The Western Washington Intravenous Streptokinase in Acute Myocardial Infarction Randomized Trial

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ABSTRACT Three hundred sixty-eight patients were randomly assigned to receive intravenous streptokinase (IVSK) (n = 191) or standard therapy (n = 177) to determine the efficacy of IVSK in the treatment of acute myocardial infarction. The mean time to treatment was 3.5 hr. At 14 days there were 12 deaths in the treatment group (6.3%) and 17 deaths in the control group (9.6%) (p = .23). Early mortality was related to infarct location. Fourteen day mortality for anterior infarctions was 10.4% for treatment with IVSK and 22.4% for control patients (p = .06) and was similar for IVSK-treated patients with inferior infarctions, 4.0% vs 1.8% (p = .32). For those randomized under 3 hr, 14 day mortality tends to be lower in treated patients, 5.2% vs 11.5% (p = .11). There was significant improvement in long-term survival for patients with anterior infarction; 2 year survival was 81% for IVSK-treated patients and 65% for control patients (p = .05). There was no improvement in survival for patients with inferior myocardial infarction (p = .27). We conclude that patients with anterior myocardial infarction have improved survival when treated within the first 6 hr of symptoms. Patients with inferior infarction do not appear to have improved survival with thrombolytic therapy. Some of this improvement in survival in patients with anterior infarction may be due to a higher frequency of revascularization procedures in the treatment group.


THROMBOLYTIC THERAPY for acute myocardial infarction became possible in the early part of this decade with the demonstration of the important role of coronary artery thrombosis as the immediate cause of acute myocardial infarction. Early reports from Russia and West Germany demonstrated the efficacy of intracoronary streptokinase in achieving coronary artery reperfusion in the setting of acute infarction. After reports of numerous pilot studies, two small randomized trials of intracoronary streptokinase were reported, demonstrating coronary artery reperfusion rates between 65% and 85%. Those that began streptokinase therapy within 3 hr of the onset of chest pain demonstrated evidence of myocardial salvage with an increase in ejection fraction and improved regional wall motion in the treated patients. These initial trials were too small to define adequately the effect of intracoronary streptokinase on survival. Two larger studies have shown a significant reduction in early mortality. These results of intracoronary streptokinase, as well as the knowledge that intracoronary therapy was not feasible for many patients and delayed the onset of treatment, led us to study intravenous streptokinase (IVSK) in the treatment of acute myocardial infarction. This trial was planned in the spring of 1982 and funded in August 1983, and patients were entered between September 1983 and August 1986.

Methods

The planned sample size of 660 patients was based on an assumed 14 day mortality of 14% in the controls and 7% in the treated patients. For these alternatives, 330 patients would be needed in each group to achieve a power of 0.80 with a significance level of .05. During the planned 3 years of patient entry, only 368 patients were randomized. As the results of other studies were reported, it was deemed inappropriate by the investigators and the Policy Advisory Board to continue patient entry beyond 3 years.

Organization of trial. Patient enrollment began September 1, 1983, and ended July 31, 1986. Twenty-seven hospitals and 80 physicians in the states of Washington and Idaho and in Vancouver, British Columbia, participated in the trial. Four of the institutions are Veterans’ Administration (VA) or Army
hospitals, four are teaching hospitals, and the remainder are community hospitals. The entry criteria and protocol for the study are outlined below.

**Patient enrollment.** Patients 75 years of age or less with signs and symptoms of acute myocardial infarction, including typical chest pain for at least 20 min, were evaluated for enrollment. Patients giving informed consent for treatment and data collection were randomized if assignment could occur within 6 hr of onset of symptoms. Patients who had atypical symptoms without a clear time of onset or a stuttering course were excluded.

**Electrocardiographic criteria.** The following electrocardiographic changes were required for enrollment: an upward bowing (convex) ST segment elevation (at least 0.15 mV in V1, V2, or V3 or 0.1 mV in other leads) in two or more leads measured 60 msec beyond the J point, and one or more leads with ST segment elevation without Q waves (40 msec duration or longer).

