
</tr>
<tr>
<td>Grade 3 (complete perfusion)</td>
<td>Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery.</td>
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</table>
Just before heparin was stopped, 75 mg dipyridamole and 325 mg aspirin, both three times daily, were begun and continued for at least 6 months. Conventional antianginal therapy was administered as needed. Patients were discharged on a β-adrenergic-blocking drug (64% of rt-PA and 61% of SK patients) unless contraindicated (or judged unnecessary after a revascularization procedure) at a dosage selected to maintain the resting heart rate at 60 beats/min or less and were followed by clinic visits at 6 weeks and 6 months and by telephone interviews every 6 months thereafter.

Randomization to thrombolytic therapy. The TIMI Data Coordinating Center generated envelopes for randomization separately for each clinical site and monitored the randomization process by telephone interview 24 hr after initiation of treatment. After informed consent was obtained, the next in the series of numbered envelopes was opened and a drug kit number provided. Each patient was randomly assigned to receive simultaneously either an infusion of 1.5 million units of SK over 1 hr and an infusion of rt-PA placebo over 3 hr or an infusion of rt-PA over 3 hr (40, 20, and 20 mg in the first, second, and third hours) and an infusion of SK placebo over 1 hr. Both regimens were selected to produce optimal opportunities for rapid and sustained lysis. SK and its placebo were supplied by Hoechst-Roussel Pharmaceuticals and Kabi Vitrum A.B.; rt-PA (GI1021) and its placebo were supplied by Genentech, Inc.

End points. The primary end point was the proportion of patients who had grade 2 or 3 reperfusion at 90 min among those who had grade 0 perfusion before treatment. Since grade 1 perfusion reflects ineffective myocardial perfusion, the same end point was sought among patients with grade 0 or 1 pretreatment perfusion.

Secondary end points included the proportion of patients with reperfusion at 30 and 60 min after initiation of thrombolytic therapy, the proportion of patients with grade 2 or 3 reperfusion at the predischARGE catheterization, the proportion of patients with successful reperfusion at 90 min who had reclosure at the predischARGE catheterization, the time to reperfusion after the start of thrombolytic therapy, and complications of therapy including hemorrhage, allergy, and arrhythmia. Clinical events such as recurrent ischemic pain, cardiac arrest, death, reinfarction, reocclusion, revascularization by coronary angioplasty or bypass operation, and heart failure were tabulated through hospital discharge or 21 days (whichever occurred first). The relationship between changes in global and regional left ventricular function and reperfusion, the effect of collateral blood flow on global and regional left ventricular function in patients with successful reperfusion, and the effect of the timing of successful reperfusion (from the onset of chest pain) on the change in global and regional left ventricular function were other secondary end points that are described elsewhere.

Coagulation tests. The Core Coagulation Laboratory measured plasma levels of fibrinogen, plasminogen, and fibrinogen degradation products in blood samples collected at baseline and at the following intervals after initiation of thrombolytic therapy: 185 min, 5 hr, 24 hr, and just before hospital discharge. Coagulation core laboratory methods are described fully elsewhere.

The Mortality and Morbidity Classification Committee reviewed case reports of all patients who received a blood transfusion, a drop in hemoglobin of 3.0 g/dl or more, or an observed blood loss, as described elsewhere. They classified the severity of hemorrhage, the primary and secondary sites, and whether it was induced by a procedure.

Hemorrhage was defined as “major” if there was a reduction of hemoglobin of 5 g/dl or more (or >15% in hematocrit) or any intracranial bleeding. Hemorrhage was classified as “minor” if there was an observed blood loss and a drop in hemoglobin of 3 to 5 g/dl (or in hematocrit from 10% to 15%) from study entry to the time of the lowest hemoglobin (hematocrit) and this was within 10 days; if there was spontaneous gross hematuria or hematemesis (>20 ml), even if the hemoglobin or hematocrit drop was less than 3 g or less than 10%, respectively; or if there was an unobserved loss 4 g/dl or more in hemoglobin or 12% or more in hematocrit. Blood loss attributable to revascularization or other surgical procedures was not classified as a TIMI hemorrhagic event.

