Intracoronary thrombolysis in patients with acute myocardial infarction: The Netherlands Randomized Trial and current status

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ANGIOGRAPHIC and pathologic studies have proved that the cause of acute myocardial infarction in most patients is coronary occlusion due to thrombosis.[1, 2] The feasibility of rapid dissolution of intracoronary thrombi by systemic or selective infusion of thrombolytic agents has been demonstrated convincingly in experimental series and in small clinical pilot studies as long as 25 years ago.[3–7] The concept of limiting infarct size by early reestablishment of antegrade flow, however, was not introduced into clinical practice until 1978.[8, 9] There have been many clinical trials of the efficacy of thrombolytic therapy in achieving reperfusion, salvaging myocardial function, and reducing mortality, but the efficacy of thrombolysis in randomized trials has varied widely in several studies.

To answer the question of whether thrombolysis is a clinically useful approach in acute myocardial infarction, 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.[10–13] 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. The intake was completed in March 1985 after entry of 533 patients. The data presented in this 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.[14]

The difference between the present study and the other randomized trials published thus far can be explained by differences in study design, by the shorter delay between the onset of symptoms and treatment, and by its larger size.[15–21]

Methods

This randomized trial of thrombolysis in acute myocardial infarction is a multicenter study supported by the Interuniversity Cardiology Institute in the Netherlands. The protocol and some initial results were published in 1982.[22–25] These preliminary data indicated that reocclusion of the coronary artery occurred predominantly in patients with severe residual stenoses.[26–28] Immediate percutaneous transluminal coronary angioplasty was therefore added to the procedure in those patients in whom visual inspection of the coronary arteriograms suggested residual stenosis in excess of 60%. When it also became evident that possibly crucial time was lost by preparation for catheterization and because other studies[12, 29, 30] reported angiographic confirmation of thrombolysis after intravenous streptokinase, it was decided (January 1984) to give intravenous streptokinase (500,000 U) at the time of admission to the hospital. Admission to the study was discontinued in March 1985.

Patient selection. During the study period all patients up to the age of 70 years with chest pain and electrocardiographic signs of typical myocardial infarction who were admitted within 4 hr after the onset of symptoms were eligible for the trial. The usual exclusion criteria for thrombolytic therapy were applied as described in detail in previous reports.[23–25, 31] The protocol is summarized in figure 1. After inclusion, patients were registered by a central telephone answering service, which also provided treatment allocation.[31] Informed consent was obtained from patients allocated to thrombolytic therapy only, as proposed by Zelen.[32] Patients who refused consent were treated according to the same guidelines as the control group.[33]

All patients were treated with heparin followed by acenocoumarol (Sintrom) until hospital discharge. After discharge, anticoagulants were continued only in patients with ventricular aneurysm, intraventricular thrombus, mitral incompetence, or large ventricles with a poor contraction pattern.

In patients assigned to streptokinase treatment, an infusion of nitroglycerin (100 μg/min) was started immediately and the patients were transferred to the catheterization laboratory as soon as possible.

Next, coronary arteriography of the artery suspected to be thrombosed was performed. Intracoronary perfusion was carried out at a rate of 4000 U/min to a maximum of 250,000 U of streptokinase. Coronary angiograms were repeated every 15 min until the vessel was patent or the chest pain had disappeared. The (re)appearance of ventricular extrasystoles or any conduction disturbance was also an indication to revisualize the artery.

After completion of the streptokinase infusion, the nitroglycerin and lidocaine infusions were interrupted and left ventricu-

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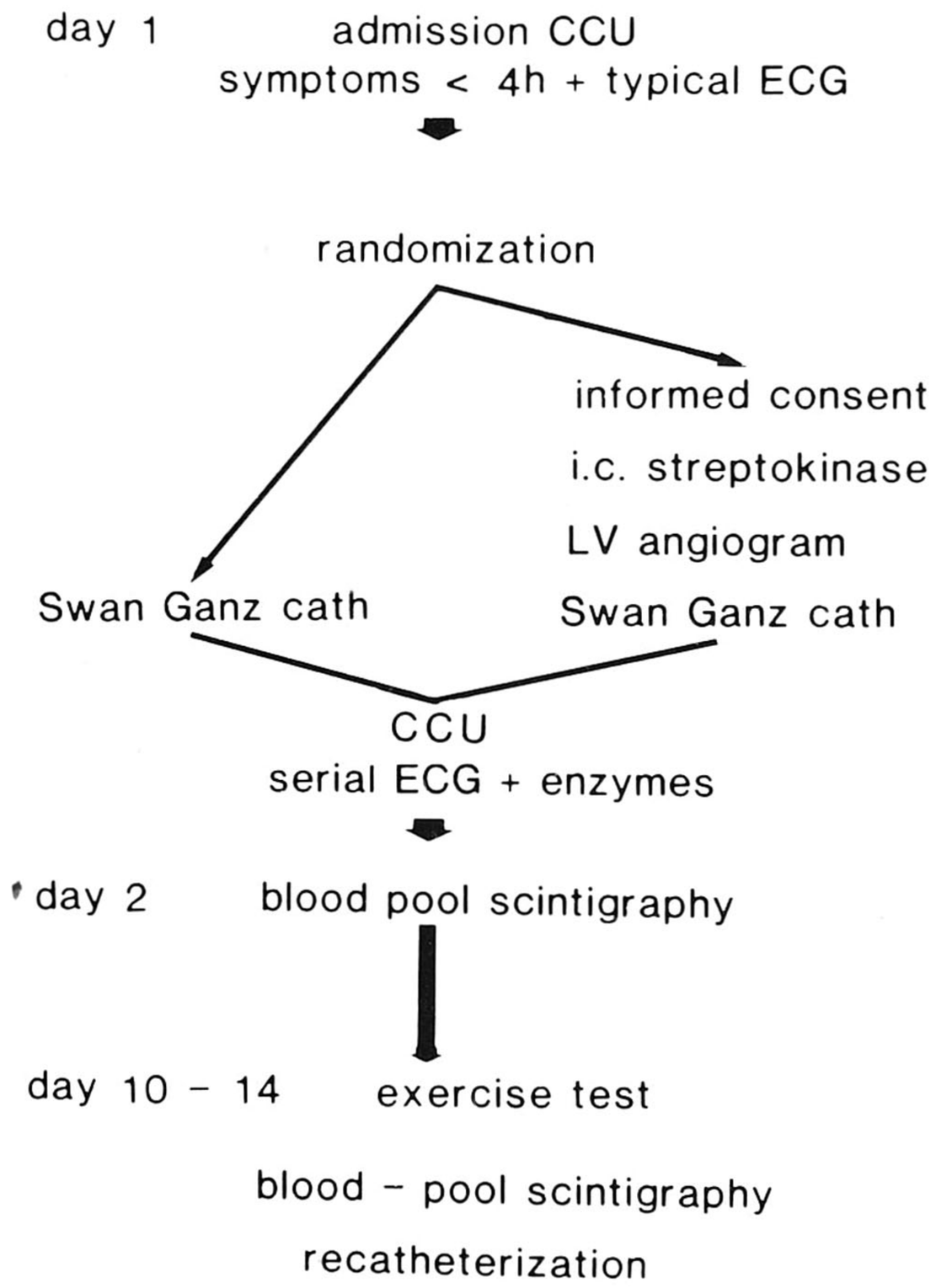

FIGURE 1. Flow chart of the procedures in the current randomized trial at the Thoraxcenter and other members of the Interuniversity Cardiological Institute. (Reproduced from ref. 14 with permission.)

lography in the right anterior oblique projection was done. Coronary arteriography and left ventricular angiography were performed both in the control group and the thrombolysis-treated group, either before discharge or 4 to 8 weeks after the acute phase.

Radionuclide angiography. Radionuclide angiography was carried out at the bedside on the first or second day after admission and repeated before hospital discharge as well as after 3 months. Gated images were obtained with 20 frames in each cycle after labeling in vivo with 15 mCi 99mTc. Data were analyzed by a fully automated computer program on a DEC-gamma 11 or an ADAC system,[34] or with an MDS or a Philips data analysis system.

Measurement of serum enzyme activities and calculation of cumulative hydroxy butyrate dehydrogenase release. Serum alpha-hydroxy butyrate dehydrogenase (HBDH) enzyme determinations were done upon admission, every 12 hr for 2 days and then every 24 hr until 5 days after admission. In 317 patients HBDH levels were obtained, whereas in 131 patients from two hospitals total lactate dehydrogenase levels were used and converted to cumulative HBDH release. Cumulative release of HBDH was calculated from these data as described earlier[35, 36] by a two-compartment model. The total HBDH activity ultimately released by the infarcted myocardium is represented by HBDHQ72, since at 72 hr after onset of chest pain the enzyme release rate has decreased to values near zero.[37]

Electrocardiographic assessment. Careful reading of the electrocardiograms, made at admission, was done independently by two experienced electrocardiographers. In cases of differing interpretation, they agreed after discussion.

