Randomized Trial of Thrombolysis Versus Heparin in Unstable Angina

Theodore L. Schreiber, MD; David Rizik, MD; Christopher White, MD; G.V.R.K. Sharma, MD; Michael Cowley, MD; Gregory Macina, MD; P.S. Reddy, MD; Louis Kantounis, MD; Gerald C. Timmis, MD; Ann Margulis, RN; Paul Bunnell, BS; Walter Barker, PhD; and Arthur Sasahara, MD

Background. The clinical usefulness of intravenous thrombolytic therapy in unstable angina is currently unknown, despite the pathogenetic similarity of this entity to acute myocardial infarction, for which thrombolysis has enjoyed great success. To compare the clinical benefit of intravenous urokinase with that of conventional antiplatelet therapy in preventing the progression of unstable angina to new myocardial infarction, intractable angina, or death within the first 96 hours after hospitalization, 149 patients with unstable angina were randomized to one of two intravenous thrombolytic strategies.

Methods and Results. Forty-nine patients received 3 million units urokinase i.v. over 90 minutes plus intravenous heparin (group A); 47 patients received unblinded 3 million units urokinase i.v. plus 325 mg aspirin p.o. daily (group B); and 53 patients received placebo thrombolytic infusion plus full-dose heparin (group C). The primary end point of this trial was 96-hour clinical status. There were no significant differences in the baseline characteristics (age, sex, previous myocardial infarction, hypertension prevalence, diabetes, tobacco use, or previous revascularization) among the three groups. Despite an excess of minor untoward reactions for the urokinase groups (chills, 26.5% and 23.4% for groups A and B versus 0% for group C; p<0.01), there was no significant difference with respect to major bleeds (two, none, and two for groups A, B, and C, respectively; p=NS). At 96 hours after presentation, no significant difference emerged in the incidence of new cardiac events: new myocardial infarctions developed in 10.2% of group A, 6.4% of group B, and 3.8% of group C (p=NS); intractable angina occurred in 6.1% of group A, 10.6% of group B, and 9.4% of group C (p=NS). There were no deaths. All three groups encountered a similar incidence of overall cardiac events: 16.3%, 17.0%, and 13.2% for groups A, B, and C, respectively (p=NS). Although trial enrollment was to extend to 600 patients, interim analysis led to early cessation of enrollment due to a negative trend in respect to outcome after thrombolysis.

Conclusions. High-dose intravenous urokinase followed by either heparin or aspirin can be safely administered to a broad, unselected group of patients with unstable angina. However, this study suggests that no clinical advantage is conferred by urokinase, with either adjunctive antiplatelet therapy over standard heparin therapy alone, when given relatively late (mean, 8.7 hours) after admission for unstable angina. A possible detrimental effect cannot be excluded. (Circulation 1992;86:1407-1414)

Key Words • urokinase • acute ischemic syndromes

Unstable angina pectoris is the leading cause of cardiac admissions to hospitals in the United States today. Despite the similar pathogenesis of unstable angina and acute transmural myocardial infarction and despite the widespread success and the established role of thrombolytic therapy for the latter condition, the use of intravenous thrombolytic therapy in unstable angina remains controversial. An enhanced systemic procoagulant state, rheological abnormalities, and excess platelet activation—all superimposed on plaque rupture— predispose to intracoronary thrombus, which is the proximate cause of coronary occlusion and consequent clinical manifestations of acute myocardial infarction, intractable chest pain, and/or cardiac death. Potential benefits of intravenous pretreatment with nonspecific thrombolytic agents in unstable angina might accrue not only from the anatomic clot lysis but also from lowering of serum viscosity and generation of fibrin-split products, which are known to be very potent antiplatelet agents, all, thus, leading to potential stabilization of the acute ischemic syndrome.

