Multicenter Patency Trial of Intravenous Anistreplase Compared With Streptokinase in Acute Myocardial Infarction

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Thrombolytic therapy has been shown to improve clinical outcome when administered early after the onset of symptoms of acute myocardial infarction; the mechanism of benefit is believed to be reestablishment and maintenance of coronary artery patency. Anistreplase is a second generation thrombolytic agent that is easily administered and has a long duration of action. To compare anistreplase (30 units/2-5 min) and therapy with the Food and Drug Administration-approved regimen of intravenous streptokinase (1.5 million units/60 min), a randomized, double-blind, multicenter patency trial was undertaken in 370 patients less than 76 years of age with electrocardiographic ST segment elevation who could be treated within 4 hours of symptom onset. Coronary patency was determined by reading, in a blinded fashion, angiograms obtained early (90–240 minutes; mean, 140 minutes) and later (18–48 hours; mean, 28 hours) after beginning therapy. Early total patency (defined as Thrombolysis in Myocardial Infarction grade 2 or 3 perfusion) was high after both anistreplase (132/183=72%) and streptokinase (129/176=73%) therapy, and overall patency patterns were similar, although patent arteries showed “complete” (grade 3) perfusion more often after anistreplase (83%) than streptokinase (72%) (p=0.03). Similarly, residual coronary stenosis, determined quantitatively by a validated computer-assisted method, was slightly less in patent arteries early after anistreplase (mean stenosis diameter, 74.0%) than streptokinase (77.2%, p=0.02). In patients with patent arteries without other early interventions, reocclusion risk within 1–2 days was defined angiographically and found to be very low (anistreplase=1/96, streptokinase=2/94). Average coronary perfusion grade was greater, and percent residual stenosis was less, at follow-up than on initial evaluation and did not differ between treatment groups. Enzymatic and electrocardiographic evolution was not significantly different in the two groups. Despite rapid injection, anistreplase was associated with only a small (4–5 mm Hg), transient (at 5–10 minutes) mean differential fall in blood pressure. In-hospital mortality rates were comparable for anistreplase and streptokinase (5.9%, 7.1%). Stroke occurred in one (0.5%) and three (1.6%) patients, respectively; one stroke was hemorrhagic. Other serious bleeding events and adverse experiences occurred uncommonly and with similar frequency in the two groups. Thus, for the end points of our study (patency, safety), anistreplase and streptokinase showed overall favorable and relatively comparable outcomes, with a few differences. When given to patients within 4 hours from onset of symptoms of acute myocardial infarction, both thrombolytic agents established high and similar total patency rates within a mean of 2.4 hours after therapy, although quantitative residual stenosis was slightly less early after anistreplase. The clinical importance of these or other differences, such as ease of drug administration, are uncertain but will be answered by ongoing comparative mortality studies and by broader clinical experience. In the interim, these data support the continued use of both of these agents in acute myocardial infarction. (Circulation 1991;83:126–140)
The central role of coronary thrombosis as an initiating mechanism in acute myocardial infarction has been well established in the past decade.\textsuperscript{1,2} Thrombolytic therapy for coronary thrombosis has progressed in parallel during the 1980s from investigational novelty\textsuperscript{3,4} to established clinical reality.\textsuperscript{5} Initially, the feasibility of coronary thrombolysis was established using intracoronary administration of the conventional plasminogen activators streptokinase\textsuperscript{3-6} and urokinase.\textsuperscript{7} Subsequently, the potential of intravenously administered agents, especially streptokinase and tissue-type plasminogen activator (t-PA), to establish coronary patency,\textsuperscript{6,8,9} to improve left ventricular function,\textsuperscript{10,11} and to reduce mortality\textsuperscript{12-14} was shown. Current investigative interest is focusing on the development of better reperfusion regimens, including new thrombolytic agents\textsuperscript{15-19} and combinations,\textsuperscript{20-22} appropriate ancillary medical therapies (e.g., thrombin and platelet inhibitors in addition to traditional agents such as nitroglycerin and \(\beta\)-blockers\textsuperscript{23,24}), and invasive procedures (e.g., angiography, angioplasty, and surgery\textsuperscript{24,25}).

Streptokinase, t-PA, and, more recently, anistreplase (anisoylated plasminogen streptokinase activator complex, APSAC\textsuperscript{19}) have been approved for intravenous use in acute myocardial infarction. Each may have relative advantages and disadvantages. In an attempt to extend and improve on these agents, additional intravenous thrombolytic agents are undergoing clinical trials, including the relatively non-fibrin-selective agents urokinase\textsuperscript{15} and anistreplase,\textsuperscript{19} the more fibrin-selective agent pro-urokinase,\textsuperscript{17} and combination regimens (e.g., t-PA with urokinase,\textsuperscript{20} streptokinase,\textsuperscript{22} or pro-urokinase\textsuperscript{21}). Goals in development of these newer regimens include improved early patency rates, reduced reocclusion risk, greater ease of administration, improved safety, and cost considerations.

Anistreplase was chemically synthesized as a custom-designed compound to overcome perceived disadvantages of the thrombolytic use of intravenous streptokinase.\textsuperscript{26} Pharmacological objectives in synthesizing anistreplase were to provide for 1) simpler administration, 2) enhanced fibrin (thrombus) affinity, and 3) longer plasma half-life.\textsuperscript{27} In anistreplase, streptokinase is combined in a 1:1 molar ratio with lys-plasminogen, which has greater fibrin affinity than the native glu-plasminogen form.\textsuperscript{28} Anistreplase is also chemically protected at its active site on the plasminogen molecule by acylation, rendering it temporarily inactive. In this form, it can be injected rapidly without causing the profound hypotension associated with bolus injection of its parent streptokinase, as observed in animal studies.\textsuperscript{29} It can also circulate in its neutral form (protected from inactivation) and find and bind in a semiselective fashion to fibrin, where it is gradually and continuously activated by hydrolysis.\textsuperscript{27,30} The long half-life of fibrinolytic activity, averaging about 90–120 minutes,\textsuperscript{27,31} compared with 20–25 minutes for streptokinase and 5–10 minutes for t-PA, offers the potential for more complete initial thrombolysis, lowered early reocclusion risk, and a simplified administration regimen, as well as an increased concern for additional bleeding risk.

Thrombolytic drug evaluation in acute myocardial infarction has focused on comparisons with placebo and standard regimens for end points of 1) coronary reperfusion or recanalization (defined by preinterventional and postinterventional angiography) or patency (defined by postinterventional angiography only), 2) left ventricular function and infarct size, and 3) mortality. Safety comparisons between different regimens are of additional importance, including rates of transfusion and intracranial hemorrhage. Recent comparisons of anistreplase with placebo or nonthrombolytic therapy for these end points have been favorable,\textsuperscript{32-35} but comparisons of the simplified anistreplase administration regimen with those of other thrombolytic agents, especially intravenous regimens, are limited.\textsuperscript{18,19}

Patency is an appealing end point for comparative studies of moderate size because in-hospital and long-term benefits of thrombolysis are believed to be most closely related to early reestablishment and maintenance of coronary blood flow.\textsuperscript{36} Thus, the purpose of this study was to compare the effects of the new agent anistreplase and standard therapy with intravenous streptokinase on early coronary patency and subsequent clinical course in patients presenting early after the onset of symptoms of acute myocardial infarction.