The following definitions were used[38]: (1) The localization of the infarct was defined as inferior if there was ST segment elevation in leads II, III, or aVF or ST segment elevation in leads I, aVL, V_5, or V_6 in combination with posterior infarction (ST segment depression in V_1 to V_4); the infarct was anterior if there was ST segment elevation in V_1 to V_4 or ST segment elevation in I, aVL, V_5, or V_6 without the presence of inferior or posterior infarction. (2) The sum of ST segment elevation on the ECG was defined for anterior infarcts as the sum of ST segment elevation in leads I, aVL, and V_1 to V_6 and for inferior infarcts as the sum of ST segment elevation in I, II, III, aVL, aVF, V_5, and V_6 and ST segment depression in V_1 to V_4.

Analysis of global and regional left ventricular function. Before hospital discharge all patients in both groups were offered cardiac catheterization.

Global and regional left ventricular function was studied from the 30 degree right anterior oblique view with an automated hardwired endocardial contour detector linked to a minicomputer. This method of analysis has been described in detail previously.[24, 39, 40] Figure 2 shows an example of the end-diastolic and end-systolic contours of the left ventriculogram as well as the segmental contribution to the global ejection fraction, as displayed by the analysis system.

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

Data 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, after original treatment allocation. Differences between the two groups were tested with the chi-square test, Student's t test, Fisher's exact test, or the Mann-Whitney rank sum test when appropriate. Multiple linear regression analysis was used for estimating the contribution of baseline data to enzymatic infarct size, left ventricular ejection fraction, and survival. All baseline data that correlated in univariate analysis with enzymatic infarct size or ejection fraction were tested in the multivariate regression model. Trends in the multivariate model were tested with the F test. Two-sided p values are reported.

Results

Five hundred thirty-three patients were entered in the study, of which 302 were treated before January 1984 (intracoronary thrombolysis) and 231 after that time (intravenous and intracoronary thrombolysis).

Baseline data. Baseline characteristics in the two groups of patients are shown in table 1. 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, maintainance therapy and therapy initiated within 24 hr preceding entry in the trial and hemodynamic state at admission was the same in both groups.

Patients were entered in the study if they arrived within 4 hr after the onset of symptoms. Forty-four control subjects and 39 thrombolysis patients were already hospitalized before onset of myocardial infarction. The median time until hospital admission was 90

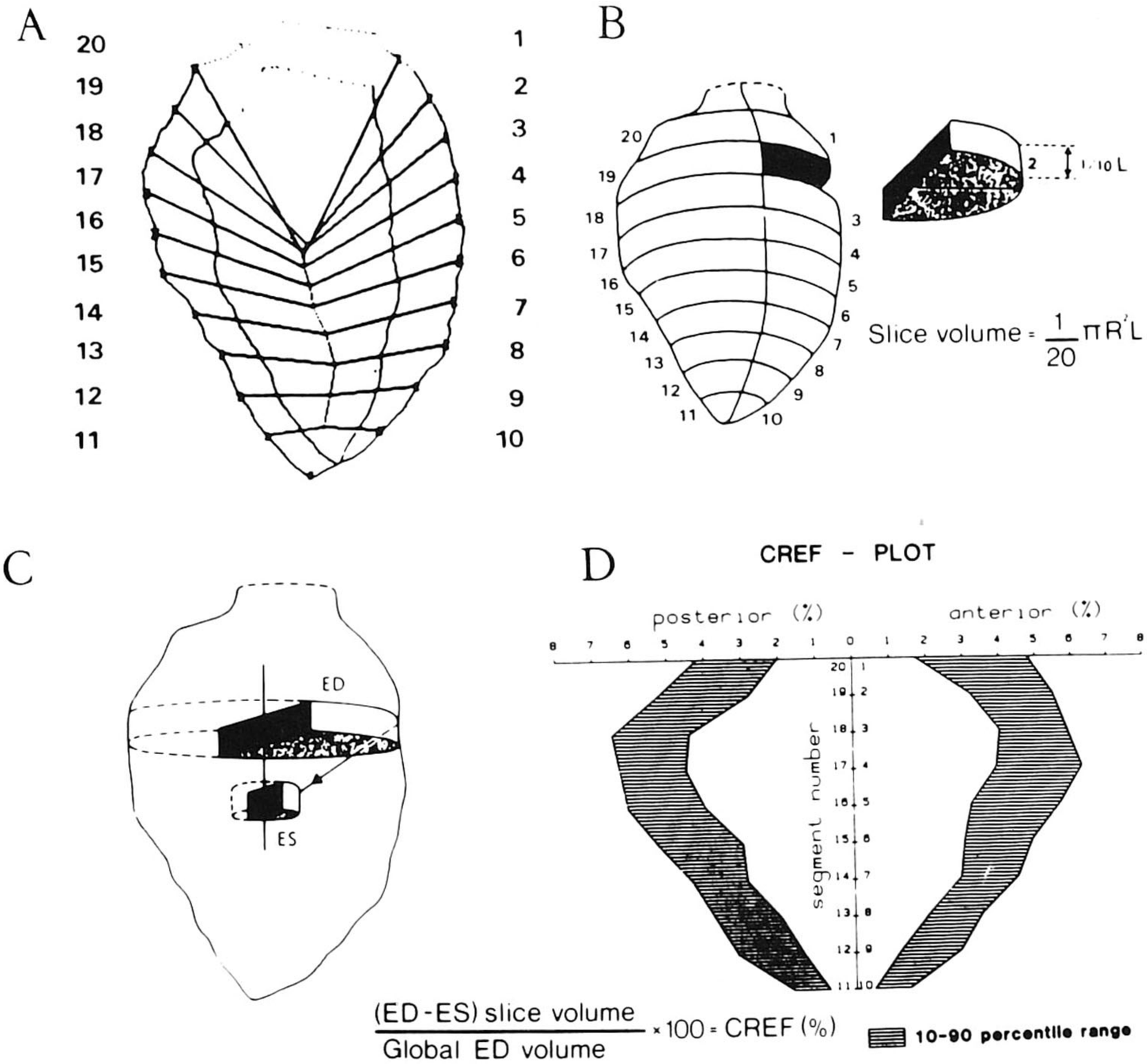

FIGURE 2. *A*, Example of the computer output showing the end-diastolic and end-systolic contours of the 30 degree right anterior oblique left ventriculogram. Systolic regional wall displacement was determined along a system of 20 coordinates on the pattern of actual endocardial wall motion in normal individuals and generalized as a mathematical expression amenable to automatic data processing.[24, 39, 40] *B*, The left ventricular end-diastolic cavity is divided into 20 half slices. The volume of each half slice is computed according to the given formula, where R is radius and L is left ventricular long-axis length. *C*, The regional contribution to global ejection fraction (CREF) is determined from the systolic decrease of volume of the half slice that corresponds to a particular wall segment. The systolic volume change is mainly a consequence of the decrease of radius of the half slice. When normalized for end-diastolic volume, the systolic segmental volume change was considered a variable of regional pump function. *D*, The shaded zones represent the 10th to 90th percentiles area of CREF values in normal individuals. On the x axis the CREF values of the anterior and inferoposterior wall areas are displayed (%), and on the y axis the segment numbers of the anterior wall (1 to 10) and of the inferoposterior wall (11 to 20) are depicted. Anterobasal = segments 1 to 5; anterolateral = segments 5 to 9; apex = segments 9 to 12; inferoapical = segments 12 to 16; inferobasal = segments 16 to 20. (Reproduced from ref. 14 with permission.)

min (table 1). Median time of arrival in the catheterization laboratory was 170 min, while streptokinase infusion was started 195 min after the onset of symptoms. These data were compared in the seven randomized trials (table 2).

Acute and late angiography. A total of 533 patients were admitted to the trial in five participating hospitals; 264 patients were assigned to receive conventional therapy and 269 patients to thrombolysis. In spite of allocation to thrombolysis, angiography could not be performed in 35 patients: informed consent was refused by 20, a contraindication occurred or was detected after randomization in three, one patient died before angiography, the coronary ostium could not be reached from the femoral artery in six, and pain and ST segment elevation resolved shortly after randomization in five. The results of early angiography are summarized in table 3. Of 234 patients who underwent early angiography, 65 had a patent infarct-related artery and in 169 this artery was occluded. In 136 patients catheterized without previous intravenous streptokinase, the infarct-related vessel was occluded in 111 (82%) and recanalization was achieved in 88 (79%) after 30 min (median) of intracoronary infusion of streptokinase. An occluded artery was found in 58 (59%) of 98 patients who received intravenous streptokinase before its intracoronary administration. Subsequently intracoronary streptokinase caused recanalization in 39

TABLE 1
Baseline data

	Thrombolysis	Controls
No. of patients	269	264
Men	217	224
Age (yr, mean ± SD)	56 ± 9	55 ± 8
Previous myocardial infarction	56	60
Known angina	69	74
Anterior infarction	129	116
Time since onset of symptoms (median, min)	90	90
Hospitalized for unstable angina	39	44
Killip class III/IV on admission	12	11
Sum of ST elevation on the ECG on admission (median, mV)	1.1	1.2

patients, whereas in five patients the thrombus was perforated by the guidewire or angioplasty catheter. Ultimately the infarct-related artery remained occluded in 36 of 234 patients who underwent angiography and at least one attempt at recanalization (15%), whereas the artery was open at study or became recanalized in 198 patients (85%). The median time between onset of symptoms and angiographic documentation of a patent infarct-related vessel was 200 min, ranging from 55 to 375 min. Differences between our data and those of the six other randomized trials are given in table 2. The infarct-related coronary artery was the left main stem in one patient, the left anterior descending artery in 102, the circumflex artery in 40, the right coronary artery in 89, and a bypass graft in two patients.

