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COOPERATIVE STUDIES

Early Thrombolysis in Acute Myocardial Infarction: Limitation of Infarct Size and Improved Survival

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The effect of thrombolysis in acute myocardial infarction on infarct size, left ventricular function, clinical course and patient survival was studied in a randomized trial comparing thrombolysis (269 patients) with conventional treatment (264 control patients). All 533 patients were admitted to the coronary care unit within 4 hours after the onset of symptoms related to the infarction. Baseline characteristics were similar in both groups. Informed consent was requested only of patients allocated to thrombolysis; no angiography was performed in 35. The infarct-related artery was patent in 65 patients and occluded in 169. Recanalization was achieved in 133 patients. The median time to angiographic documentation of vessel patency was 200 minutes after the onset of symptoms.

The clinical course in the coronary care unit was more favorable after thrombolysis. Infarct size, estimated from myocardial enzyme release, was 30% lower after thrombolysis. In patients admitted within 1 hour after the onset of symptoms the reduction of infarct size was 51%, in those admitted between 1 and 2 hours it was 31% and in those admitted later than 2 hours it was 13%. Left ventricular function measured by radionuclide angiography before hospital discharge was better after thrombolysis (ejection fraction 48 ± 15%) than in control patients (44 ± 15%). Similar improvement was observed in patients with a first infarct only (thrombolysis 50 ± 14%, control subjects 46 ± 15%), in patients with anterior infarction (thrombolysis 44 ± 16%, control subjects 35 ± 14%) and in those with inferior infarction (thrombolysis 52 ± 12%, control subjects 49 ± 12%). Similar results were obtained by contrast angiography.

Mortality was lower after thrombolysis. After 28 days 16 patients allocated to thrombolysis and 31 control patients had died. One year survival rates were 91 and 84%, respectively. On the other hand, nonfatal reinfarction occurred more frequently after thrombolysis (36 patients) than in control subjects (16 patients). Early thrombolysis by intracoronary streptokinase leads to a smaller infarct size estimated by enzyme release, preserves left ventricular function at the second week and leads to improved 1 year survival.

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Myocardial infarction in most patients results from a thrombotic occlusion of a major coronary artery. Recently, Rentrop and other investigators (1–4) have demonstrated that rapid recanalization can be achieved by intracoronary infusion of streptokinase in approximately 80% of patients. Because early editorials called for caution (5–7), we initiated in May 1981 a randomized trial to compare a strategy aimed at early recanalization by intracoronary administration of streptokinase with conventional treatment in the coronary care unit. The primary objective was to study the effect of the intervention on mortality and morbidity after myocardial infarction. In addition we analyzed the effect of attempted thrombolysis on infarct size and left ventricular function measured by various methods.

Because the aim of thrombolysis is rapid restoration of blood flow to the jeopardized myocardium to preserve cel-

*A listing of Participating Centers and Collaborators is presented at the end of the text.

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Table 1. Distribution of Patients and Results of Angiography and Thrombolysis in the Four Participating Hospitals

	Control Group	Thrombolysis Group	No Angiography*	Coronary Patency†		
				○ → ○	● → ○	● → ●
Thoraxcenter	118	119	13	24	69	13
St. Annadal	62	61	7	17	26	11
Free University	46	47	9	10	19	9
Zuiderziekenhuis	28	33	6	11	15	1
Leiden University	10	9	—	3	4	2
Total	264	269	35	65	133	36
Intracoronary thrombolysis	150	152	16	25	88	23
Intravenous and intracoronary thrombolysis	114	117	19	40	45	13

*Angiography was refused by or contraindicated in 35 patients. †The infarct-related vessel was open and remained open in 65 patients (○ → ○); recanalization of an occluded vessel was achieved in 133 patients (● → ○), while the occlusion persisted in 36 patients (● → ●). Coronary angioplasty was attempted in 46 patients and succeeded in 44. Note the greater fraction of patients with an open infarct-related vessel at angiography after pretreatment with intravenous streptokinase (40 [41%] of 98 patients) than in patients without such treatment (25 [18%] of 136 patients).

Table 2. Baseline Data in 533 Patients

	Control Group	Thrombolysis Group
Number of patients	264	269
Male	224 (85)	217 (81)
Age (yr) (mean ± SD)	55 ± 8	56 ± 9
History		
Angina longer than 4 weeks	74 (28)	69 (26)
Angina less than 4 weeks	91 (34)	89 (33)
Previous myocardial infarction	60 (23)	56 (21)
Previous bypass surgery	8 (3)	5 (2)
Maintenance therapy		
None	143 (54)	146 (54)
Anticoagulant therapy	11 (4)	20 (7)
Beta-blockers	64 (24)	62 (23)
Calcium antagonists	31 (12)	31 (12)
Long-acting nitrates	47 (18)	49 (18)
Digoxin	6 (2)	8 (3)
Diuretic drugs	16 (6)	30 (11)
Therapy before admission		
None	134 (51)	133 (49)
Analgesics	57 (22)	57 (21)
Antiarrhythmic agents	14 (5)	11 (4)
Beta-blockers	17 (6)	13 (5)
Calcium antagonists	24 (9)	28 (10)
Nitrates	87 (33)	79 (29)
Resuscitation	5 (2)	7 (3)
Hemodynamic state		
Heart rate (beats/min)	74 ± 16	74 ± 17
Systolic blood pressure (mm Hg)	131 ± 27	131 ± 30
Diastolic blood pressure (mm Hg)	84 ± 20	83 ± 20
Mild heart failure (no.)	40 (15)	40 (15)
Acute congestive failure (no.)	2 (1)	1 (0.5)
Shock (no.)	9 (3)	11 (4)

The actual numbers in each group are presented; percentages are shown in parentheses.

lular integrity and function, time must be a crucial factor limiting the salutary effects of thrombolysis. When it became evident that preparation of the catheterization laboratory and introduction of the catheter delayed streptokinase infusion by approximately 1 hour, pretreatment with intravenous streptokinase was given to patients who entered the trial after December 31, 1983 (4,8–10). The intake was completed in March 1985 after entry of 533 patients. Details of the design of the study and preliminary data were reported in 1982 (11–13).