**Exclusion criteria.** Factors that excluded patients from enrollment in the trial included (1) presence of severe disease of other organ systems likely to reduce longevity or ability to cooperate or give informed consent (e.g., cancer, severe kidney or liver disease, sepsis, coma, emotional illness), (2) prior streptokinase therapy, (3) any contraindication to anticoagulation therapy, including active peptic ulcer disease, diabetic retinopathy, and hypertension with diastolic blood pressure over 120 mm Hg, (4) recent major surgical procedure (2 weeks) or neurosurgical procedure or history of stroke (4 weeks), (5) trauma likely to result in bleeding, (6) presence of central venous lines placed in uncompressible entry sites such as subclavian or internal jugular veins, and (7) prior coronary artery bypass surgery.

**Patient management.** Patients who met entry criteria were given a detailed explanation of the purpose of the trial and were asked to sign an informed consent statement approved by the Institutional Human Subjects Review Committee at each hospital. When possible, a family member participated in the consent process.

Patients randomly assigned to streptokinase therapy were given 50 mg benadryl and 100 mg hydrocortisone intravenously, followed by 1.5 million IU IVSK over 1 hr. In addition, treated patients received intravenous heparin starting at 1000 U/hr beginning 2 hr after the completion of the streptokinase infusion and were continued on heparin until stabilized on oral anticoagulation with warfarin. Participating physicians were advised to continue oral anticoagulation when appropriate for 3 months after hospital discharge. Control patients received routine coronary care as defined by their physicians, which may or may not have included heparin or warfarin anticoagulation.

Both treatment and control patients had serial creatine kinase (CK) levels determined at the time of randomization and every 4 hr for 24 hr. A 12 lead electrocardiogram was done at the time of hospital discharge. At the discretion of their physicians, patients were encouraged to undergo left heart catheterization, coronary arteriography, and left ventriculography before hospital discharge or shortly thereafter. Finally, patients living in the Seattle area were invited to undergo resting tomographic thallium-201 myocardial imaging for infarct sizing and radioisotope determination of ejection fraction. These studies were done in a central laboratory 6 to 8 weeks after patients entered the study and will be reported separately.

**Randomization procedure.** At the beginning of the study, patients at each hospital were randomly assigned to treatment and control groups within the following strata: (1) anterior myocardial infarction less than 3 hr from onset of symptoms, (2) anterior myocardial infarction 3 to 6 hr from symptom onset, (3) inferior myocardial infarction less than 3 hr from onset of symptoms, and (4) inferior myocardial infarction 3 to 6 hr from symptom onset. Four sets of opaque, sealed envelopes were used to randomly assign patients to treatments. Each envelope contained the patient identification number and therapeutic assignment. This number, when reported to the data coordinating center, was used to ascertain that envelopes had been opened in the proper sequence and the therapeutic assignment was correct.

**Clinical data collection.** Baseline information obtained for all patients included age, sex, history of prior myocardial infarction, and history of congestive heart failure requiring therapy. In addition, the times of symptom onset, admission to the hospital, and initiation of therapy were recorded. The clinical status at time of entry was categorized as ongoing ischemic pain, hemodynamically stable, hypertensive (systolic pressure under 90 mm Hg but without evidence of low cardiac output or shock), cardiogenic shock (persistent systolic pressure under 80 mm Hg with clinical evidence of inadequate cardiac output to sustain vital functions), pulmonary edema, and the use of direct current cardioversion for ventricular tachycardia or fibrillation. These categories were not mutually exclusive. Serial electrocardiograms and cardiac enzyme measurements were collected every 4 hr for the initial 24 hr of hospitalization. At the time of hospital discharge, angina, as defined by the Canadian Cardiovascular Society classification, and the presence and severity of congestive heart failure were determined.

For those patients who underwent coronary angiography, all available films were reviewed by an angiographic reading committee. Ejection fractions were determined by experienced technicians who were blinded to the treatment assignment. The committee classified the occlusions in infarct-related vessels according to severity and location, and when possible measured residual diameter stenosis with a digital caliper. The presence and adequacy of collateral circulation to the distal bed of the infarct-related vessel was graded on a scale of 0 to 3 as previously defined. The extent of disease in the noninfarct arteries was also classified. Reperfusion was measured as in the TIMI trial: grade 0, no reperfusion; grade 1, penetration of the thrombus with minimal perfusion; grade 2, partial perfusion; grade 3, complete perfusion. The angiographic reading panel was blinded to treatment assignment.

A 6 month and a second follow-up carried out at 1 or more years were accomplished by mail and/or phone. Vital status and interim coronary bypass surgery and coronary angioplasty were ascertained. Information concerning hospitalization for reinfarction, chest pain, congestive heart failure, arrhythmia, and cardiac catheterization was collected. Questions concerning the presence and frequency of angina were also asked. To date, 6 month and late follow-up have been completed for 99.7% and 98% of eligible patients.