To improve recanalization, percutaneous transluminal coronary angioplasty (PTCA) was attempted in 46 patients with severe stenosis of the infarct-related artery after thrombolysis in whom it was judged to be technically and organizationally feasible.[26] In 44 patients this additional procedure was successful, while reocclusion of a subtotal lesion occurred after PTCA in two patients. No differences in final patency were observed between anterior infarcts (83%) and inferior infarcts (88%). Final patency decreased slightly since more time had elapsed between onset of symptoms and admission. Final patency was 96% in patients already hospitalized before onset of symptoms, 85% in patients admitted within 1 hr after onset of symptoms, 89% after more than 1 hr and within 2 hr, and 76% after 2 or 4 hr. Sum of ST segment elevation, previous myocardial infarction, known angina, or Killip class at admission did not affect final patency rate. Late coronary angiograms were available in 199 patients assigned to receive thrombolytic therapy and in 205 patients treated conventionally (table 3). These data were missing in 42 patients who died in the intervening period, 24 patients who underwent early bypass surgery, 22 patients who were transferred to another hospital, and 41 patients who refused the second angiogram; in 72 patients late angiography was performed, but the left ventricular angiograms were inadequate for quantitative analysis. Angiograms were thus available in 332 patients. These angiograms were obtained before discharge in 279 patients (median 11 days) and after discharge in 124 patients (median 42 days). During follow-up angiography, patency rates in the control and thrombolysis groups were 52% (106/205) and 79% (157/199) ($p = .0001$). The reocclusion rate in patients who had recanalization by intracoronary streptokinase was 20% (22/109 patients), while late occlusion in the patients with a patent infarct-related vessel at first angiogram was 6% (3/49 patients).

Clinical course. Complications during the clinical

TABLE 2
Previously reported data in literature

					Time (min) to:				
	n	Previous MI	Killip III/IV	Admission/ randomization	Treatment	Patency[A]	Occlusion (%)	Reperfusion (%)	Reocclusion (%)
ICI	533	116 (22%)	23 (4%)	90	195	200	83	79	20
Anderson et al.[16]	50	4 (8%)	—	152	238	259	100	79	0
Leiboff et al.[19]	40	—	—	84	242	286	100	68	45
Kennedy et al.[17]	250	32 (13%)	17 (7%)	134	276	—	86	68	—
Khaja et al.[15]	40	—	4 (10%)	—	324	—	100	60	—
Raizner et al.[21]	64	5 (8%)	7 (11%)	212	337	—	55	50	—
Rentrop et al.[20]	124	22 (18%)	—	246	354	—	67	74	17

Baseline characteristics in the seven randomized trials of thrombolysis. The actual numbers are presented, with percentages in parentheses.
MI = myocardial infarction; ICI = Interuniversity Cardiology Institute, The Netherlands.
[A]In patients with successful recanalization.

TABLE 3
Results of early and late angiography

Early angiography			Late angiography missing					Late angiography		
			Patient refusal	Death before angio	CABG	Inadequate quality of LV angio	Other[A]	Adequate LV angio	Coronary patency	
									Patent	Occluded
264 controls			19	27	4	31	9	174	106	99
	35 no angiography		5	4	2	8	2	14	13	9
269 thrombolysis	→ 65 patent	→ 65 patent	1	1	9	13	5	36	46	3
	169 occluded → 133 patent		11	4	4	18	5	91	87	22
	36 occluded		5	6	5	2	1	17	11	8
533 patients			41	42	24	72	22	332	263	140

CABG = coronary artery bypass graft surgery.

[A]For example, due to transfer to another hospital.

course in the hospital are summarized in table 4 and compared with the other randomized trials. 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 the incidence of reinfarction, angina pectoris, or heart failure. Ventricular fibrillation was more prominent in the controls, as well as pericarditis, characterized by posture-related chest pain and a friction rub, whereas bleeding occurred 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, but this was of borderline significance.[31] For example cardiogenic shock ($p = .08$) and treatment with dopamine and dobutamine ($p = .04$) occurred more frequently in controls. Similarly, heart failure during convalescence was more frequent in controls ($p = .05$). Treatment after hospital discharge was similar in both groups, including β-blockers in 101 controls and in 113 patients allocated to thrombolysis and anticoagulants in 80 controls and 79 patients.[31]

Myocardial enzyme release. Infarct size was estimated from serial serum enzyme measurements during the first 72 hr. Cumulative data in figure 3 indicate a 30% smaller infarct size in the treated group ($p = .0001$, Mann-Whitney test). This difference was also apparent when patients with a first infarct only ($p = .0001$), patients with anterior wall infarction ($p = .005$), and patients with inferior wall infarction ($p = .007$) were analyzed separately. Furthermore, similar results were obtained when the patients who died within 72 hr were not included in the analysis and when data from the five hospitals were analyzed separately. Median values for HBDH infarct size in control and thrombolysis-treated patients were 1100 and 770 U/liter. These values were 1140 and 790 U/liter in those with a first infarct, 1280 and 840 U/liter in those with anterior wall

TABLE 4
Clinical course in hospital: review of the randomized trials[A]

	n		Mortality		Reinfarction		CABG/PTCA		VF		Bleeding	
	C	T	C	T	C	T	C	T	C	T	C	T
ICI	264	269	26	14	9	12	9	13	60	36	7	53
Anderson et al.[16]	26	24	4	1	2	1	2	7	5	3	—	—
Leiboff et al.[19]	18	22	1	2	—	—	—	—	—	3	—	5
Kennedy et al.[17]	116	134	13	5	3	4	9	13	—	—	1	7
Khaja et al.[15]	20	20	2	1	—	—	5	1	—	—	—	—
Raizner et al.[21]	35	29	2	4	2	5	5	5	—	—	0	2
Rentrop et al.[20]	61	63	4	10	—	—	—	—	—	—	13%	

C = control group; T = thrombolysis group; CABG = coronary artery bypass graft surgery; PTCA = percutaneous transluminal coronary angioplasty; VF = ventricular fibrillation.

[A]Summary of the clinical course in hospital in the seven randomized trials. Values refer to number of patients, except as otherwise noted.

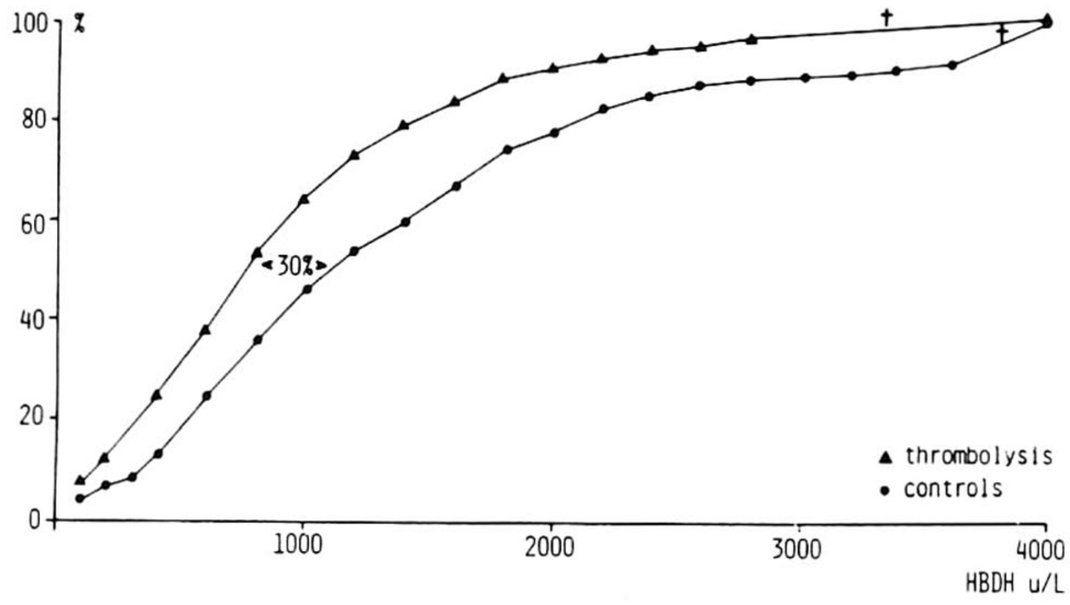

FIGURE 3. Cumulative distributions of infarct size determined from serial HBDH measurements. Data were available in controls and in patients assigned to thrombolysis. Patients who died before completion of the measurements have been included as the largest infarct sizes (†) as discussed in the text. The median reduction of infarct size after thrombolysis is 30% (p = .0001, Mann-Whitney test). (Reproduced from ref. 31 with permission.).

infarction, and 970 and 670 U/liter in those with inferior wall infarction.