Two large-scale prospective randomized clinical trials in the past decade have demonstrated that intravenous heparin clearly reduces progression to new myocardial...
infarction and intractable angina pectoris after admission for unstable angina.9,10 Thus, the gold standard against which intravenous thrombolytic therapy in unstable angina must be compared in the decade of the 1990s is full-dose intravenous heparinization with or without adjunctive oral aspirin.9–11 A plethora of both observational and small prospective, randomized, placebo-controlled trials have studied intravenous and intracoronary thrombolytic agents12–23 in unstable angina, but only five studies have been presented to date comparing fibrinolytic therapy with full-dose intravenous heparin therapy in unselected patients with this entity.24–28 These studies have been small, and the evidence for clinical benefit has been unclear.

Given the epidemiological importance of developing optimal pharmacological therapy for unstable angina, a multicenter study group to assess intravenous pretreatment with a nonspecific fibrinolytic agent, urokinase, in unstable angina was assembled in 1989 to prospectively assess whether intravenous urokinase pretreatment soon after hospital admission would lower the short-term risk of progression of unstable angina to new infarction, intractable angina, or death compared with the emerging conventional therapy with intravenous heparin. Urokinase was chosen because of previous extensive clinical experience of this agent and its excellent safety profile.29–32 A pilot trial of intravenous urokinase previously suggested its clinical efficacy in unstable angina.19 A secondary hypothesis was that either aspirin or heparin might then be the preferred adjunctive antithrombotic agent after intravenous urokinase in unstable angina, either from a safety or an efficacy point of view. The current report details the clinical end point and safety data of our multicenter, placebo-controlled, partially blinded study.

Methods

This multicenter randomized trial was conducted at five clinical sites and one angiographic core laboratory. The data coordinating center and statistical analysis were provided by Abbott Laboratories in Abbott Park, Ill. All patients presenting to the emergency department or inpatient floors of any of the cooperating centers with a clinical history compatible with unstable angina were screened by one of the investigators for eligibility for randomization. Patients were entered into the study between May 1, 1989, and September 1, 1990, when enrollment was ceased pursuant to a decision of the Data Monitoring and Safety Committee of this trial.

To be eligible for entry, the patient must have had a history of unstable angina in which an acute, transmural, myocardial infarction has been excluded. The patient was expected to present with typical anginal chest, neck, or arm pain that had occurred within 24 hours before screening. The pain must have occurred at rest, have had a duration of >10 minutes, be produced with substantially less exertion than previously required, or be unresponsive to the patient's prescribed therapeutic regimen of antianginal therapy. Eligibility also required ECG evidence of 1) subendocardial ischemia characterized by either ST segment depression or symmetric T wave inversion in at least two adjacent leads or 2) reversible ST segment elevation and/or hyperacute T waves occurring only during anginal chest pain and not present when asymptomatic. In the event of a nondiag-

![FIGURE 1. Flow chart of study design.](http://circ.ahajournals.org/)

nostic ECG, the patient could still be eligible for randomization if a clear history of coronary artery disease evidenced by documented previous infarction or prior coronary arteriography displaying >50% stenosis in any coronary artery was present. In the event of a normal ECG during anginal chest pain, the patient was excluded from the study.

Exclusion criteria were 1) age of <18 or >75 years, 2) general exclusion to thrombolytic therapy as defined in the Thrombolysis in Myocardial Infarction (TIMI) II-B trial,3 3) coronary artery bypass surgery or angioplasty at any time during the 6 months before randomization, and/or 4) known or suspected sensitivity to aspirin, urokinase, or heparin.

