Coronary arterial thrombolysis with combined infusion of recombinant tissue-type plasminogen activator and urokinase in patients with acute myocardial infarction

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ABSTRACT To determine whether tissue-type plasminogen activator (t-PA) and urokinase (UK) act synergistically to achieve coronary thrombolysis, incremental doses of both drugs were infused intravenously over 60 min. In 146 consecutive patients treated 3.0 ± 1.0 hr from symptom onset, coronary angiography was performed 90 min after the start of the infusion and at 7 days. The groups of patients treated by different dose regimen were as follows: group I, 14 patients treated with t-PA 25 mg and UK 0.5 million U; group II, 20 patients given t-PA 25 mg and UK 1.0 million U; group III, 24 patients given t-PA 1.0 mg/kg and UK 0.5 million U; group IV, 33 patients treated with t-PA 1.0 mg/kg and UK 1.0 million U; and group V, 55 patients given t-PA 1.0 mg/kg and UK 2.0 million U. In groups I and II, patency of the infarct-related vessel at 90 min was only 36% and 42%, respectively. With 1 mg/kg t-PA and increasing doses of UK (groups III to V), patency ranged from 72% to 75% (overall 73%). Repeat catheterization at 7 days demonstrated reocclusion in groups III to V in 10 of 110 (9%). The patency and reocclusion rates in groups III to V were not significantly different from those in our previous study of 386 patients treated with t-PA alone (150 mg over 6 to 8 hr). In that study the patency rate of the infarct-related vessel at 90 min was 75% (p = .66) and reocclusion occurred in 15% (p = .11). Patients in groups III to V who failed fibrinolytic therapy and underwent “rescue” coronary angioplasty had a higher patency rate at follow-up (22 of 23, 96%) as compared with patients treated with t-PA alone (56 of 81, 69%; p = .017) and lower in-hospital mortality (0/27 vs 10/96, 10.4%; p = .075). We conclude that t-PA and urokinase do not act synergistically in achieving coronary thrombolysis and that 75% patency of the infarct-related vessel at 90 min may represent a plateau value for thrombolytic therapy. However, with the combined infusion of these agents, the bleeding frequency was not increased whereas the reocclusion rates were lower, particularly in patients who failed thrombolytic therapy and underwent emergency angioplasty.


THE MAJOR OBJECTIVES of fibrinolytic therapy for acute myocardial infarction are to achieve rapid and sustained patency in the highest proportion of patients, with avoidance of rethrombosis and bleeding episodes. With the introduction of intravenous tissue-type plasminogen activator (t-PA), a relatively clot-selective agent, early recanalization of the infarct-related vessel has been achieved in 66% to 83% of patients.1–5 In two randomized trials, intravenous t-PA achieved higher rates of patency with less fibrinogenolysis as compared with streptokinase.3, 6–8 Despite the superior thrombolytic efficacy of t-PA, a high frequency of reocclusion2, 3, 5 led to the recommendation of a prolonged maintenance infusion.4 Furthermore, bleeding problems have not been significantly lower than with
streptokinase, 3, 6, 9 and in one study a 150 mg dose of t-PA, given to achieve rapid and complete recanalization, was associated with an increased incidence of intracranial hemorrhage.10

The concept of improved efficacy and safety of thrombolytic therapy with the use of synergistic combinations of fibrinolytic agents was recently introduced.11–14 Experiments in vitro have not been consistent with regard to whether additivity or synergism exists.11, 14 In rabbit and canine preparations, synergism was demonstrated for t-PA and urokinase (UK)12 as well as t-PA and single-chain urokinase-type plasminogen (pro-urokinase).12, 15 Preliminary results obtained in small groups of patients with myocardial infarction treated with low-dose combination therapy have also been encouraging.13, 16

The primary purpose of the current multicenter trial was to determine whether t-PA and UK act synergistically to achieve coronary thrombolysis. The results obtained in 146 patients were compared with the findings of our previous trial in which 386 patients received t-PA monotherapy.17

