A randomized trial of intravenous and intracoronary streptokinase in patients with acute myocardial infarction

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ABSTRACT The clinical effects of intravenous streptokinase in patients with acute myocardial infarction were compared with those of intracoronary streptokinase in a randomized, prospective study. Comparisons were also made with a historical control group. Fifty patients were entered into the study at 2.4 ± 1.2 hr after onset of pain, and 27 were assigned to intravenous and 23 to intracoronary therapy. The doses of streptokinase averaged 212,000 U ic and 845,000 U iv (0.75 × 10^6 U/5 hr, n = 14 or 10^6 U/1 hr, n = 13). Results of studies of the two intravenous dosage schedules were similar and so were combined. Streptokinase was administered at 2.8 ± 1.0 hr after onset of pain in the intravenous and at 4.3 ± 1.4 hr in the intracoronary drug group (p < .001). Convalescent (day 10) radionuclide ejection fractions were 54 ± 14% for the intravenous and 50 ± 16% for the intracoronary drug group. Change in ejection fraction from day 1 to 10 tended to be greater after intravenous drug: 5.1% (p < .08) vs 1.2% (NS). Semiquantitative regional wall motion indexes in the infarct zone showed significant and similar modest improvement from admission to day 10 in both groups (p < .02). Accelerated enzyme-release kinetics were noted after both therapies. Times of peak enzyme levels for patients on intravenous and intracoronary drug were, respectively, 12.5 ± 5.0 and 11.5 ± 4.3 hr for creatine kinase MB isoenzyme and 31.7 ± 11.8 and 28.1 ± 12.7 hr for lactic dehydrogenase (LDH). Peak LDH-I level was lower in patients receiving intravenous drug than in the historical control group (p < .05). Electrocardiographically summed ST segments diminished rapidly after therapy in both groups; Q wave development was similar and overall R wave loss was equivalent and less extensive compared with in historical control subjects. Infarct pain requiring morphine was diminished similarly in both treatment groups. Incidence of early arrhythmias and heart failure also did not differ. Posttherapy ischemic events and early surgery tended to be more common in the intracoronary group and bleeding was more common in the intravenous group. Intravenous drug did not decrease early hospital mortality (intravenous drug = 5, historical control = 4, intracoronary drug = 1); the differences in this parameter among groups were not significant. At convalescent angiographic evaluation, anterograde perfusion was present in 73% of those receiving intravenous and 76% of those receiving intracoronary drug. Thus, favorable relative effects were noted on cardiac function, clinical evaluations, and hospital course after intravenous streptokinase in early survivors of myocardial infarction and use of intravenous drug has the advantage of earlier and easier application. Additional studies will be required to address effects on mortality.


MYOCARDIAL INFARCTION represents the most important pathologic entity in Western society in terms of morbidity and mortality. Attempts to reduce the size of myocardial infarction with drugs that reduce myocardial functional demand have, in general, been dis-appointing.1 Recently, the feasibility of restoring coronary perfusion by administration of intracoronary thrombolytic agents has been demonstrated.2–5 Results of nonrandomized studies have also suggested the possibility of cardiac functional improvement,6–10 but controlled trials have given mixed results, reporting either no effect11,12 or a modest relative improvement in ventricular function13 after application of streptokinase at 4 to 6 hr after onset of symptoms. Recent studies have also suggested a potential reduction in mortality in patients undergoing reperfusion with intracoronary
streptokinase. These results are leading to more widespread application of thrombolytic therapy. However, a minority of hospitals have coronary angiographic laboratories, and even these are not all prepared to provide 24 hr coverage. Moreover, it is unlikely that intracoronary administration of streptokinase at an average of less than 3 to 4 hr after onset of symptoms will be feasible.

These considerations have stimulated interest in the use of short-term, relatively high-dose intravenous streptokinase. Large-scale studies of effects of standard doses of intravenous streptokinase on patients with acute myocardial infarction have been performed in the past decade. While the relative safety of these infusions was established, the study designs were flawed and the results mixed. Intravenous streptokinase has not to date been approved for general use in this application. The feasibility of coronary thrombolysis by high-dose, short-term infusion of streptokinase was recently confirmed by Schroder et al. However, as with intracoronary streptokinase, randomized studies are needed to adequately assess safety and potential benefit with respect to hospital course.

We recently demonstrated that early application of intracoronary streptokinase may be associated with a beneficial overall effect on in-hospital course of patients with acute myocardial infarction. In an effort to allow earlier, easier application of thrombolytic therapy, we next undertook a prospective, randomized study to compare the intravenous with the intracoronary drug in treatment of patients with acute myocardial infarction. Results were also compared with those in our comparable historical control group of patients that did not receive thrombolytic therapy.

Methods

Recruitment of patients. Patients with ischemic chest pain of less than 4 hr duration and with electrocardiographic ST segment elevation of at least 2 mm (0.2 mV) that was unresponsive to nitroglycerin were candidates for inclusion in the study. Exclusion criteria included hemodynamic (shock) or rhythm instability precluding possible immediate catheterization and specific contraindications to thrombolytic therapy. After consent was obtained from physician and patient, a letter was opened that contained each patient's random treatment assignment to catheterization with infusion of intracoronary streptokinase, administered at coronary angiography, or to intravenous streptokinase administered in the coronary care unit. Approximately 80% of hospitalized patients qualifying for the study could be recruited. Six patients initially randomly assigned to therapy (two to intravenous and four to intracoronary drug) were excluded within the first 24 hr because they subsequently refused to undergo catheterization (two patients) or because there was inadequate historical or electrocardiographic evidence on entry of acute transmural myocardial infarction, as determined on investigator review (four patients). (One of the excluded patients initially assigned to the intracoronary drug group and presenting with heart failure later died. Her initial ST elevation was due to a ventricular aneurysm from an old infarction.) No patient who qualified for study died between entry and the beginning of thrombolytic therapy, and all patients who qualified and received therapy were followed until death or hospital discharge. Standard medical therapy provided to both groups included prophylactic lidocaine for the first 24 hr of hospitalization, morphine sulfate as required for pain, and oxygen and nitroglycerin as indicated.