Global left ventricular function determined from contrast angiography. When the hemodynamic data of the control group were compared with those of the thrombolysis group, almost all the variables listed in table 5 showed significant differences. The global left ventricular ejection fraction in the thrombolysis group was on average 6% higher (p = .0001) than in the control group, mainly because of a smaller end-systolic volume in the thrombolysis group (41 vs 53 ml/m^2 in the control group; p = .0004). In addition, the end-diastolic volume was significantly higher and abnormal in the control group compared with the thrombolysis group (95 vs 84 ml/m^2; p = .006), whereas mean aortic pressure and heart rate were not different at the time of the hemodynamic investigation. The differences observed in the entire group (n = 332) between conventional and thrombolytic therapy remained present to a significant degree after exclusion of those 65 patients who had had a previous infarction (40 in the control group and 25 in the thrombolysis group).

Global and segmental function in anterior or inferior infarction: thrombolysis vs conventional treatment. Table 5 and figure 4 show the data from patients with inferior infarction. The global ejection fraction shows an 8% difference (p = .0001) in favor of the thrombolysis group, and this difference in ejection fraction is due to a significantly (p = .007) smaller end-systolic volume (37 ml/m^2) when compared with that of the control group (48 ml/m^2). In figure 4, *A*, the regional contribution to ejection fraction values of the patients with inferior infarction assigned to thrombolysis are compared with those assigned to conventional treatment. Depressed regional contribution to ejection fraction values was observed in the inferoposterior wall (segments 11 to 18) as expected, whereas regional pump function was significantly better in patients assigned to thrombolysis, although it was not (yet) normal. In these patients no difference was observed in regional function of the anterior wall. Thus when the recanalization is successful and the infarct-related vessel remains patent, there is a significant improvement of function of the inferior wall associated with the subsidence of the initially compensatory augmented functioning of the anterior wall. This latter phenomenon was particularly prominent in the patients who underwent the combined procedure of recanalization and angioplasty (figure 4, *B*) in the acute phase.

In table 5 and figure 5, global and regional left ventricular function of patients with anterior myocardial infarction is shown. A significant (p = .0025) 7% difference in global ejection fraction was found between both groups due to a smaller end-systolic volume in the thrombolysis group (45 vs 60 ml/m^2 in the control group; p = .006). As figure 5 clearly indi-

TABLE 5
Left ventricular hemodynamics before discharge

	Controls	Thrombolysis	p value[A]
All patients (n = 332)			
n	174	158	
HR (bpm)	78 ± 15	76 ± 13	NS
Mean AoP (mm Hg)	88 ± 13	90 ± 15	NS
EDP (mm Hg)	20 ± 9	20 ± 8	NS
EDV (ml/m^2)	95 ± 37	84 ± 33	.006
ESV (ml/m^2)	53 ± 31	41 ± 27	.0004
EF (%)	47 ± 14	53 ± 13	.0001
Inferior infarction (n = 184)			
n	105	79	
HR	77 ± 16	74 ± 12	NS
Mean AoP	88 ± 13	91 ± 15	NS
EDP	19 ± 8	18 ± 8	NS
EDV	91 ± 35	82 ± 32	.07
ESV	48 ± 28	37 ± 24	.007
EF	49 ± 13	57 ± 11	.0001
Anterior infarction (n = 148)			
n	69	79	
HR	79 ± 13	77 ± 13	NS
Mean AoP	87 ± 13	89 ± 14	NS
EDP	21 ± 10	21 ± 9	NS
EDV	101 ± 39	86 ± 34	.02
ESV	60 ± 34	45 ± 29	.006
EF	43 ± 14	50 ± 13	.0025

Values are expressed as means ± SD.

HR = heart rate; AoP = aortic pressure; EDP = end-diastolic pressure; EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction.

[A]Student test for unpaired data. Only p values below .1 are tabulated.

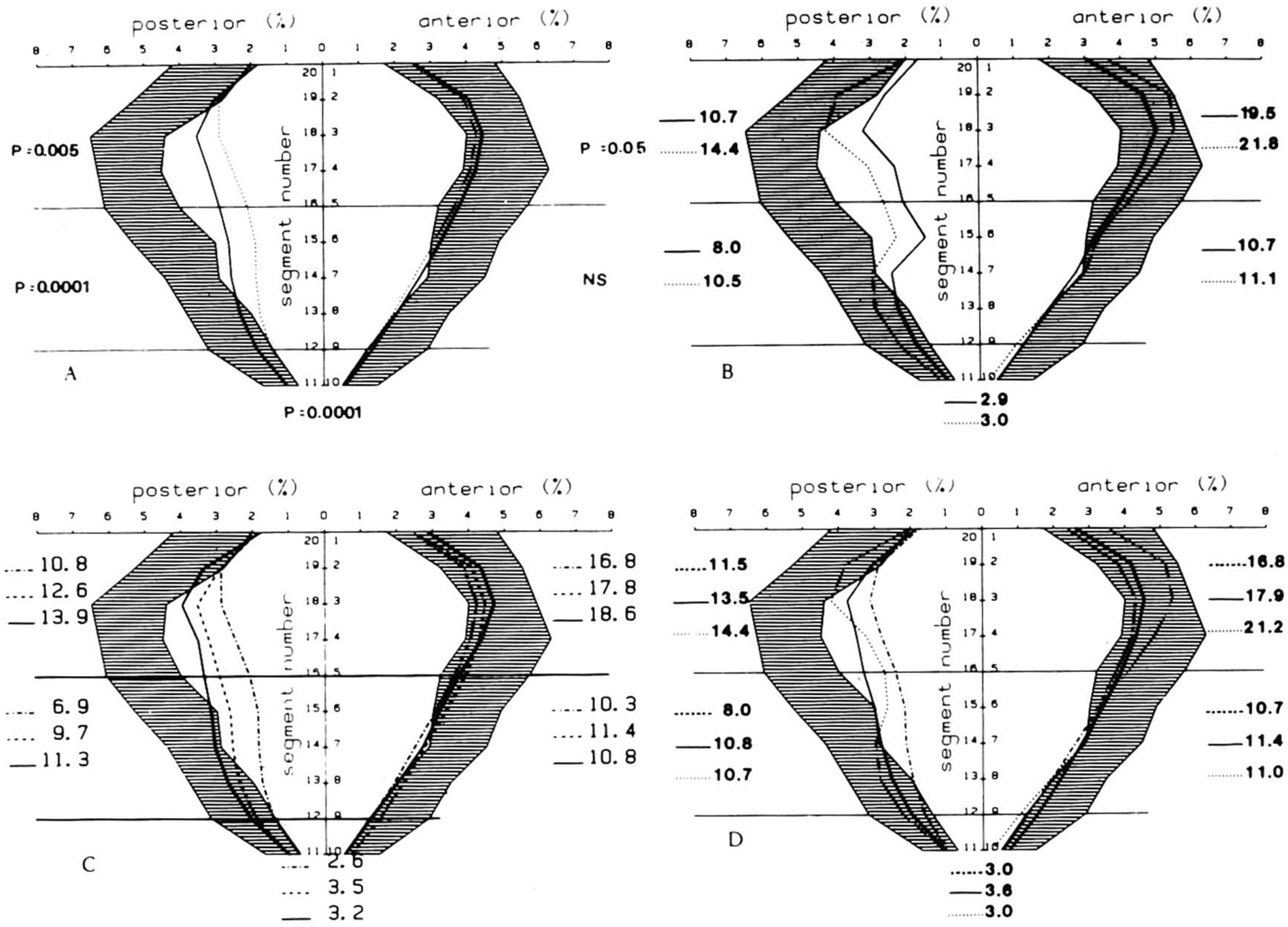

FIGURE 4. *A*, Regional contribution to global ejection fraction in 20 segments of the left ventriculogram in patients with inferior infarction. Shaded areas represent the normal range. The regional pump function of the inferior wall (segments 11 to 20) in the thrombolysis-treated group (n = 79, solid line) is markedly less depressed than in the conventionally treated group (n = 105, dotted lines). *B*, Change in regional contribution to global ejection fraction from the acute (solid line) to the chronic stage (dotted line) in patients with an inferior infarction who underwent a combined procedure of thrombolysis and angioplasty (n = 6). *C*, Regional contribution of the inferior wall to global ejection fraction at the chronic stage in the control group and in the thrombolysis group, according to the success of the recanalization at the acute stage and to the time elapsed from the onset of symptoms to treatment. -.-.-, Control (n = 105); ————, thrombolysis > 180 min (n = 41); ——, thrombolysis ≤ 180 min (n = 22). *D*, Regional contribution of the inferior wall to global ejection fraction at the chronic stage in the thrombolysis group (n = 79), according to the initial success and late patency after thrombolysis either with or without angioplasty. -.-.-, Unsuccessful thrombolysis (n = 31); ——, successful thrombolysis (n = 41); . . . . ., angioplasty after successful thrombolysis (n = 7). (Reproduced from ref. 14 with permission.)

cates, this 7% difference in global ejection fraction in favor of the thrombolysis group is essentially due to a better regional pump function of the anterior wall and, to a smaller extent, to better regional pump function of the inferoapical segment (11 to 15) of the inferior wall (figure 5, *A*).