Recently, we reported (14) that short-term and 1 year survival rates were significantly improved after thrombolysis. The data presented in this final report demonstrate that improved survival after early thrombolysis in acute myocardial infarction is indeed associated with a reduction of infarct size and with preservation of global left ventricular function. Furthermore, regional wall motion after thrombolysis appeared to be better than in the control group (15).

Methods

Patient selection. Patients were eligible for the trial if they were admitted to one of the participating coronary care units within 4 hours after the onset of chest pain lasting 20 minutes or more and with electrocardiographic signs compatible with myocardial infarction (11–14). ST segment elevation of 0.2 mV or greater had to be present in one of the precordial leads or 0.1 mV in a limb lead, or both, despite treatment with oral or intravenous nitroglycerin or nifedipine, or both. In addition, patients were included with 0.2 mV or greater ST segment depression in precordial leads, compatible with posterior wall infarction.

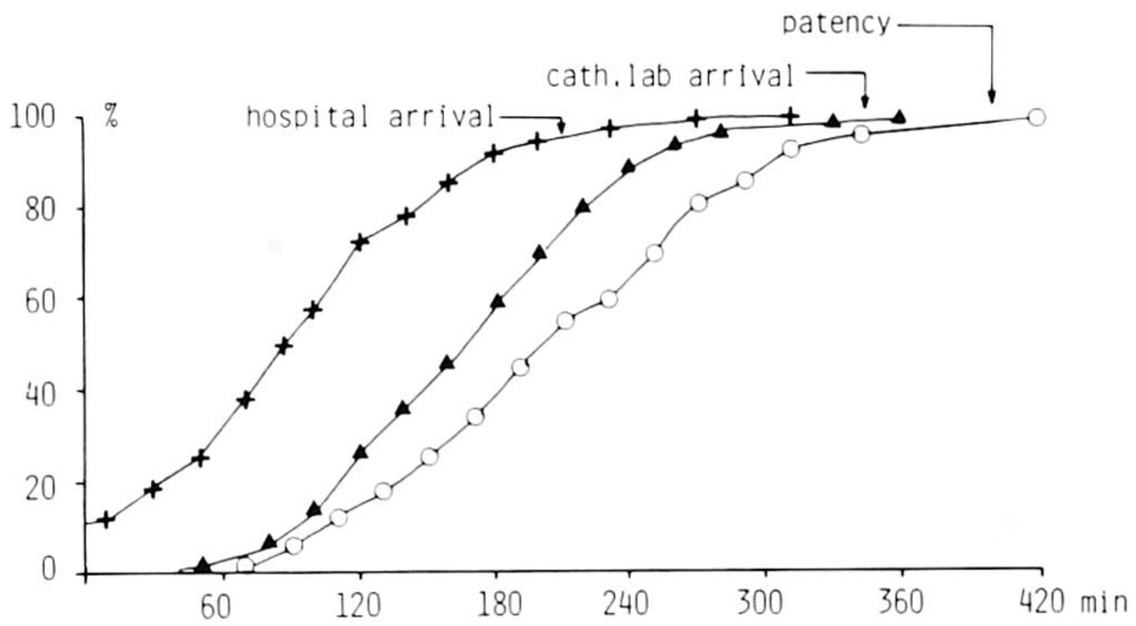

Figure 1. Cumulative distributions of the intervals between the onset of symptoms and hospital arrival (+—+), arrival in the catheterization laboratory (cath. lab) (▲—▲) and angiographic confirmation of a patent infarct-related artery (○—○) when appropriate.

Exclusion criteria were: 1) age over 70 years; 2) previous treatment with streptokinase; 3) bypass surgery of the vessels corresponding to the infarct location; 4) recent trauma including traumatic resuscitation; 5) a history of gastrointestinal bleeding, ulcer, hematuria or a cerebrovascular accident within 3 months; 6) pregnancy or menstruation; and 7) mental confusion that precluded informed consent.

Treatment protocol. Eligible patients who did not meet the exclusion criteria were registered by a central telephone answering service. The responsible physician provided administrative data including hospital name, patient's initials, sex, date of birth and clinical state. The answering service then opened the randomization envelope and provided treatment allocation. Informed consent was asked only of patients allocated to thrombolytic treatment (16). Patients who refused consent were treated according to the conventional treatment protocol, but were included in the analysis according to original treatment allocation. The study protocol was approved by the board of the Netherlands Interuniversity Cardiology Institute.

In all patients treatment was directed to an "optimal" hemodynamic state characterized by sedation, a heart rate between 60 and 90 beats/min, systolic blood pressure between 100 and 140 mm Hg and absence of left ventricular failure, including pulmonary capillary wedge pressure less than 12 mm Hg when hemodynamic monitoring was used. Guidelines for treatment have been described in detail (17) and included the use of intraaortic balloon counterpulsation for treatment of cardiogenic shock.

All patients were treated with intravenous heparin followed by acenocoumarol (Sintrom) until hospital discharge. After discharge anticoagulant agents were continued only in patients with ventricular aneurysm, mitral incompetence or a large left ventricle with a poor contraction pattern. Beta-receptor blockers were prescribed in the majority of patients starting between 7 and 14 days unless contraindications were present. Other therapy was prescribed as needed.

Thrombolytic therapy. After giving informed consent, patients received intravenous nitroglycerin in a dose that reduced systolic blood pressure to 100 to 120 mm Hg, as well as lidocaine, 2 mg/min, 5,000 U heparin, 250 mg acetylsalicylic acid and 100 mg prednisolone (13). Coronary angiography was performed with the Judkins technique. If the infarct-related artery was occluded, streptokinase was given at a rate of 4,000 U/min until all visible clot disappeared. Usually a maximum of 250,000 U was given. Subselective catheterization of the occluded coronary branch of the left coronary artery or mechanical perforation of the clot was employed in a few patients. After completion of streptokinase infusion, complete left and right coronary arteri-

Table 3. Degree of Obstruction* in the Coronary Arteriograms Before and After Attempted Reperfusion

	First Angiogram	After Streptokinase	After Streptokinase Plus Coronary Angioplasty†
Infarct-Related Artery Without Intravenous Streptokinase			
Normal	—	—	—
Less than 50%	1	5	26
50 to 90%	5	40	31
90 to 99%	19	69	56
Occlusion	111	22	23
With Prior Intravenous Streptokinase			
Normal	2	2	2
Less than 50%	2	5	19
50 to 90%	11	28	27
90 to 99%	25	45	37
Occlusion	58	18	13

*Visual analysis of the severity of the lesion in the infarct-related vessel, expressed as percent diameter stenosis. †Percutaneous transluminal coronary angioplasty was attempted in 27 patients without and in 19 patients after pretreatment with intravenous streptokinase.