**Objectives of the study.** The primary end point of the trial was 14 day mortality, and secondary end points reported here included long-term survival and the effect of treatment on coronary artery patency, left ventricular function, and the patient’s initial clinical course. The results of follow-up (8 week) measurements of infarct size, segmental wall motion, and global left ventricular function will be reported later.

**Statistical methods.** The chi-square and Fisher’s exact tests were used to test for statistical significance for categorical variables. For continuous variables, the two-tailed t test was used to determine statistical significance. Continuous variables were expressed as mean ± 1 SD. The product limit method was used to test for differences in survival between treatment and control groups.

**Results**

Three hundred sixty-eight patients were enrolled by 80 physicians; 27 hospitals contributed an average of
TABLE 1
Patients’ characteristics

<table>
<thead>
<tr>
<th></th>
<th>IVSK</th>
<th>Control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>191</td>
<td>177</td>
<td>368</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>57.0±11.0</td>
<td>57.1±10.1</td>
<td>57.0±10.6</td>
</tr>
<tr>
<td>% female</td>
<td>17.8%</td>
<td>14.1%</td>
<td>16.0%</td>
</tr>
<tr>
<td>Anterior</td>
<td>35.1%</td>
<td>37.9%</td>
<td>36.4%</td>
</tr>
<tr>
<td>Inferior</td>
<td>64.9%</td>
<td>62.1%</td>
<td>63.6%</td>
</tr>
<tr>
<td>Prior MI</td>
<td>13.7%</td>
<td>13.0%</td>
<td>13.4%</td>
</tr>
<tr>
<td>Time to hosp.</td>
<td>107±75</td>
<td>125±89</td>
<td>116±82*</td>
</tr>
<tr>
<td>Randomized ≤3 hr</td>
<td>50.8%</td>
<td>54.2%</td>
<td>52.4%</td>
</tr>
<tr>
<td>Randomized &gt;3 hr</td>
<td>49.2%</td>
<td>45.8%</td>
<td>47.6%</td>
</tr>
<tr>
<td>Time to treatment</td>
<td>209±84</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemodynamic state</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>90.1%</td>
<td>85.9%</td>
<td>88.0%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>(SBP&lt;90 mm Hg)</td>
<td>8.4%</td>
<td>8.5%</td>
</tr>
<tr>
<td>Shock</td>
<td>2.1%</td>
<td>1.1%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Ongoing chest pain</td>
<td>94.2%</td>
<td>88.6%</td>
<td>91.6%</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>6.3%</td>
<td>3.4%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Postcardioversion</td>
<td>2.1%</td>
<td>2.8%</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

MI = myocardial infarction; SBP = systolic blood pressure. *p = .046, IVSK vs control.

13.6 patients with a range of one to 64. Six community hospitals enrolled at least 20 patients and accounted for 57% of the total enrollment. Only 15% of the patients were entered from teaching hospitals.

Baseline characteristics were similar for patients assigned to IVSK and to standard treatment (p > .05) as shown in table 1. One hundred ninety-one patients were randomly assigned to the treatment group and 177 to the control group; 134 (36%) had anterior wall and 234 (64%) had inferior wall myocardial infarctions. There were 309 men and 59 women and their mean age was 57 years. The time from onset of symptoms to hospital admission averaged 107 min for the treatment group and 125 min for the controls (p = .046). Whereas 8.0% of treated patients were in the hospital when myocardial infarction occurred, only 3.0% of control patients were hospitalized at the time of onset of infarction. When these hospitalized patients were excluded, the difference in the time to hospitalization was no longer significant (p = .17). Although 52% of the patients were randomized less than 3 hr after symptoms onset, only 42.9% began therapy within 3 hr of symptom onset. The average time for starting IVSK was 209 min after the onset of symptoms.

A prior myocardial infarction had occurred in 13.4% of patients. At the time of enrollment, chest pain was present in 94% of treated patients and 89% of the controls. Hypotension, pulmonary edema, and cardionic shock were present in 8.4%, 4.9%, and 1.6%, respectively. Emergency direct-current defibrillation or cardioversion was required in 2.4% of patients. The average dose of streptokinase was 1,488,000 ± 122,000 IU given over a period of 60 ± 10 min.