The preceding analysis was based on original treatment allocation, disregarding whether treatment was actually given and whether reperfusion was achieved. The actual effects of reperfusion can be better understood when four subgroups of patients are compared: (1) patients who refused the intervention or otherwise did not undergo early angiography; (2) patients with either unsuccessful recanalization or late reocclusion; (3) patients with successful recanalization and late patency of the infarct-related vessel, and (4) patients who underwent a successful recanalization, immediately followed by angioplasty. For the patients in whom recanalization could not be achieved, the segmental function of the anterior wall was the worst, whereas the highest preservation of regional function of the anterior wall was observed in those patients who underwent a combined procedure of thrombolysis and angioplasty (figures 4, *D*, and 5, *D*). The magnitude of change in regional function at the infarct site was also related to the time from the onset of chest pain to treatment. Patients treated with thrombolytic therapy within 3 hr had a significantly greater improvement than patients treated later (figures 4, *C*, and 5, *C*). The regional contribution to ejection fraction of the infarct zone, either anterior or inferior, improved by at least 1.5%.

Follow-up. Clinicial follow-up ranged from 1 to 48 months after admission. Data presented in table 6 show a 45% reduction of mortality after thrombolysis. This was offset by a higher incidence of late reinfarction

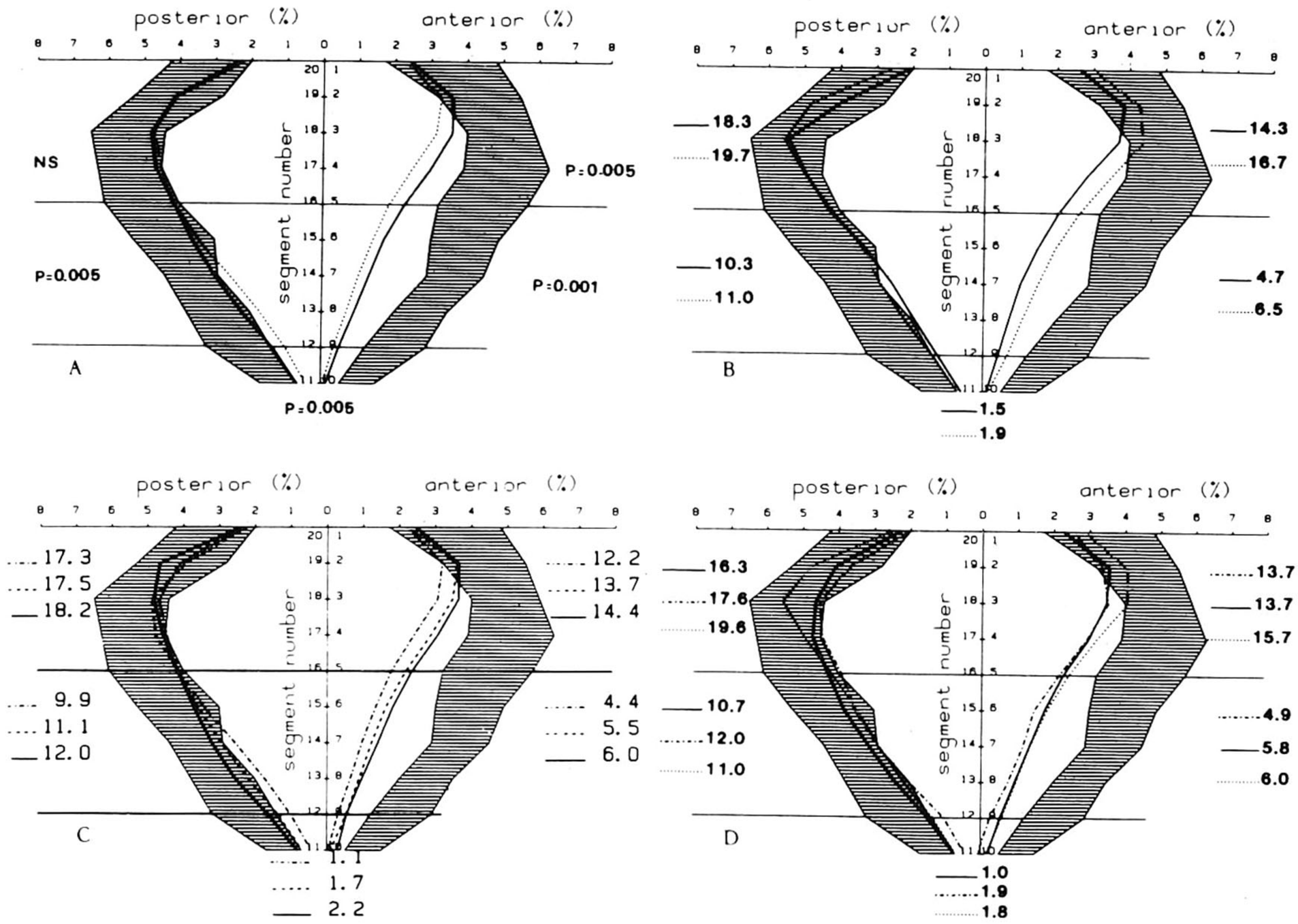

FIGURE 5. *A*, Mean values of regional contribution to ejection fraction in patients with anterior infarction (format as in figure 4). The regional pump function of the anterobasal, anteroapical, and inferoapical segments (1 to 10, 11 to 15) is significantly better in the thrombolysis group (n = 79, solid line) compared with the group receiving conventional treatment (n = 69, dotted line). *B*, Change in regional contribution to ejection fraction from the acute (solid line) to the chronic stage (dotted line) in patients with an anterior infarction who underwent a combined procedure of recanalization and angioplasty (n = 17). *C*, Regional contribution of the anterior wall to global ejection fraction at the chronic stage in the control and in the thrombolysis group, according to the success of the recanalization at the acute stage and to the time elapsed from the onset of symptoms to treatment. -.-.-, Control (n = 69); ----, thrombolysis > 180 min (n = 40); ———, thrombolysis ≤ 180 min (n = 24). *D*, Regional contribution of the anterior wall to global ejection fraction at the chronic stage in the thrombolysis group (n = 79), according to the initial and late patency after successful thrombolysis either with or without angioplasty. -.-.-, Unsuccessful thrombolysis (n = 15); ———, successful thrombolysis (n = 44); . . . . ., angioplasty after successful thrombolysis (n = 20). (Reproduced from ref. 14 with permission.)

and more frequent performance of late angioplasty or bypass surgery after thrombolysis. The reduction in mortality was present in all subgroups.

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 one death in 65 patients with patent infarct-related vessels at angiography and one 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. In spite of treatment with anticoagulants and nifedipine, he developed postinfarction angina. After 7 days, the artery was reoccluded at the same site and repeat coronary angioplasty was carried out. After 31 days the patient developed a new anteroseptal infarction and died from intractable cardiogenic shock.

Infarct size and treatment delay. In figure 6, HBDH release is shown in relation to the interval between onset of symptoms and hospital admission. In patients assigned to the control group, HBDH release was independent of the interval between onset of symptoms and admission. On the other hand, we found lower enzyme levels in patients assigned to thrombolysis within 2 hr after the onset of symptoms. These data indicate a 51% reduction of infarct size by thrombolysis in patients admitted within 1 hr, a 31% reduction of infarct size between 1 and 2 hr, and a 13% reduction between 2 and 4 hr after the onset of symptoms.

Infarct size and electrocardiographic assessment. The correlation between the ST segment elevation and cumulative HBDH release is almost linear in both groups, and limitation of infarct size by streptokinase is greater in patients with a high sum of ST segment elevation on the ECG at admission.[41]

TABLE 6
Clinical follow-up

	Controls	Thrombolysis	None	Patent/ patent	Occluded/ patent	Occluded/ occluded
n	264	269	35	65	133	36
Reinfarction	16	36	4	9	21	3
Early PTCA	—	46	—	13	31	2
Late PTCA/CABG	40	62	9	18	28	7
Total mortality	42	23	5	1	8	9
IC	23	17	4	—	6	7
IV + IC	19	6	1	1	2	2
First MI only	26	11	2	1	3	5
Anterior MI	25	12	3	—	4	5
Inferior MI	17	11	2	1	4	4

Major complications (mortality and nonfatal recurrent infarction) and bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA) in patients with acute myocardial infarction (MI) allocated to conventional treatment (controls) or thrombolysis. Mortality is shown for patients admitted before (IC thrombolysis) or since (IV + IC thrombolysis) January 1984. Patients assigned to thrombolytic treatment are subdivided according to the results of the intervention (see also table 3).

The combination of ST segment elevation and duration of symptoms is given in figure 7. This shows that limitation of infarct size is greatest in patients admitted within 2 hr after onset of symptoms with an ST segment elevation of 12 mm or more (620 U/liter). Limitation of infarct size was less pronounced in patients admitted after 2 to 4 hr with ST segment elevation of 12 mm or more (460 U/liter) and in patients admitted within 2 hr with ST segment elevation less than 12 mm (300 U/liter). In the subset of patients with ST segment elevation less than 12 mm, admitted after 2 to 4 hr, no limitation of infarct size was observed.