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Table 4. Clinical Course in Hospital

	Control Group	Thrombolysis Group	p Value
No. of patients	264	269	
Hospital mortality (14 days)	26	14	0.05
Recurrent infarction (14 days)	9	12	
Angina pectoris	55	57	
Heart failure (coronary care unit)			
Mild	55	54	
Severe	12	10	
Shock	24	13	
Dopamine/dobutamine treatment	42	26	0.03
Respiratory support	11	6	
Intraaortic balloon pump	10	16	
Heart failure during convalescence	53	37	0.05
Ventricular fibrillation	61	38	0.01
Pericarditis	46	19	0.0004
Bleeding	7	53	0.0001
Coronary angioplasty	9	59*	
Bypass surgery	16	29	

Percutaneous transluminal angioplasty was performed more frequently in the thrombolysis group when the 46 patients with angioplasty immediately after thrombolysis are included (*). Only p values of 0.05 or less are reported.

ography was performed. In some of the patients with severe residual stenosis of the infarct-related coronary artery, percutaneous transluminal coronary angioplasty was attempted as part of the recanalization procedure. Subsequently, nitroglycerin and lidocaine infusions were withdrawn. Administration of heparin was started as soon as measured recalcification time was less than 6 minutes. Starting in January 1984 thrombolytic treatment was instituted immediately after informed consent was obtained with injections of acetylsalicylic acid and prednisolone followed by 500,000 U streptokinase intravenously over 10 to 20 minutes. The patient was then prepared for cardiac catheterization and treated as described earlier.

Post-therapy procedures. Serum alpha-hydroxybutyric dehydrogenase enzyme determinations were made on admission, every 12 hours during 2 days and then every 24 hours until 5 days after admission. Cumulative release of alpha-hydroxybutyric dehydrogenase was calculated from these data as described earlier (18). In two hospitals total lactate dehydrogenase was measured instead and converted to alpha-hydroxybutyric dehydrogenase by exchange of standards.

Radionuclide angiography was carried out at the bedside on the first, second or third day after admission and repeated before hospital discharge and after 3 months. Gated images were obtained with 20 frames in each cycle after in vivo labeling with 15 mCi technetium-99m. Data were analyzed by a fully automated computer program on a DEC-gamma 11 or an ADAC system (19) or with an MDS or Philips data analysis system.

Before hospital discharge all patients in both groups were offered coronary arteriography. From the left cineventriculogram in the right anterior oblique projection, left ventricular ejection fraction and regional wall motion were measured (15).

Follow-up. All patients were followed up at the outpatient clinic for at least 1 year after admission. Recurrent myocardial infarction, angina pectoris, cardiac failure, bypass surgery and coronary angioplasty as well as prescribed medication were recorded. In addition, survival status was assessed for all patients at 6 month intervals.

Statistical analysis. Data analysis was based on the "intention to treat" principle. Thus, patients who refused early angiography were analyzed as part of the thrombolysis group, according to the original treatment allocation. Differences between the two groups were tested with the chi-square test, Student's *t* test or Mann-Whitney test when appropriate. Two-sided p values are reported.