Patients assigned to treatment with intracoronary streptokinase were catherized shortly after admission to the hospital by the Judkins (femoroarterial) approach and heparin (5000 units) was given to each after arterial entry. Aortic and left ventricular pressures were measured and left ventriculography and selective coronary angiography were performed in which the presumably uninvolved vessel was visualized first. After occlusion (total or subtotal) of the vessel supplying the infarct zone had been confirmed, streptokinase (1000 U/ml dextrose or saline) was administered through the selective coronary arterial catheter. An initial bolus of 10,000 to 20,000 U streptokinase was given, followed by an infusion of 5,000 U/min (range 3000 to 6000). A soft angiographic guidewire was used to probe obstructs not reopening by 45 to 60 min. After reperfusion was established, the infusion rate was decreased to 3500 U/min (range 2000 to 5000) for an additional 30 to 45 min. Coronary angiography was repeated at intervals of 10 to 15 min during administration of streptokinase. Subtotal occlusion was treated with an infusion of 100,000 U. The left ventriculographic examination was repeated at the end of the study.

Patients assigned to intravenous streptokinase therapy received the drug according to one of two regimens. The initial group of patients (n = 14) was given 750,000 according to a standard protocol consisting of a 250,000 U loading dose (over 10 to 15 min) and then 100,000 U/hr for 5 hr. After the safety of intravenous dosing had been established, a high-dose, shorter term infusion was used in another group of 13 patients. This consisted of a 500,000 U loading dose (over 10 to 15 min) and 10,000 U/min for 50 min (total 1,000,000 U over 1 hr). There were no significant differences between the slow- and fast-rate infusion groups with respect to patient characteristics, enzyme kinetics, ejection fraction, or clinical evidence of reperfusion; the groups were thus combined for comparison with the group receiving intracoronary drug.

After streptokinase (intracoronary or intravenous), a heparin infusion was initiated (800 to 1000 U/hr) when the partial thromboplastin time fell to 80 to 100 sec; the dose was titrated to maintain thromboplastin time in this range for 3 days. Antiplatelet drugs (aspirin, 300 mg twice daily and dipyridamole, 75 mg twice daily) or warfarin were then given for the rest of the hospital stay and during the first 3 outpatient months. Decisions regarding other medical therapy, cardiac surgery, and coronary balloon angioplasty were not specified by the study but were left to the attending physician and were not keeping with common clinical practice.

Laboratory testing. Serum concentrations of the cardiac enzymes creatine kinase (CK), creatine kinase MB isoenzyme (CK-MB), lactate dehydrogenase (LDH), LDH isoenzymes 1 to 5, and SGOT were measured. Determinations were made at admission; at 3, 8, 12, and 18 hr; and at 1, 1.5, 2, 3, 4, and (for LDH) 7 days. Total enzyme determinations were based on standard spectrophotometric analyses. Isoenzymes (CK, LDH) were separated electrophoretically on cellulose acetate and quantitated. Twelve-lead electrocardiograms were obtained at admission, after thrombolytic therapy (or about 3 hr), at 8 hr, twice on the first postinfarct day, and after 2, 3, 4, and 10 days or before discharge (mean 8.9 days). Two-dimensional echocardiographic examination, performed with an 80 degree elec-
trronically phased sector scanner, was done on admission (pre-
therapy, day 0), after 24 hr (day 1), and on day 10 or before 
discharge (mean 9.5 days). Equilibrium-gated radionuclide 
ventriculography ([99mTc]-pyrophosphate red cell label) 
was performed on day 1 (within 24 hr after thrombolytic 
therapy) and on day 10 or before discharge (mean 9.5 days). Details of 
our radionuclide ventriculographic method and information on 
reproducibility of results have been previously published.

A 24 hr arrhythmia-monitor recording was also obtained on 
day 10 or before discharge (mean 9.7 days). All surviving patients 
were requested to undergo coronary angiography and left 
ventriculography before discharge (mean day 11.0). Enzymatic, 
electrocardiographic, and ventriculographic analyses (echo-
cardiography, radionuclide, and radiocontrast methods) were 
interpreted by independent observers who were blinded to treat-
ment assignment and hospital course of the patients. Global 
echocardiographic regional wall motion index was assessed by 
two independent observers as an average segment score, with 
the use of 15 left ventricular segments. Segments were scored 
as normal (score of 5), mildly hypokinetic (4), severely hypo-
kinetic (3), akinetic (2), or dyskinetic (1). The interobserver 
difference in mean index change was 0.01 index units and in 
individual patient variables, the difference was 0.2 index units. 
An index was also serially computed for segments initially 
involved (on day 1) by the acute infarction (infarct index).