Methods

Patient selection. Inclusion criteria were less than 4 hr of chest discomfort with diagnostic electrocardiographic ST segment elevation (>0.1 mV in two or more contiguous leads). Patients with more than 4 but less than 6 hr of symptoms were considered if they had severe, ongoing chest discomfort. Patients were excluded if they were more than 75 years of age, had recent (less than 3 months) trauma, stroke, or major surgery, had previous myocardial damage in the infarct territory, had systolic blood pressure less than 80 mm Hg unresponsive to fluids, or had evidence of recent or active bleeding (e.g., peptic ulcer, hemoptysis). The protocol was approved by the institutional review board at each of the clinical sites. Permission to administer the two investigational fibrinolytic agents concomitantly was obtained from the Food and Drug Administration. All patients provided informed consent before participation in the study.

Combination fibrinolytic therapy. The predominant single chain form of t-PA (Genentech, Inc., South San Francisco, CA)5, 18 and the low molecular weight form of UK (Abbott, Chicago) were used. Both drugs were reconstituted and administered via a separate intravenous infusion line. Five sequential groups of patients, each with at least 25 patients, were allocated prospectively to receive doses of the lytic agents as shown in table 1. For groups I and II, no bolus of t-PA was given because of the low total dose. In the remaining groups, 10% of the t-PA was administered as a bolus. The t-PA dose for groups III to V was 1 mg/kg with a maximum of 90 mg. A UK bolus was not employed as in the previous synergism experiments.12, 13 All fibrinolytic doses were given over 60 min. In each patient, the t-PA infusion was started second just before the UK infusion. No fibrinolytic therapy was administered intravenously after 60 min.

Cardiac catheterization and coronary angioplasty. After initiation of thrombolytic therapy, patients were transferred to the cardiac catheterization laboratory where angiography of the infarct-related vessel was performed at 90 min. Arterial access was obtained via the femoral or brachial route. Heparin (5000 U) was administered immediately after access was established. To standardize the number of injections, one contrast angiogram was obtained at 60 min of therapy if the patient had arrived in time. At 90 min, up to four angiograms in various orthogonal and hemiangular views were obtained. Angiography of the noninfarct vessels and the left ventricle was also performed.

The flow pattern of the infarct-related vessel was graded according to the TIMI classification.3, 19 The final angiogram obtained at 90 min was used for triage for angioplasty. Patients with persistent occlusion at 90 min of therapy (TIMI 0 or 1 grade) were eligible for coronary angioplasty, performed at the discretion of the investigator. For patients with TIMI grade 2 or 3 patency of the infarct-related vessel and a significant residual stenosis, coronary angioplasty was performed at the same catheterization if there was evidence of ongoing ischemia or reduced coronary blood flow (chest pain, presence of collaterals or >0.2 mV ST segment elevation) or was deferred until follow-up catheterization or until the patient developed clinical evidence for ischemia. When angioplasty was performed at the same catheterization, an additional 5000 U of heparin was given. Balloon dilatation of stenoses in the infarct-related vessel was accomplished by two to three inflations at 5 to 8 atm. If residual thrombus was present after coronary angioplasty, as identified by definite filling defects and a delayed flow pattern, patients were eligible to receive intracoronary t-PA (30 mg) over 15 min, and if this failed intracoronary UK (500,000 U) was given over 15 min.

Medical therapy. Patients were treated with intravenous heparin, beginning at 500 to 800 U/hr, adjusted to prolong the partial thromboplastin time 2 to 2.5 times, for at least 3 days. One aspirin tablet (325 mg) and diltiazem 30 to 60 mg four times per day were given. During the first 24 hr, patients received intravenous lidocaine and nitroglycerin unless contraindicated. β-Blockers were not administered unless specifically required to treat supraventricular tachycardia, hypertension, or angina. Urgent repeat cardiac catheterization was performed for recurrent ischemia, defined as 20 min or more of chest discomfort associated with electrocardiographic ST segment elevation. In patients with a stable clinical course, a submaximal treadmill test was performed before the repeat catheterization.