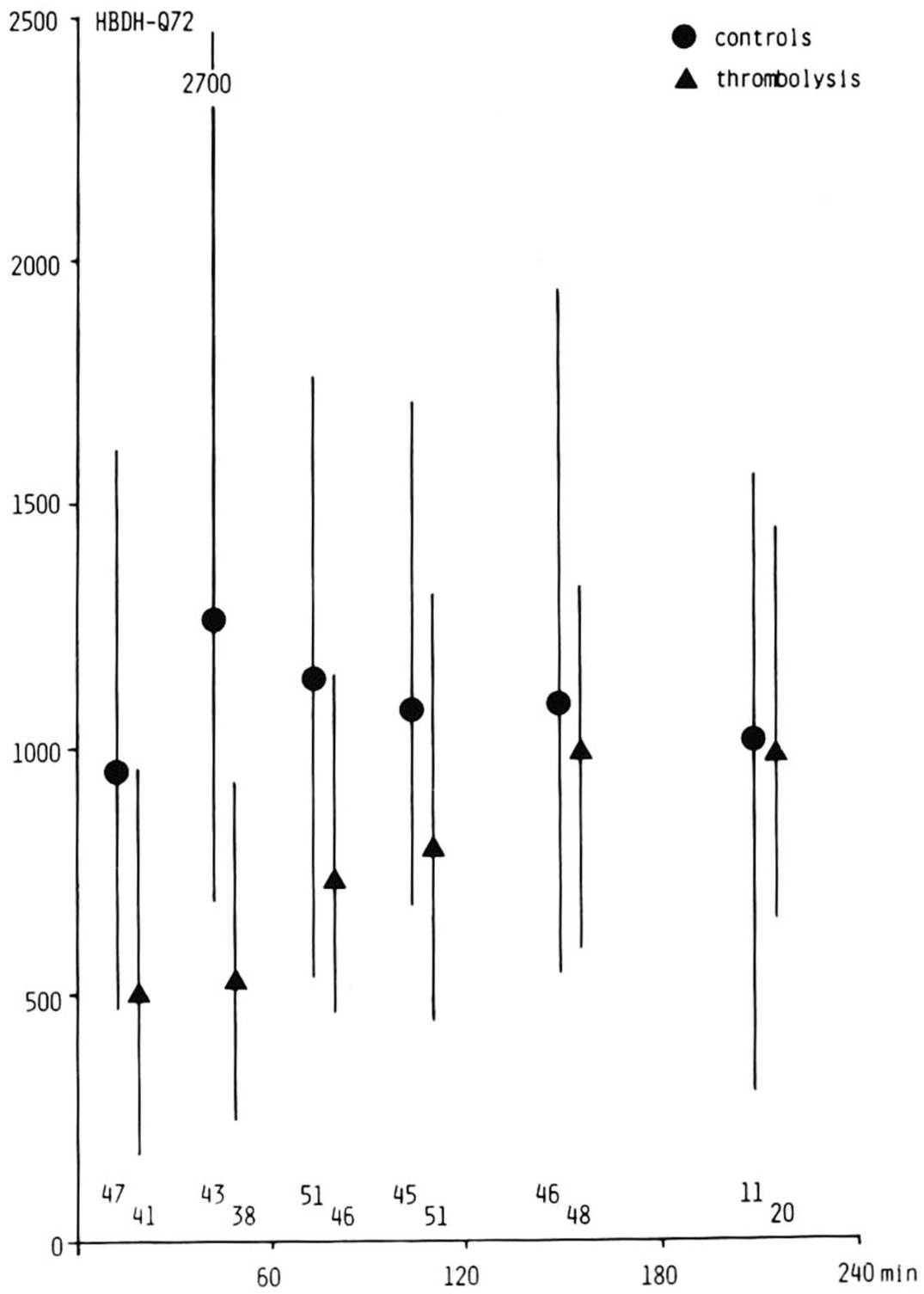

FIGURE 6. Median and 50% range (first to third quartile) of HBDHQ72 in patients assigned to thrombolysis or conventional treatment in relation to the time interval between onset of symptoms and randomization. The numbers denote the number of patients in each time interval. (Reproduced from ref. 31 with permission.)

Infarct size and prognosis. Among a total of 533 patients randomized in the study, 65 (12%) died within 1 year after onset of chest pain. In 32 of them, 3 day survival data made it possible to calculate HBDHQ72 in patients who died in the first year after infarction; median HBDHQ72 was 84% higher ($p = .0001$) in patients who died within 1 year than in 1 year survivors.[36]

Global left ventricular function determined from radionuclide angiography. Left ventricular ejection fraction was measured by radionuclide angiography between days 2 and 4 in 416 patients and before hospital discharge in 360 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. The results in table 7 indicate no change in global left ventricular ejection fraction between the second day and hospital discharge in the control group. In thrombolysis-treated patients left ventricular ejection fraction before discharge was between $3.7 \pm 9.0\%$ higher than at the first measurement. Accordingly, left ventricular 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

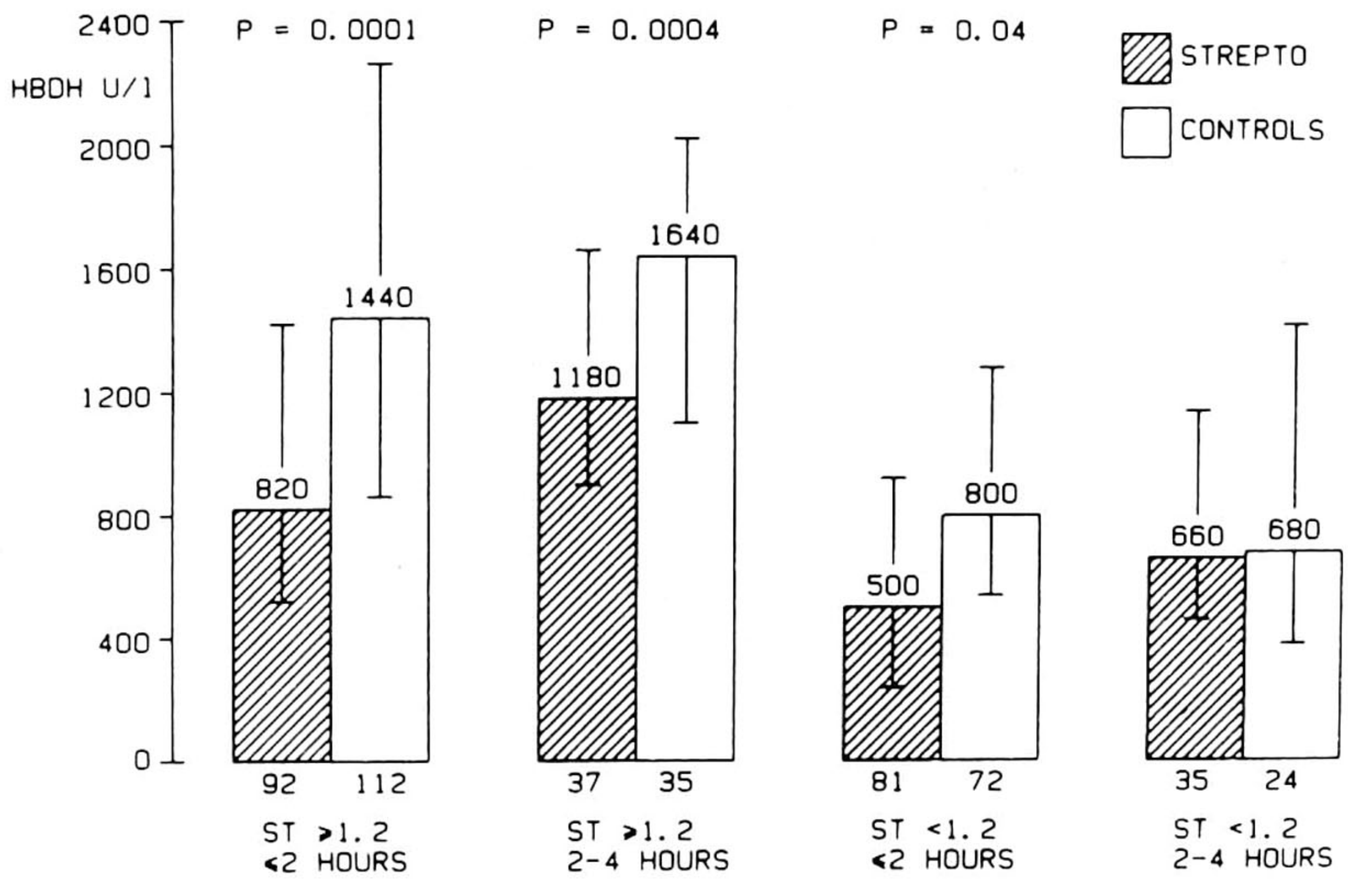

FIGURE 7. Median values and quartiles of enzymatic infarct size in four subsets of patients in both treatment groups. Limitation of infarct size is most prominent in patients with a high sum of ST segment elevation on the ECG at admission and in patients admitted within 2 hr after onset of symptoms. (Reproduced from ref. 41 with permission.)

group, in patients treated with intracoronary thrombolysis only, in patients with a first infarction, and in patients with anterior and inferior 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 or inferior wall infarction upon admission and in both treatment protocols.