Reinfarction was defined as two or more of the following: (1) recurrence of chest pain attributable to ischemia of 30 or more minutes duration and unresponsive to nitroglycerin, (2) new ST segment elevation (0.1 mV) in at least two contiguous electrocardiographic leads but in no more than seven leads or new Q waves, and (3) new plasma creatine kinase elevation (accompanied by the appearance of creatine kinase–MB isoenzymes) to 50% above the average of consecutive normal values or 50% above the previous value if the creatine kinase value had not returned to within the normal range.

Statistical evaluation. Because it was not the purpose of the study to test a statistical hypothesis concerning the relative efficacy of rt-PA and SK, traditional sample size calculations based on type I errors and power were not carried out. Instead, study size was based on the desired precision of the estimate of the difference in proportion of patients with the primary end point. The desired sample size in each of the two treatment groups was 136 patients with total occlusion of the infarct-related artery at time of initiation. This sample size was required to ensure that 90% confidence limits for observed difference in proportions of patients in the two treatment groups having the primary end point would have a half-length of no more than 10 percentage points. It was further assumed that approximately 20% of the eligible patients would have partial occlusion, yielding a total of 170 patients required in each treatment group.

An early stopping rule was established assuming two interim data reviews, the first after 50% and the second after 75% of the required number of patients had been treated and observed for the primary end point. The stopping rule was based on finding at an interim review a difference between rt-PA and SK so extreme that the probability of a complete reversal of trend leading to the opposite decision at the scheduled end of the trial was miniscule (i.e., less than .001).

Group differences in baseline characteristics were assessed by the two-sample t or chi-square test for continuous and dichotomous variables, respectively. Differences in coronary reopening were assessed by the two-sample test of proportions. All reported p values were two-sided and they were not adjusted for baseline differences or multiple testing. The multiple linear regression model was used to correct for modest baseline differences in variables related to reperfusion.

Results

Of 316 patients assigned randomly to thrombolytic therapy, 26 were not treated (14 rt-PA, 12 SK); eight patients (three assigned to rt-PA, five assigned to SK) had less than a 50% stenosis and were discharged alive. Technical difficulties that precluded completion of the protocol were encountered in six patients (four assigned to rt-PA, two assigned to SK); five of these patients were discharged alive, and one died 9 days after admission. Nine patients (six assigned to rt-PA, three assigned to SK) became sufficiently unstable to require other emergency therapy and withdrawal from
TABLE 2
Baseline characteristics

<table>
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<tr>
<th></th>
<th>Randomized patients</th>
<th>Treated patients</th>
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<tr>
<td></td>
<td>rt-PA</td>
<td>SK</td>
</tr>
<tr>
<td>No. of patients</td>
<td>157</td>
<td>159</td>
</tr>
<tr>
<td>Age&lt;65 (%)</td>
<td>78</td>
<td>72</td>
</tr>
<tr>
<td>Male (%)</td>
<td>80</td>
<td>79</td>
</tr>
<tr>
<td>MI diagnosis (%)</td>
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<tr>
<td>Confirmed</td>
<td>98</td>
<td>97</td>
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<tr>
<td>ECG consistent</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>CK-MB consistent</td>
<td>95</td>
<td>94</td>
</tr>
<tr>
<td>History (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Angina pectoris</td>
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<td>50</td>
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<tr>
<td>Stroke</td>
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<td>3</td>
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<tr>
<td>Hypertension</td>
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<td>51</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>13</td>
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<tr>
<td>Gastrointestinal disease</td>
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<td>9</td>
</tr>
<tr>
<td>Smoking status (%)</td>
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<tr>
<td>Current</td>
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<td>55</td>
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<tr>
<td>Exsmoker</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Hematocrit&lt;40% (%)</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;100 mm Hg (%)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Rales present (%)</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>S1 present (%)</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Treatment with (\beta)-blocker within 1 week (%)</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Location of ST elevation (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior</td>
<td>54</td>
<td>46</td>
</tr>
<tr>
<td>Anterior</td>
<td>45</td>
<td>52</td>
</tr>
<tr>
<td>Lateral</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

MI = myocardial infarction; RCA = right coronary artery; LAD = left anterior descending artery; LCx = left circumflex coronary artery; ER = emergency room.