**Methods**

The aims of the Second Thrombolytic Trial of Eminase (anistreplase) in Acute Myocardial Infarction (TEAM-2) study group were 1) to determine the therapeutic effects of anistreplase on patency, assessed qualitatively and quantitatively, early after myocardial infarction, 2) to compare these patency results with a standard thrombolytic regimen of intravenous streptokinase, 3) to determine absolute and relative reocclusion rates within 1–2 days after the two regimens, and 4) to assess patient safety and tolerance.

**Patient Selection**

Patients who were admitted to the 27 enrolling centers of TEAM-2 (listed in "Appendix") were selected for study entry based on the following criteria: age less than 76 years; symptoms of acute ischemia (chest pain) lasting more than 30 minutes but 4
hours or less from onset to treatment; and ST segment elevation of 0.1 mV or more in one or more limb leads or 0.2 mV or more in one or more precordial (V) leads suggestive of ischemic injury and not relieved by sublingual (or intravenous) nitroglycerin.

Exclusion criteria were age 76 years or more; ongoing cardiogenic shock (systolic blood pressure of 80 mm Hg or less, or vasopressor- or intra-aortic balloon-dependent state); coronary bypass surgery at any time or coronary balloon angioplasty within 1 month; and contraindications to thrombolytic therapy, including recent history (<6 months) of thrombotic cerebrovascular accident or intracranial or intraspinal surgery, hemorrhagic cerebrovascular accident (at any time), active internal bleeding, history of hemorrhagic diathesis, peptic ulceration within 6 months, long-term full-dose anticoagulation with warfarin or heparin, external chest massage or other injury (e.g., traumatic intubation) for this episode of infarction, other major trauma or injury within 10 days, pregnancy or lactation or childbearing potential, prosthetic valves or dilated cardiomyopathy or ventricular aneurysm with thrombus, streptokinase or anistreplase therapy within 6 months, other investigational drug therapy within 2 months, and systolic blood pressure greater than 200 or diastolic blood pressure greater than 120 mm Hg confirmed on one or more additional readings during pretreatment (screening) observations.

Initial Study Plan and Drug Dosing

Patients who met inclusion and exclusion criteria and who gave written, informed consent were randomized in a blind fashion to therapy with anistreplase or streptokinase (double-dummy method). Randomization was achieved by use of consecutively numbered treatment kits according to a block design schedule so that two of every four sequentially enrolled patients would receive anistreplase. Blinding was maintained by administering matching placebo for the treatment that the patient did not receive, that is, anistreplase placebo for patients receiving active streptokinase and streptokinase placebo for those receiving active anistreplase. Lyophilized anistreplase (30 units) was reconstituted to 5 ml with sterile water or saline and administered intravenously during 2–5 minutes within 30 minutes of reconstitution. Two vials (750,000 units/vial) of lyophilized streptokinase were each reconstituted with 5 ml physiologic saline or 5% dextrose and further diluted to a total volume of at least 45 ml. The total dose of 1.5 million IU was administered intravenously by infusion pump throughout a 60-minute period.

Patency Determination

Coronary perfusion status was determined at early angiography, performed as close to 90 minutes after start of therapy as possible, but within a maximum of 240 minutes. Protocol coronary patency was assessed by reading all angiograms in a blind fashion at a central laboratory by one of us (S.G.S.) using the Thrombolysis in Myocardial Infarction (TIMI) criteria.8 Interobserver variability was previously shown to be small in our laboratory for the determination of patency (TIMI grade 2 or 3 perfusion) versus occlusion (grade 0 or 1 perfusion).37

TIMI perfusion grades are defined in detail elsewhere.8,37 However, in brief, grade 0 perfusion is no antegrade flow beyond the point of occlusion; grade 1 perfusion is minimal, incomplete perfusion of dye around clot; grade 2 perfusion (“partial perfusion”) is complete but delayed perfusion of the distal coronary bed; and grade 3 perfusion (“complete perfusion”) is antegrade flow to the entire distal bed at a normal rate. Total patency rate was defined as the proportion of patients with grade 2 plus 3 perfusion, and complete perfusion rate as the proportion with grade 3 perfusion.

Maximum infarct-related artery luminal diameter and area of stenosis were quantitatively determined by one of us (F.L.M.) reading in a blinded fashion the coronary angiographic films using a validated technique38 modified after the method of Brown and averaged from duplicate or triplicate measures of the optimal views (maximal stenosis) and orthogonal views.

Guidelines for Early Mechanical Intervention

A conservative strategy was adopted for the application of mechanical interventions at early angiography. No intervention was allowed for grade 3 perfusion or adequate grade 2 perfusion, unless signs or symptoms of reocclusion were observed. For patients with grade 0, 1, or poor grade 2 flow (typically with >90% residual stenosis), mechanical intervention before the 18–48-hour angiogram was allowed at the discretion of the investigating physicians.

Angiographic Method and Follow-up Study

Patients with initially patent (grade 2 or 3) infarct-related coronary arteries who did not undergo early mechanical intervention (angioplasty, surgery) were given medical therapy (heparin, etc.) and returned for coronary angiography at approximately 24 hours (18–48 hours) to assess the continued course of patency or reocclusion.

At least two views of the infarct-related artery (defined with assistance of the pretreatment electrocardiogram and left ventriculography) were taken. These included the optimal view for maximizing percent stenosis and its orthogonal (right angle) view. When there was a discrepancy in patency grade among different injections, the final grade (grade on last injection) was used for study purposes.

Ancillary Medications

Heparin was given in a loading dose of 5,000–10,000 units at the start of catheterization. An intravenous infusion (usual initial dose 1,000 units/hr) was commenced after the angiogram and before the thrombin time or activated partial thromboplastin time had decreased to less than about twice the upper limit of the normal range (normally about 2–8 hours after the start of lytic therapy). The optimal
duration of heparin therapy after thrombolysis is unknown but appears to be at least 24 hours.\textsuperscript{39-43} Heparin infusion was, thus, required to be administered for at least 24 hours after dosing (the time of repeated angiogram) and adjusted to keep partial thromboplastin time or thrombin time at about two to three times the upper limit of the normal range. In this study, which was begun before the results of the International Study of Infarct Survival (ISIS-2) were known, aspirin or other antiplatelet therapy was not routinely administered within 24 hours of thrombolytic therapy.

Administration of an antihistamine (diphenhydramine 25–50 mg i.v.) was recommended but not required before thrombolytic therapy. Additional concomitant medications, for example, anti-ischemic therapy, analgesics, antiarrhythmics, oxygen, and so on, were administered in accordance with usual hospital practice.