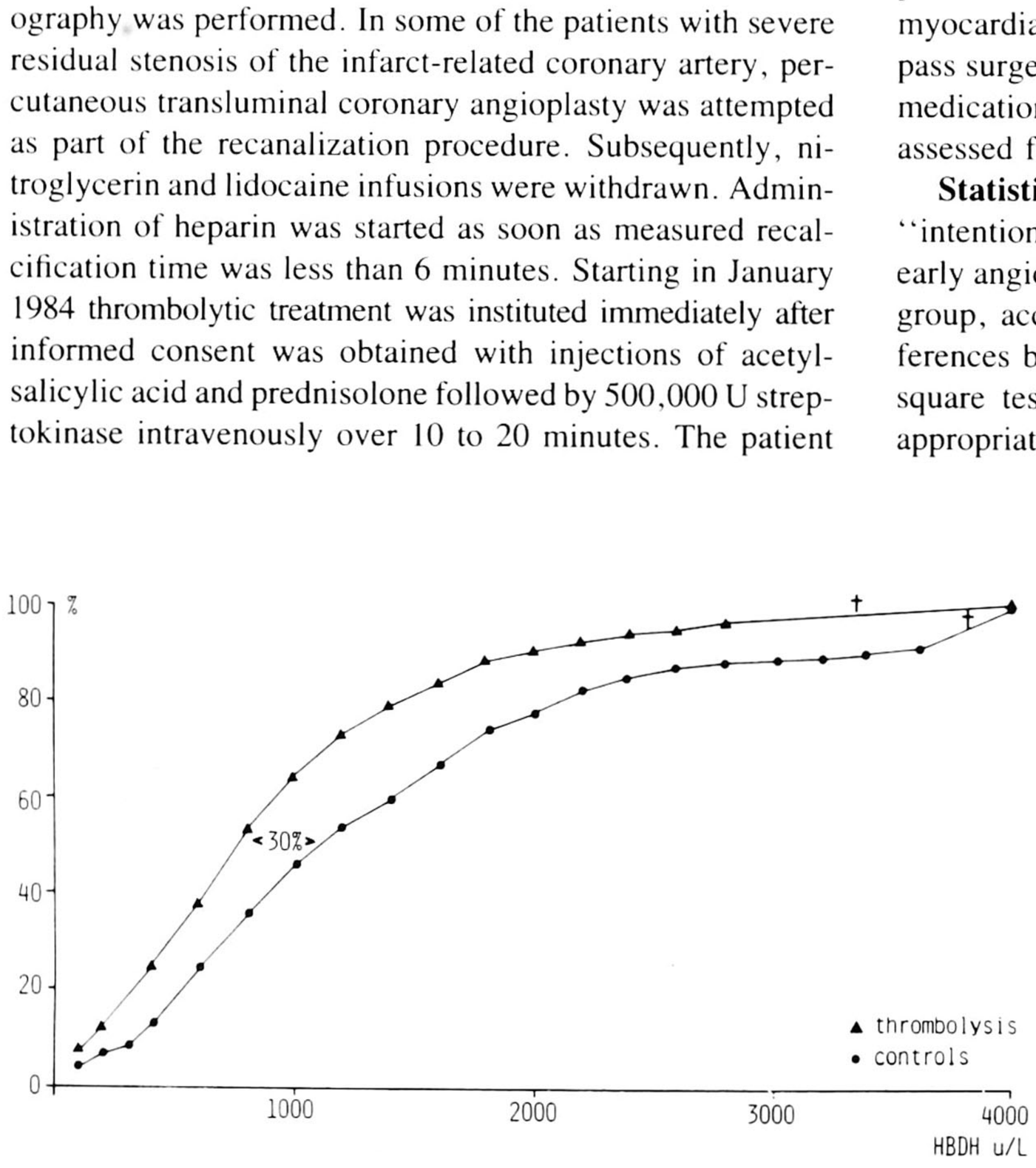

Figure 2. Cumulative distributions of infarct size determined from serial alpha-hydroxybutyric dehydrogenase measurements in control patients (●—●) and in patients allocated to thrombolysis (▲—▲). Patients who died before completion of the measurements have been included as the largest infarct sizes (†) as discussed in the text. The median reduction of infarct size after thrombolysis is 30% (p = 0.0001 Mann-Whitney test).

Results

There were 533 patients entered in the study, of whom 302 were treated before January 1984 (intracoronary thrombolysis) and 231 after that time (intravenous and intracoronary thrombolysis). Of the 533 patients, 264 were randomized to the thrombolysis group and 269 to the control group. In Table 1 the number of patients in each study center is presented with the results of acute angiography in the thrombolysis group. The largest number of patients (237) was submitted by the Thoraxcenter, where the study was initiated in May 1981. The Zuiderziekenhuis, the Free University and the St. Annadal Hospital joined the study in 1983, and the University of Leiden joined in 1984.

Baseline characteristics in the two groups of patients (Table 2). All baseline data were distributed evenly, including a history of previous myocardial infarction in 116 patients (22%) and previous bypass surgery in 13 patients (2%). Similarly, maintenance therapy and therapy initiated within 24 hours preceding entry in the trial and the hemodynamic state at admission were the same in both groups.

Patients were entered in the study if they arrived within 4 hours after the onset of symptoms. Forty-four control and 39 thrombolysis patients were already hospitalized before the onset of myocardial infarction. The median time to hospital admission was 90 minutes. The median time of arrival in the catheterization laboratory was 170 minutes, whereas streptokinase infusion was started 195 minutes after the onset of symptoms (Fig. 1). These data were similar in the four participating hospitals.

Acute coronary angiography and thrombolysis. Thirty-five (13%) of the 269 patients allocated to thrombolytic treatment did not undergo coronary angiography. Twenty of these refused the intervention, two patients were resuscitated after randomization, one was later found to have a contraindication, one died and in six the catheter could not be passed through the aorta. Angiography was performed in the remaining 234 patients. In 136 patients who underwent catheterization without previous intravenous streptokinase, the infarct-related vessel was occluded in 111 (82%) and recanalization was achieved in 88 (79%) of these after 30 minutes of streptokinase infusion (median). After intravenous streptokinase administration an occluded artery was found in 58 of 98 patients. Intracoronary streptokinase caused recanalization in 39 patients whereas in 5 patients the thrombus was perforated by guide wire or angioplasty catheter. Thus, a patent artery was ultimately achieved in 85% of patients by combined intravenous and intracoronary thrombolysis. The median time from the onset of symptoms to angiographic documentation of patency of the infarct-related artery was 200 minutes (range 55 to 375). There were no significant differences among the angiographic data in the four centers (Table 1). The infarct-related coronary artery was the left main stem in 1 patient, the left anterior descending artery in 102 patients, the left circumflex artery in 40, the right coronary artery in 89 and a bypass graft in 2. To improve recanalization, coronary angioplasty was attempted in 46 patients with severe stenosis of the infarct-related artery after thrombolysis in whom the procedure was judged to be technically and organizationally feasible (3). In 44 patients this additional procedure was successful, while reocclusion of a subtotal lesion occurred after angioplasty in 2 patients. The severity of the lesion in the infarct-related vessels is presented in Table 3.