\( ^a \)p < .05, compared with SK.

\( ^b \)Stenosis of 70% or more of lumen diameter of a major coronary artery or one of its major branches, based on core laboratory visual assessment of the artery before thrombolytic therapy.

\( ^c \)Median value parentheses.

This study before administration of the assigned thrombolytic agent; five died within 24 hr of admission, one died 5 days after admission, and three were discharged alive. Three patients (one assigned to rt-PA, two assigned to SK) were found ineligible before treatment was given. All were alive at discharge. These 26 patients are included among the randomly assigned patients in table 2.

**Baseline characteristics.** For the 157 and 159 patients assigned randomly to rt-PA and SK, respectively (table 2), the distributions of baseline characteristics were similar. Only the proportion of patients with a history of hypertension before entry was significantly greater in the rt-PA patients. The groups of treated patients were also very comparable except with regard to a history of hypertension before entry and the baseline ejection fraction (which was not available for patients who were not treated). The baseline ejection fraction was more often below 35% in patients treated with SK (p<.05).

Intracoronary nitroglycerin changed the perfusion grade from grade 0 to 2 in one patient in the rt-PA group and in two patients in the SK group and from grade 1 to 2 in three patients in the rt-PA group and in one patient in the SK group. It did not change perfusion from grade 0 or 1 to 3 in any patient. The perfusion grade after nitroglycerin was used as the baseline for thrombolytic therapy. Before treatment, the proportions of patients in each treatment group with perfusion grades 0, 1, 2, and 3 were similar (figure 1).
Reperfusion. Among patients with totally occluded (grade 0) infarct-related arteries, successful reperfusion (grades 2 or 3) at 90 min occurred in 56% (52/93) of those treated with rt-PA compared with 26% (27/103) of those treated with SK (p<.001; figures 2 and 3). Although in these patients with grade 0 at baseline, nine of 93 (10%) in the rt-PA and 14 of 104 (13%) in the SK group progressed to grade 1 reperfusion at 90 min, this was not considered achievement of reperfusion. An additional four patients receiving rt-PA and two receiving SK with grade 0 perfusion at baseline had transient grade 2 or 3 reperfusion within 90 min but reocclusion by 90 min. Thus, they were not considered to exhibit successful reperfusion.

Among patients with infarct-related arteries with grades 0 or 1 perfusion at baseline, successful reperfusion (grades 2 or 3) at 90 min occurred in 62% (70/113) of those treated with rt-PA compared with 31% (37/119) of those treated with SK (figures 2 and 3). The proportion of arteries (grades 0 or 1 at baseline) that were successfully recanalized (grades 2 or 3) at 60 min after the start of thrombolytic therapy was 48% (54/113) in the rt-PA and 23% (27/119) in the SK group (p<.001) and at 30 min after the start of thrombolytic therapy it was 24% (27/113) in the rt-PA and 8% (9/119) in the SK group (p<.001; figure 4, A). In patients in whom reperfusion was achieved, the mean time to reperfusion from the initiation of thrombolytic therapy in grade 0 or 1 arteries at baseline was 49 min (median 45) for those receiving rt-PA compared with 55 min (median 60) for those given SK (p = NS).

Infarct-related arteries in both groups that were grade 1 at baseline exhibited recanalization (grades 2 or 3) at 90 min in a high proportion (90% or 18/20 rt-PA group and 63% or 10/16 SK group; figure 3). Reocclusion within 90 min did not occur in any patient who had grade 1 perfusion at baseline.