\textbf{Clinical and Laboratory Observations}

Vital signs, adverse reactions to drug, and clinical conditions suggesting coronary reocclusion, heart failure, bleeding, and other complications associated with acute myocardial infarction or its therapy were closely monitored for 24 hours after dosing and also followed until hospital discharge. Pulse and blood pressure were measured at least twice before dosing, at 5–10-minute intervals for the first 30 minutes, at 15–30-minute intervals for the next 90 minutes, at 3, 4, and at 12 hours after dosing, and then as customarily obtained clinically. Temperature was measured at pretreatment, at 12 hours after dosing, and then at least daily until discharge.

A standard 12-lead electrocardiogram was obtained before study entry, after the 90–240-minute angiogram, at 8 hours after dosing, and at discharge. Additional 12-lead electrocardiograms were obtained on suspicion of coronary artery reocclusion or reinfarction.

Blood was collected for measurement of serum creatine kinase (CK) and its MB isoenzymes (MB CK) before dosing and at 4, 8, 12, 18, 24, and 36 hours after dosing. Sampling for lactic dehydrogenase and its cardiac isoenzyme (LDH-1) were measured before treatment and at 12, 24, 36, 48, and 72 hours. Routine clinical chemistry and hematology assessments were made before dosing, at 24 and 72 hours after dosing, and at discharge. Additional testing was undertaken for unexplained, persisting abnormalities. Urine samples were collected between 24 and 72 hours after dosing for determination of urine hemoglobin or blood. Samples for fibrinogen and plasminogen were collected before dosing, at 90–240 minutes (at initial catheterization), and at 24 hours after dosing; measurements were made at a central laboratory (V.J.M.).

\textbf{Study Hypothesis and Statistical Analysis}

The primary study aim was to test the hypothesis that early coronary patency observed after anistreplase exceeds that after streptokinase. Determined qualitatively and quantitatively. A recruitment goal of 350–400 evaluable patients was set to allow detection of a significant difference ($p<0.05$) in patency rates between streptokinase and anistreplase of 12–15% points (for example, 55% versus 70%\textsuperscript{44}) with a power of 0.8.

Data gathered from the 27 individual sites were pooled before analysis. The major efficacy variables, defined prospectively in order of importance, were 1) patency rates (both total and complete perfusion rates) of the infarct-related coronary artery at 90–240 minutes after dosing graded by TIMI angiographic criteria\textsuperscript{8}; 2) the degree of stenosis of the patent infarct-related coronary artery at 90–240 minutes after dosing measured by a previously validated, computer-assisted quantitative method\textsuperscript{38}; 3) the rate of reocclusion and the TIMI grades (and quantitative degree) of stenosis at about 24 hours after dosing; and 4) frequency, timing, and outcome of mechanical interventions. Prospectively defined secondary efficacy measures of interest included assessment of infarct size by QRS score on discharge electrocardiogram, comparative kinetics of cardiac enzymes (time to peak, value of peak measures), and patency comparisons by length of time from onset of symptoms to therapy and also by length of time from the start of dosing until the initial angiogram (dichotomized at median times). Of additional interest were comparisons of safety and adverse experiences, including bleeding and intracranial hemorrhage.

Results for continuous variables are presented as mean and root mean squared error. Analysis of variance was used to assess treatment differences in continuous variables. Categorical variables were analyzed with logit analysis if they were not ordinal. If there was a natural ordering to the variables, a categorical analysis with an ordinal response was performed. A probability less than 0.05 was considered significant.

\textbf{Results}

\textbf{Entry Characteristics of Study Groups}

A total of 370 patients meeting entry criteria and giving informed consent were entered into the study and randomized, 188 to anistreplase (APSAC) and 182 to streptokinase. Entry characteristics did not differ between groups, except that there was a marginally significant excess of women in the anistreplase group ($p=0.05$) (Table 1). A minority in each group had suffered previous infarction (13%, 14%). A comparable percentage of patients in both groups had histories of hypertension, angina, and diabetes. Time from onset of symptoms to therapy averaged 158 minutes and was nearly identical in each group (anistreplase, 159; streptokinase, 158 minutes). The distribution of time to treatment, also similar in the two groups, is presented in Figure 1. The sum of ST segment elevation on the 12-lead electrocardiogram at entry was also comparable between groups.
A total of 359 patients received assigned therapy, had no major protocol violations, underwent coronary angiography, and had films available for patency determination (anistreplase, 183; streptokinase, 176). The right and left anterior descending coronary arteries were predominantly and approximately equally involved (each in 40–45% of patients in each group). The infarct-related artery was the left circumflex in only 11% and 12% of patients, respectively.

Reasons for exclusion of the 11 patients (3%) from the efficacy assessment were as follows: in the anistreplase group (n=5), intervention (angioplasty or guidewire manipulation) was undertaken before 90 minutes in two, and catheterization was technically unsuccessful (catheter could not be passed to coronary artery) in three; in the streptokinase group (n=6), hemodynamic instability precluding early angiography developed in two, angiographic films were lost in one, the incorrect treatment was given by mistake in one, the catheter could not be passed in one, and the catheterization laboratory was not available in one. Of these patients, one in the anistreplase and two in the streptokinase group subsequently died. All patients, including these, are included in the safety analysis.

**Early Angiographic Patency Results**

The early (90–240 minutes) angiographic assessment was undertaken at a mean (±SD) of 2.4±1.0 hours (median, 2.1 hours). Both the mean time to assessment (anistreplase, 2.34 hours; streptokinase, 2.39 hours; RMSE=0.96, p=0.66) and the distribution of times (Figure 2) were almost identical in the two groups.

As shown in Table 2 and Figure 3, a high and nearly identical rate of total coronary patency was observed at early angiography for the two treatment arms: 72% (anistreplase) and 73% (streptokinase). However, grade 3 (complete) perfusion tended to be higher after anistreplase (60% of patients) than after streptokinase (53% of patients) administration. Thus, of patients with patent arteries at early angiography, 83% showed grade 3 perfusion in the anistreplase group versus 72% in the streptokinase group (p=0.03).

Early patency success by infarct-related artery and treatment group is also shown in Table 2. The small differences observed in patency by treatment for each artery were not significant. However, the overall

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Bar graphs of distributions of times to treatment (in hours) from onset of symptoms in the two groups. Distributions are statistically similar. AN, anistreplase; SK, streptokinase.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Bar graphs of distributions of time from treatment to early angiography (in minutes) in the two groups. Distributions are not statistically different. AN, anistreplase; SK, streptokinase.
distribution of patency rates did differ somewhat among the three arteries: 66% for the left anterior descending artery, 79% for the right coronary artery, and 69% for the circumflex artery ($p=0.03$). The slightly greater patency rate for the right coronary artery, noted here, contrasts with the slightly greater reperfusion rates for the left anterior descending artery, noted in previous reperfusion studies of anistreplase and streptokinase; reasons for these differences are unknown but may be due to chance or to differences in biological responses or study design.