Study Design

After confirming eligibility, the patient was asked to provide informed consent. Next, a randomized, partially blinded, three-arm design was used for administration of study drug therapy as outlined in Figure 1. At the inception of the study, enrollment of 200 patients into each of the three arms was planned to detect a 25% reduction in aggregate end points (assumed to be 30% for the "conventional therapy" group) with a power of >80% at the p<0.05 level. However, on September 1, 1990, the Data Safety Monitoring Board analyzed the interim results of the first 150 patients, and because of the absence of a trend favoring active therapy, further randomization was not felt to be justified on an ethical basis. Group A (49 patients) received blinded, active urokinase study drug and full-dose intravenous heparinization. Specifically, 3 million units urokinase was administered intravenously over 90 minutes, of which the first 1.5 million units were given as a "bolus" over 3–5 minutes. An open-label heparin bolus of 5,000 units was administered coincident with the bolus administration of the urokinase study drug via separate intravenous line. After the administration of the 90-minute urokinase study drug, continuous infusion of heparin was started at 1,000 units/hr. The heparin infusion rate was adjusted to maintain the activated partial thromboplastin time (aPTT) at 1.5–2 times control. The aPTT was determined within 4–6 hours after heparinization and again at 12–24 hours on day 1. For the remainder of the 96-hour study period, the aPTT was determined at least daily. Group B (47 patients) received open-label urokinase, 3 million units i.v. over 90 minutes and 325 mg aspirin orally at the time of study drug initiation and daily in the morning for the remainder of the study period. Group C (53 patients) received a placebo infusion over 90 minutes together with a heparin bolus of 5,000 units. At the end of the study drug infusion,
heparin infusion was started and continued in a manner identical to group A.

The primary end point of the study was clinical status at 96 hours after admission in respect to new major cardiac events. Specifically, the incidence of new myocardial infarction, intractable angina requiring emergency interventional therapy, or death was monitored by a specific study nurse at each center during the period of the investigation. ECGs were performed daily and during each episode of chest pain occurring during the study period. Serial creatine kinase (CK) and MB bands were obtained every 12 hours for the first 48 hours of the study and then daily for the remainder of the study. In the event of new chest pain, CK and MB bands were obtained every 12 hours for an additional 48 hours. New myocardial infarction was defined as a protracted episode of chest pain accompanied by a subsequent elevation of the CK >1.5 times normal together with a corresponding elevation of the CK-MB. Chest pain was defined as intractable if it persisted for >20 minutes despite intravenous nitroglycerin.

Coronary arteriography was prohibited for the first 96 hours of the study by protocol unless symptoms were deemed by the investigators to warrant emergency invasive therapy. Each patient’s clinical course was evaluated carefully, both prospectively and retrospectively, for bleeding and/or untoward drug-related complications. Other anticipated adverse effects included but were not limited to bleeding, exacerbation of angina, bradycardia or tachycardia, hypertension or hypotension, new cerebrovascular accident, nausea, vomiting, dizziness, vertigo, dyspnea, diaphoresis, renal failure, chills, fever, headache, or an anaphylactic reaction. When clinical hemorrhage occurred, it was categorized according to site and severity. Mild bleeding was categorized as that leading to no clinical consequence not requiring transfusion and <250 ml estimated blood loss. Moderate bleeding was defined as otherwise mild bleeding but leading to 250–500 ml of observed blood loss. Severe bleeding was characterized by >500 ml blood loss, requiring transfusion. Life-threatening bleeding was defined as intracranial bleeding or any internal or external bleeding that led to hemodynamic instability.

Concomitant Therapy

The thrombolytic and adjunctive antithrombotic regimen was determined by study protocol. Antianginal therapy consisted of maximally tolerated nitrates and stepwise addition of calcium channel blockers and then β-blockers in conjunction with the patient’s outpatient drug regimen, if compatible with this study. The use of each class of antianginal and other medications was carefully monitored by the study research nurse and appropriately tabulated.

Statistical Analysis

Baseline variables were analyzed by an F test using a two-way ANOVA for continuous variables; the Mantel-Haenszel test was used for discrete variables for comparison among the three treatment groups.34 Angiographic data were analyzed for statistical significance using one-way ANOVA. The incidences of primary end point events in each of the three groups were compared using the χ² test. All values are expressed as the mean±SD for continuous variables. A two-tailed value of p<0.05 was considered significant.

Results

All data were analyzed according to the intention-to-treat principle.