TABLE 7
Radionuclide angiography

	n	Controls	n	Thrombolysis	p value
All patients					
Days 2–4	199	42 ± 15	217	45 ± 14[B]	.05
Days 10–20	171	44 ± 15	189	48 ± 15[B]	.003
ΔLVEF	140	0.9 ± 11[A]	160	3.7 ± 9[A]	.0001
Intracoronary thrombolysis					
Days 2–4	113	41 ± 14	123	45 ± 14[B]	.04
Days 10–20	93	42 ± 14	96	48 ± 14[B]	.003
ΔLVEF	78	0.6 ± 10[A]	82	3.9 ± 8[A]	.0001
Intravenous + intracoronary thrombolysis					
Days 2–4	86	44 ± 14	94	46 ± 14[B]	
Days 10–20	78	45 ± 16	93	48 ± 15[B]	
ΔLVEF	62	1.3 ± 13[A]	78	3.6 ± 11[A]	.005
First infarction					
Days 2–4	159	44 ± 14	179	47 ± 13[B]	.04
Days 10–20	137	46 ± 15	158	50 ± 14[B]	.009
ΔLVEF	112	1.2 ± 12[A]	137	3.6 ± 9[A]	.0001
Anterior infarction					
Days 2–4	86	34 ± 13	99	39 ± 13[B]	.02
Days 10–20	67	35 ± 14	89	44 ± 16[B]	.0004
ΔLVEF	57	1.2 ± 9[A]	70	4.9 ± 9[A]	.0001
Inferior infarction					
Days 2–4	113	49 ± 12	118	50 ± 12[B]	
Days 10–20	104	49 ± 12	100	52 ± 12[B]	.07
ΔLVEF	83	0.7 ± 13[A]	90	2.8 ± 9[A]	.005

Radionuclide left ventricular ejection fraction (LVEF) measured 2 to 4 days after infarction and before hospital discharge (10 to 20 days).

ΔLVEF = sequential change in ejection fraction between the two measurements in patients in whom both were available.

[A]p value, paired t test for ΔLVEF; [B]p value, unpaired t test for comparison of controls and thrombolysis. Only p values less than .05 are reported. No significant differences were observed in controls, while LVEF improved in thrombolysis treated patients. In the control group ΔLVEF did not reach statistical significance in any subgroup.

The 46 patients who underwent a subsequent attempt at angioplasty after intracoronary streptokinase showed a dramatic increase in the ejection fraction from days 2 to 4 (40 ± 13%) to days 10 to 20 (48 ± 14%; p = .05) and to 3 months (53 ± 12%; p = .05). This increase was even more pronounced in the 29 patients with anterior wall infarction from days 2 to 4 (35 ± 11%) to days 10 to 20 (43 ± 14%; p = .05) and to 3 months (52 ± 16%; p = .05).

Discussion

These results show for the first time in a large randomized multicenter trial that early recanalization of an occluded coronary artery in the acute phase of a myocardial infarction leads to recanalization of an occluded coronary artery, limitation of infarct size, improvement of left ventricular function, and reduction of 1 year mortality. Most benefit of recanalization was observed in patients with extensive myocardial ischemia, as reflected by a high sum of ST segment elevation on the ECG at admission, who were admitted within 2 hr after onset of symptoms.

Criticisms of study design. Although several open clinical trials[42–48] have aroused great interest and rekindled enthusiasm for reperfusion, their interpretation is fraught with difficulty as selected patients with successful thrombolysis were compared with patients with persistent occlusions. Such interpretation can carry considerable bias, which can be overcome only by means of randomized trials and analysis of the data on an "intention to treat" basis. However, in such a trial it is difficult to follow the sequence: determination of

patient eligibility, coronary arteriography, randomization, and attempted reperfusion of patients randomly assigned to special therapy. In this sequence, patients with evolving infarcts who are assigned to conventional therapy would be obliged to undergo emergency coronary arteriography without sufficient potential benefit to outweigh the attendant risk. To overcome this difficulty we randomized all patients who were eligible on clinical grounds but obtained consent for performing coronary arteriography only from those assigned to reperfusion therapy. This procedure has been proposed by Zelen[32] for the comparison of a new method of treatment with an accepted mode of therapy. Data analysis was based on original treatment allocation. Therefore the 35 patients who did not undergo early 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: five out of 35 patients (table 6). Since 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.

The interpretation of this study might be questioned because of changes in the protocol in January 1984, the inclusion of percutaneous transluminal coronary angioplasty in some of the patients, missing data, the lack of coronary arteriography at admission in the control group, and the absence of direct measurement 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 hr, while several reports indicated that recanalization could be achieved by intravenous streptokinase.[11–13] Direct perforation of the thrombus was attempted in five 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, since earlier observations indicated that patients with residual subtotal stenosis after thrombolysis are at increased risk for reocclusion, which would negate the effect of thrombolysis.[26] Angioplasty was not associated with complications. In fact, HBDH release after angioplasty was lower and left ventricular ejection fraction was higher than in patients in whom only thrombolysis was carried out. Therefore it is likely that the beneficial effects of thrombolysis in the present study would have been less apparent without additional angioplasty. No patients were lost to follow-up with respect to mortality or major clinical events, which represent the major end points of the study. Data on left ventricular function were missing because of 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, since missing data were equally distributed between the two groups and since similar differences were observed between patients allocated to thrombolysis and controls in various subgroups. Moreover, there were no differences in baseline data between patients with or without measurements of left ventricular function.

In contrast with other trials,[15–21] no early angiography was performed in the control group. Therefore the coronary anatomy at admission in these patients could not be studied. This procedure was elected because early angiography is not 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.[22] Similarly, it was not attempted to determine left ventricular function by radionuclide angiography upon admission, since this would have delayed the intervention that could diminish the possible salutary effects of recanalization.

Myocardial enzyme release. Total HBDH release in 72 hr was calculated as a measure of infarct size by a two-compartment model,[35–37] which enables us to calculate the cumulative activity released from the infarcted myocardium into the plasma space for each cytoplasmic (iso)enzyme. The method has proved its value to assess myocardial damage induced by surgical and cardioplegic procedures[49, 50] and to assess the relationship between enzymatic infarct size and occurrence of pump failure, electrocardiographic changes, conduction and rhythm disturbances, global left ventricular function, wall motion abnormalities, and 1 year survival.[35]

In the present study a 30% median reduction of HBDH release was observed in the thrombolysis group. This supports the hypothesis that myocardial tissue can be salvaged by early thrombolysis.

Anderson et al.,[51] who measured serial activities of several (iso)enzymes in serum, calculated the integrat-

ed concentrations of serum LDH and serum LDH-1 and did not find significant differences between thrombolysis-treated and control patients. However, recalculation of released quantities of LDH and LDH-1 with the method used in the present study yielded a smaller infarct size after thrombolysis of 20% and 40% with LDH and LDH-1 respectively. This is in agreement with the better left ventricular ejection fraction after thrombolysis reported by Anderson et al.[51] It is evident that reported enzyme washout data cannot be readily compared without adequate background information.

Left ventricular function. Global left ventricular ejection fraction was measured by contrast and radionuclide angiography. Both methods showed higher ejection fractions at 2 weeks after thrombolysis compared with conventional therapy. 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 patients with recurrent infarction. Some difference between the two groups was already apparent in left ventricular ejection fraction measured by radionuclide angiography after 2 to 4 days (table 7), although these were of borderline significance. Although no measurements of ejection fraction were done at admission, we may presume that these were similar in both groups, since other baseline data were also evenly distributed. The data thus indicate a gradual recovery of left ventricular function during the first 2 weeks after reperfusion.[52] 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 of 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.