**Hypothesis.** Our hypothesis was that results would be similar 
in the group receiving intravenous streptokinase and in the 
group treated with intracoronary streptokinase with respect to 
changes in left ventricular ejection fraction and regional wall 
motion, cardiac enzyme kinetics, electrocardiographic evolu-
tion, and overall hospital course. A primary outcome variable 
was the change in radionuclide left ventricular ejection fraction 
from day 1 to day 10. An ancillary hypothesis was that the 
results of intravenous therapy would be favorable in comparison 
with those in patients randomly allocated to treatment in a 
standard coronary care unit alone (historical control group). This 
group consisted of patients with similar characteristics on entry 
who were enrolled in our previous randomized study. The 
referral base and treatment approach to myocardial infarction, 
except for thrombolytic therapy, did not change between 
study groups. Patient characteristics at entry were also similar for 
the previous and current patient groups (table 1).

**Statistical analysis.** Averaged data are generally presented 
as mean ± SD; the SEM was used to express variance in the 
figures and in table 3 (enzyme kinetics). Student’s t test (paired 
or unpaired) was used to compare two groups with approximating 
normal distributions, and analysis of variance was used for 
comparison of more than two data groups. Global enzyme kinetic 
was compared initially with Hotelling’s T2 test to establish 
differences. Nonparametric group comparisons were made 
when appropriate with use of the Mann-Whitney test. Chi-
square analysis was performed for data in 2 x 2 contingency 
tables. Significance was claimed at the level of p < .05 (gener-
ally by two-tailed analysis). Patient responses were analyzed by 
initial treatment assignment rather than by success of therapy 
(reperfusion).

**Results**

**Patient characteristics (table 1).** Entry into the study 
occurred 2.4 ± 1.2 hr after the onset of symptoms. Twenty-seven 
patients were assigned to intravenous and 23 to intracoronary streptokinase therapy. The two 
groups were comparable with respect to age, sex, Killip 
class at entry, and location of infarct as well as with 
regard to history of previous myocardial infarction,

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IV (n = 27)</th>
<th>IC (n = 23)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (range)</td>
<td>60.5 (36–77)</td>
<td>61.8 (20–84)</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex</td>
<td>24(89)</td>
<td>18(78)</td>
<td>NS</td>
</tr>
<tr>
<td>Killip class</td>
<td>1.5 ± 0.6</td>
<td>1.4 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Location of infarct</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>11(41)</td>
<td>11(48)</td>
<td>NS</td>
</tr>
<tr>
<td>Inferior</td>
<td>16(59)</td>
<td>12(52)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous infarction</td>
<td>4(15)</td>
<td>3(13)</td>
<td>NS</td>
</tr>
<tr>
<td>Time randomized (hr from onset of symptoms)</td>
<td>2.1 ± 0.9</td>
<td>2.8 ± 1.4</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Admission vital signs</td>
<td></td>
<td></td>
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<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Systolic</td>
<td>130 ± 25</td>
<td>130 ± 23</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic</td>
<td>83 ± 16</td>
<td>84 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>79 ± 15</td>
<td>79 ± 21</td>
<td>NS</td>
</tr>
<tr>
<td>Serum glucose (mg/dl)</td>
<td>185 ± 73</td>
<td>191 ± 179</td>
<td>NS</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td>227 ± 37</td>
<td>228 ± 54</td>
<td>NS</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive family history</td>
<td>10(37)</td>
<td>9(39)</td>
<td>NS</td>
</tr>
<tr>
<td>Obesity</td>
<td>7(26)</td>
<td>5(22)</td>
<td>NS</td>
</tr>
<tr>
<td>β-blocker therapy</td>
<td>4(15)</td>
<td>2(8)</td>
<td>NS</td>
</tr>
<tr>
<td>Diuretic therapy</td>
<td>5(19)</td>
<td>8(35)</td>
<td>NS</td>
</tr>
</tbody>
</table>

IV = patients receiving intravenous drug; IC = patients receiving intracoronary drug.

- Figures outside parentheses are numbers of patients; figures within parentheses are percentages.
- Mean ± SD.
- On arrival in emergency ward.
- Determined on admission in samples from nonfasting patients.
- Clinical coronary artery disease in first-degree relative at ≤60 years of age.

smoking habits, family history, obesity, blood pressure and heart rate, and levels of serum glucose and 
cholesterol. Diuretics or β-blockers were used by a similar 
minority of patients in each group. Patients assigned to intravenous therapy were randomized at 
a slightly earlier time (2.1 vs 2.8 hr, p < .05). Incidences of coronary anatomic disease and initial ventricular 
function were also shown to be comparable in 
the groups (see below).

**Results of blinded observation**

**Comparative changes in ejection fraction.** Early (day 1) 
and late (day 10) posttreatment left ventricular ejection 
fractons, assessed by radionuclide ventriculography, 
are illustrated in figure 1 for surviving patients (two 
refused restudy). Ejection fractions on day 1 were 
similar in the two groups: for the left ventricle, 47.7 ± 
12.5% (intravenous drug, n = 22) vs 48.5 ± 12.8% 
(intracoronary drug, n = 21); for the right ventricle,
FIGURE 1. Radionuclide ejection fractions on days 1 and 10 in the two streptokinase (SK) groups. Bars connect pairs of data for individual studies. Dots indicate isolated studies. Circles give mean data (±SEM).

42.1 ± 12.0% (intravenous drug, n = 17) vs 43.3 ± 12.6% (intracoronary drug, n = 16). On day 10, ejection fractions were as follows: for the left ventricle, 53.8 ± 14.0% (intravenous drug, n = 22) and 49.7 ± 15.6% (intracoronary drug, n = 20); for the right ventricle, 45.2 ± 8.9% (intravenous drug, n = 17) and 42.6 ± 12.2% (intracoronary drug, n = 14). These values also were not significantly different by group. The average percentage point increase in left ventricular ejection fraction between days 1 and 10 approached significance only in the intravenous drug group (increase of 5.1%; p < .08, n = 21 pairs). However, this change was significantly better than that noted in the historical control group: ejection fraction decreased by 3.0 ± 8.4% in the control group (n = 22) compared with an increase of 5.1 ± 12.4% in the intravenous streptokinase group, an average differential of 8.1 absolute percentage points (p < .02). The smaller differential, 4.5 percentage points, between the intracoronary streptokinase (current study) and historical control groups did not achieve significance.