Population

One hundred forty-nine patients were randomized during the period of the study from May 1, 1989, through September 1, 1990. Group A consisted of 49 patients who received blinded urokinase plus heparin. Group B consisted of 47 patients who received open-label urokinase plus aspirin. Group C received blinded urokinase placebo plus heparin. The epidemiological descriptors of these 149 patients are listed on Table 1. No significant difference was seen in respect to mean age, percent male sex, race (percent Caucasian), history of previous hypertension, previous myocardial infarction, or diabetes mellitus. Only a very small proportion of our population had a history of previous angioplasty or bypass at any time before 6 months from enrollment, although a nonsignificant surfeit of these procedures was observed in group C. A very small proportion of patients in each of the three groups had a history of previous congestive heart failure. Non–Q wave myocardial infarction was documented as the etiology of the qualifying episode of chest pain by an elevated CK-MB within the first 24 hours in 4.1%, 6.4%, and 5.7% of patients in groups A, B, and C respectively (p=NS).

Table 2 details the antianginal regimen that patients received during the period of the study. No significant difference among the three groups was noted in respect to use of any antianginal agents. Specifically, a similar proportion of patients in each group received intravenous or oral β-blockers, nitrates intravenously or sublingually, verapamil, diltiazem, or nifedipine.

Safety of the Study Drugs

The side effects observed in each of the three treatment groups are summarized in Table 3. Although chills were substantially more common in patients receiving urokinase, fever was equally rare in each of the three groups. No patient in any of the three groups developed
an anaphylactic reaction. Two percent of patients in group A and C but none in group B experienced a major bleed. There was no intracranial or other life-threatening bleeding in any of the three treatment groups. One patient in group C developed a retroperitoneal bleed. Minor bleeds were seen in 14% of group A, 8% of group B, and 5% of group C. Although this difference was not statistically significant, it suggests a trend toward increased minor bleeding in the urokinase-and-heparin group.

Clinical Outcome

Table 4 details the primary end points of the trial on an intention-to-treat basis. A slight excess of patients in groups A and B, 10.2% and 6.4%, respectively, in comparison to 3.8% of group C experienced a new myocardial infarction during the study (p=NS). No significant difference emerged in the incidence of new intractable angina pectoris requiring mechanical revascularization among the three groups (6.1% for group A, 10.6% for group B, and 9.4% for group C). There were no deaths in any group. The likelihood of any new major cardiac event was slightly greater in groups A (16.3%) and B (17%) than in group C, the placebo-plus-heparin group (13.2%), but this difference did not reach statistical significance. These data demonstrate that although large-dose intravenous urokinase may be administered safely essentially in a bolus fashion over 90 minutes in a nonselected population of patients with unstable angina, no major clinical benefit may be expected using thrombolysis with either adjunctive therapy (heparin, or aspirin) over conventional therapy (heparin) for unstable angina at our institutions.