Repeat catheterization and revascularization. Patients underwent a repeat cardiac catheterization at 7 days, even if an interim urgent study had been necessary. Follow-up angiography was performed to determine late patency of the infarct-related vessel and ventricular function. Angioplasty of the infarct-related artery was performed during the repeat catheterization when there was a significant residual stenosis, a positive exercise test, or both. Patients underwent coronary artery bypass surgery if they had either severe, multiple-vessel disease or lesions of the infarct-related vessel not amenable to angioplasty.

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**Table 1**

<table>
<thead>
<tr>
<th>Patient groups</th>
<th>Intravenous dose over 60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>t-PA</td>
</tr>
<tr>
<td>I</td>
<td>25 mg</td>
</tr>
<tr>
<td>II</td>
<td>25 mg</td>
</tr>
<tr>
<td>III</td>
<td>1.0 mg/kg</td>
</tr>
<tr>
<td>IV</td>
<td>1.0 mg/kg</td>
</tr>
<tr>
<td>V</td>
<td>1.0 mg/kg</td>
</tr>
<tr>
<td>TAMI-I</td>
<td>150 mg/6–8 hr</td>
</tr>
</tbody>
</table>

*In groups III to V, 10% of the t-PA dose was given as a bolus.*
was performed emergently when angioplasty had induced closure of the infarct-related vessel or when there was ongoing or severe ischemia with the appropriate underlying anatomy.

**Bleeding and coagulation variables.** Bleeding was categorized as major if it was intracranial or required transfusion of 2 units or more of packed red blood cells. The site of bleeding, baseline and nadir hematocrit, and units transfused were recorded for all patients.

Blood samples collected on 0.01M citrate and 200 kIU/ml aprotinin at baseline and 1, 4, and 24 hr after fibrinolytic therapy were immediately processed and kept frozen at −20°C until assayed in the core laboratory. Fibrinogen was determined by a coagulation rate assay. Fibrinogen degradation products were analyzed by the tanned red cell agglutination inhibition technique. t-PA and UK antigen levels were measured with specific enzyme-linked immunosorbent assays.

**Core angiographic laboratory.** All cineangiograms were forwarded to the Core Radiographic Laboratory for blinded single observer review of infarct-related vessel perfusion status, quantitative stenosis, and ventricular function. Global ventricular function was determined by the area-length method and expressed as ejection fraction; regional wall motion of the infarct zone was quantified as standard deviation/chord by means of the centerline chord method. Technically inadequate studies due to lack of opacification or frequent ventricular extrasystoles were not included in the analysis.

**Comparison with t-PA monotherapy (TAMI-I).** The results of combined t-PA and UK therapy in the current study were compared with those of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI-I) cohort of 386 patients treated with single-agent t-PA. In the previous study, the same overall protocol was used except for the fibrinolytic therapy (t-PA at a total dose of 150 mg over 6 to 8 hours with 10% of the first hour dose as a bolus) and randomization of the timing of coronary angioplasty for patients with a patent vessel and high-grade residual stenosis at the early catheterization.

**Data analysis.** Values are expressed as means ± 1 SD unless otherwise specified. Because of the multiple possible comparisons of baseline characteristics and outcomes and the nonrandomized nature of the comparisons between TAMI-I and TAMI-II studies, limited numbers of variables were specified for statistical comparison. For discrete variables, these comparisons were performed with the chi-square test. For continuous variables, the Wilcoxon rank-sum test was used. Comparison of early 7-day global and regional left ventricular function in the TAMI-II patients was performed with the Wilcoxon signed-rank test.

Case report forms were completed by the clinical research nurse coordinators and reviewed by the principal investigator at each site before submission to the Duke Data Coordinating Center. The data were verified independently by study monitors from review of the clinical records. The Data Monitoring Board met regularly to review the outcome of each patient and to ensure the safety of the various thrombolytic combinations. When the 95% confidence limits for 90 min patency of the infarct-related vessel for each combination dose dropped below 70%, patient entry into that dose group was terminated. Bleeding complication rates were monitored carefully throughout the trial.