Regional wall motion (table 2). Echocardiographic regional wall motion indexes for global and infarct segments were similar in both treatment groups on admission, day 1, and before discharge (day 10). Changes (improvement) in global wall motion index from admission to discharge, determined with paired data, were minor and not significant (average of two observers). (Changes in index after 1 day transiently favored the intracoronary group [p < .01]). In contrast, significant improvement became evident when restricting analysis to the infarct zone: an improvement of 0.3 of an index unit occurred in both intravenous and intracoronary drug groups between admission and day 10 (both p < .02).

Myocardial enzyme kinetics (table 3; figures 2 and 3). Similar accelerated enzyme-release kinetics were associated with both intravenous and intracoronary therapies, and kinetics in each group differed significantly from those in historical control subjects. Times to peak en-

<table>
<thead>
<tr>
<th>Regional wall motion index</th>
<th>Change in index</th>
<th>Day 1–10</th>
<th>p value</th>
<th>Day 10–1</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV drug group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Segments indexed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global (n)</td>
<td>4.18 ± 0.70 (26)</td>
<td>4.25 ± 0.58 (24)</td>
<td>4.47 ± 0.55 (22)</td>
<td>-0.11 ± 0.25 (22)</td>
<td>NS</td>
</tr>
<tr>
<td>Infarct zone (n)</td>
<td>3.61 ± 0.74 (25)</td>
<td>3.66 ± 0.72 (23)</td>
<td>4.12 ± 0.80 (21)</td>
<td>-0.09 ± 0.57 (22)</td>
<td>NS</td>
</tr>
<tr>
<td>IC drug group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Segments indexed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global (n)</td>
<td>4.21 ± 0.59 (21)</td>
<td>4.29 ± 0.59 (21)</td>
<td>4.24 ± 0.59 (20)</td>
<td>0.09 ± 0.24 (21)</td>
<td>NS</td>
</tr>
<tr>
<td>Infarct zone (n)</td>
<td>3.54 ± 0.77 (21)</td>
<td>3.74 ± 0.90 (21)</td>
<td>3.83 ± 0.80 (21)</td>
<td>0.19 ± 0.43 (21)</td>
<td>NS</td>
</tr>
</tbody>
</table>

The global wall motion index was based on an average of 15 left ventricular segments and was graded as follows: 5 = normal; 4 = mildly hypokinetic; 3 = severely hypokinetic; 2 = akinetic; 1 = dyskinetic. Infarct zone analysis included serial analysis of an average of 6.7 involved segments.

Changes in the index were determined with paired data; positive numbers indicate improvement and negative numbers, deterioration. (Global changes represent average of two observers.)

n indicates the number of patients successfully imaged at each determination.
enzyme concentrations did not differ according to route of administration of drug (table 3). In contrast, substantially later peaks were observed in the historical control group for each enzyme (p < .05 to .001). Peak serum enzyme concentrations were similar after intravenous and intracoronary therapy. However, enzyme peaks for LDH and myocardial isoenzyme LDH-1 were significantly lower after intravenous streptokinase than after the therapy that the control patients received (p < .05). Integrating concentrations of serum enzyme activities over time yielded similar areas for the intravenous and intracoronary drug groups. Because of the large interpatient variance, area differences for LDH and LDH-1 in treated groups vs the historical control group were not significant.
Coronary drug groups, with early loss, then stabilization; R wave amplitudes at the time of discharge from the hospital were greater after thrombolytic therapy than after the treatment that the control group received (p < .002, figure 5). The number of leads with pathologic Q waves was identical during convalescence in intravenous and intracoronary drug groups; Q waves were slightly but not significantly more frequent in historical control patients (figure 6).

Unblinded results of randomized study

Hospital course by treatment group (table 4). Streptokinase therapy was associated with significant and similar pain relief, as measured by the reduced need for morphine in patients receiving streptokinase by either route. Posttreatment morphine requirements for historical control patients was greater (p < .01, control vs intravenous drug).12 Killip heart failure class was similar for patients in both streptokinase groups on admission and in the coronary care unit. (Patients dying in shock were included as class 4.) Incidence of arrhythmias was also generally similar in the groups; however, there was a statistically lower frequency of ventricular ectopy in the intravenous drug group at hospital discharge (p < .05). At least one recurrent ischemic syndrome (extension, threatened occlusion, or angina) was present in three patients receiving intravenous and eight patients receiving intracoronary drug (p < .1).

Correspondingly, coronary bypass surgery was performed during the hospital course in four patients in the intravenous and eight in the intracoronary group. In addition, two patients receiving intracoronary drug underwent successful coronary balloon angioplasty. No mortality or perioperative infarction was associated with surgery, which was performed 1 to 14 days (mean 5.3 days) after infarction. The specific indication for additional interventions (surgery, balloon dilatation) included recurrent ischemic pain in nine and anatomic reasons (high-grade residual lesion, multivessel disease, and good apparent salvage) in five patients. Con-

**FIGURE 4.** Summation of ST segment elevations on 12-lead electrocardiograms in the two streptokinase and historical control groups. The dark bar on the abscissa represents the time of therapeutic intervention (streptokinase). Asterisk denotes significant difference (p < .05) between intravenous drug and historical control groups on day 10. Vertical bars denote ± SEM. ADM = admission.