The number of patients treated at each hourly interval or within 4 hr after onset of symptoms was similar in each group (table 3). The proportion of infarct-related arteries recanalized at each hourly interval from onset of symptoms to initiation of thrombolytic therapy was always greater for patients receiving rt-PA than for those given SK at each interval within and
FIGURE 3. Flow diagrams for the angiographic outcome of randomized patients in the rt-PA (A) and SK (B) groups. Numbers of patients are within the circles. The denominator used to calculate a percentage is in parentheses. Clinical events and their frequency are listed for each angiographic subgroup. One patient in each treatment group underwent predischarge angiography beyond 21 days after admission (at 25 days). ND = not done; HD = hospital discharge; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass graft operation; CHF = congestive heart failure.
beyond 4 hr for patients with grade 0 before treatment or grades 0 or 1 before treatment (table 3; figure 4). The proportion of arteries open after thrombolytic therapy with rt-PA was the same whether or not treatment was initiated within 4 hr of symptom onset. This was not the case after SK therapy; a much smaller proportion (approximately 50% less) of arteries were open if therapy was initiated 4 or more hours after symptom onset (table 3; figure 4). At the dosage of rt-PA used, a significantly greater proportion of patients with anterior infarction and occlusion of the left anterior descending coronary artery exhibited reperfusion compared with the proportion of patients with inferior infarction and involvement of the right or left circumflex coronary arteries (table 4) who exhibited reperfusion.

Perfusion grade 2 or 3 at 90 min was present in 70% (100/143) of all patients treated with rt-PA and in 43% (63/147; p<.001) of all patients treated with SK, inde-
TABLE 3
Reperfusion by treatment and time from symptom onset

<table>
<thead>
<tr>
<th>Hours from symptom onset to Rx</th>
<th>rt-PA No./total</th>
<th>SK No./total</th>
</tr>
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<tbody>
<tr>
<td>&lt;1</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>1-2</td>
<td>3/67</td>
<td>2/10</td>
</tr>
<tr>
<td>2-3</td>
<td>10/86</td>
<td>19/17</td>
</tr>
<tr>
<td>3-4</td>
<td>40/55</td>
<td>27/10</td>
</tr>
<tr>
<td>4-5</td>
<td>36/66</td>
<td>37/8</td>
</tr>
<tr>
<td>5-6</td>
<td>19/54</td>
<td>35/8</td>
</tr>
<tr>
<td>6-7</td>
<td>20/61</td>
<td>14/8</td>
</tr>
<tr>
<td>&gt;7</td>
<td>15/67</td>
<td>13/2</td>
</tr>
<tr>
<td>Total</td>
<td>143/70</td>
<td>147/37</td>
</tr>
</tbody>
</table>

Rx = treatment; BL = baseline; GR = grade.

Table 3 shows the reperfusion rate by treatment and time from symptom onset to treatment. The table indicates that the reperfusion rate for rt-PA is significantly higher than for SK, especially within the first 2 hours of symptom onset.

The proportion of patients with recanalization of the infarct-related artery did not differ with respect to locus (proximal, mid, or distal) of the coronary occlusion. Gender did not affect the incidence of reperfusion. Multiple linear regression analysis taking into account baseline distributions of patient characteristics before treatment did not affect the calculated occurrence of reperfusion.

Reocclusion. Sixty-two of the 70 patients in the rt-PA group with grades 0 or 1 perfusion at baseline and grades 2 or 3 at 90 min were restudied before hospital discharge; 24% or 15 of 62 exhibited reocclusion (the other eight patients were not restudied; figure 3, A). Twenty-nine of the 37 patients in the SK group with reperfusion (grade 0 or 1 at baseline to grade 2 or 3 at 90 min) were restudied before hospital discharge; 14% or four of 29 exhibited reocclusion (the other eight patients were not restudied; figure 3, B). If the episodes of reinfarction or death within 21 days are assumed to be attributable to reocclusion in patients who were not catheterized again at hospital discharge, the estimated reocclusion rate is 29% (20/70) in the rt-PA and 30% (11/37) in the SK group.