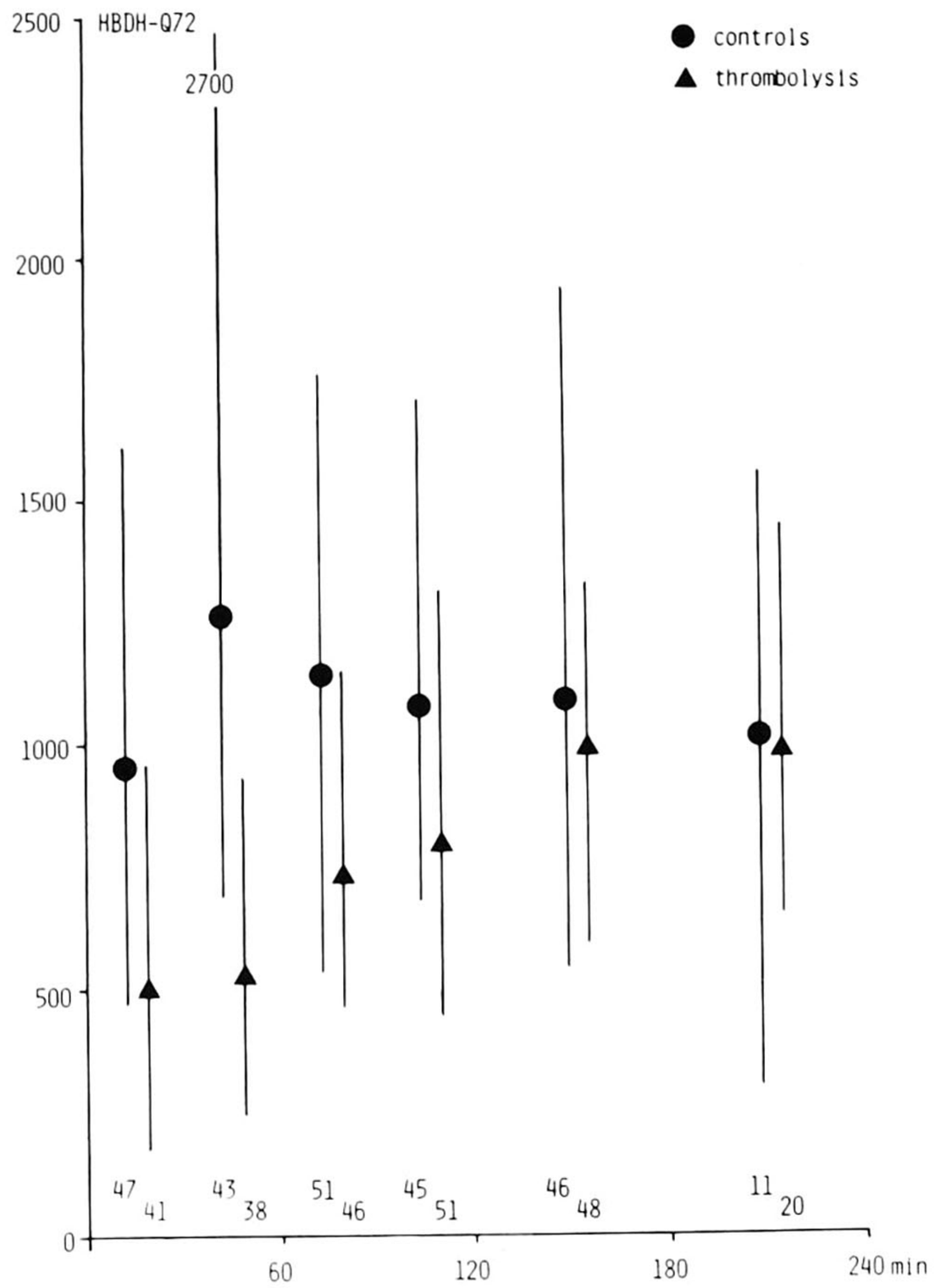

Figure 3. Median and 50% range (first to third quartile) of hydroxybutyric dehydrogenase Q72 in patients allocated to thrombolysis (▲) or conventional treatment (●), in relation to the time interval between onset of symptoms and randomization. The numbers denote the number of patients in each time interval.

Clinical course. Complications during the clinical course in the hospital are summarized in Table 4. These data include all events up to 14 days after admission, in the coronary care unit, in the catheterization laboratory or in the medium care unit. There were no differences in reinfarction, angina pectoris or heart failure in the two treatment groups. Ventricular fibrillation occurred more frequently in the control patients, as did pericarditis, characterized by posture-related chest pain and a friction rub, while bleeding occurred

Table 5. Left Ventricular Ejection Fraction on Radionuclide Angiography Before Hospital Discharge

	Control Group		Thrombolysis Group		
	No.	Ejection Fraction	No.	Ejection Fraction	p Value
All patients					
Days 2 to 4	200	43 ± 14	218	45 ± 14†	0.05
Days 10 to 20	172	44 ± 15	189	48 ± 15†	0.003
Δ LVEF	141	0.9 ± 11	161	3.7 ± 9*	0.0001
Intracoronary thrombolysis					
Days 2 to 4	113	41 ± 14	123	45 ± 14†	0.04
Days 10 to 20	93	42 ± 14	96	48 ± 14†	0.003
Δ LVEF	78	0.6 ± 10	82	3.9 ± 8*	0.0001
Intravenous plus intracoronary thrombolysis					
Days 2 to 4	87	44 ± 15	95	46 ± 14†	NS
Days 10 to 20	79	45 ± 16	93	48 ± 15†	NS
Δ LVEF	63	1.3 ± 13	79	3.5 ± 11*	0.005
First infarction					
Days 2 to 4	159	44 ± 14	179	47 ± 13†	0.04
Days 10 to 20	138	46 ± 15	158	50 ± 14†	0.009
Δ LVEF	113	1.3 ± 12	137	3.6 ± 9*	0.0001
Anterior infarction					
Days 2 to 4	86	34 ± 13	100	39 ± 13†	0.02
Days 10 to 20	68	35 ± 14	89	44 ± 16†	0.0006
Δ LVEF	58	1.3 ± 9	71	4.9 ± 9*	0.0001
Inferior infarction					
Days 2 to 4	114	49 ± 12	118	50 ± 12†	NS
Days 10 to 20	104	49 ± 12	100	52 ± 12†	NS
Δ LVEF	83	0.7 ± 13	90	2.8 ± 9*	0.005

*p Value, paired *t* test for difference in ejection fraction measurements; †p value, unpaired *t* test for comparison of control and thrombolysis patients. Only p values of 0.05 or less are reported. Δ LVEF = difference between the two measurements of ejection fraction in patients in whom both measurements were available. LVEF = left ventricular ejection fraction; NS = not significant. In the control group the difference in ejection fraction measurements did not reach statistical significance in any subgroup, but ejection fraction improved in thrombolysis patients.

more frequently after thrombolysis. In most cases bleeding was limited to the puncture site for angiography. Several observations related to heart failure in the acute phase were more frequent in control patients; this was, however, of borderline significance. For example, cardiogenic shock ($p = 0.08$) and treatment with dopamine and dobutamine ($p = 0.03$) occurred more frequently in control patients. Similarly, heart failure during reconvalescence was more frequent in control patients ($p = 0.05$). Treatment after hospital discharge was similar in both groups, including beta blockers in 101 control patients and 113 allocated to thrombolysis and anticoagulant agents in 80 and 79 patients, respectively.