**FIGURE 5.** R wave heights in leads with ST segment elevation, according to the electrocardiogram on admission, in the two streptokinase and historical control groups. Asterisk denotes significant difference (p < .05) between streptokinase and control groups on day 10. Vertical bars denote ± SEM. ADM = admission.

**FIGURE 6.** Number of leads with pathologic Q waves (ΣQw) over time in the two streptokinase and historical control groups. Vertical bars denote ± SEM. ADM = admission.
TABLE 4
Characteristics of hospital course in the two groups of patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IV drug group (n = 27)</th>
<th>IC drug group (n = 23)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine sulfate requirement (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before therapy (0–3 hr)</td>
<td>5.1 (0–35)</td>
<td>5.2 (0–42)</td>
<td>NS</td>
</tr>
<tr>
<td>After therapy (3 hr–3 days)</td>
<td>3.0 (0–67)</td>
<td>1.4 (0–36)</td>
<td>NS</td>
</tr>
<tr>
<td>Killip heart failure class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission</td>
<td>1.5 ± 0.6</td>
<td>1.4 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>In coronary care unit (maximum)</td>
<td>1.8 ± 1.1</td>
<td>1.8 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Arrhythmias</td>
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<tr>
<td>Primary ventricular tachycardia/fibrillation</td>
<td>2</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Bradycardias (problematic, requiring repeated drug therapy or paced)</td>
<td>2</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial fibrillation, paroxysmal</td>
<td>4</td>
<td>1</td>
<td>NS</td>
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<tr>
<td>Ventricular ectopic beats (late, day 10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total/24 hr</td>
<td>8 (0–1703)</td>
<td>52 (1–2257)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Successive or early (No. patients positive/No. studied)</td>
<td>5/20</td>
<td>11/20</td>
<td>.05</td>
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<tr>
<td>Recurrent ischemia</td>
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<tr>
<td>Infarct extension/coronary reocclusion</td>
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<td>NS</td>
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<tr>
<td>Threatened/transient coronary reocclusion</td>
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<td>NS</td>
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<td>Postinfarct angina</td>
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<tr>
<td>Early coronary bypass surgery</td>
<td>4</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Day of surgery</td>
<td>7.0 (1–14)</td>
<td>4.4 (1–14)</td>
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</tr>
<tr>
<td>Clinical bleeding problem</td>
<td>4</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital deaths</td>
<td>5</td>
<td>1</td>
<td>NS</td>
</tr>
</tbody>
</table>

aMedian (range).
bMean ± SD
cGeometric mean (range).
dMean (range).
eDoes not include cardiac rupture, felt to be unrelated.

Valescent ventriculographic evaluations were obtained after surgery or angioplasty in 11 of 14 patients.

Clinically apparent bleeding (upper gastrointestinal source) was noted in four patients after intravenous and one patient after intracoronary streptokinase. Source of bleeding was a gastric (in a patient receiving intracoronary drug), pyloric, and duodenal ulcer in one patient each, was associated with the nasogastric tube in one, and was unidentified in one (coffee grounds emesis).

All were successfully treated with fluid or blood-component replacement. Aminocaproic acid was used in two. Bleeding occurred within 6 hr of streptokinase infusion in three patients (all receiving intravenous drug) and during subsequent heparin therapy in two. Anemia ascribed to other causes was also noted in three patients receiving intravenous and two receiving intracoronary drug. One patient developed an urticarial rash 1 day after intravenous therapy.

Mortality in our elderly population requires discussion. In the historical control group, four hospital deaths occurred (15% mortality rate) and among the 50 patients undergoing thrombolytic therapy in this study, six deaths occurred (12% mortality). This mortality was age related: 3.6% (1/22) in patients age 65 years old or younger; 23% (5/22) in those over 65. Five patients in the intravenous drug group died, a rate similar to that among the historical control patients. One patient in the intracoronary drug group died. The trend toward fewer deaths in the intracoronary vs intravenous drug group was not statistically significant, however. All deaths were associated with pump failure, with or without terminal arrhythmia. Deaths in the intravenous drug group occurred at 1, 4, and 8 hr and 2 and 3 days and could not be specifically ascribed to thrombolytic therapy. Postmortem examinations were performed in three patients in the intravenous drug group and demonstrated rupture of the ventricular septum in one (this patient died after 8 hr, with intracoronary clot still occluding the anterior descending), free wall rupture in another (dying after 2 days), and extensive infarction in the third (dying after 3 days). Progressive shock and arrhythmia were noted in the patient receiving intravenous drug who died at 1 hr. Cardiogenic shock and limited gastrointestinal bleed-
ing (blood volume maintained) characterized the course in the patient receiving intravenous drug who died at 4 hr. The single death in the intracoronary drug group, in a patient initially near shock and successfully reperfused, occurred 1 hr after thrombolysis and may have been the result of reocclusion (postmortem declined).

**Angiographic and therapeutic observations (table 5).** In the intracoronary drug group acute coronary angiography documented total occlusion in 21 (91%) and subtotal occlusion in two patients. Reperfusion was established in 87% (20/23) of patients overall and 86% (18/21) of those with totally occluded vessels. (Initial reperfusion was accomplished by contrast injection in one and guidewire manipulation in two.) Intracoronary streptokinase was administered 4.3 ± 1.4 hr after onset of symptoms, representing an average delay of 1.4 hr after admission. Total streptokinase dose averaged 210,000 U. Occluded vessels were reperfused after an average of 23 min (range 0 to 60); total infusion time averaged 56 ± 20 min. In therapeutically reperfused patients with paired, interpretable angiograms, ejection fraction increased immediately after therapy from 53.9 ± 5.2% to 61.5 ± 11.2% (p < .07, n = 11).