The proportion of patients with successful reperfusion (grades 0 or 1 at baseline to 2 or 3 at 90 min) who had angiographic patency at hospital discharge represents 42% (47/113) of the rt-PA group (8/113 or 7% unknown; figure 3, A) with occlusion (grade 0 or 1) at baseline and 21% (25/119) of the SK group (8/119 or 7% unknown; figure 3, B) with occlusion at baseline (p<.001). If patients without a predischarge angiogram and no reinfarction or death are considered as having patent arteries, 44% (50/113) of the rt-PA group and 22% (26/119) of the SK group can be considered to have patent arteries (figure 5; p<.001). Thus, patients treated with rt-PA not only exhibited successful reperfusion more often at 90 min, but also maintained greater patency of the infarct-related artery (by angiographic and clinical observations) at discharge.

Left ventricular function. There were no significant changes in global or regional left ventricular function in either of the two treatment groups from pretreatment baseline to hospital discharge.

Coagulation variables. The largest percent reduction in fibrinogen observed at 3 or 5 hr after the start of thrombolytic treatment was 33% in the rt-PA group and 58% in the SK group; the corresponding reductions in plasminogen were 63% and 83%. The highest mean value of fibrinogen/fibrin degradation products was 111 and 257 for rt-PA- and SK-treated patients, respectively. The results of the studies on the effects of these two agents on coagulation variables are described in detail elsewhere.

Clinical course in hospital. Patients were discharged from hospital at a mean of 16 and 15 days (range 0 to 55 days) for the rt-PA and SK groups, respectively.

Hypotension within 24 hr of treatment not associated with arrhythmia occurred in four (3%) and eight (5%) patients treated with rt-PA and SK, respectively. Fever or chills of uncertain cause occurred in six (4%) patients in the rt-PA and 22 (15%) patients in the SK group (p<.01); urticaria of uncertain cause occurred in one patient in the rt-PA and three patients in the SK group. No patient developed anaphylaxis. Nausea or vomiting during the first 24 hr were frequent in both groups (41% in the rt-PA and 46% in the SK group) and often appeared to be related to the injection of THERAPY AND PREVENTION--THROMBOLYSIS

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contrast medium. During the early days of hospitalization, transient renal insufficiency, probably related in part to contrast medium, occurred in 5% of patients in each group.

Death occurred in six (4%) patients in the rt-PA and eight (5%) patients in the SK group within 21 days (during more prolonged hospitalization to 30 and 27 days, respectively, death occurred in an additional one rt-PA- and four SK-treated patients). Three of the six deaths in the rt-PA and two of the eight deaths in the SK group followed initially successful reperfusion and subsequent prolonged chest pain presumably attributable to reocclusion. The other three deaths in the rt-PA and six deaths in the SK group (plus three of the four deaths during prolonged hospitalization) occurred in patients without reperfusion. No deaths occurred in the patients presenting with subtotal occlusion (baseline perfusion grade 2 or 3; figure 3). Thus, death was associated with failure to reperfuse, reinfarction, or recurrent ischemia. The observed 21-day mortality for all randomized patients was 7.0% (11/157) for those assigned to rt-PA and 6.3% (10/159) for those assigned to SK.

Cardiogenic shock occurred in four patients (3%) in the rt-PA compared with 10 patients (7%) in the SK group and occurred primarily in patients in whom reperfusion was not achieved (figure 3, B). Cardiac arrest occurred in 13% and 10% of the patients in the rt-PA and SK groups, respectively, and within 24 hr of admission in at least half. The incidence of heart failure was similar in the rt-PA (15%) and the SK (19%) group. The incidence of clinical reinfarction was similar in the rt-PA (13%) and the SK (12%) group, and was distributed evenly throughout the first 11 days of hospitalization, but was higher in patients with initial recanalization and subsequent angiographically documented reocclusion (figure 3). Recurrent pain attributed to ischemia occurred in a high proportion of both rt-PA– (46%) and SK-treated (44%) patients (figure 3). Pericarditis occurred in 10% of patients in both groups. In the rt-PA group, it was more frequent in those who did not exhibit recanalization (figure 3).