Discussion

This randomized partially blinded trial of the nonselective thrombolytic agent urokinase for intravenous therapy of unstable angina pectoris compared with full-dose intravenous heparin as conventional therapy is the largest trial reported to date of nonselective fibrinolytic therapy in this disease entity. Despite clear documentation of overall safety of large-dose intravenous urokinase in a broad unselected population of unstable angina patients, we failed to detect any clinical advantage in the two thrombolytic arms of the trial when compared with standard heparin therapy alone. Furthermore, despite failing to reach statistical significance, an unfavorable trend emerged toward more myocardial infarctions in both urokinase groups compared with heparin alone. Despite a large number of observational trials of thrombolytic therapy in unstable angina, there were five relatively large randomized trials of intravenous thrombolytic therapy to full-dose intravenous heparin24–28 in unselected patients. Heparin infusion, due to its documented clinical efficacy, must be considered benchmark therapy when evaluating any.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>A (UK + Hep)</th>
<th>B (UK + ASA)</th>
<th>C (placebo + Hep)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.1±11.5</td>
<td>59.8±9.2</td>
<td>59.9±10.8</td>
<td>0.276</td>
</tr>
<tr>
<td>Male (%)</td>
<td>71</td>
<td>70</td>
<td>62</td>
<td>0.955</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>90</td>
<td>81</td>
<td>77</td>
<td>0.955</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>34.7</td>
<td>40.4</td>
<td>34.0</td>
<td>0.510</td>
</tr>
<tr>
<td>History MI (%)</td>
<td>30.6</td>
<td>25.5</td>
<td>26.4</td>
<td>0.938</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>16.3</td>
<td>19.1</td>
<td>11.3</td>
<td>0.559</td>
</tr>
<tr>
<td>Previous PTCA or CABG (%)</td>
<td>6.1</td>
<td>4.3</td>
<td>13.2</td>
<td>0.098</td>
</tr>
<tr>
<td>Non-Q MI on presentation (%)</td>
<td>4.1</td>
<td>6.4</td>
<td>5.7</td>
<td>0.995</td>
</tr>
<tr>
<td>CHF by history (%)</td>
<td>0.0</td>
<td>4.3</td>
<td>3.8</td>
<td>0.921</td>
</tr>
<tr>
<td>History of tobacco use (%)</td>
<td>10.2</td>
<td>14.9</td>
<td>18.9</td>
<td>0.552</td>
</tr>
</tbody>
</table>

UK, urokinase; Hep, heparin; ASA, aspirin; MI, myocardial infarction; PTCA, coronary angioplasty; CABG, coronary artery bypass surgery; non-Q MI, non-Q wave myocardial infarction; CHF, congestive heart failure

Table 2. Concomitant Antianginal Therapy

<table>
<thead>
<tr>
<th>Group</th>
<th>A (UK + Hep)</th>
<th>B (UK + ASA)</th>
<th>C (placebo + Hep)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>49</td>
<td>47</td>
<td>53</td>
<td>NS</td>
</tr>
<tr>
<td>Nitrates (oral or topical)</td>
<td>34</td>
<td>36</td>
<td>43</td>
<td>NS</td>
</tr>
<tr>
<td>Nitrates (IV)</td>
<td>27</td>
<td>33</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>β-Blocker (oral)</td>
<td>25</td>
<td>26</td>
<td>23</td>
<td>NS</td>
</tr>
<tr>
<td>β-Blocker (IV)</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Verapamil</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>22</td>
<td>20</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>NS</td>
</tr>
</tbody>
</table>

UK, urokinase; Hep, heparin; IV, intravenous; NS, not significant at p<0.05.
new intervention. The landmark Montreal Heart Institute study demonstrated unequivocal superiority of heparin over aspirin or placebo for the control of additional anginal episodes in unstable angina.10 Both heparin and aspirin separately were effective at decreasing the incidence of acute myocardial infarction, but an addendum to the study25 demonstrated that heparin was even more effective than aspirin at reducing the incidence of new myocardial infarction in unstable angina, holding it to approximately 1%. This low incidence would be very difficult to top with any new intervention.

Previous Studies

Details of the five prospective studies comparing intravenous thrombolytic therapy in unstable angina to full-dose heparin therapy are presented in Table 5. The largest of these, the UNASEM European trial of anistreplase,27 administered thrombolytic therapy after a baseline coronary arteriogram demonstrated significant coronary artery disease. Inpatient clinical outcome and follow-up catheterization outcome at 12–48 hours after admission were the primary end points. These investigators noted that absolutely no clinical benefit was conferred by anistreplase over heparin alone. Angiographic benefit alone was noted in only that subgroup of patients having total obstruction due to coronary thrombosis at baseline coronary arteriography. Two smaller European studies analyzed the benefit of streptokinase given to patients with unstable angina and compared this with full-dose heparin alone.25,26 These two studies differed in clinical outcome, with one showing modest clinical benefit favoring the thrombolytic. Two prospective clinical trials compared recombinant tissue-type plasminogen activator (rt-PA) with full-dose heparin in unstable angina.24,28 Both found that conventional therapy with heparin was either clinically more effective or associated with less adverse secondary end points. In the study of Freeman et al, thrombolytic therapy was associated with deterioration in an aggregate index of ischemia as measured by 201T1 scintigraphy.28 Furthermore, there were more episodes of silent ischemia on continuous 24-hour monitoring. The ongoing TIMI-III megatrial of intravenous thrombolytic therapy of t-PA in unstable angina has not yet been completed.