During the first 14 days after myocardial infarction, 13 patients in the treatment group (6.8%) and 10 in the control group (5.6%) underwent coronary artery bypass graft surgery. Twelve treatment patients (6.3%) and five control patients (2.8%) had coronary balloon angioplasty during the same period (p = .11).

By 1 year, 17.3% of the treatment and 14.1% of the control patients had undergone coronary artery bypass graft surgery (CABG), whereas 9.9% of treatment and 4.5% of control patients had had coronary artery angioplasty. Thus 27.2% of treatment patients and 18.6% of controls had a revascularization procedure by 1 year (p = .05). There were no hospital deaths related to these procedures. One patient who had CABG died 1 week after discharge from the hospital.

Fourteen day mortality. The 14 day mortality is presented in figures 1 and 2. Overall, the mortality was 7.9%. Twelve of 191 IVSK-treated patients (6.3%) and 17 of 177 control patients (9.6%) died; this difference was not statistically significant (p = .23). Of the 19 deaths, 23 died of shock, three of arrhythmias, two of cardiac rupture, and one of suicide. This latter patient was incorrectly randomized to the anterior control group and did not have a myocardial infarction. Two patients randomized to IVSK therapy did not receive therapy; one died before treatment was initiated, and the other developed ventricular fibrillation and after

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FIGURE 1. Time of death for the patients who died within the first 14 days of the study. The cause of death is indicated as shock, arrhythmia, or cardiac rupture. The closed triangles represent three patients of note. Two in the treatment group did not receive streptokinase, as noted in the text, and one with anterior infarction in the control group died of suicide.
resuscitation had contraindications to receiving streptokinase. This patient died 2 days later.

Mortality was related to the location of the infarction, as shown in figure 1. After anterior infarction, mortality was 10.5% in the treatment group and 22.4% in the control group (p = .06). Among those with inferior infarction, mortality was similar in the treatment and the control groups (4.0% vs 1.8%; p = .32). There were 34 women in the treatment group, and one died (2.9%), while four of 25 women (16.0%) in the control group died (p = .08). The mortality rates for men assigned to treatment and control were more similar, 7.0% vs 8.6% (p = .61). Among all patients with prior myocardial infarction, none of 26 treated patients and five of 23 (21.7%) control patients died (p = .02). The influence of time of randomization on 14 day survival is shown in figure 2. For patients randomized by less than 3 hr, the treatment group had a 5.2% mortality compared with the control patients’ mortality of 11.5% (p = .11). There was no difference in the 14 day mortality for those randomized after 3 hr (7.5% for both groups).

Clinical status. The clinical status of patients at the time of hospital discharge is shown in table 2 and is presented according to treatment group. There were no apparent differences in the status of treatment and control groups. The length of stay, angina class, presence of congestive heart failure, peak CK level, and incidence of non–Q wave infarction were similar in both treatment and control groups (p > .05). The time to peak CK level was significantly earlier in treated compared with control patients (p < .0001).

At the time of late follow-up, IVSK-treated and control patients did not differ with respect to rehospitalization for chest pain, 13.4% vs 12.1% (p = .74), congestive heart failure, 2.0% vs 5.3% (p = .14), arrhythmia, 4.8% vs 8.9% (p = .15), or cardiac catheterization, 9.4% vs 5.3% (p = .19). However, patients did differ with respect to rehospitalization for myocardial infarction, 9.6% of treated patients and 2.7% of controls (p = .01). Finally, the presence of angina was similar in both groups at 6 month and late follow-up. At late follow-up, 39.3% of IVSK-treated and 37.6% of control patients had at least some episodes of angina pectoris.

Complications of therapy. Complications occurred in 23.0% of the treatment group and in 14.1% of the control group (p = .03). Bleeding, although infrequent, tended to occur more often in the streptokinase group (13.1% vs 6.5%; p = .07), as did allergic reactions (2.1% vs 0%; p = .07). The incidence of ventricular fibrillation was similar in both groups, but ventricular tachycardia occurred more frequently in the IVSK-treated patients (11.0% vs 4.5%; p = .02). There was one serious nonfatal intracerebral hemorrhage resulting in severe permanent neurologic disability in a 66-year-old man in the IVSK group.

