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COOPERATIVE STUDIES

Long-Term Benefit of Early Thrombolytic Therapy in Patients With Acute Myocardial Infarction: 5 Year Follow-Up of a Trial Conducted by the Interuniversity Cardiology Institute of the Netherlands

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Patients (n = 533) who participated in the Interuniversity Cardiology Institute of the Netherlands Trial were followed up for 3 to 7 years. The 5 year survival rate after thrombolytic therapy with intracoronary streptokinase was 81% (269 patients) compared with 71% after conventional therapy (264 patients). The greatest improvement in survival was observed in patients with anterior infarction (81% versus 64% with thrombolytic therapy or conventional therapy, respectively), in those with heart failure on admission or a previous infarction and in those with extensive myocardial ischemia on admission. Left ventricular ejection fraction at the time of hospital discharge was better after thrombolytic therapy. In the hospital survivors, long-term outcome was related to left ventricular function at the time of discharge and, to a lesser extent, to the underlying coronary artery disease. The initial therapy (thrombolysis or conventional) was not an independent additional determinant of long-term survival when left ventricular function and coronary status at the time of hospital discharge were taken into account. Thus, the salutary effects of thrombolytic therapy appear to be the result of myocardial salvage.

Reinfarction within 3 years was observed more frequently after thrombolytic therapy, particularly in patients with inferior wall infarction and those with ≥90% stenosis of the infarct-related vessel at discharge. Coronary bypass surgery and coronary angioplasty were performed more frequently after thrombolytic therapy than in conventionally treated patients. At 5 years, approximately 40% of patients in both groups had an uneventful course without reinfarction or additional revascularization procedures.

These observations demonstrate that the benefits of thrombolytic therapy are maintained throughout 5 years of follow-up. Treatment after hospital discharge of patients who underwent thrombolytic therapy on admission should not necessarily be different from conventional management after myocardial infarction.

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Early thrombolytic therapy with intracoronary streptokinase (1–3), intravenous streptokinase (4–6), anisoylated streptokinase-plasminogen complex (APSAC) (7) or recombinant tissue-type plasminogen activator (rt-PA) (8–10) improves early and 1 year survival rates in certain groups of patients with acute myocardial infarction. To verify whether the improved survival after thrombolytic therapy is maintained over time, survival status was assessed after 3 to 7 years in the 533 patients who were enrolled in the Interuniversity Cardiology Institute of the Netherlands Trial comparing treatment with intracoronary streptokinase and conventional therapy. Univariate and multivariate analyses were performed to determine which baseline characteristics were related to long-term survival. Furthermore, similar analyses were performed to identify those factors that determined long-term survival in patients who were discharged after thrombolysis or conventional therapy.

Methods

Patient recruitment. Between May 1981 and March 1985, a total of 533 patients were enrolled in a randomized trial comparing early thrombolytic therapy with intracoronary streptokinase (269 patients) and conventional treatment (264

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patients). Patients with electrocardiographic (ECG) evidence of myocardial infarction (1,2) who were admitted within 4 h of the onset of symptoms were included in the trial. Details of patient characteristics (1), angiography and other procedures (2,11) and ECG findings (12,13) have previously been reported. Briefly, patients in five participating hospitals were randomly allocated to conventional therapy or intracoronary streptokinase (250,000 U in 1 h). In 98 patients admitted after January 1984, angiography and intracoronary streptokinase were preceded by streptokinase (500,000 U) given intravenously. Angiography was not performed in 35 patients despite allocation to streptokinase therapy because of patient refusal, early death or technical reasons (1). Immediate coronary angioplasty was attempted as part of the reperfusion procedure in 46 patients (2).

Data analysis was based on initial treatment allocation. Coronary arteriography and left ventriculography were performed between 10 and 40 days after admission. Left ventricular ejection fraction could be measured and the status of the infarct-related vessel could be assessed in 422 patients. Angiographic data were not available in 44 patients who died, 37 patients who underwent coronary bypass surgery before discharge and 30 patients for various other reasons.

Follow-up. In May 1988, survival status was assessed in all patients through the municipal registries. In addition, cardiologists or general practitioners, or both, were contacted to obtain information on hospital admissions, reinfarction and revascularization procedures.

Statistical analysis. Survival curves for the different subgroups were obtained, as described by Kaplan and Meier (14). Cox's proportional hazard mode (15) was used to identify factors that were related to long-term survival or reinfarction. In a stepwise procedure, variables were included in the model if the probability (p) value for inclusion was <0.10. A variable was removed if the p value for removal was >0.15.