Overall review of these five trials together with the present study further strengthens the conclusion that fibrinolytic therapy in a broad, unselected population of unstable angina confers no clinical benefit over intravenous heparin. Moreover, the possibility that thrombolysis in unstable angina may actually adversely affect outcome must be seriously entertained, given our findings showing a trend toward more myocardial infarctions in the thrombolytic groups in this study as well as more extant ischemia in the study of Freeman et al.28 Why this may be the case must necessarily remain the subject of speculation at the current time. Hypothesizes center around three major directions of thought. The first supposes that the clinical benefit conferred by fibrinolytic therapy in unstable angina is relatively small or nonexistent compared with heparin alone, whereas the clinical detriment due to either bleeding complications or worsening of either culprit vessel anatomy or platelet and/or coagulation activation may be significant and exceed the small clinical benefit. The Third Inter-

Table 3. Side Effects of Therapy

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients</th>
<th>A (UK + Hep)</th>
<th>B (UK + ASA)</th>
<th>C (placebo + Hep)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>49</td>
<td>47</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Chills (%)</td>
<td></td>
<td>26.5</td>
<td>23.4</td>
<td>0.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fever ≥38°C (%)</td>
<td></td>
<td>0</td>
<td>2.1</td>
<td>1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Nausea (%)</td>
<td></td>
<td>4.1</td>
<td>6.4</td>
<td>3.8</td>
<td>NS</td>
</tr>
<tr>
<td>Vomiting (%)</td>
<td></td>
<td>14.3</td>
<td>14.9</td>
<td>0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Anaphylaxis (%)</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Anemia (%)</td>
<td></td>
<td>0</td>
<td>0</td>
<td>2.0</td>
<td>NS</td>
</tr>
<tr>
<td>Serious bleed (%)</td>
<td></td>
<td>0</td>
<td>0</td>
<td>2.0</td>
<td>NS</td>
</tr>
<tr>
<td>Intracranial</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td></td>
<td>0</td>
<td>0</td>
<td>2.0</td>
<td>NS</td>
</tr>
<tr>
<td>Minor bleed (%)</td>
<td></td>
<td>14</td>
<td>8</td>
<td>5.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

UK, urokinase; Hep, heparin; ASA, aspirin; *anemia, hemoglobin <10 at any time during study period.

Table 4. Primary End Points by Intention to Treat

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients</th>
<th>A (UK + Hep)</th>
<th>B (UK + ASA)</th>
<th>C (placebo + Hep)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>49</td>
<td>47</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>MI (%)</td>
<td></td>
<td>5 (10.2)</td>
<td>3 (6.4)</td>
<td>2 (3.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Intractable angina (%)</td>
<td></td>
<td>3 (6.1)</td>
<td>5 (10.6)</td>
<td>5 (9.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Death (%)</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Any of above (%)</td>
<td></td>
<td>8 (16.3)</td>
<td>8 (17.0)</td>
<td>7 (13.2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