### Table 2. Early (90–240 Minutes) Patency Results

<table>
<thead>
<tr>
<th>Measure</th>
<th>Anistreplase</th>
<th>Streptokinase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow grade (percent)</td>
<td>(n)</td>
<td>(n)</td>
</tr>
<tr>
<td>0</td>
<td>20 (37)</td>
<td>19 (34)</td>
</tr>
<tr>
<td>1</td>
<td>8 (14)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>2</td>
<td>12 (22)</td>
<td>20 (36)</td>
</tr>
<tr>
<td>3</td>
<td>60 (110)</td>
<td>53 (93)</td>
</tr>
<tr>
<td>Total patency (grade 2/3)</td>
<td>72.1 (132/183)</td>
<td>73.3 (129/176)</td>
</tr>
<tr>
<td>Patency by time from symptom onset to treatment (grade 2/3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq$2.7 hr</td>
<td>76 (69/91)</td>
<td>73 (66/90)</td>
</tr>
<tr>
<td>$&gt;2.7$ hr</td>
<td>68 (63/92)</td>
<td>73 (63/86)</td>
</tr>
<tr>
<td>Patency by time from treatment to angiography (grade 2/3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq$2.1 hr</td>
<td>75 (62/83)</td>
<td>69 (64/93)</td>
</tr>
<tr>
<td>$&gt;2.1$ hr</td>
<td>70 (70/100)</td>
<td>78 (65/83)</td>
</tr>
<tr>
<td>Patency by infarct-related artery (grade 2/3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right coronary</td>
<td>81 (68/84)</td>
<td>78 (55/71)</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>63 (47/75)</td>
<td>69 (56/81)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>65 (13/20)</td>
<td>73 (16/22)</td>
</tr>
</tbody>
</table>

*Logistic regression with treatment as a factor and response equal to 0, 1, 2, and 3.
†Logit analysis with treatment as a factor.
‡Logistic regression where patency (0/1, 2/3), treatment, median time, and treatment-by-median time interaction (NS) are factors.
§χ² analysis with Yates' correction.

**Relation of Patency to Time From Symptom Onset to Therapy and From Therapy to Angiography**

Because reperfusion rates after streptokinase and anistreplase have been shown to decline when therapy is initiated after 4 hours from symptom onset, we examined whether time to treatment within 4 hours influenced patency rates. Time to therapy was dichotomized at the median of 2.7 hours. Only small differences were observed within and between groups, and these were not significant (Table 2). Overall, average patency rates were 75% for those treated with either agent in 2.7 hours or less and 71% after 2.7 hours from symptom onset.

Because reperfusion may continue to occur up to and beyond 90 minutes, we also examined the effect of time from treatment to angiography on patency rates (Table 2). Time to angiography was dichotomized at the median of 2.1 hours after dosing. Differences observed between early and later angiography were not significant, either for within-group or between-group comparisons. Overall, 72% of patients had patent arteries when studied earlier than 2.1 hours and 74% when studied later.

**Maintenance of Patency and Reocclusion 1 Day After Thrombolytic Therapy**

One hundred ninety patients with initially patent arteries without interventions were restudied angiographically to assess continued patency or reocclusion after 1 day (18–48 hours; mean±SEM, 28.0±1.0). Only one of 96 anistreplase (1.0%) and two of 94

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**Figure 3.** Bar graph of early (90–240 minutes) coronary patency rates for the two treatment arms. Open bars, rates of total (grade 2 and 3) patency. Hatched bars, rates of complete (grade 3) patency. APSAC, anistreplase; SK, streptokinase.
TABLE 3. Later (18–48 Hours) Patency/Reocclusion in Patients Achieving Early (90–240 Minutes) Patency

<table>
<thead>
<tr>
<th>Late patency grade</th>
<th>Anistreplase n (%)</th>
<th>Streptokinase n (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1 (1)</td>
<td>2 (2.1)</td>
<td>0.60†</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6 (6.3)</td>
<td>6 (6.4)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>89 (93)</td>
<td>86 (91)</td>
<td></td>
</tr>
<tr>
<td>No angiogram*</td>
<td>36 [27]</td>
<td>35 [27]</td>
<td>0.98‡</td>
</tr>
</tbody>
</table>

Only patients achieving grade 2 or 3 flow at 90–240-minute angiogram without early interventions were stipulated by protocol to undergo 18–48-hour follow-up angiogram.

*Angiogram was not obtained primarily because of mechanical intervention or adverse experiences that precluded the 24-hour angiogram. Number in bracket is percent of total patients.
†Logit analysis with treatment as a factor and response equals 0, 2, and 3.
‡Logit analysis with treatment as a factor.

streptokinase (2.1%) patients had reoccluded (Table 3). Among patients with continued patency, grade 3 perfusion was found in 93% in the anistreplase and, similarly, in 91% in the streptokinase group.

Quantitative Assessment of Patency

Residual percent diameter stenosis for patent infarct-related arteries was slightly less after anistreplase therapy (mean, 74.0%) than after streptokinase (77.2%, p=0.02; Table 4). At the 1-day (mean, 28 hours) assessment of patients whose arteries were patent at the initial angiographic assessment and who had not undergone further coronary interventions, further favorable changes in percent stenosis were observed in both treatment groups; a −3.5 percentage point change (n=91) for anistreplase patients and −4.0% (n=92) for streptokinase (both p<0.001); the residual percent diameter stenosis was also similar in the two treatment groups (Table 4).

Perfusion grade correlated with percent stenosis: for the early study (all patients), r=−0.74, p<0.0001; and for the late study, r=−0.47, p<0.0001.

Ancillary Medical Therapies

Ancillary therapies were given before thrombolysis equally to patients in the two groups. Before hospitalization, nitrates were being taken by 28 (15%) of patients in the anistreplase group (n=188) and by 22 (12%) in the streptokinase group (n=182); β-blockers were being taken by 24 (13%) and 25 (14%) of these patients, respectively. Before thrombolysis, nitroglycerin was administered in hospital to 168 (89%) and 167 (92%), and β-blockers to only eight (4%) and nine (5%), respectively.
Intravenous heparin therapy was required by protocol to be given for at least one day. On average, heparin discontinuation occurred on day 3 (median, day 2; 95% range, days 1–8) and was similar in the two groups (mean time of discontinuation, ≤2.9 days for the anistreplase group; ≤3.0 days for the streptokinase group).

Early and Overall Mechanical Interventions in the Treatment Groups

Early mechanical intervention (guidewire manipulation, angioplasty, or bypass surgery), performed before the follow-up (18–48 hours) angiogram, occurred in 23 (17.4%) anistreplase and 25 (19.4%) streptokinase patients initially achieving a patent (grade 2 or 3) artery whose perfusion was judged by the attending cardiologist to be inadequate.

Overall during hospitalization, coronary balloon angioplasty was performed in 89 (49%) of anistreplase and 92 (52%) of streptokinase patients, and coronary bypass surgery was performed in 39 (21%) of anistreplase and 37 (21%) of streptokinase patients in the efficacy population.