Myocardial enzyme release. Infarct size was estimated from serial serum enzyme measurements during the first 72 hours. In 317 patients alpha-hydroxybutyric dehydrogenase levels were obtained, while in 131 patients from two hospitals total lactate dehydrogenase levels were used and converted to cumulative alpha-hydroxybutyric dehydrogenase release. In 28 patients alpha-hydroxybutyric dehydrogenase was both measured directly and estimated from total lactate dehydrogenase levels. The regression equation between measured (M) and estimated (E) alpha-hydroxybutyric dehydrogenase was $E = 0.994 \times M - 3$ and the standard error of the estimate was 334 U. Because there was no systematic difference between estimated and measured alpha-hydroxybutyric dehydrogenase release, both were combined in the analysis. Data were incomplete in 30 patients who died within 72 hours after admission, in 17 patients without serum creatine kinase elevation and in 38 other patients. Because most patients who died within 72 hours had pump failure, these were entered in the analysis as having the largest infarcts (18). Similarly, patients without creatine kinase elevation, who did not develop an infarct, were entered as having the smallest infarcts based on alpha-hydroxybutyric dehydrogenase levels.

Cumulative data in Figure 2 indicate a 30% smaller infarct size in the treated group ($p = 0.0001$, Mann-Whitney test). This difference was also apparent when patients with a first infarct only ($p = 0.0001$), patients with anterior wall infarction ($p = 0.005$) and patients with inferior wall infarction ($p = 0.007$) were analyzed separately. Further-

more, similar results were obtained when the patients who died within 72 hours were not included in the analysis and when data from the five hospitals were analyzed separately. Median values for alpha-hydroxybutyric dehydrogenase infarct size in control and thrombolysis patients were 1,100 and 770 U/liter, respectively. In patients with a first infarct these values were 1,140 and 790 U/liter, respectively, in anterior wall infarction 1,280 and 840 U/liter, respectively and in inferior wall infarction 970 and 670 U/liter, respectively. In Figure 3 alpha-hydroxybutyric dehydrogenase release is shown in relation to the interval between the onset of symptoms and hospital admission. In patients allocated to the control group, alpha-hydroxybutyric dehydrogenase release was independent of the interval between the onset of symptoms and admission. On the other hand, we found smaller enzyme release in patients allocated to thrombolysis within 2 hours after the onset of symptoms. These data indicate a 51% reduction of infarct size by thrombolysis in patients admitted within 1 hour, a 31% reduction of infarct size in those admitted between 1 and 2 hours and a 13% reduction in patients admitted between 2 and 4 hours after the onset of symptoms.

Left ventricular function (Table 5). Left ventricular ejection fraction was measured by radionuclide angiography between day 2 and day 4 in 418 patients and before hospital discharge in 361 patients. Missing data were equally distributed between the two treatment groups and were due to death, transfer to other hospitals, patient refusal, unavailability of the gamma camera or other administrative reasons. There was no change in global left ventricular ejection fraction between the second day and hospital discharge in the control group. In the thrombolysis group left ventricular ejection fraction before discharge was 3.7 ± 9.0% higher than the first measurement. Accordingly, ejection fraction after 10 to 20 days was approximately 4% higher when thrombolysis was compared with conventional treatment. This difference was significant in the whole group, in patients treated with intracoronary thrombolysis only, in patients with a first infarction and in those with anterior infarction. Similarly, a 6% greater ejection fraction was found during cardiac catheterization in the thrombolysis group. Again these differences were similar in patients with a first infarct only and in patients with anterior wall or inferior wall infarction on admission and in both treatment protocols (15).

Follow-up (Tables 6 and 7). Clinical follow-up ranged from 1 to 48 months after admission. There was a 45% reduction of mortality after thrombolysis. This was offset by a higher incidence of late reinfarction and more frequent performance of late coronary angioplasty or bypass surgery after thrombolysis. The reduction in mortality was present in all subgroups, and it was similar in all five hospitals.

The subgroup of patients without early angiography and those in whom recanalization failed fared worse than those in whom recanalization was achieved. On the other hand, there was only 1 death in 65 patients with a patent infarct-related vessel at angiography and also 1 death in 46 patients in whom coronary angioplasty was performed immediately after thrombolysis. This particular patient underwent thrombolysis and angioplasty of the left anterior descending artery. Despite treatment with anticoagulant agents and nifedipine, he developed postinfarction angina. After 7 days the artery was reoccluded at the same site and coronary angioplasty was repeated. After 31 days the patient developed a new anteroseptal infarction and died from intractable cardiogenic shock.

Discussion

The primary aim of the present study was the analysis of the effect of early thrombolysis on the clinical course and survival of patients with acute myocardial infarction. The results demonstrate that thrombolysis in the first hours after the onset of infarction can reduce myocardial damage and thus preserve part of the function of the left ventricle and improve patient survival. In one other randomized trial (20,21) there was a similar improvement in survival, although left ventricular function and infarct size appeared

Table 6. Clinical Follow-Up

	Control Group	Thrombolysis Group	No Angiography*	Thrombolysis		
				○ → ○	● → ○	● → ●
No. of patients	264	269	35	65	133	36
Death	42	23	5	1	8	9
Reinfarction	16	36	4	9	21	3
Acute PTCA	—	46	—	13	31	2
Late PTCA/CABG	40	62	9	18	28	7

*Patients who were allocated to the thrombolysis group but did not undergo acute angiography. Major complications (mortality and nonfatal recurrent infarction) and coronary artery bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA) in patients allocated to conventional treatment (control) or thrombolysis. Symbols as in Table 1.