Two different models were developed. In the first model, the association between long-term survival and patient characteristics was analyzed, including the patient history, delay between onset of symptoms and hospital admission, baseline ECG, clinical state on admission and allocation to thrombolysis or conventional therapy. Forty-five patients were excluded from this analysis because the ST segment elevation in the baseline ECG could not be interpreted (12,13). A second model was developed to predict long-term survival in 422 hospital survivors in whom all information at the time of discharge (including the angiographic data) was available.

Results

Medication during follow-up. Three year follow-up data were complete in all except in two patients in whom the last available follow-up data were used. Medication used at different follow-up intervals is presented in Table 1. All patients were treated with heparin or coumarin until hospital discharge. Aspirin was not routinely prescribed after discharge. Prophylactic long-term beta-adrenergic blockade was advised, unless contraindicated. Nevertheless, only 20% of patients used a beta-blocker at 1 year. There were more patients without medication in the thrombolysis group, although this was not statistically significant.

Table 1. Medication at 1, 3 and 5 Year Follow-Up Study*

Medical Therapy (%)		Follow-up Year 1	3	5
Coumarin	C	16	16	16
	T	15	14	13
Platelet aggregation inhibitors	C	3	4	3
	T	7	5	6
Beta-blockers	C	21	18	17
	T	20	18	14
ACE inhibitors	C	1	2	4
	T	1	2	4
Digoxin	C	6	5	5
	T	5	4	3
Diuretic drugs	C	15	12	12
	T	11	10	12
None	C	7	9	10
	T	9	15	17

*The percent of patients using a given class of drugs is presented for 1, 3 and 5 year survivors allocated to conventional therapy (C) or thrombolysis (T). ACE = angiotensin-converting enzyme.

Survival (Fig. 1). Of the 269 patients allocated to thrombolytic therapy, 233 (87%) were alive at the 3 year follow-up study, while only 207 (79%) of the 264 patients given conventional therapy survived to 3 years. Estimated 5 year survival rates were 81 and 71%, respectively. Overall reduction in mortality during the 5 year follow-up period was 39%,

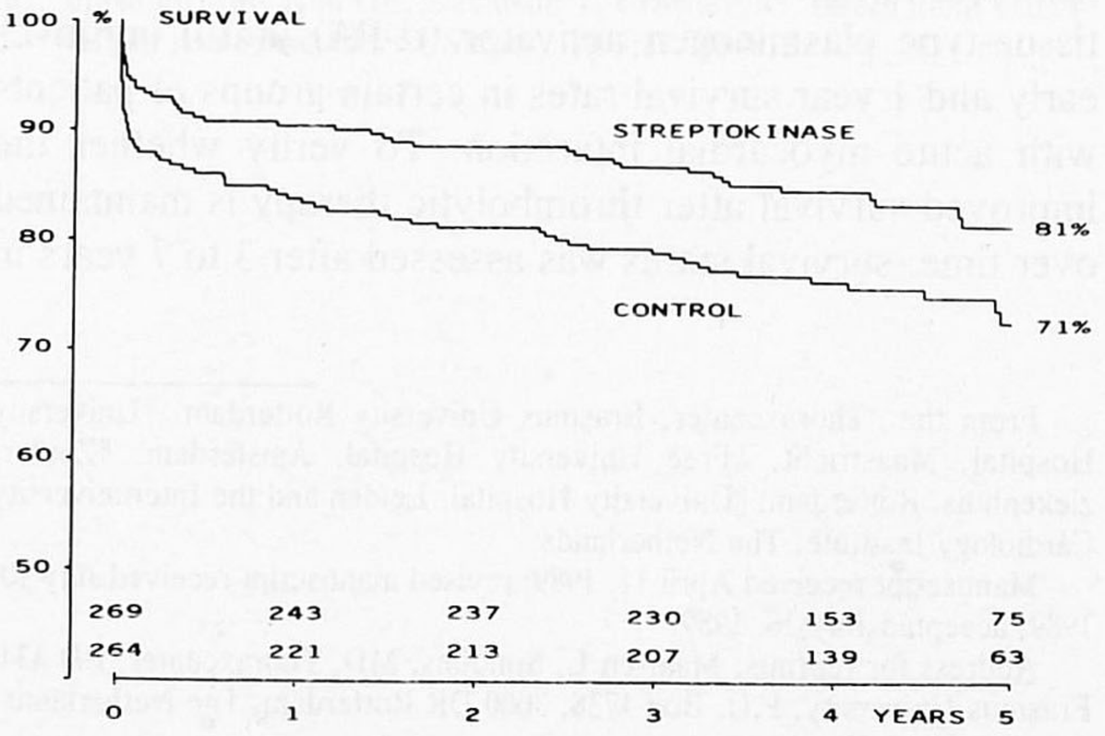

Figure 1. Survival analysis of all 533 patients allocated to intracoronary streptokinase or conventional therapy (control). Numbers denote patients at risk at the various intervals after treatment with streptokinase (**top**) or conventional therapy (**below**). Follow-up data were complete at 3 years.