Hemodynamic, Laboratory, and Safety Evaluations

Changes in blood pressure. A comparison of blood pressure effects of rapidly injected anistreplase and those of slowly infused streptokinase was of interest. Changes in blood pressure overall were statistically similar for the two regimens and included modest reductions in the early minutes and hours after therapy. These reductions may also be due to other concomitant medications (such as nitroglycerin, β-blockade, morphine), to myocardial infarction itself, and to lytic therapy (Figure 4). A difference between groups of nominal significance was observed only at 10 minutes for systolic and 5–10 minutes for diastolic pressure. These differences of 4–5 mm Hg were small and comparable to the blood pressure differences observed between anistreplase and placebo in the Anistreplase Intervention Mortality Study (AIMS).46

Changes in blood coagulation variables with therapy. Observed changes in hemoglobin, fibrinogen, and plasminogen after both therapies were comparable and of expected degree, based on previous studies (Table 5). Streptokinase (1.5 million units) and anistreplase (30 units, equivalent to a streptokinase dose of 1.1 million units) caused substantial decreases in fibrinogen and plasminogen levels from baseline. Fibrinogen fell to an average of 24% of baseline after anistreplase and to 21% of baseline after streptokinase. Plasminogen fell to 18% and 14% of baseline in the two treatment groups, respectively. The slightly greater decreases after streptokinase were significant for fibrinogen (p=0.05) but not plasminogen.

Decreases in hematocrit and hemoglobin levels after anistreplase and streptokinase therapy were similar at 24 hours and 3 days, as were nadir values. After 3 days, slightly greater declines were observed after streptokinase and were significant for changes in hematocrit (p=0.03) but not hemoglobin (p=0.26).

### Table 5. Hematologic Measurements

<table>
<thead>
<tr>
<th>Measure</th>
<th>Anistreplase n</th>
<th>Mean</th>
<th>Streptokinase n</th>
<th>Mean</th>
<th>RMSE</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pretherapy</td>
<td>164</td>
<td>351</td>
<td>164</td>
<td>368</td>
<td>120</td>
<td>0.21</td>
</tr>
<tr>
<td>90 min (mean difference)†</td>
<td>158</td>
<td>-266</td>
<td>157</td>
<td>-294</td>
<td>126</td>
<td>0.05</td>
</tr>
<tr>
<td>24 hr (mean difference)‡</td>
<td>151</td>
<td>-145</td>
<td>151</td>
<td>-129</td>
<td>129</td>
<td>0.26</td>
</tr>
<tr>
<td>Plasminogen (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pretherapy</td>
<td>168</td>
<td>104</td>
<td>165</td>
<td>101</td>
<td>30.5</td>
<td>0.46</td>
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<td>90 min (mean difference)†</td>
<td>162</td>
<td>-85</td>
<td>155</td>
<td>-87</td>
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<td>0.52</td>
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<tr>
<td>24 hr (mean difference)‡</td>
<td>155</td>
<td>-63</td>
<td>152</td>
<td>-61</td>
<td>31.4</td>
<td>0.62</td>
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Fall in hematocrit (n, % of patients)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Anistreplase n</th>
<th>Mean</th>
<th>Streptokinase n</th>
<th>Mean</th>
<th>RMSE</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretherapy to 24 hr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5% point</td>
<td>65</td>
<td>37%</td>
<td>60</td>
<td>34%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5 to 10% point</td>
<td>80</td>
<td>45%</td>
<td>81</td>
<td>47%</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>≥10% point</td>
<td>32</td>
<td>18%</td>
<td>33</td>
<td>19%</td>
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<td></td>
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</table>

Pretherapy to 3 days

<table>
<thead>
<tr>
<th>Measure</th>
<th>Anistreplase n</th>
<th>Mean</th>
<th>Streptokinase n</th>
<th>Mean</th>
<th>RMSE</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5% point</td>
<td>58</td>
<td>34%</td>
<td>37</td>
<td>23%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5 to &lt;10% point</td>
<td>52</td>
<td>31%</td>
<td>51</td>
<td>32%</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>≥10% point</td>
<td>60</td>
<td>35%</td>
<td>70</td>
<td>44%</td>
<td></td>
<td></td>
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</table>

Nadir hematocrit (%)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Anistreplase n</th>
<th>Mean</th>
<th>Streptokinase n</th>
<th>Mean</th>
<th>RMSE</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(median, range)</td>
<td>184</td>
<td>335</td>
<td>178</td>
<td>33.9</td>
<td>5.51</td>
<td>0.48</td>
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</tbody>
</table>

Fall in hemoglobin (n, % of patients)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Anistreplase n</th>
<th>Mean</th>
<th>Streptokinase n</th>
<th>Mean</th>
<th>RMSE</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretherapy to 24 hr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2 g/dl</td>
<td>81</td>
<td>46%</td>
<td>80</td>
<td>46%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2 to &lt;4 g/dl</td>
<td>76</td>
<td>43%</td>
<td>72</td>
<td>41%</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>≥4 g/dl</td>
<td>20</td>
<td>11%</td>
<td>22</td>
<td>13%</td>
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<td></td>
</tr>
</tbody>
</table>

Pretherapy to 3 days

<table>
<thead>
<tr>
<th>Measure</th>
<th>Anistreplase n</th>
<th>Mean</th>
<th>Streptokinase n</th>
<th>Mean</th>
<th>RMSE</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2 g/dl</td>
<td>66</td>
<td>39%</td>
<td>48</td>
<td>31%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2 to &lt;4 g/dl</td>
<td>58</td>
<td>34%</td>
<td>64</td>
<td>41%</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>≥4 g/dl</td>
<td>46</td>
<td>27%</td>
<td>45</td>
<td>29%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Nadir hemoglobin (g/dl)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Anistreplase n</th>
<th>Mean</th>
<th>Streptokinase n</th>
<th>Mean</th>
<th>RMSE</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(median, range)</td>
<td>184</td>
<td>11.3</td>
<td>179</td>
<td>11.5</td>
<td>1.88</td>
<td>0.30</td>
</tr>
</tbody>
</table>

*Analysis of variance where treatment is a factor.
†Mean difference between paired treatment and pretreatment values.
‡Categorical analysis with response as an ordinal value where treatment is a factor.
RMSE, root mean squared error.

Bleeding complications, other adverse reactions, and mortality. Serious morbidity and mortality occurred infrequently in both study groups. There were 11 in-hospital deaths in the anistreplase group (5.9%) and 13 in the streptokinase group (7.1%) (Table 6). Deaths occurred in nine patients who received thrombolytic therapy only, three who also had guidewire intervention, six who underwent angioplasty, three who had coronary bypass surgery, and three who underwent both angioplasty and bypass surgery. Among patients undergoing intervention, 13 who received early interventions (within the first day) died in-hospital, and two who received later interventions died in-hospital. The distribution of deaths in
patients undergoing the various procedures was similar in the two groups. Stroke occurred in one (0.5%) and three (1.6%) patients in the anistreplase and streptokinase groups, respectively. One stroke (in the anistreplase group) was hemorrhagic but occurred 2 days after dosing during heparin infusion. One stroke was fatal (in the streptokinase group).