UK, urokinase; Hep, heparin; ASA, aspirin; MI, new myocardial infarction; NS, not significant at p<0.05.
national Study of Infarct Survival (ISIS-III) investigators have shown\(^{3,36}\) that irrespective of the agent used (streptokinase, t-PA, or anistreplase) in the first 24 hours, there is excessive clinical hazard (death) and that clinical benefit of the agent becomes apparent only after 24 hours. Conceivably, by a variety of mechanisms, including activation of the highly thrombogenic, ulcerated, endothelial surface of an active plaque and/or the exposure of such surfaces to direct platelet and thrombin activation, and so on, thrombolysis in unstable angina may lead to a paradoxical increase in ischemic episodes, which may then be associated with a potentially adverse outcome.\(^{37}\) Finally, preliminary angiographic evaluation of thrombus in unstable angina patients suggests that it primarily consists of platelets and fibrin ("white thrombus"), is nonobstructive, and is largely resistant to lytics\(^{38}\) in contrast to the erythrocyte-rich occlusive, "red" thrombus commonly present in acute myocardial infarction. Such a finding, if confirmed, would then speak strongly against use of lytics in unstable angina.

Yet another hypothesis to explain the outcome in this trial revolves about the heterogeneity of unstable angina. It has been well demonstrated that many patients who are medically refractory in unstable angina "harbor" thrombus at coronary arteriography; a clustering of such patients might then be associated with an enhanced clinical outcome after thrombolysis.\(^{39,40}\) Alternatively, we and others have recently demonstrated that unstable patients with new-onset exertional angina or acceleration of previous stable exertional angina is associated with an extremely low rate of progression to new ischemic events, and consequently, any clinical benefit to be conferred by thrombolysis over the already low risk associated with conventional heparin therapy in this disease entity would, again, require a much larger study population. We believe that future trials of thrombolytic therapy in unstable angina should be confined only to those patients with coronary insufficiency syndrome and/or new-onset rest angina, which we and others have shown to be associated with a risk of clinical progression to a new ischemic end point >25% and as high as 40%.\(^{39,41}\) Confinement of randomization to such patients in a thrombolytic trial might then answer the question as to whether thrombolitics in a highly selected population may confer clinical benefit. Observational trials from Europe detailing small cohorts of patients suggest that urokinase and streptokinase may be of clinical benefit in patients refractory to nitrates, calcium blockers, and \(\beta\)-blockers and anticoagulation.\(^{18,42}\)

Our secondary hypothesis was that either full-dose heparin or full-dose aspirin might lead to a preferential clinical outcome in unstable angina when added to high-dose urokinase. Neither clinical benefit nor excess bleeding risk was evident when one adjunctive agent was compared with the other. Accordingly, if thrombolytic therapy is to be used in unstable angina, aspirin alone might suffice from the convenience point of view. Caution is indicated, however, because in absence of thrombolytic therapy, heparin clearly appears superior to aspirin at prevention of infarction after admission for unstable angina.\(^{35}\)

**Study Limitations**

The choice of agent, urokinase, was based on the extensive previous clinical experience with urokinase in treating pulmonary embolism, extending to deep venous thrombosis and acute myocardial infarction. Because of its human origin, untoward allergic effects of this agent would ordinarily have been expected to be minimal. Indeed, we found that a substantial minority of patients developed chills during the rapid administration of the agent, although these were easily terminated with either intravenous diphenhydramine or meperidine. This side effect, although well tolerated, should be weighed in the selection of urokinase for unstable angina. Nevertheless, a superb safety record was demonstrated in the study notwithstanding the high dose of urokinase (3 million units) administered rapidly in our study. Comparison with trials of t-PA, anistreplase, and streptokinase in unstable angina revealed that the serious side effects of urokinase are relatively infrequent and hence compare very favorably with these other agents.\(^{3,6,36}\)

Although the number of patients randomized by this trial exceeds any of the previously published trials, it is conceivable that a larger trial of some 600–1,200 patients may have confirmed the superiority of heparin over urokinase with respect to clinical outcome. The relatively late administration of thrombolytic in this study (8.6 hours) compared with acute myocardial infarct trials also remains a serious limitation. Conceivably, at the time of presentation to the emergency department, some unstable angina patients are in a true preinfarction state, and if such patients were treated with thrombolytic agents, clinical benefit might be demonstrable. In this connection, patients in ISIS-II, with suspected acute myocardial infarction, who did not "rule in" for myocardial infarction experienced an enhanced clinical outcome with streptokinase;\(^{4}\) in the ASSET trial, patients presenting with nonspecific ECG patterns and, hence, assumed to have unstable angina in retrospect also enjoyed same clinical benefit.\(^{5}\) These subgroups of patients were clinically suspected to have acute myocardial infarction because of their presenting complaint of protracted severe chest pain. These pa-