**Results**

**Patients.** Of the 146 patients enrolled, treatment began 3.0 ± 1.0 hr from onset of symptoms. The mean age was 55 ± 9 years, 83% were men, and the infarct-related vessel was the left anterior descending artery in 58, the right coronary artery in 64, and the left circumflex artery in 20, and a saphenous vein bypass graft in one patient; in one patient the infarct-related artery was unidentifiable. Two patients died before reaching the cardiac catheterization laboratory because of intratable arrhythmias in one patient (group II) and early, progressive cardiogenic shock in the other patient (group III).

**Patency of the infarct-related vessel.** The 90 min angiographic patency results for groups I to V are presented in figure 1 and compared with the results of our previous trial with t-PA alone. The patency rates in groups I and II were only five of 14 (36%) and eight of 19 patients (42%), respectively, which resulted in the Policy Board recommendation to terminate recruitment in these groups before reaching the projected number of 25 patients. These results for patency of the infarct-related vessel were significantly lower than those in our previous study with t-PA alone (mean patency rates 75%; 95% confidence intervals 67% to 83%). When t-PA at a dose of 1 mg/kg was combined with increasing doses of UK (groups III to V), no trend toward increased patency was observed. The patency rate for t-PA and UK in combination was very similar to that observed with t-PA alone (groups III to V: 82/112, 73.2%; TAMI-I: 288/384, 75%; p = .66).

**Reocclusion.** The reocclusion rates in groups I and II were 0 and 20%, respectively, but there were few patients who had recanalization induced by fibrinolytic therapy. The results for groups III, IV, and V were 11%, 6%, and 11%, respectively. Cumulatively, with 1 mg/kg t-PA and incremental UK, the rate of reocclusion was 9% as compared with 15% in the TAMI-I patients (p = .11).

**Coronary angioplasty in patients with persistent occlusion.** In groups III to V, consisting of 112 patients, 27 demonstrated TIMI grade 0 or 1 at the 90 min angiogram. Coronary angioplasty was performed in 22 of these patients with successful recanalization in all but
three (86.4%). Only seven patients received intracoronal t-PA and UK for persistent evidence of thrombus after immediate angioplasty. At repeat angiography of 23 patients in groups III to V, 22 (95.7%) of these patients had sustained patency. These results compare favorably with our previous experience with t-PA only, where sustained patency was demonstrated in only 56 of 81 patients (69.1%) who had failed therapy and had undergone immediate angioplasty (p = .015). A detailed comparison of demographic, angiographic, and clinical course variables of these two patient groups is shown in table 2. Patients receiving t-PA and UK in whom lytic therapy failed and who underwent angioplasty had a significant improvement in ejection fraction (49.2 ± 12.1% at baseline, 54.5 ± 9.7% at follow-up; p = .008) and regional wall motion (-2.56 ± 1.12 SD/chord at baseline, -2.12 ± 1.32 at follow-up; p = .004). In contrast, patients who did not respond to infusion of t-PA only and who underwent sequential angioplasty did not experience improvement in left ventricular function (27) (table 3).

Bleeding and coagulation variables. The hematocrit and transfusion data are summarized in table 4. One patient in group V had a limited intracranial hemorrhage in the posterior fossa and experienced near complete neurologic recovery. Occult gastrointestinal bleeding occurred in 27 of 146 patients (18.4%) but there was no frank emesis of blood or melena. Significant periaccess bleeding requiring 2 units of transfused blood or more occurred in six patients (4.1%), and one patient (0.7%) had gross hematuria. Two retroperitoneal hemorrhagic episodes (1.3%) occurred. Transfusions of 2 or more