Any bleeding event was reported frequently in each group (about one half of patients), was attributed to thrombolytic therapy in about 20% of patients, but was judged to be severe in only 4% of patients in each treatment group as shown in Tables 6 and 7.

Other reactions were common but minor, and no anaphylaxis occurred. A summary of all adverse reactions occurring with a frequency of more than 5% is shown in Table 6 for the two groups. In Table 7, reactions believed to be treatment related are shown and graded by severity. Both total and treatment-related adverse reactions were generally similar for the two treatment groups in frequency and severity. Minor rash/pruritus reactions were reported as treatment related in 3% of anistreplase compared with none of the streptokinase patients, but overall, the occurrence of rash/pruritus was similar for the two groups (nine [5%] versus seven [4%]). Ventricular extrasystoles were reported less frequently after anistreplase than after streptokinase administration (7% versus 17%), but the occurrence of any arrhythmia/conduction disturbance was similar for the two groups. Given the multiple comparisons, these minor differences are probably due to chance.

**Enzymatic comparisons.** Myocardial infarction, defined as elevation of CK to 1.5 times or more the upper limit of normal during serial testing, was confirmed enzymatically in 97% of anistreplase patients (180 of 186) and 96% of streptokinase patients (171 of 179). In contrast, elevations were present on the initial sample (at study entry) in only 9% (16 of 171) and 11% (19 of 167) of these patients, respectively, confirming the early acquisition of patients into the study. (The expected initial rise in CK occurs at 4–6 hours or more after symptom onset.) Peak values and times to peaks of serum cardiac enzymes are given in Table 8 and were not significantly different in the two groups although peak values tended to be lower in the anistreplase group.

**Discussion**

**Study Summary**

Documentation of early establishment and maintenance of coronary artery patency after myocardial infarction is believed to be of importance because of the widely held belief, supported by numerous observations, that it represents the major mechanism of clinical benefit of thrombolytic therapy (patent artery hypothesis). In the present study, anistreplase was shown to establish and maintain high patency rates when given to myocardial infarction patients admitted to the hospital within 4 hours of symptom onset, a group standing to benefit most from thrombolytic therapy. Unexpectedly, total patency rates were equally high with streptokinase, although of slightly lower quantitative degree.

Early rates of patency of 70–75%, as observed in this study, approach the ceiling of patency rates achieved to date in the larger, better-controlled, and prospective studies of thrombolytic regimens. Such patency rates have also been described for regimens of t-PA and t-PA plus urokinase. Patency grades increased further during 1–2 days, and reocclusion was rare (1–2% rate) in the studied cohort of patients not undergoing immediate interventions. Safety was good and comparable in both regimens, consistent with previous reports and mortality rates were low compared with previous studies.

Blood pressure effects of the rapid administration regimen of anistreplase were carefully documented in the present study and were modest. Clinical hypotension occurred but was uncommon; overall, the
response to rapid injections of anistreplase (plus ancillary therapies) was similar to that of slow infusions of streptokinase.

**Literature Comparisons for Anistreplase**

The patency result for anistreplase in the present study is supported by an overview of other, smaller studies of varying design.\(^4^8\) Data for seven studies, available in either final or preliminary reports, gave angiographic results for anistreplase treatment in a total of 402 patients treated within 4–6 hours of onset of symptoms and studied angiographically at about 90 minutes, 0.5–4 hours after therapy. Patency occurred in 288 patients (72%). This overall patency rate is identical with the 72% rate observed in the present study and suggests that substantial confidence may be given to an early patency rate estimate of 70–75% for anistreplase.

These rates of patency after anistreplase, defined by postinterventional angiography, are, as expected, greater than rates of reperfusion (recanalization), defined by preinterventional and postinterventional angiography and measured in earlier studies.\(^4^5,4^8,4^9\) Reperfusion requires pretreatment confirmation of coronary occlusion (defined as grade 0 or 1 perfusion). Because about 10–20% of patients admitted to the hospital within 4–6 hours of symptom onset show patency at the time of initial study\(^1\) (believed to be a manifestation of spontaneous reperfusion), studies that select patients for treatment by clinical and electrocardiographic criteria (“patency” studies) typically show higher rates (by about 10–20%) than studies in which patient selection is made by angiographic criteria for coronary occlusion. Thus, reperfusion (recanalization) rates averaging 55–60%, according to previous studies,\(^4^5,4^8,4^9\) are entirely consistent with the patency rates of 70–75% of this and previous studies.\(^4^4,4^8\) As with studies of streptokinase, studies of anistreplase have shown lower (or slower) rates of reperfusion when therapy was begun more than 4 hours after symptom onset.\(^4^5\) The present study focuses on patients admitted to the hospital within 4 hours of symptom onset, those who are most likely to show optimal clinical benefit,\(^12,1^3\) and does not show a significant relation of time to treatment and patency outcome in this cohort.

---

**Table 7. Adverse Reactions Attributed to Treatment and Categorized by Severity**

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Group</th>
<th>Mild</th>
<th></th>
<th></th>
<th>Moderate</th>
<th></th>
<th></th>
<th>Severe</th>
<th></th>
<th></th>
<th>Total</th>
<th></th>
<th></th>
<th>p*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td><strong>Bleeding problems</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall†</td>
<td>APSAC</td>
<td>188</td>
<td>12</td>
<td>6</td>
<td>17</td>
<td>9</td>
<td>8</td>
<td>4</td>
<td>37</td>
<td>20</td>
<td>0.70</td>
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<td></td>
<td>SK</td>
<td>182</td>
<td>13</td>
<td>7</td>
<td>13</td>
<td>7</td>
<td>7</td>
<td>4</td>
<td>33</td>
<td>18</td>
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<td></td>
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<tr>
<td>Puncture site bleeding</td>
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<td>5</td>
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<td>4</td>
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<td>21</td>
<td>12</td>
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<td></td>
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<tr>
<td>Other site bleeding</td>
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<td>8</td>
<td>4</td>
<td>11</td>
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<td>2</td>
<td>23</td>
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<td>1</td>
<td>1</td>
<td>6</td>
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<td>8</td>
<td>4</td>
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<td>1</td>
<td>14</td>
<td>8</td>
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<td>188</td>
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<td>0</td>
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<td>2</td>
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<tr>
<td>Fever or chills</td>
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<td>188</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<td>2</td>
<td>0.35</td>
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<td>0</td>
<td>0</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash or pruritus</td>
<td>APSAC</td>
<td>188</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
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<td>6</td>
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<td>&lt;0.01$</td>
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<tr>
<td></td>
<td>SK</td>
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<td>0</td>
<td>0</td>
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<td>0</td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Logistic analysis based on total.
†The sum of puncture site bleeding and bleeding at other sites may exceed that in the overall bleeding category because a patient could have both puncture site and nonpuncture site bleeding.
‡Hypotension or shock
$\S$Fisher’s exact test
APSAC, anistreplase; SK, streptokinase.