The intravenous drug group was characterized by a substantially shorter delay occurring between entry and drug administration (0.7 ± 0.3 hr), leading to delivery of drug an average of 2.8 ± 1.0 hr after onset of pain (p < .001, intravenous vs intracoronary drug). Using a combination of indirect clinical indexes27 (change in pain or rhythm, early enzyme peak, rapid ST segment resolution) we estimated that 59% (n = 16) of the patients in the intravenous drug group reperfused early (<1 hr), 26% (n = 7) reperfused with some delay (1 to 4 hr), and 15% (n = 4) failed to reperfuse. Relatively early peaking of levels of CK-MB isoenzyme (at <14 hr after entry) occurred in a similar high percentage of patients receiving intrave-

### Table 5

**Selected therapeutic and angiographic end points in the two patient groups**

<table>
<thead>
<tr>
<th>Observation</th>
<th>IV drug</th>
<th>IC drug</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hours, symptom onset to streptokinase</td>
<td>2.8 ± 1.0(^a)</td>
<td>4.3 ± 1.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hours, entry to drug administration</td>
<td>0.7 ± 0.3</td>
<td>1.4 ± 0.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total coronary occlusion present(^b)</td>
<td>—</td>
<td>91 (21/23)</td>
<td>—</td>
</tr>
<tr>
<td>Units of streptokinase given × 10(^{-3})(^c)</td>
<td>845 (500–1,000)</td>
<td>212 (75–330)</td>
<td>—</td>
</tr>
<tr>
<td>Minutes, streptokinase infusion until recanalization(^d)</td>
<td>—</td>
<td>24.2 ± 14 (0–60)</td>
<td>—</td>
</tr>
<tr>
<td>Reperfusion established</td>
<td></td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Early (day 0)</td>
<td></td>
<td>87 (20/23)</td>
<td></td>
</tr>
<tr>
<td>Late (predischarge)(^f)</td>
<td>73 (16/22)</td>
<td>76 (16/21)</td>
<td>NS</td>
</tr>
<tr>
<td>Antegrade via infarct artery(^h)</td>
<td>86 (19/22)</td>
<td>86 (18/21)</td>
<td>NS</td>
</tr>
<tr>
<td>Via infarct artery, bypass graft, or collaterals(^h)</td>
<td>5</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Uncertain or undetermined (No. patients)</td>
<td>5</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Number of diseased vessels (≥70% coronary artery obstruction)(^h,(^f)</td>
<td>55 (11/22)</td>
<td>57 (13/23)</td>
<td>NS</td>
</tr>
<tr>
<td>1</td>
<td>41 (9/22)</td>
<td>35 (8/23)</td>
<td>NS</td>
</tr>
<tr>
<td>3</td>
<td>5 (1/22)</td>
<td>9 (2/23)</td>
<td>NS</td>
</tr>
<tr>
<td>Early enzyme peak (peak CK-MB% at &lt;14 hr)(^h,(^g)</td>
<td>92 (23/25)</td>
<td>86 (19/22)</td>
<td></td>
</tr>
<tr>
<td>Infarct-related coronary artery</td>
<td></td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>8</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>4</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Right</td>
<td>10</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Uncertain/undetermined</td>
<td>5</td>
<td>1</td>
<td>NS</td>
</tr>
</tbody>
</table>

\(^a\) Mean ± SD.
\(^b\) In percentage (proportion of patients).
\(^c\) Mean (range).
\(^d\) Median of 9.2 days IV, 9.6 days IC group at angiography.
\(^e\) Determined angiographically (n = 42) or at postmortem examination (n = 3). Five patients receiving intravenous drug not studied (death without postmortem or refusal).
\(^f\) In patients surviving more than 24 hr.
nous and intracoronary drug who survived through 24 hr. Late patency could be assessed in 22 patients, either angiographically (in 19) or at postmortem examination (in three). Perfusion was present to the infarct zone in 73% (16/22) by antegrade flow and in an additional 14% (n = 3) by visible collateral filling. Late results were comparable in the intracoronary drug group. A similar distribution of infarct-related arteries was observed by treatment group, and the extent of coronary artery disease was comparable. Information on predischARGE angigraphic left ventricular ejection fraction was incomplete, but paralleled radionuclide data, with ejection fraction averaging 58.8 ± 16.2% in the intracoronary (n = 12) and 61.4 ± 13.7% (n = 18) in the intravenous drug group.

Subgroup observations in the patients receiving intravenous drug. No significant differences in characteristics or major end points were observed between the low- (n = 14) and high-rate (n = 13) infusion groups. Mean ages were 63 ± 12 and 58 ± 13 years, respectively. Time of entry into the study averaged 2.1 and 2.1 hr. Anterior infarction occurred in 43% and 38%. Increases in radionuclide ejection fraction averaged 5.2 and 6.4 percentage points. Times to peak level of CK-MB were 13.7 and 10.0 hr and to peak level of LDH-1, 31.7 and 30.6 hr. Electrocardiographic predischARGE Q waves averaged 3.7 vs 3.4 and relative R wave amplitudes, 44% and 44%. Bleeding problems occurred in two in each group. A similar number were believed to have both early (n = 8, 8) and intermediate reperfusion (n = 4, 3), and similar late patency rates (75%, 70%) were observed. Deaths by group numbered one (low rate) and four (high rate) (p = NS).