Table 2. Factors Related to Survival After Conventional Therapy (C) or Intracoronary Streptokinase (T) in 533 Patients

		No.	Survival (%) at Follow-up Year* 1	3	5
All patients	C	264	84	79	71
	T	269	90	87	81
Infarct location (on admission ECG)					
Anterior	C	116	78	71	64
	T	130	89	85	81
Inferior	C	148	89	85	76
	T	130	91	88	82
Admission delay (h)					
<2	C	200	83	78	72
	T	192	91	89	79
2 to 4	C	64	84	79	67
	T	77	90	87	83
ST segment deviation (on admission) (mV)					
Σ ST <1.2	C	96	87	87	78
	T	116	92	92	86
Σ ST >1.2	C	147	82	75	65
	T	129	89	84	78
Subgroups of thrombolysis					
No ic therapy	T	35	86	83	75
ic SK only	T	112	88	86	83
iv + ic SK	T	76	92	85	–
ic SK + PTCA	T	46	96	94	78

*Three year follow-up data were complete; 5 year data were estimated by Cox regression analysis. Note that ST segment elevation could not be assessed in 45 patients, as described previously (13,14). In the lower part of the table, survival data are presented as related to the actual therapy administered in patients allocated to thrombolysis: patients who did not undergo intracoronary therapy (ic), patients with intracoronary therapy only, those in whom intracoronary therapy was preceded by intravenous streptokinase (iv SK) and patients who underwent immediate coronary angioplasty (PTCA) as part of the reperfusion strategy (1). Intravenous administration of streptokinase was started in 1984; thus, 5 year follow-up data are not available in this subgroup. ECG = electrocardiogram.

as estimated by Cox analysis (95% confidence interval 12 to 58%).

The difference between survival in the two treatment groups increased somewhat over time (Fig. 1). In fact, in those patients who were alive after 1 year, the 5 year survival rate was 87% after thrombolysis and 81% after conventional therapy. In patients with inferior infarction, a small but statistically nonsignificant difference in survival was maintained, favoring thrombolytic therapy (Table 2). Patients with anterior infarction particularly benefited from thrombolytic therapy, with 14% greater survival at 3 years and 17% at 5 years. The gain in 3 year survival with thrombolytic therapy appeared greater in patients treated within 2 h of the onset of symptoms and in patients with extensive myocardial ischemia (ST segment elevation >1.2 mV) on admission. At 5 years, these effects were less

Table 3. Prediction of 3 Year Survival From Baseline Characteristics in 488 Patients

	No. of Patients C	T	3 Year Survival (%) C	T	Regression Coefficient (Cox analysis)
Killip class					−1.52
1–2	232	235	81	88	
3–4	11	10	29	66	
Previous myocardial infarction					−1.02
No	189	200	83	91	
Yes	54	45	67	70	
Σ ST segment elevation (mV)					−0.61
<1.2	96	116	84	90	
>1.2	147	129	76	85	
Infarct location					−0.60
Inferior	138	129	84	89	
Anterior	105	116	73	85	
Treatment					−0.56
Conventional	243	–	79	–	
Thrombolysis	–	245	–	87	
Age (yr)					−0.45
<55	103	103	84	90	
>55	140	142	76	85	
Delay (h)					−0.33
<2	184	173	78	89	
2 to 4	59	72	79	87	

Abbreviations as in Table 1.

apparent, but these data are less reliable because of incomplete follow-up information. In patients allocated to thrombolytic therapy, the 3 year survival rate was 96% in 65 patients whose infarct-related artery was patent on immediate angiography. The survival rate was 89% in 133 patients whose artery opened during intracoronary administration of streptokinase with or without mechanical perforation of the occlusion. The lowest 3 year survival rate (67%) was found in 36 patients with a persistent occlusion despite the intervention.

As explained in "Methods," four different modes of therapy were actually administered to patients allocated to thrombolysis. The 3 year survival rate was lowest (83%) in 35 patients to whom intracoronary streptokinase was not given. There was no difference between patients treated with or without intravenous streptokinase before intracoronary thrombolysis (85 versus 86% 3 year survival, respectively). The highest 3 year survival rate (94%) was observed in 46 selected patients who underwent angioplasty as part of the reperfusion strategy.