---

**Table 8. Comparative Peak and Time to Peak Serum Enzyme Concentrations**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Anistreplase</th>
<th>Streptokinase</th>
<th>RMSE</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to peak (hr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to peak from time of treatment (hr)</td>
<td>173 11.1 163</td>
<td>11.1 163</td>
<td>5.4</td>
<td>0.94</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>167 28.9 151</td>
<td>28.3</td>
<td>13.8</td>
<td>0.71</td>
</tr>
<tr>
<td>Lactic dehydrogenase</td>
<td>167 31.5 151</td>
<td>30.9</td>
<td>13.7</td>
<td>0.69</td>
</tr>
<tr>
<td>Peak enzyme value (IU/l)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>173 2,455 163</td>
<td>2,772</td>
<td>1,979</td>
<td>0.14</td>
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<td>Lactic dehydrogenase</td>
<td>167 621 151</td>
<td>701</td>
<td>400</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Analysis of variance where treatment is a factor.
Literature Comparisons for Streptokinase

Patency rates observed in this study were higher for streptokinase than those suggested by some previous patency evaluations.5,6,8,9,44 In a European comparison of t-PA and streptokinase, patency rates were 70% and 55%, respectively, after 90 minutes (p=0.05).9 In a preliminary report of a smaller French patency study of anistreplase versus streptokinase (on which power calculations for the present study were based), patency was observed after 90 minutes in 72% (28 of 39) of anistreplase patients compared with 56% (24 of 43) of streptokinase patients after 90 minutes.44

A recently published Scottish study also compared patency in a group of 128 patients randomized to anistreplase or streptokinase.50 Patency rates were similar for the two agents but, unlike this study, were lower for both (55%, 53%, respectively). Differences in design of that study compared with the present study included entry of patients for up to 6 hours after symptom onset (versus 4 hours) and assessment at 90 minutes (versus 90–240 minutes; mean, 140 minutes).

Reasons for differences in the streptokinase results in this study compared with others are not immediately apparent, although wide ranges of reperfusion and patency rates have been previously published for streptokinase, ranging from 31% to 92%.5,6 These earlier studies of streptokinase were of varying size and design and used varying methods of measuring perfusion. We hypothesize that the higher patency rates observed in TEAM-2 for streptokinase may have resulted from 1) treatment of patients at an earlier average time than in other studies, 2) delay of angiographic assessment to a somewhat later mean time after therapy (2.4 hours), allowing streptokinase, which may reperfuse some arteries at a slower rate, time to “catch up,” 3) use of the final (rather than initial) angiogram to define patency, and 4) inclusion of grades 2 and 3 perfusion in the definition of overall patency rate. However, both qualitative and quantitative measures of coronary patency grade indicated a somewhat greater effect of anistreplase than streptokinase. This is consistent with the overall literature impression of greater activity of anistreplase on early coronary patency, although the effect of streptokinase was greater than previously believed.

Other Interdrug Comparisons of Thrombolytic Therapy

In contrast to differences in the rates of early patency between thrombolytic agents in some comparisons, later patency rates (at 1–3 days and beyond) have been similar among agents in most comparisons.8,16,20 We also noted equivalent (and improved) patency rates at 1 day after both anistreplase and streptokinase. How other important clinical outcomes (i.e., cardiac function and mortality) are affected by differences in rates of early patency are unknown and must await the outcome of direct comparative trials for these end points. Preliminary results of a mortality comparison between t-PA and streptokinase showed no difference (International Study Group43). The equivalence of effect of streptokinase and t-PA on mortality is surprising if 90-minute reperfusion rates from earlier studies are used as predictors8,9 but may be explained by the higher patency rates at 2–3 hours or more after streptokinase than previously supposed, as demonstrated in the present study. Use of a heparin regimen that was suboptimal for t-PA may also have been a factor in the outcome.43 A large three-way comparison of the effects of streptokinase, t-PA, and anistreplase on mortality is underway (ISIS-3).

Differences in outcome have been difficult to show using the end point of left ventricular ejection fraction, both for comparisons with placebo6 and especially for interdrug comparisons. No differences in convalescent ejection fraction have been shown for comparisons of t-PA with streptokinase51 and t-PA with urokinase and with t-PA plus urokinase.20 Improvement in ejection fraction after anistreplase has been shown in comparisons with placebo (heparin),34 similar to those of placebo comparisons with other agents (i.e., 6 percentage points).

Hemodynamic Tolerance of Anistreplase and Streptokinase

Evaluation of the effects on blood pressure of rapidly injected doses of anistreplase is of clinical interest. In canine studies, bolus injection of large doses of streptokinase-plasminogen (equivalent to 2 million units in humans) led to rapid and profound reductions in blood pressure (mean fall, 50%), whereas bolus injections of anistreplase (50 units) had negligible effects.29 These blood pressure changes correlated with differences in the generation of circulating plasmin and bradykinin. After streptokinase, abrupt generation of large quantities of plasmin and bradykinin were observed, whereas anistreplase caused only gradual and controlled plasmin generation.

In clinical studies, Lew et al52 showed mean reductions in systolic and diastolic blood pressure of 35 and 19 mm Hg, respectively, 15 minutes after standard rate (750,000 units/30 min) infusions of streptokinase. Hall53 gave 600,000 units streptokinase during 10 minutes and observed transient hypotension in 30–40% of patients. Kohler et al54 tested rapid injections of streptokinase (750,000–1,500,000 units in 5–10 minutes). Hypotension occurred in 50%, and decreases in mean blood pressure averaged about 40 mm Hg.

Compared with standard, slow (1-hour) infusions of streptokinase, the mean additional reduction in blood pressure of only 4–5 mm Hg at 5–10 minutes after the 2–5-minute anistreplase injection in our study is favorable. Occasionally, hypotension was of sufficient magnitude to require temporary postural or fluid therapy. Thus, careful clinical observation is recommended.
Safety of Anistreplase and Streptokinase

Safety of anistreplase and streptokinase was good in the present study and comparable to that observed in other trials.\cite{33,45,49} As with other lytic agents, bleeding represents the most common and important adverse event. In other studies, hemorrhagic events occurred overall in 15% of patients treated with anistreplase (n>5,000 patients).\cite{33} Only 1.6% of these events were described as serious. In invasive trials requiring routine catheterization, such as the present one, the incidence of reported hemorrhagic events has averaged 22%, the majority occurring at the puncture site. Hemorrhagic or possibly hemorrhagic cerebral vascular accidents have occurred with an incidence of 0.3−0.6%. Anaphylaxis, reported in 0.2% after anistreplase (Eminase package insert) or streptokinase, was not observed in the present study.

The net outcome of anistreplase therapy was shown recently in the AIMS to be decidedly beneficial, resulting in a 48% reduction in mortality risk at 30 days\cite{34} with a maintained benefit at 1 year.\cite{46} Aspirin was not used concurrently in AIMS nor in the present study, because both were begun before the publication of ISIS-2,\cite{13} which first clearly suggested additional benefit (about 20%) for aspirin coadministered with streptokinase. The potential of aspirin to further improve outcome for other lytic agents is being tested in trials including ISIS-3 and TEAM-3 (comparing the effects of anistreplase and t-PA on coronary patency and left ventricular function).