Before hospital discharge, 10% and 14% of patients underwent percutaneous transluminal coronary angioplasty and 13% and 10% of patients underwent coronary artery bypass operations in the rt-PA and SK groups, respectively. Thirty-five percent of patients in both groups with subtotal occlusion at baseline (grade 2 or 3 perfusion) underwent revascularization (figure 3).

**Bleeding complications.** Observed bleeding, ecchymosis, or hematoma at the catheterization site occurred in 95 or 66% and 98 or 67% of patients in the rt-PA and SK groups, respectively. A major decrease in hematocrit occurred in 15% and 16% of rt-PA– and SK-treated patients, respectively. A minor decrease in the hematocrit occurred in 16% of patients in each group. Of those suffering a bleeding event (major or minor) the primary site of bleeding was the catheterization or arterial puncture site in 78% and 80% of rt-PA– and SK-treated patients, respectively. No intracranial bleeding occurred in these patients. Spontaneous blood loss (not
Discussion

In this study, pretreatment coronary arteriography and seven repeated angiographic observations were carried out within 90 min of the onset of treatment with the thrombolytic agents. Intravenous administration of rt-PA compared with SK recanalized a significantly higher proportion of occluded infarct-related arteries at each interval up to 90 min after initiation of treatment. We chose rapid administration of the highest dose of SK that had proven safe and effective in previous studies for comparison with an 80 mg dose of rt-PA (G11021). Because rt-PA has a relatively short circulating half-life of minutes, a 3 hr infusion was used in an effort to lyse residual thrombus and reduce the risk of reocclusion. In contrast to rt-PA, SK has a longer circulating half-life. Furthermore, it induces prolonged changes in hemostasis associated with persistence of circulating degradation products. Thus, effects of prolonged infusions of rt-PA are likely to be biologically comparable to prolonged effects after somewhat briefer infusions of SK.

rt-PA recanalized a higher proportion of occluded arteries than SK at each hour of administration after the onset of chest pain (table 3), with a continued high proportion of recanalization even when treatment was started more than 4 hr after the onset of symptoms. In contrast, SK exhibited diminished efficacy when initiated 4 hr or more after the onset of chest pain. Rates of recanalization with SK in our large group of homogeneously defined patients with the same ECG and entry criteria may have been low because of the strict definitions of occlusion and successful reperfusion, requiring grades 2 or 3 after baseline grades 0 or 1. Previous studies with baseline angiography were small with variable patient populations (some subtotal occlusion or ST segments depressed or undefined) and used variable criterion for successful reperfusion that was undefined, included grade 1 perfusion after grade 0 at baseline (13% of our SK group), or included transient reperfusion (2% of our SK group) at 60 min with reocclusion within the next 30 min. Inclusion of the latter two groups would increase reperfusion in our SK group (baseline grade 0) from 26% to 41%. If these two groups were included in our rt-PA groups (baseline grade 0), successful reperfusion would increase from 56% to 70%. Our findings are also consistent with those in laboratory studies demonstrating lysis with t-PA (but not urokinase) of 50% of thrombi as old as 1 week. This suggests that rt-PA may be useful for lysis of residual mural and layered coronary thrombi of variable age associated with plaque rupture.

The lower rates of recanalization with rt-PA in right and circumflex coronary arteries compared with left anterior descending coronary arteries may be attributable to decreased branching of the former with increased stasis proximal to the occlusion, and consequently larger volumes of thrombi for lysis in a higher proportion, but not necessarily all, of these arteries. This difference was not seen for SK but would not be expected within 90 min with an agent that lyse thrombus more slowly and opens so few arteries within the first 90 min. This interpretation is supported by finding that more than 50% of infarct-related arteries that were totally occluded at 90 min were successfully recanalized 24 hr after thrombolytic therapy was started.