The results of the five reported but smaller randomized trials with intracoronary streptokinase[15, 17, 19–21] conflict with the data presented here (table 8). Khaja et al.[15] found that intracoronary streptokinase was more effective than placebo (intracoronary infusion of dextrose) in achieving reperfusion, but they detected no difference in left ventricular function at 12 days and at 5 months. Kennedy et al.,[17] Leiboff et al.,[19] and Raizner et al.[21] also demonstrated no difference in the radionuclide ejection fraction at discharge in patients with anterior or inferior myocardial infarction treated with intracoronary streptokinase or controls, although they achieved reperfusion and decreased mortality. In

TABLE 8
Radionuclide left ventricular ejection fraction (%) of the seven randomized trials

	Controls			Thrombolysis		
	Early	Late	Δ	Early	Late	Δ
ICI	43	44	1	44	48	4
Anderson et al.[16]	42	39	−3	43	47	4
Leiboff et al.[19]	42	41	−1	46	43	−3
Kennedy et al.[17]	46	47	1	47	48	1
Khaja et al.[15]	36	37	1	45	45	0
Raizner et al.[21]	48	50	2	43	46	3
Rentrop et al.[20]	—	—	−1	—	—	2

See also table 2.

all these studies the intervention was instituted much later than the current one (table 2). The median interval between the onset of symptoms and angiographic documentation of a patent infarct-related vessel in the present study was 200 min whereas the other two major trials included patients up to 12 hr after the onset of symptoms. In the studies of Khaja et al.[15] and Raizner et al.,[21] the time periods between chest pain and onset of streptokinase infusion were 5.4 and 5.6 hr, respectively; in the Western Washington Trial the mean time until randomization and the start of streptokinase infusion was 276 min,[17, 18] whereas Rentrop et al.[20] started intracoronary streptokinase an average of 350 min after the onset of symptoms.[20]

The shorter delay achieved in our study is also reflected by the higher recanalization rate (79%) compared with that of the Western Washington Trial (68%) (table 2). These differences with this only other large randomized trial (250 patients) may be crucial, since they confirm experimental data that recovery of ischemic myocardium cannot be achieved after 4 hr of coronary occlusion.[53]

Schwartz et al.[46] clearly demonstrated no benefit from late reperfusion (4 hr), which is in agreement with all animal experiments.[54, 55] They,[46] Anderson et al.[16] and we agree in demonstrating streptokinase to have a major beneficial effect on the left ventricular function provided it is given within 4 hr after onset of symptoms.

The magnitude of change in regional function in the infarct zone was also significantly influenced by the time elapsed between the onset of chest pain and the actual recanalization. Patients with an infarct-related vessel recanalized within 3 hr had significantly greater improvement than patients treated later. The regional contribution to ejection fraction of the infarct zone improved by at least 1.5% in patients treated within 3 hr with either anterior or inferior infarction. As recent-

ly demonstrated by Mathey et al.,[56] thrombolysis should be administered within 2 hr after the onset of symptoms to obtain maximal recovery of ventricular function. Improvement of left ventricular function was related to the same factors as limitation of enzymatic infarct size. However, the clinical implication of an improvement in global ejection fraction was greater in patients with impaired left ventricular function than in patients with normal left ventricular function.[14] The most important clinical improvement was seen in patients with anterior infarction (46% vs 34%; p = .0001) and in patients with previous myocardial infarction (41% vs 34%; p = .09). The greatest improvement was found in patients with ST segment elevation of 12 mm or more, whereas in the subset of patients with less than 12 mm ST segment elevation and admitted 2 to 4 hr after the onset of symptoms, no improvement in global ejection fraction was seen.[41]

The inclusion of mechanical perforation and coronary angioplasty as part of the recanalization procedure and the introduction of intravenous administration of streptokinase in the second treatment arm before the cardiac catheterization provide another major difference with previously reported studies. Angioplasty was used in two of the five participating hospitals that had extensive experience with this procedure. It was carried out when residual obstruction was considered to be 60% or more after thrombolysis[26, 27] to prevent reocclusion. Patients so treated had a lower mortality and a lower incidence of reinfarction than patients treated successfully with streptokinase alone. Although these results may be biased by the selection of patients with lesions suitable for angioplasty and who were hemodynamically stable after thrombolysis, these findings are in agreement with earlier observations that the recovery of regional left ventricular function is greatest in patients with a minimal residual stenosis after the intervention.[57, 58] Experimental studies have also shown that restriction of flow during reperfusion results in relative underperfusion of, and continued ischemia in, the subendocardium.[59]

These results also indicate that reperfusion may need to be supplemented by additional revascularization procedures such as angioplasty to optimize the chances of obtaining full functional recovery. Its beneficial effects evident in this large series of patients studied over an extended period might help to explain the observed reduction (from 16% to 9%) in 1 year mortality.[31, 60]

Clinical course and follow-up. Survival was improved significantly by early thrombolysis. Three month mortality was high in patients admitted with Killip class III or IV at admission (64%), in patients with high ST segment elevation (16%), in patients with previous myocardial infarction (41%), and in patients with anterior infarction (18%) who were allocated to conventional treatment.[41] Clinically important reduction of early mortality was found only in these groups of patients. In the other subgroups early mortality was below 5% in the control group, so no important reduction of early mortality could be expected. 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 the Western Washington Trial,[61] although these authors did not find differences in infarct size or left ventricular function.[17]

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.[60] Since reinfarction occurred in some of the patients in spite of adequate anticoagulation or after successful 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.[62]

Prognostic implications. The Multicenter Postinfarction Research Group[63] reported better 1 year survival after myocardial infarction in patients with higher global ejection fraction, independent of the extent of coronary disease. Similar data were found in a follow-up study of 449 hospital survivors at the Thoraxcenter (personal communication, P. Fioretti). When the results of these studies are pooled, a curvilinear relationship between the one year mortality rate and global ejection fraction can be constructed (figure 8). When the currently observed improvement of left ventricular ejection fraction from 47% in controls (estimated probability of cardiac death 0.050) vs 53% in patients allocated to thrombolysis (estimated probability of cardiac death 0.037) is interpreted in this manner, the 1 year mortality should indeed be reduced by 24% after thrombolysis, a projection that corresponds to our observations. Thus the explanation for the reduced mortality must in the main be ascribed to the restoration of left ventricular function rather than by any other mechanism. 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 oth-

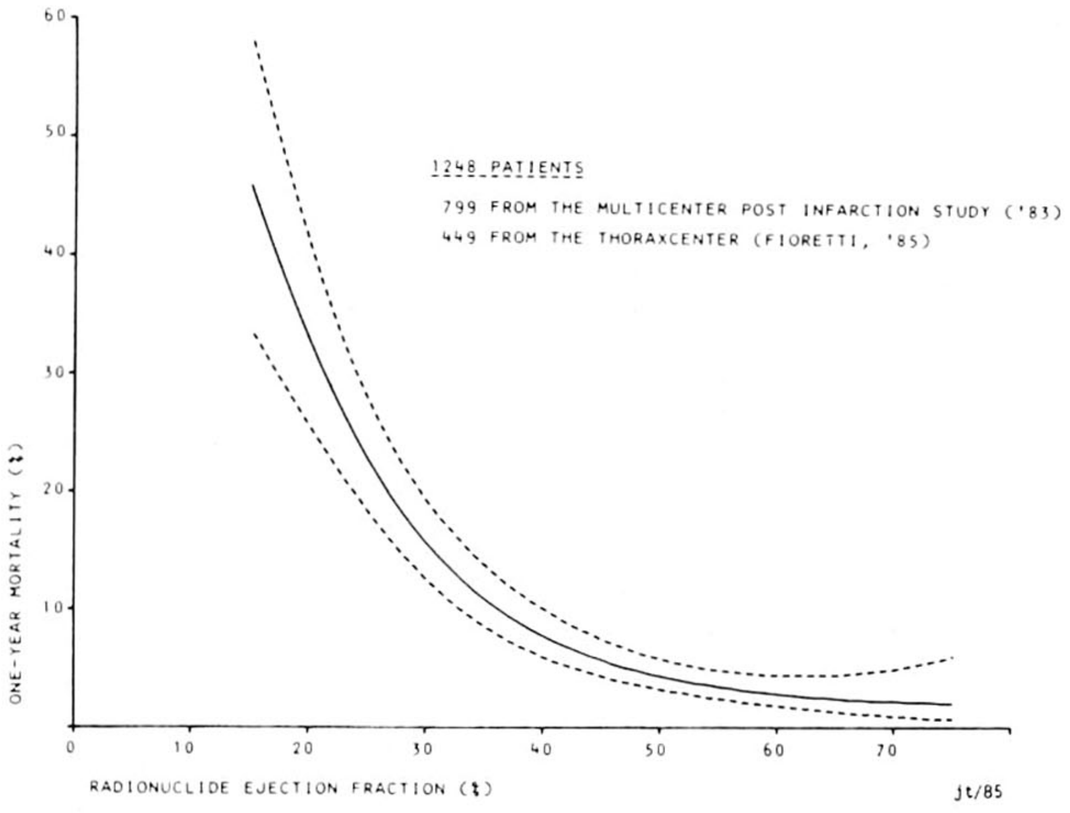

FIGURE 8. One year mortality as a function of radionuclide ejection fraction (%) measured at hospital discharge after acute myocardial infarction. Dotted lines represent the corresponding 95% confidence interval. The calculations are based on pooled data from the Multicenter Postinfarction Research Group[63] and the Thoraxcenter (personal communication; P. Fioretti, 1985). (Reproduced from ref. 14 with permission.)

er studies that were either too small[11, 15, 16, 19] or initiated treatment later after the onset of symptoms,[17, 18, 20] our data 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 assigned to early thrombolytic therapy and a reduction of early and late mortality. Future studies should investigate whether similar results can be obtained by intravenous infusion of newer thrombolytic drugs such as tissue-type plasminogen activator.[64–66]

Finally, strategies should be developed for early recognition of the symptoms of myocardial infarction by the patient and for immediate intervention, since myocardial salvage is attainable only if myocardial blood flow is restored within the first few hours of infarction.

Appendix

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