### TABLE 2

<table>
<thead>
<tr>
<th>Characteristics of patients with persistent coronary artery occlusion after thrombolytic therapy</th>
<th>TAMI-II (groups III-V)</th>
<th>TAMI-I t-PA + UK</th>
<th>TAMI-I t-PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>27</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>55.4 ± 8</td>
<td>56.4 ± 8</td>
<td></td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>74</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Time to Rx (hr)</td>
<td>2.9 ± 1.1</td>
<td>2.9 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>Infarct-related vessel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>42%</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>LCX</td>
<td>18%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>38%</td>
<td>51%</td>
<td></td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>37%</td>
<td>48%</td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>129 ± 23</td>
<td>131 ± 25</td>
<td></td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>77 ± 15</td>
<td>80 ± 19</td>
<td></td>
</tr>
</tbody>
</table>

HR = heart rate; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; SBP = systolic blood pressure.

### TABLE 3

<table>
<thead>
<tr>
<th>Outcome of patients with persistent coronary artery occlusion after thrombolytic therapy</th>
<th>t-PA and UK</th>
<th>t-PA alone</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful PTCA</td>
<td>19/22 (86.4%)</td>
<td>63/86 (73.3%)</td>
<td>.199</td>
</tr>
<tr>
<td>Patency at follow-up</td>
<td>22/23 (95.7%)</td>
<td>56/81 (69.1%)</td>
<td>.017</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>0%</td>
<td>10.4%</td>
<td>.075</td>
</tr>
<tr>
<td>Ventricular function</td>
<td>17</td>
<td>68</td>
<td>—</td>
</tr>
<tr>
<td>LVEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (%)</td>
<td>49.2 ± 12.1</td>
<td>50.6 ± 11.4</td>
<td>—</td>
</tr>
<tr>
<td>Follow-up (%)</td>
<td>54.5 ± 9.7</td>
<td>49.3 ± 11.8</td>
<td>—</td>
</tr>
<tr>
<td>(Change) (median)</td>
<td>+5</td>
<td>-1</td>
<td>.008</td>
</tr>
<tr>
<td>RWM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (SD/chord)</td>
<td>-2.56 ± 1.1c</td>
<td>-2.70 ± 1.0</td>
<td>—</td>
</tr>
<tr>
<td>Follow-up (SD/chord)</td>
<td>-2.12 ± 1.3c</td>
<td>-2.59 ± 1.0</td>
<td>—</td>
</tr>
<tr>
<td>(Change) (median)</td>
<td>0.44 ± 0.85</td>
<td>0.12 ± 0.98</td>
<td>.165</td>
</tr>
</tbody>
</table>

LVEF = left ventricular ejection fraction; PTCA = coronary angioplasty; RWM = regional wall motion.

aThe denominators refer to the number of patients in each group who underwent predischarge coronary angiography.

bThe numbers of patients with technically adequate, paired left ventriculographic studies for global and regional wall function, at baseline and 7 days, are listed.

cp = .004.

units of packed red cells were given to 24 of 112 (21%) group III to V patients, of whom 11 received transfusion as part of coronary bypass surgery. The transfusion rate was lower than the 31.1% overall rate in the TAMI-I trial, in which a higher proportion (23%) of patients underwent bypass surgery. When patients undergoing surgery were excluded, there were no differences in the transfusion requirement for patients treated with the combination vs t-PA monotherapy (12% vs 17%; p = .20).

The results of fibrinogen assays are presented in figure 2. Minimal fibrinogenolysis occurred with the low-dose combinations (groups I and II). When 1 mg/kg t-PA was combined with increasing doses of UK, there was progressively more fibrinogen deple-
thrombolytic combination therapy with full doses of t-PA and UK was associated with a lower reocclusion rate than observed with t-PA alone, as defined by systematic repeat angiography performed before hospital discharge. In addition, patients in whom thrombolytic therapy had failed appeared to benefit most from the combination when angioplasty was performed. Previously, Califf et al. reported a poor prognosis for patients who fail therapy with intravenous t-PA. Despite “rescue” coronary angioplasty, these patients had a 29% reocclusion rate, a 10.4% in-hospital mortality, and no improvement in left ventricular global or regional infarct zone wall motion. In contrast, in the present study, there was only a 7% reocclusion rate, no mortality, and significantly improved ventricular function. Although these two treatment protocols were not compared in a randomized manner, the very similar demographic and angiographic profiles of the two study groups and the similar ancillary treatment protocols after thrombolysis allow a preliminary conclusion that the combination therapy is more beneficial to this patient group.