The fact that such a high proportion of baseline grade 1 arteries opened at 90 min in both groups (90% for rt-PA and 63% for SK) also supports the hypothesis that a smaller volume of thrombus and the ability of a lytic agent to envelop the thrombus are important determinants of rapid recanalization. These two conditions are probably best met when treatment is initiated very early after the onset of symptoms. If the rate of lysis is dependent on the dose of lytic agent, then a higher dose of rt-PA may have increased recanalization of right and circumflex coronary arteries, and may have decreased the risk of reocclusion due to improved
arterial dimensions and flow and decreased residual thrombus.30–33

Although the dose selection of the lytic agents in this study can be criticized,34 recent experience with intravenous SK does not show a relationship between the dose of SK and the recanalization rate,4–9 as recently reviewed.2 Our observations at five time intervals within the first hour of administration do not support the suggestion that unequal duration of administration of the lytic agents accounts for the superiority of rt-PA compared with SK.34

The proportion of patients with grade 2 or 3 perfusion at 90 min independent of results of baseline pretreatment angiography (72% in the rt-PA and 46% in the SK group), despite inclusion of the eight patients with less than 50% stenosis who were excluded from treatment after baseline angiography, is similar to the 90 min incidence of patency in the European study comparing rt-PA and SK (70% with rt-PA and 55% with SK).30 The European study used a 0.75 mg/kg dose of rt-PA, a slightly smaller dose of rt-PA, and did not obtain pretreatment arteriography; thus, it was able to deliver thrombolytic therapy earlier at the price of lack on knowledge of pretreatment coronary vascular patency. The importance of pretreatment angiography is reflected by the wide range in the occurrence of subtotal occlusion at baseline, i.e., from 5% to 33%.2

Intravenous SK was modestly effective in recanalizing occluded coronary arteries, judging from our results and those of others who obtained baseline angiograms. Its clinical effects are therefore only modest.35–37 Our study was not designed with sufficient statistical power to examine clinical outcome in the two treated groups. The very large GISSI study including 11,712 randomized patients from Italian community hospitals reported an 18% reduction of hospital mortality compared with a control group that received no thrombolytic therapy. Survival was enhanced especially in those treated within 1 hr, and a mild reduction of mortality from 12.0% to 9.2% was present in those treated within 3 hr.35 Smaller trials from the Netherlands and Germany (ISAM) have reported similar trends.36,37 Taken together, these three trials provide strong evidence for the modest clinical benefit of intravenous administration of SK in the early hours (especially the first) of myocardial infarction.

Decreases in fibrinogen and plasminogen and increases in fibrin(ogen) degradation products at 3 and 24 hr after onset of therapy are less marked after rt-PA than with SK.9,11,27 However, the incidences of major or minor bleeds did not differ in the two groups we studied, probably because the vast majority of bleeds were associated with invasive procedures, such as arterial puncture, and because of the extensive anticoagulation with heparin to prevent reocclusion. Results of a retrospective study suggest that heparin therapy should be continued for at least 3 days to minimize reocclusion.38 However, continued reocclusion events in our patients beyond 3 days and up to 11 days after admission (in spite of continued therapy with heparin alone) and the supernormal rebound increase in fibrinogen at hospital discharge27 suggest that anticoagulation should be continued in combination with platelet inhibition throughout hospitalization and possibly longer.32

Because reocclusion is also associated with high-grade residual stenosis,31 early reduction of the high-grade residual lesions by coronary angioplasty may be beneficial. It appears to reduce the otherwise high incidence of recurrent pain attributable to ischemia (figure 3) seen after thrombolysis.39 The role and timing of coronary angioplasty after thrombolysis is being evaluated in Phase II of the TIMI trial.

The thrombolytic effects of intravenous rt-PA and achievement of clot lysis as frequently as that seen with intracoronary SK4,5,14 support the utility of this agent for early intravenous administration as a first step for maximizing myocardial salvage in a high proportion of patients. The overall impact of rt-PA with respect to myocardial salvage and reduction of mortality will probably be greatest among patients who can be treated early and those in whom reocclusion and reinfarction can be minimized.

TIMI

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References
ant human tissue-type plasminogen activator: a prospective, randomized, placebo-controlled trial. Circulation 70: 1012, 1984
Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge.

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