Angiographic findings. One hundred thirty-eight (72.3%) treated and 112 (63.3%) control patients underwent follow-up cardiac catheterization an average of 10.4 ± 7.4 days after infarction. The baseline clinical characteristics of patients undergoing cardiac catheterization were evaluated. The average age of those undergoing catheterization was 55, compared with 60 for those not undergoing catheterization (p < .01). Patients with catheterization were also more

![Graph](chart.png)

**FIGURE 2.** Fourteen day mortality for patients randomized less than 3 hr and from 3 to 6 hr from the onset of symptoms of acute myocardial infarction.

**TABLE 2**

<table>
<thead>
<tr>
<th>Discharge characteristics (survivors only)</th>
<th>IVSK</th>
<th>Control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>179</td>
<td>160</td>
<td>339</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>11 ± 7</td>
<td>11 ± 7</td>
<td>11 ± 7</td>
</tr>
<tr>
<td>Angina class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No angina</td>
<td>66.5%</td>
<td>65.0%</td>
<td>65.8%</td>
</tr>
<tr>
<td>I</td>
<td>11.7%</td>
<td>11.3%</td>
<td>11.5%</td>
</tr>
<tr>
<td>II</td>
<td>7.3%</td>
<td>8.8%</td>
<td>8.0%</td>
</tr>
<tr>
<td>III</td>
<td>3.9%</td>
<td>2.5%</td>
<td>3.2%</td>
</tr>
<tr>
<td>IV</td>
<td>2.2%</td>
<td>0.0%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Unknown</td>
<td>8.4%</td>
<td>12.5%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>9.5%</td>
<td>7.5%</td>
<td>8.6%</td>
</tr>
<tr>
<td>Peak CK (U/liter)</td>
<td>1859 ± 1431</td>
<td>1828 ± 1213</td>
<td>1844 ± 1331</td>
</tr>
<tr>
<td>Time to peak CK (hr)</td>
<td>16.1 ± 5.6</td>
<td>20.8 ± 5.4*</td>
<td>18.3 ± 6.0</td>
</tr>
<tr>
<td>Non–Q wave infarction</td>
<td>10.2%</td>
<td>5.7%</td>
<td>8.0%</td>
</tr>
<tr>
<td>NO CK elevation</td>
<td>2.8%</td>
<td>1.9%</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

*p < .0001, IVSK vs control.
likely to have received IVSK (55% vs 48%), more likely to be men (87% vs 74%), more likely to have had a prior infarction (15% vs 10%), and more likely to have congestive heart failure (10% vs 5%). None of these differences was statistically significant.

Of the films available for review by the angiographic committee, 170 (70.5%) had left ventricular angiograms judged of adequate quality to determine ejection fractions. The results of some of these analyses are reported in table 3. Treatment-control comparisons for reperfusion were significant for patients with anterior infarctions (p = .04), for those with inferior infarctions (p = .006), and for all patients (p = .003). Reperfusion was graded angiographically in 130 treated and in 105 control patients. No reperfusion was present in 26.9% of treated patients and in 47.6% of the controls. There was adequate reperfusion (grade II or III) in 68.5% of the treatment group and 44.7% of the controls. For patients with patent infarct-related vessels, the residual coronary artery stenosis for treatment and control groups did not differ (p = .13). Since these angiograms were obtained 1 to 3 weeks after entry into the trial, the incidence of initial total occlusion and the time that reperfusion may have occurred are not known.

For all patients, the ejection fraction tended to be higher in the 93 IVSK-treated patients as compared with the 77 controls (54 ± 12% vs 51 ± 13%; p = .06) and was significantly higher for treated patients (53 ± 14%) than for controls (44 ± 14%; p = .03).

**Long-term survival.** The survival of the treatment and control patients up to 3 years is displayed in figure 3. The mean follow-up for all patients was 1.4 years. For the group as a whole, there was a small trend toward a reduction in mortality but the difference is not significant (p = .35). This is in contrast to the survival of the patients with anterior myocardial infarction as shown in figure 4. Survival for IVSK-treated patients was 83% vs 70% for the controls at 1 year and 81% vs 65% at 2 years. This difference in survival was significant (p = .05) and was primarily due to the large reduction in mortality for those randomized by less than 3 hr, in whom the 1 year survival was 82% vs 60% for controls. On the other hand, there was no benefit for the patients with inferior myocardial infarction, with 1 year survival of 91% vs 95% for controls and 2 year survival of 89% vs 93% (p = .27). Patients with inferior myocardial infarction who were randomized