Table 7. Mortality

	Control Group	Thrombolysis Group	No Angiography	Thrombolysis ○ → ○	Thrombolysis ● → ○	Thrombolysis ● → ●
Total mortality	42	23	5	1	8	9
Intracoronary thrombolysis	23	17	4	—	6	7
Intravenous and intracoronary thrombolysis	19	6	1	1	2	2
First infarct only	26	11	2	1	3	5
Anterior wall infarction	25	12	3	—	4	5
Inferior wall infarction	17	11	2	1	4	4
Thoraxcenter	20	11	4	—	4	3
St. Annadal	10	7	—	1	2	4
Free University	6	3	1	—	1	1
Zuiderziekenhuis	6	1	—	—	1	—
Leiden University	—	1	—	—	—	1

Mortality in patients admitted before or since January 1984 and mortality data in the five participating hospitals. Patients allocated to thrombolytic treatment are grouped according to the results of the intervention. Note that similar trends are present in all subgroups. Symbols as in Table 1.

unaltered (22), while results of several smaller randomized trials were inconclusive (23–28). The difference between the results of the present trial and those of other studies can be explained by differences in study design, by the shorter delay between the onset of symptoms and treatment and by its larger size.

Study design. The study was designed to compare a new method of treatment (thrombolysis) with the accepted mode of therapy. Informed consent was asked only from patients allocated to angiography and thrombolysis as proposed by Zelen (16). This design was chosen to prevent extensive discussions of the risk and potential benefits of acute angiography and thrombolysis in half of these critically ill patients who were eventually allocated to conventional coronary care unit treatment. Data analysis was based on original treatment allocation. Therefore, the 35 patients who did not undergo acute angiography were analyzed as part of the thrombolysis group. This subgroup included a few patients in shock who refused the intervention "because they wanted to be left alone." This is reflected by the relatively high mortality in this group (5 of 35 patients) (Table 6). Because similar patients must be part of the control group, removal of this subgroup from the intervention group would falsely favor the effect of thrombolytic treatment. Yet it is evident that these deaths are not related to the thrombolytic therapy.

Possible limitations. The interpretation of this study might be questioned because of changes in the protocol in January 1984, the inclusion of coronary angioplasty in some of the patients, missing data, the lack of coronary arteriography on admission in the control group and the absence of direct measurements of baseline left ventricular function. These points will therefore be discussed in detail.

Because the aim of the trial was not to study the effect of intracoronary streptokinase itself, but rather to study the effect of early reperfusion, we decided to combine both intravenous and intracoronary thrombolysis in the later patients when it became apparent that the preparation of the catheterization laboratory, the introduction of catheters and the first angiogram delayed the administration of streptokinase by approximately 1 hour, while several reports (8–10) indicated that recanalization occurred in a considerable number of patients with administration of intravenous streptokinase.

Direct perforation of the thrombus was attempted in 5 patients and coronary angioplasty was performed in addition to the streptokinase infusion in 46 patients. This intervention was considered an integral part of the recanalization procedure because earlier observations indicated that patients with residual subtotal occlusion after thrombolysis are at increased risk for reocclusion, which would negate the effect of thrombolysis (3). Coronary angioplasty was not associated with complications. In fact, alpha-hydroxybutyric dehydrogenase release after coronary angioplasty was decreased and left ventricular ejection fraction was higher than in patients in whom only thrombolysis was carried out (15). Therefore, it is likely that the beneficial effects of thrombolysis in the present study would have been less apparent without additional coronary angioplasty.

No patients were lost to follow-up with respect to mor-

tality or major clinical events, which represent the major end points of the study. Missing data on left ventricular function were due to death of the patients, patient refusal, transfer to other hospitals, lack of technical facilities at the required time or intervening bypass surgery. It is unlikely that this would invalidate the results because missing data were equally distributed between the two groups and because similar differences were observed between patients allocated to thrombolysis and control patients in various subgroups. Also, there were no differences in baseline data between patients with or without measurements of left ventricular function.

In contrast with other trials (20–28), early angiography was not performed in our control group. Therefore, the coronary anatomy on admission could not be studied in these patients. This procedure was elected because acute angiography is not a part of conventional management of myocardial infarction. In fact, angiography might expose these patients to a small but pertinent risk, which could worsen prognosis in the control group (13). Similarly, determination of left ventricular function by radionuclide angiography was not attempted on admission because this would have delayed the intervention and thus diminish the possible salutary effects of recanalization.

Angiography in acute myocardial infarction. Earlier data from pilot studies performed at the Thoraxcenter (13) indicated that the risk of mortality, directly related to intracoronary infusion of streptokinase in patients with acute myocardial infarction, might be as high as 5%. However, despite 5 deaths during the catheterization procedure, 14 day mortality in patients allocated to thrombolysis was lower (14 deaths [5%]) than in the control group (26 deaths [10%]). In our experience the risk of the intervention is not so much associated with early angiography itself as with the actual recanalization. We thus agree with DeWood et al. (29), who reported that early angiography can be performed without excessive risk in patients with myocardial infarction. The 82% incidence of coronary occlusion at angiography and the 79% recanalization rate in patients treated with intracoronary streptokinase in the present study are consistent with other reports on early angiography and intracoronary thrombolysis (1–4,20,23–28).

Myocardial enzyme release. Total alpha-hydroxybutyric dehydrogenase release in 72 hours was calculated as a measure of infarct size using a two compartment model (30). This model takes into account the fractional catabolic rate or clearance of the enzymes from the blood and is insensitive to faster washout after reperfusion (30,31). Earlier studies (32) demonstrated similar results when infarct size was estimated from different enzymes including creatine kinase, creatine kinase-MB isoenzyme, alpha-hydroxybutyric dehydrogenase and aspartate aminotransferase. In the present study, alpha-hydroxybutyric dehydrogenase release was measured because it can be computed accurately from samples taken at 12 hour intervals, whereas creatine kinase should be sampled more frequently. Furthermore, the error in the computed total enzyme release due to biologic variations in the fractional catabolic rate of alpha-hydroxybutyric dehydrogenase is smaller than for creatine kinase, creatine kinase-MB isoenzyme or aspartate aminotransferase (32). Although estimation of infarct size by enzyme release is controversial, earlier studies (18) demonstrated a relation between total alpha-hydroxybutyric dehydrogenase release and the clinical sequelae of myocardial infarction. Furthermore, an autopsy study (33) in 84 patients who died of acute myocardial infarction demonstrated that peak levels of lactate dehydrogenase or thermostable lactate dehydrogenase correlated better with anatomic infarct size than did peak aspartate aminotransferase. Actually, the correlation between thermostable lactate dehydrogenase and anatomic infarct size ($r = 0.79$) was similar to that in a recent study (34) comparing anatomic infarct size with peak creatine kinase ($r = 0.79$) or total creatine kinase infarct size ($r = 0.86$). Other investigators have used peak creatine kinase values (20,23) or peak lactate dehydrogenase measurements (27), which appeared not to be reduced after thrombolysis. In fact, peak creatine kinase in the Western Washington trial (20) was 30% higher in the streptokinase group than in control patients. However, such peak measurements are not reliable estimates of myocardial enzyme release because enzyme washout is faster after reperfusion. In the present study we observed a faster washout of alpha-hydroxybutyric dehydrogenase, lactate dehydrogenase and creatine kinase after thrombolysis.