Discussion

The present study compared the effects on hospital course of intravenous and intracoronary streptokinase in patients presenting with acute myocardial infarction. Results after intravenous streptokinase were also compared with those after standard therapy in a comparable historical control group not treated with thrombolytic therapy. Overall, our study suggests that intravenous and intracoronary streptokinase have approximately equivalent overall effects on hospital course and clinical and laboratory variables used to evaluate patients with myocardial infarction surviving the first 8 hr. In a comparison with a historical control group not treated with the drug, several variables indicated a significant benefit of streptokinase therapy. Our study does not provide evidence for a reduction in early mortality after intravenous streptokinase compared with therapy that the historical control patients received, but this analysis was limited by the small study population. The use of intracoronary streptokinase has several disadvantages that might limit its widespread and effective application. A small minority of hospital centers have cardiac catheterization facilities able to provide 24 hr coverage. Even in these, inevitable delays prolong the time to application of streptokinase, jeopardizing the potential beneficial effects of reperfusion. Intravenous streptokinase, if proved effective, could be applied readily and rapidly in virtually every medical care facility.

Recently, Schroder et al. demonstrated the feasibility of thrombolysis with short-term intravenous infusions of streptokinase. In 11 of 21 patients (52%) studied angiographically, occluded coronary arteries were opened within 1 hr after starting the infusion. In 84% of a larger group (93 patients), eventual patency of the infarct-related coronary artery was demonstrated by angiography in the fourth week. Early peaking serum CK-MB curves suggested that recanalization may have occurred in most patients within 1 to 2 hr of application. Myocardial salvage was suggested by improvement in local contraction disorders in the recanalized group and by a significant relationship between infarct size and time from onset of symptoms to treatment, with benefit being particularly evident in patients treated within 3 hr of symptom onset. Streptokinase doses were 500,000 or 1,500,000 U and clinically evident bleeding was not problematic. Intravenous streptokinase had previously been applied to patients with myocardial infarction in several large trials undertaken during the 1970s. Generally, these trials were flawed by errors in study design, but some of the larger trials suggested a potential beneficial effect on mortality. In these trials, the level of safety of standard doses of streptokinase appeared acceptable.

Our study documented the ability to apply thrombolytic therapy substantially earlier by the intravenous route in patients with acute myocardial infarction, with a relatively favorable effect on ventricular function. Intravenous streptokinase was applied by 2.8 hr (vs 4.3 hr for intracoronary drug). The 5.1 percentage point average increase in ejection fraction during convalescence, as determined by radionuclide ventriculography, was significant in comparison with the average decrease in function (−3.0%) noted in the historical control group. Improved global function after streptokinase was also observed by Schroder et al. The small improvement in ejection fraction after intracoronary streptokinase did not achieve significance in the present study. This result is consistent with randomized
trials from Michigan and is slightly inferior to that noted in our previous trial. Intracoronary drug was applied slightly later in the present study and a somewhat greater incidence of posttherapy ischemic events occurred. Echocardiographic regional wall motion in the infarct zone showed similar overall improvement in both groups. Compensatory changes in opposite wall motion may explain the insignificant global index change, as observed by others.

The kinetics of myocardial enzyme release were similar in the two treatment groups and differed from that in the control group. Early peaking of levels of myocardial enzymes appears to be a consistent finding after coronary thrombolysis and was also noted in the present study. Clinical and animal studies suggest that rapid release of CK-MB, whether therapeutically or spontaneously achieved, is a marker of early reperfusion. Rapid enzyme release has also been associated with differential improvement in left ventricular function in treated and untreated patient groups. The similar times to enzyme peaks in our intravenous and intracoronary drug groups provide evidence for a similar average time to reperfusion. Results of animal and human studies suggest an increase in the total amount of CK released into the serum after reperfusion. The result is greater total enzyme release (by up to two to three times) for equivalent infarct volumes. Thus, the finding of roughly equivalent peak and time-integrated CK enzyme values for the two streptokinase-treated groups and the historical control group in our study is consistent with myocardial salvage. The lower peak levels of LDH and LDH-1 in the intravenous drug vs the control group are also suggestive of salvage. However, the mechanisms of myocardial LDH release during myocardial infarction and reperfusion require further experimental study, especially since nonmyocytic components (including white cells and red cells) participating in the exudative and hemorrhagic responses to ischemic injury may be a substantial source of LDH.

Electrocardiographic evolutionary changes were favorable after intravenous streptokinase and this is consistent with previous observations. Reperfusion initially accelerates electrocardiographic evolution, but final electrocardiographic indexes have favored treated groups after successful therapy. Injury currents, (summed ST segment) were rapidly reduced by both therapies (especially intravenous therapy, compared with historical control), and R waves were better preserved at convalescence. Q wave development was slightly but insignificantly less than in historical controls. Electrocardiographic scoring indexes have been recently developed based on R wave loss and Q wave development and have been correlated with left ventricular function after myocardial infarction. The observed electrocardiographic results in our study may thus be interpreted as supporting a modest reduction in infarct size. The reason for initially rapid electrocardiographic evolution on reperfusion is unclear. The possibility of reperfusion injury has recently been considered and is leading to experimental attempts to limit its extent.