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Angiographic characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anterior</td>
</tr>
<tr>
<td></td>
<td>IVSK</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>52.6 ± 13.7</td>
</tr>
<tr>
<td>Residual stenosis (total occlusions excluded)</td>
<td>66.1 ± 17.3</td>
</tr>
<tr>
<td>Reperfusion</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>III (complete)</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

The number of patients in each group is in parentheses.
between 3 and 6 hr had a trend toward reduced survival with IVSK therapy, with 1 year survival of 87% for treated patients and 96% for controls and 2 years survival of 84% vs 96% (p = .07). The initial differences in mortality for women and those with prior myocardial infarction receiving IVSK therapy were no longer evident at the time of last follow-up.

Discussion

This randomized trial was stopped after the entry of 368 patients over the prescribed period of 36 months. The decision to halt the trial was made after the publication of the early results of two large IVSK trials, the ISAM trial from the Federal Republic of Germany\textsuperscript{12, 13} and the much larger GISSI from Italy.\textsuperscript{8, 14} The ISAM study entered patients between March 1982 and March 1985, whereas GISSI enrolled patients from February 1984 to June 1985. This Western Washington trial enrolled patients between September 1983 and August 1986. Both ISAM and GISSI randomized patients in multiple hospitals according to a relatively simple protocol. Patients were entered up to the age of 75 years in the ISAM study, but 10% of the patients in GISSI were older than 75. Patients were entered up to 6 hr after the onset of symptoms in the Western Washington and the ISAM study, whereas 17% of GISSI patients were entered 6 and 12 hr after symptoms onset. In both studies, approximately 80% of the patients were men. The dose of streptokinase was 1.5 million U given over 1 hr in all three studies. Angiography at the time of hospital discharge was carried out in 68% of the patients in this study and in 49% of the ISAM patients and was not performed in the GISSI. Mortality has been reported in numerous subsets of patients by the Italian investigators but in only a few subsets by the German investigators. Mortality is reported at 14 days in this study and at 21 days in the other two studies.

Since there were no deaths between 14 and 21 days in this trial, the data are comparable. For patients treated at less than 6 hr, the early mortality for treated and control patients was 6.3% vs 9.6% (p = .23) in this trial, 6.3% vs 7.1% (p = NS) in the ISAM study, and 10.7% vs 13.0% (p = .0002) in GISSI. A preliminary report of a large multicenter randomized trial of intravenous streptokinase vs control known as ISIS-2 is now available.\textsuperscript{15} These investigators report that, as of January 1987, a cohort of nearly 4000 patients has been entered into the trial within 4 hr of the onset of symptoms of acute myocardial infarction. The in-hospital mortality was about 8% in those receiving 1.5 million U of IVSK and about 12% in those entered into the control groups. These preliminary results are considered to demonstrate an important difference in early survival, although no statistical analysis was provided in this report. These results represent a reduction in early mortality of 34% in this study, 11% in the ISAM study, 18% in GISSI, and approximately 33% in ISIS-2. A positive trend in mortality was therefore present in each trial but varied in magnitude and achieved statistical significance in the two largest trials.

The major benefit of IVSK in this trial was in patients with anterior infarction and in those randomized by less than 3 hr from onset of symptoms. This corresponds to those treated patients who had higher ejection fractions at 1 to 3 week angiography. These were also the groups of patients who benefited most in GISSI. Equally important, as in GISSI, this trial demonstrated no benefit from IVSK in patients with inferior myocardial infarctions. As demonstrated by GISSI, the time to onset of IVSK therapy is of major importance. The prolonged interval between hospitalization and onset of therapy of more than 1.5 hr in this trial no doubt reduced the potential efficacy of IVSK therapy and highlights the need for the expeditious management of these patients.

The trend toward reduced 14 day mortality in the subsets of patients with prior myocardial infarction and women in this trial is of interest. It is important, however, to recognize the small numbers of patients in these subgroups. The German study did not report mortality for these subsets. In GISSI, the mortality for women was reduced with therapy from 22.6% in the controls to 18.5% (p = .01) in treated patients. In this study there was a strong trend in the same direction, with the control women having a mortality of 16.0% and the treated patients 2.8% (p = .08). This is in contrast to the mortality for patients with a history of prior myocardial infarction. In this group there was a statistically significant reduction in mortality in the treated patients.
in this study, 0% in the treated patients and 21.7% (p = .02) in the controls. There was no such trend in the GISSI study, with the mortality being 16.9% in the treated and 16.5% in the control patients (p = NS).