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>No. of patients</th>
<th>Agent</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>NeriSerneri et al(^{24})</td>
<td>1990</td>
<td>97</td>
<td>t-PA</td>
<td>No clinical benefit</td>
</tr>
<tr>
<td>Steffenino et al(^{25})</td>
<td>1990</td>
<td>40</td>
<td>Streptokinase</td>
<td>No clinical benefit</td>
</tr>
<tr>
<td>Saran et al(^{26})</td>
<td>1990</td>
<td>48</td>
<td>Streptokinase</td>
<td>Clinical benefit</td>
</tr>
<tr>
<td>UNASEM(^{27})</td>
<td>1991</td>
<td>159</td>
<td>APSAC</td>
<td>No clinical benefit; angiographic improvement</td>
</tr>
<tr>
<td>Freeman et al(^{28})</td>
<td>1992</td>
<td>70</td>
<td>t-PA</td>
<td>No clinical benefit and thrombolysis</td>
</tr>
</tbody>
</table>

t-PA, tissue-type plasminogen activator; APSAC, anisoylated plasminogen streptokinase activator complex.
tients were generally treated soon after their last episode of chest pain, and it is conceivable that if our study population had similarly received thrombolitics much sooner than 8.5 hours after pain, an enhanced outcome may have been demonstrated.

Although some of the other randomized trials used baseline angiography, the investigators in this current trial expressly chose not to use angiography since the end point of the trial was clinical and angiography soon after the study drug administration might be associated with hemorrhagic complications. Although we cannot comment on the serial effect on culprit vessel anatomy, as a result of any of the three study drug arms in this trial, the effects of therapy on clinical outcome are independent, in our view, of the performance of such angiography. Indeed, no significant difference amongst the three treatment groups in respect to global left ventricular function or severity of culprit stenosis of the ischemia-related artery could be documented at posttherapy angiography performed at the mean of 105 hours after study entry in the current study.

Conclusions

This randomized study of a nonselective fibrinolytic agent, urokinase, administered in a large dose intravenously soon after presentation with unstable angina failed to detect any clinical benefit at 96 hours after admission compared with conventional full-dose intravenous heparin therapy in a broadly representative population of patients with unstable angina. Despite the clinical safety of urokinase, even when given with either concomitant aspirin or full-dose heparin over a 96-hour period, such therapy cannot be routinely recommended for unselected patients with unstable angina. Future trials of thrombolytic therapy in unstable angina should be focused only on high-risk patients, which may be identified by presentation with coronary insufficiency or new-onset rest angina pattern, substantial ST segment displacement and/or those in whom baseline assessment of fibrinolytic system function documents ongoing thrombosis.

Acknowledgments

We acknowledge the enthusiastic participation of the physicians and nurses at the participating institutions. Mrs. Faye Colando is especially credited with the preparation of this manuscript. We also wish to express our gratitude to Abbott Laboratories for its support of this study.

References


36. ISIS-3 (Third Interventional Study of Infarct Survival) Collaborative Group: Presented at the 40th Annual Scientific Session of the American College of Cardiology, Atlanta, Georgia, March 1991


Randomized trial of thrombolysis versus heparin in unstable angina.
T L Schreiber, D Rizik, C White, G V Sharma, M Cowley, G Macina, P S Reddy, L Kantounis,
G C Timmis and A Margulis

_Circulation_. 1992;86:1407-1414
doi: 10.1161/01.CIR.86.5.1407

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 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/86/5/1407

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/