The hospital course in surviving patients was favorable in those receiving intravenous streptokinase. A marked decrease in pain (assessed by the need for morphine) has been observed after reperfusion and was similarly noted after intravenous and intracoronary therapy in this study. Average change in Killip heart failure class was comparable in both treatment groups. Incidence of acute arrhythmias did not differ significantly between treatment groups, and late ventricular arrhythmias were actually less frequent in patients in the intravenous drug group. The occurrence of postinfarct ischemic events favored the intravenous group, although the reason for this is unclear. Bleeding episodes tended to be more common in the intravenous drug group, but were successfully managed. The greater frequency of interventions (surgery, balloon dilatation) in the intracoronary drug group could be related to more frequent pain recurrence and the fact that there was anatomic information available as a result of early angiography. Because interventions were often performed before the final convalescent evaluations, they must be considered, together with acute streptokinase, as part of the overall therapeutic intervention. However, any presumed beneficial effects of surgical intervention would, if anything, bias the study against the intravenous streptokinase group since more interventions were performed in the intracoronary drug group.

Our study is too small to assess significant differences in mortality, but overall and age-related rates were generally similar to average rates reported in other studies. Mortality after intravenous streptokinase was similar to that in historical control patients (five vs four deaths). The lower mortality after intracoronary drug (one death) was not significant. Four patients who received the higher dose of intravenous streptokinase died. However, we could not confirm or exclude the possibility of an effect of intravenous streptokinase on mortality. One free wall rupture was documented in both the intravenous streptokinase and historical control groups. A septal rupture was noted in the intravenous drug group, but occurred in a patient.
who did not undergo reperfusion to the infarct zone. Two deaths (without postmortem evaluation) occurred in patients who may have undergone early reperfusion (early CK peaks). Although hemorrhagic infarction after reperfusion is not believed to cause more extensive necrosis, transient deleterious effects of reperfusion on ventricular function in patients with large infarctions have occasionally been reported.\textsuperscript{4, 41, 42} The relatively earlier recruitment of patients in the intravenous group may have also been significant. It is well established that cohort mortality during acute infarction increases as time from onset of symptoms decreases. Three of five deaths in the intravenous drug group occurred in patients recruited early (<2 hr) who showed progressive hemodynamic instability that would have precluded them from study entry had they been recruited at a slightly later time (i.e., 3 to 8 hr, as for other studied groups). Thus, their deaths may have occurred in spite rather than because of early administration of streptokinase. The elderly are known to have a higher mortality rate after myocardial infarction with\textsuperscript{45} or without streptokinase. We recruited a more elderly population than have others,\textsuperscript{12, 15, 43} with an average age of 61 years and a range to 84 years, and the patients who died were older (average age 68 years, three over 76 years) so that concerns about risk/benefit ratio may be best directed toward the elderly (>65 years). It is relevant that larger studies of standard-dose intravenous streptokinase in patients with myocardial infarction have not shown excessive mortality.\textsuperscript{16, 17} Further controlled studies will thus be required to assess the safety of and questions about mortality after high-dose, short-term intravenous streptokinase.

Certain limitations of our study should be recognized. Catheterization data were not obtained in the intravenous drug group on admission to the hospital since our protocol was designed to mimic the clinical situation. Also, early coronary angiography in the intravenous drug group was sacrificed in favor of earlier institution of therapy, with the potential for greater clinical benefit. Our control study group was a historical rather than a concurrent one. However, these patients showed excellent matching, were similarly recruited and evaluated, and received otherwise similar therapy.\textsuperscript{13} Other studies have documented the acute kinetics of coronary thrombolysis after intravenous streptokinase.\textsuperscript{15, 28, 43-45} a 50% to 60% reperfusion rate in the first hour has been consistently observed.

Evidence for early reperfusion in our study included similarities in clinical course, enzyme kinetics, and electrocardiographic evolution in the intravenous and intracoronary streptokinase groups. Similar rates of infarct zone perfusion were also present at convalescent angiographic examination. However, it is recognized that patency rates of infarcted vessels at convalescent angiographic examination represent the sums of streptokinase-related and spontaneous recanalization rates, minus rates of persistent and recurrent occlusions. Spontaneous patency rates have been variable in post-infarction angiographic studies (range about 10% to 60%).\textsuperscript{46-50} Indirect, but not direct, evidence provided by our study suggests that patency in our intravenous drug group may be explained primarily by streptokinase therapy.

Two different intracoronary drug regimens were used. The higher dose rate was instituted to mimic current trends\textsuperscript{15, 27, 43, 44} after safety had been established with standard-rate infusions. Although subgroup analysis was performed and revealed no differences, other (larger) studies will be required to fully answer the question of ideal dose. Our earlier administration of intravenous streptokinase may explain our more favorable results in comparison with those of the study of Rogers et al., in which the early reperfusion rate after intravenous streptokinase was only approximately 30%.\textsuperscript{43} Our study, unlike that of Rogers et al., however, does not provide a strong rationale for extremely high-dose therapy; significant differences were not noted in clinical course in subgroups receiving standard vs higher rate regimens. Time of application may thus be as critical to successful reperfusion as the dose of intravenous drug.\textsuperscript{15, 28} Despite the favorable comparisons between the streptokinase-treated and untreated (historical control) groups, the gains suggested are generally modest. Approaches that allow even earlier and more efficient intervention\textsuperscript{51} and the application of adjunctive therapies that assist in salvaging greater amounts of myocardium are indicated.\textsuperscript{52}

In summary, the clinical effects of intravenous and intracoronary streptokinase in patients with acute myocardial infarction were compared in a randomized, prospective fashion. Indirect evidence suggested a roughly similar rate of early reperfusion. Similar or superior effects on left ventricular function, incidence of arrhythmias, and postinfarction ischemic complications were noted in survivors in the intravenous drug group. Although early mortality in this group tended to be higher, this could not be ascribed to drug. These results should stimulate additional studies of intravenous streptokinase in patients with acute myocardial infarction to further assess questions of safety and efficacy.

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