The mechanism for the possible benefit of combined t-PA and UK therapy is unclear. Possible explanations include more extensive clot lysis, more extensive sys-

### Discussion

These results do not support the preliminary observations that t-PA and UK act synergistically on coronary arterial thrombolysis in patients with acute myocardial infarction. At low doses of both agents representing approximately 25% of the therapeutic dose of each agent, patency rates of the infarct-related vessels were below 45%, which necessitated early termination of patient entry to these groups. With the full therapeutic dose of t-PA (1 mg/kg) and incremental doses of UK (0.5 to 2.0 million U) no further increase in patency rate was observed as compared with our previous experience of t-PA infusion alone. The data thus apparently do not fulfill the Berenbaum criteria for synergism between these thrombolytic agents.

The demonstration of 75% patency of the infarct-related vessel at 90 min of combined high-dose t-PA and UK supports the “plateau” concept for pharmacologic coronary thrombolysis. Prior trials of intracoronary or intravenous thrombolysis with a variety of thrombolytic agents used alone at varying doses have failed to consistently yield patency rates higher than 75%. The mechanism for resistance in approximately one-fourth of patients is not known, but our findings contradict the possibility of a higher short-term thrombolytic efficacy.

Despite the lack of clear evidence for a synergistic effect on the reperfusion rates, combination therapy with full doses of t-PA and UK was associated with a lower reocclusion rate than observed with t-PA alone, as defined by systematic repeat angiography performed before hospital discharge. In addition, patients in whom thrombolytic therapy had failed appeared to benefit most from the combination when angioplasty was performed. Previously, Califf et al. reported a poor prognosis for patients who fail therapy with intravenous t-PA. Despite “rescue” coronary angioplasty, these patients had a 29% reocclusion rate, a 10.4% in-hospital mortality, and no improvement in left ventricular global or regional infarct zone wall motion. In contrast, in the present study, there was only a 7% reocclusion rate, no mortality, and significantly improved ventricular function. Although these two treatment protocols were not compared in a randomized manner, the very similar demographic and angiographic profiles of the two study groups and the similar ancillary treatment protocols after thrombolysis allow a preliminary conclusion that the combination therapy is more beneficial to this patient group.

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### Table 5

<table>
<thead>
<tr>
<th>Group</th>
<th>t-PA</th>
<th>UK (×10^6 U)</th>
<th>FDP (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25 mg</td>
<td>0.5</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>25 mg</td>
<td>1.0</td>
<td>345</td>
</tr>
<tr>
<td>3</td>
<td>1mg/kg</td>
<td>0.5</td>
<td>649</td>
</tr>
<tr>
<td>4</td>
<td>1mg/kg</td>
<td>1.0</td>
<td>1139</td>
</tr>
<tr>
<td>5</td>
<td>1mg/kg</td>
<td>2.0</td>
<td>1609</td>
</tr>
<tr>
<td>TAMI-I</td>
<td>150 mg</td>
<td>-</td>
<td>195</td>
</tr>
</tbody>
</table>

### Figure 2

Plasma fibrinogen values (percent baseline to nadir) for each thrombolytic dose regimen.

### Figure 3

Median peak fibrinogen degradation product titers for each thrombolytic dose regimen.