We have no explanation for these differences. We anticipated that the patients at highest risk would be the group that would benefit most from thrombolytic therapy. This has been the case in the subsets of patients in this trial and in our prior intracoronary streptokinase trial, but it is difficult to discard the results obtained by GISSI. Possibly a more detailed analysis of the GISSI study will help to provide an explanation. It should be remembered that GISSI accepted patients up to 12 hr after the onset of symptoms as well as those over 75 years of age. The subset analysis available at this time does not take into account the time of treatment or the age of the patients. For the purpose of this discussion, we are therefore comparing the results in our patients under age 76 and treated at less than 6 hr from the onset of symptoms with an older group of patients treated up to 12 hr. Thus the difference in the patient populations may account for some of the differences in results.

Both this study and the German study show improvements in the ejection fraction for patients receiving early therapy. For those randomized by less than 3 hr from the onset of symptoms, in this trial the ejection fraction was 56% for treated patients and 52% for control patients (p = .20). For those treated by less than 3 hr in the German study the ejection fraction was 57% vs 54%, respectively (p < .005). The difference was most striking for patients with anterior infarction in this trial (53% vs 44%; p = .03). The data for this subset have not been reported by the ISAM investigators.

This trial has demonstrated improved long-term survival in patients with anterior myocardial infarction who received IVSK within 6 hr of the onset of symptoms. Patients with inferior infarction, on the other hand, did not benefit from thrombolytic therapy. The GISSI investigators have recently published 1 year data on survival. The early benefits of therapy have been maintained over the first year of follow-up. In contrast, the ISAM investigators have reported reduced long-term survival for patients with anterior infarction who received thrombolytic therapy. These latter investigators believe that failure to follow thrombolytic therapy with revascularization procedures may account for reduced late survival in this group. In this study, 27.2% of the treated patients and 18.6% of the control patients had revascularization procedures during the first year (p = .05). Thus one-third more patients receiving IVSK had revascularization procedures. This rate of revascularization (27.2%) in the treatment group during the first year after myocardial infarction was more than twice that in the ISAM trial (12.5%) and may in part explain the sustained long-term survival of patients in this study as compared with the ISAM experience.

The trend toward reduced heart failure in treated patients at late follow-up is consistent with the observed improvement in ejection fraction. This benefit is partially offset by the higher reinfarction rate for IVSK-treated patients. More frequent reinfarction among treated patients has also been reported by ISAM and GISSI investigators. It is not known whether more aggressive use of revascularization procedures after thrombolysis can further minimize the occurrence of reinfarction.

In summary, the Western Washington IVSK trial has demonstrated improved survival in patients with anterior myocardial infarction. IVSK did not improve survival of patients with inferior myocardial infarction. Patients in the treatment group also had higher rates of coronary artery patency at 1 and 3 week angiography as compared with controls, and this was most evident in the patients randomized in less than 3 hr in whom the left anterior descending coronary artery was the infarct vessel. Left ventricular function was significantly improved in patients with anterior myocardial infarctions and in those with patent infarct vessels at the time of follow-up angiography with a trend toward improved function in the treatment group as a whole.

Based on the results of this randomized trial, we conclude that IVSK, when given within the first few hours of evolving anterior myocardial infarction, improves early and late survival. This improved survival may depend on the relatively frequent use of additional revascularization procedures after therapy. The efficacy of IVSK in the treatment of patients with inferior myocardial infarction has not been demonstrated by this or other trials and cannot be recommended at this time.

The investigators and their associates wish to give special thanks to the patients and their families who made this study possible. The streptokinase (KabiKinase) used in this trial was generously supplied by KabiVitrum, Inc.

Appendix

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References
15. ISIS Steering Committee: Intravenous streptokinase given within 0-4 hours of onset of myocardial infarction reduced mortality in ISIS II. Lancet 1: 502, 1987 (letter to the Editor)
The Western Washington Intravenous Streptokinase in Acute Myocardial Infarction Randomized Trial.
J W Kennedy, G V Martin, K B Davis, C Maynard, M Stadius, F H Sheehan and J L Ritchie

*Circulation*. 1988;77:345-352
doi: 10.1161/01.CIR.77.2.345
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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