In our study a 30% median reduction of alpha-hydroxybutyric dehydrogenase release was observed in the thrombolysis group. This supports the hypothesis that myocardial tissue can be salvaged by early thrombolysis. The estimation of alpha-hydroxybutyric dehydrogenase release from lactate dehydrogenase measurements in two hospitals did not affect the difference between the thrombolysis and control groups, because similar differences between these two groups were observed in all five hospitals. Although these methods have not been validated in patients after coronary reperfusion, it is unlikely that myocardial salvage is overestimated by computation of alpha-hydroxybutyric dehydrogenase release. In fact, total creatine kinase release in dogs was approximately 10% greater after reperfusion than without reperfusion at the same anatomic infarct size, whereas enzyme breakdown in the circulation was not affected by the presence of streptokinase (35). If the data from such studies apply to alpha-hydroxybutyric dehydrogenase release in patients with acute myocardial infarction, the actual salvage of myocardium would even be underestimated. The observed reduction of alpha-hydroxybutyric dehydrogenase release is in agreement with data reported by Anderson et al. (28). From their Figure 6 we computed a 40% reduction of total lactate dehydrogenase-1 isoenzyme release in the thrombolysis group com-

pared with conventionally treated patients. Thus both studies are consistent with a reduction of enzymatic infarct size after thrombolysis.

Left ventricular function. Global left ventricular ejection fraction was measured by contrast angiography and radionuclide angiography. Both methods showed a higher ejection fraction 2 weeks after thrombolysis than after conventional therapy (15). This improvement was seen in inferior wall as well as in anterior wall infarction and applied to patients with a first infarct as well as to those with recurrent infarction. Some differences between the two groups in left ventricular ejection fraction measured by radionuclide angiography were already apparent after 2 to 4 days (Table 5), although these differences were of borderline significance. Although no measurements of ejection fraction were performed on admission, we may presume that these data were similar in both groups because other baseline data were also evenly distributed. The data then indicate a gradual recovery of left ventricular function during the first 2 weeks after reperfusion (36). The differences in ejection fraction between the two groups of patients were small (4%). However, the global left ventricular ejection fraction is related to the function of both the infarcted myocardium and other areas. Thus, changes in the infarcted area may be underestimated because of compensatory changes elsewhere. The improvement in left ventricular function after thrombolysis is supported by analysis of regional wall motion and by the smaller end-diastolic and end-systolic volumes after thrombolysis, measured by contrast angiography (15).

Earlier experiments have demonstrated salvage of myocardial function after early coronary reperfusion in dogs (37–39). In addition, several studies reported a higher ejection fraction in patients with successful thrombolysis than in patients whose infarct-related coronary artery remained occluded (40–43) or in historical control patients (44). In other randomized trials, only Anderson et al. (28) reported a beneficial effect on ejection fraction after streptokinase treatment. Although the lack of a beneficial effect in other series may be due to the small number of patients studied, the different results between our trial and those of two other larger trials (20–23) can be explained by the longer delay until treatment in the latter studies because it is less likely that recanalization after 4 or 6 hours of occlusion will salvage significant amounts of myocardium in the majority of patients (38,39). In fact, the data from the present trial indicate that a marked reduction of infarct size can be achieved only in patients admitted within 2 hours after the onset of symptoms.

Clinical course and follow-up. Survival was improved significantly by early thrombolysis. Furthermore, there was a borderline significant reduction of heart failure and shock in patients allocated to thrombolysis. These data are in agreement with the observed reduction of infarct size and preservation of left ventricular function. Actually, the 1 year survival rates are very similar to those reported by investigators in the Western Washington Trial (21), although these investigators did not find differences in intermediary measurements, such as infarct size or left ventricular function (20).

Unfortunately, these beneficial effects of thrombolytic therapy on survival were offset by a higher incidence of reinfarction, particularly in patients with an inferior wall infarction (14). Because reinfarction occurred in some of the patients despite adequate anticoagulant therapy or after successful coronary angioplasty, further studies are warranted to determine the optimal mode of treatment after thrombolysis. Bleeding after thrombolytic treatment occurred frequently at puncture sites, but did not result in significant morbidity (45).

Conclusions. The aim of recanalization in patients with acute myocardial infarction is rapid restoration of blood flow to the jeopardized myocardium to preserve viable myocardial cells. Ultimately this should result in preservation of myocardial function and improved prognosis after the infarction. Although the measurements of infarct size and left ventricular function used in this study might be criticized, the consistency of the observations supports the true benefits of early thrombolysis in patients with myocardial infarction. In contrast with other studies that either were too small (24–27) or initiated treatment later after the onset of symptoms (20–23), we demonstrated a 30% smaller infarct size estimated from myocardial enzyme release as well as preservation of left ventricular function documented by contrast angiography and radionuclide angiography in patients allocated to early thrombolytic therapy, as well as a reduction of early and late mortality. Future studies should investigate whether intracoronary administration of a thrombolytic agent is indeed mandatory, or whether similar results can be obtained by intravenous infusion of newer thrombolytic drugs such as the tissue plasminogen activator (46–48). Finally, strategies should be developed for early recognition of the symptoms of myocardial infarction by the patient and for immediate intervention, because myocardial salvage is only attainable if myocardial blood flow is restored within the first few hours of infarction.

Appendix

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