Study Limitations

As with other patency and reperfusion studies, only a limited number of observations are possible, although perfusion and occlusion are dynamic processes that occur throughout a period of several hours to days. However, the slightly later time of initial angiography probably allowed for near-optimal assessment of early patency after streptokinase within a clinically relevant time frame.

As in other studies, the evaluation of reocclusion is complicated by the exclusion of a number of subjects who undergo early angioplasty or who fail initial therapy and are inappropriate to restudy clinically. Thus, the reported reocclusion rates relate to a select subgroup and not to all patients. Left ventricular function was not evaluated but is a less sensitive end point for differentiating between thrombolytic agents. Also, the high rate of intervention during hospitalization confounds comparisons of relative differences between medical therapies, especially those occurring after the follow-up (1−2-day) catheterization. Interventions were performed after the initial angiogram in only 18% of patients achieving early patency but in 31% of the total population. Overall, 49% of the total population underwent eventual angioplasty and 21% eventual bypass surgery before discharge. Of note, this study antedated the publication of important trials (TIMI 2B\cite{24} and SWIFT\cite{55}) that argued against additional benefit from "routine" angioplasty during hospitalization in patients with residual stenosis postthrombolysis.

The impact of the modest differences in patency rates or grades on other important clinical end points such as cardiac functional class, left ventricular function, infarct size, and mortality cannot be deduced from this study but must be established by other trials. Despite these reservations, this study presents a useful comparison; it is one of the largest patency studies of intravenous streptokinase and is the single largest experience with anistreplase. Observations were made in a blinded fashion by experienced readers and were confirmed by validated, quantitative methods. Concordance with results from an overview of several smaller trials suggests that confidence may be placed in the findings for anistreplase.

Summary of Advantages and Limitations of the Two Thrombolytic Agents

In selecting a thrombolytic for use in acute myocardial infarction, both streptokinase and anistreplase have advantages and limitations.

Streptokinase, the oldest thrombolytic, is also the most extensively studied. Streptokinase also has the advantage of being the least expensive among thrombolytic agents (approximate pharmacy cost: streptokinase, $100−200; anistreplase, $1,700; alteplase [t-PA], $2,200). The addition of aspirin to streptokinase therapy has resulted in greater mortality reductions than the modest rates reported for streptokinase alone.\cite{12,13}

Disadvantages of streptokinase include its antigenicity, which occasionally causes allergic reactions (in about 2−5%,\cite{43} usually mild) and elicits neutralizing antibodies that may reduce reperfusion efficacy; therefore, reuse within 5 days to 1 year should probably be avoided. Streptokinase may cause hypotension that is dependent, in part, on the rate of administration.\cite{52−54} However, severe hypotension is uncommon when the agent is given during a 1-hour period and usually responds to standard measures. Another limitation is that the rate of thrombolysis with streptokinase is slowed with advancing clot age, leading to lower recanalization rates at 90 minutes for patients with longer (>4 hours) symptom duration.\cite{8} However, the present study and a previous study\cite{16} show that there is "catch-up" in perfusion rates during the subsequent hours to days. Fibrinogen depletion has been previously viewed as a limitation, but a higher overall bleeding risk for streptokinase has not been confirmed in direct comparison trials with t-PA, which is relatively fibrin selective.\cite{8,43} The anticoagulant effects of fibrinogen depletion and fibrinogen degradation product generation may be advantageous in reducing the risk of subsequent reocclusion.\cite{8,20,43}

Anistreplase has the advantage of a simplified administration regimen: it can be given as a single, rapid injection. In-hospital time delays to thrombolytic therapy are substantial, averaging 90 minutes.\cite{56} Simplified administration may facilitate ear-
lier usage in settings less sophisticated than the coronary care unit, such as the emergency ward or physician’s office and, perhaps in the near future, in mobile care units. Anistreplase has greater in vitro fibrin affinity than does streptokinase, increasing bioavailability at the site of the clot. 

Its longer half-life (90 minutes) compared with streptokinase (20 minutes) and t-PA (10 minutes) leads to a longer duration of fibrinolytic activity, allowing a single injection to be substituted for longer or continuous infusions to provide ongoing fibrinolytic effects. Anticoagulant actions of both anistreplase and streptokinase persist much longer, however, because 1–2 days are required for fibrinogen to be regenerated. As shown in animal studies, the hypotensive effects of bolus doses of streptokinase are markedly blunted by acylation, which leads to much more gradual plasmin and kinin production.

The present study shows that the clinical blood pressure effects of rapid (2–5 minutes) anistreplase injections are similar to those of slowly infused (1 hour) doses of streptokinase. Clinically, as reviewed above, patency rates for anistreplase have been reported by others to be both greater than or equal to streptokinase; in our study population, differences in the patency profile by 2.4 hours were small. As is the case with streptokinase and t-PA, anistreplase is associated with a significant reduction in acute myocardial infarction mortality compared with placebo. The odds reduction in 30-day mortality was 51% in AMS, and the initial survival benefit was maintained at 1 year.

Although this odds reduction is greater than in several trials with other thrombolytic agents, direct comparisons, such as in the International Study Group and ISIS-3 studies, are necessary to demonstrate superiority of one agent over another.

Anistreplase shares the same allergic risks and limitations as streptokinase. The bleeding risk of anistreplase, despite its longer half-life, is similar to that of streptokinase, as confirmed in the present study.

Ongoing, direct comparisons should allow a more accurate profiling of anistreplase with t-PA, a relatively fibrin-selective agent, and better answer questions about relative reperfusion efficacy, recollection risk, and safety, both in patients receiving and not receiving subsequent interventions.

Conclusion

In conclusion, when given to acute myocardial infarction patients within 4 hours from onset of symptoms, intravenous anistreplase and streptokinase establish high and comparable total patency rates within a mean of 2.4 hours (median, 2.1 hours) after therapy. Grade 3 perfusion tends to occur more frequently and the residual stenosis is slightly less early after anistreplase. In patients in both groups not undergoing other interventions, angiographic recolclusion during the subsequent 1–2 days occurs rarely (<1–2%), and a further improvement in average perfusion grade (to grade 3 in 92%) and decline in percent stenosis (by 

–4% points) is observed. Overall, for the end points of patency and safety in our study, anistreplase and streptokinase show favorable and mostly comparable outcomes with a few differences. The clinical importance of these or other differences, such as ease of drug administration, will be answered by ongoing comparative mortality studies (such as ISIS-3) and by broader clinical experience. In the interim, these data support the continued use of these agents in acute myocardial infarction.

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Appendix

Investigators of the Second Multicenter Thrombolytic Trials of Eminase in Acute Myocardial Infarction (TEAM-2) were:


SmithKline Beecham Laboratories Research Staff. H.W. Eckerson, PhD; R.N. Daly, PhD; J. Barnes; J. Becker; S. Hamm; E. Medler, MS; P. Mullins; S. Zinsser.

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