### Table 5

<table>
<thead>
<tr>
<th>Predischarge status of the infarct-related vessel</th>
<th>n</th>
<th>Patent ≤50%</th>
<th>Patent &gt;50%</th>
<th>Bypass graft</th>
<th>Occluded</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAMI-I</td>
<td>356</td>
<td>50%</td>
<td>11%</td>
<td>22%</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>TAMI-II</td>
<td>104</td>
<td>70%</td>
<td>8%</td>
<td>5%</td>
<td>4%</td>
<td>3%</td>
</tr>
</tbody>
</table>

χ² = 14.85, p = .005

*Patients with a follow-up angiogram at 7 to 10 days are classified by residual stenosis of the infarct-related vessel, presence of a bypass graft to the infarct zone, or occlusion. TAMI-II data refer to group III to V patients. The in-hospital mortality rates are also indicated.
temic fibrinolytic activation, and prolonged fibrinogen depletion, potentially associated with reduced blood viscosity \(^{29,30}\) and more intense inhibition of platelet function. \(^{31-33}\) Since the patients who appeared to benefit most were those in whom lytic therapy had failed, it is not likely that a more extensive clot lysis was a major contributing factor. It is possible that a more intense thrombolytic state was beneficial to prevent reclosure after angioplasty had restored antegrade flow. Although the disposition rates of both t-PA and UK are rapid (a \(t_{1/2}\) in plasma of less than 10 min), the rheologic advantages of a lower blood viscosity may have played a role. \(^{29,30}\) Recent studies have suggested that t-PA has the potential to increase platelet activation and aggregation. \(^{32,33}\)

In the current study, combination t-PA and UK therapy led to an eightfold elevation of fibrinogen degradation products compared with t-PA monotherapy. These protein fragments have been demonstrated previously to have an important platelet disaggregatory effect. \(^{34}\) Thus, more intense inhibition of platelet function may account for the improvement in sustained patency of the infarct-related vessel. The favorable results of low reclosure after thrombolytic failure are similar to those reported by Stack et al. \(^{35}\) in a large series of patients treated with high-dose intravenous streptokinase and immediate angioplasty.

In the present study, the frequency of bleeding complications was surprisingly low, despite the simultaneous use of two thrombolytic agents at high doses and the associated extensive systemic fibrinolytic state. This observation suggests a few potentially important characteristics of the bleeding associated with fibrinolytic therapy. First, the avoidance of a prolonged t-PA maintenance infusion, which has been observed to predispose to bleeding, \(^{31}\) may be beneficial. Second, the apparent paradox between extensive fibrinogen breakdown and a low frequency of bleeding is emphasized by the present findings. Finally, with the combined use of full doses of two thrombolytic agents in addition to aspirin and heparin and in the presence of invasive arterial punctures, less than 10% of patients who did not undergo bypass surgery required transfusion, primarily for correction of a decreased hematocrit and not for major clinical bleeding.

The present study has several significant limitations. It represents a sequential experience with relatively small numbers of patients in each group who are compared with the historical controls of the TAMI-I trial. Our present observations therefore need to be verified and extended in a larger prospective, randomized trial. With limited data in the literature on the effects of intravenous UK therapy \(^{36,37}\) and the lack of a study group randomized to infusion of UK alone, no firm conclusions can be drawn concerning the relative efficacy of the combination of t-PA and UK as compared with UK alone. Furthermore, in the absence of a pretreatment angiogram and serial early angiographic studies, the current study did not allow us to evaluate the possibility of a synergistic effect of t-PA and UK with respect to the time to recanalization.

In conclusion, we found no evidence for significant synergism between t-PA and UK with respect to coronary artery reperfusion. However, the previously identified high-risk subset \(^{27}\)—patients with persistent occlusion of the infarct-related vessel treated with immediate angioplasty—appeared to benefit from combined t-PA and UK in terms of low reclosure (4%), low mortality (0%), and improvement of left ventricular function (5.3 point increase in ejection fraction). Since there was no increased bleeding tendency with the combination therapy, the use of UK as an alternative for a prolonged t-PA infusion deserves further prospective evaluation.

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Coronary arterial thrombolysis with combined infusion of recombinant tissue-type plasminogen activator and urokinase in patients with acute myocardial infarction.

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