The results of multivariate analysis (using the Cox model) of the effect of thrombolytic therapy on survival are presented in Table 3. The greatest gain in survival was achieved in patients with impaired left ventricular function (Killip

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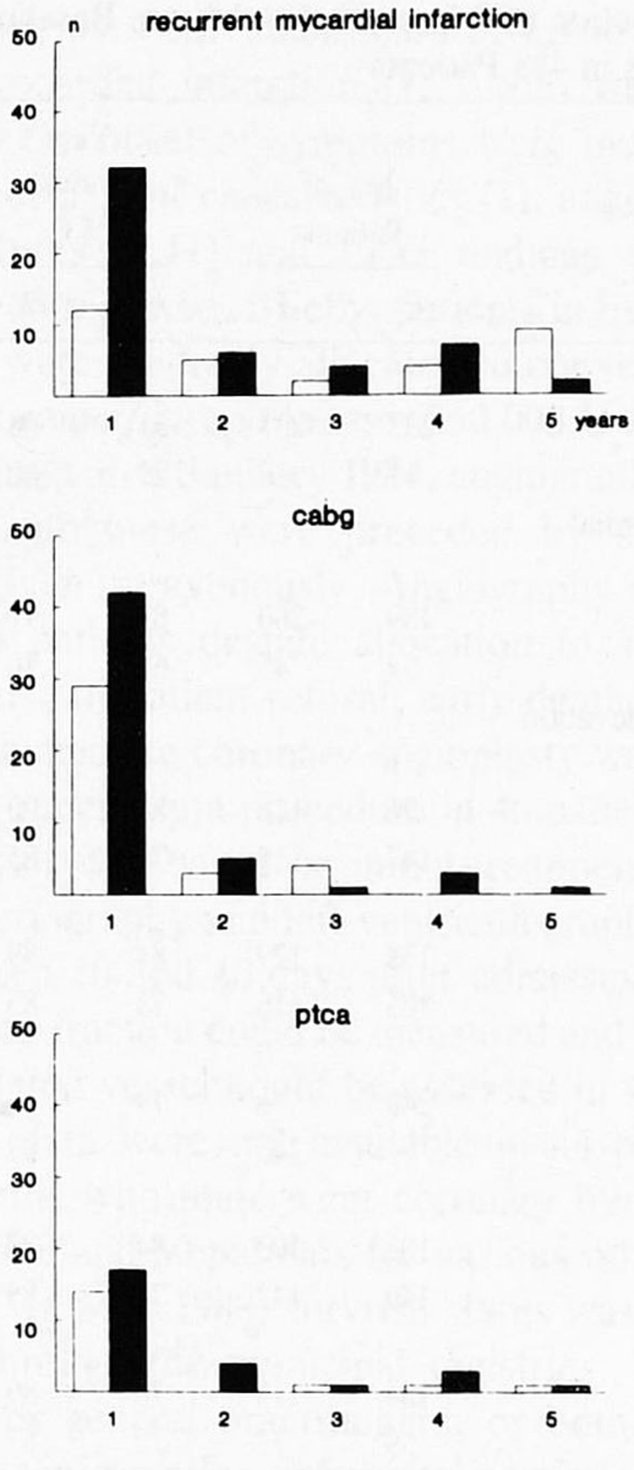


Figure 2. Distribution of new events during the follow-up period: recurrent myocardial infarction, coronary bypass surgery (cabg) and coronary angioplasty (ptca) at 1 year intervals. **Bars** indicate the number of events in each year. **Open bars** = conventional therapy; **solid bars** = streptokinase.

class 3 or 4 and previous infarction) and extensive anterior wall ischemia (ST segment elevation). Furthermore, age and the delay between symptom onset and hospital admission (and treatment) were predictors of late mortality.

Reinfarction (Fig. 2 and 3). Early reinfarction (within 1 year after admission) was more frequent after thrombolysis compared with conventional therapy (13 versus 5%) (Fig. 2), particularly in patients with inferior infarction (1). Few reinfarctions were reported in the subsequent 2 years, while the rate seemed to increase during years 4 and 5 in conventionally treated patients (Fig. 3). The total incidence of reinfarction after 5 years was the same in the two treatment groups. A predischarge exercise test was performed in 400 patients and showed angina or ST segment depression, or both, in 167. Recurrent infarction occurred in 30 (18%) of the 167 patients with ischemia during exercise and 50 (21%) of the 233 patients without ischemia. Also, the risk of the combined end point (reinfarction or death) was not enhanced in patients with ischemia during exercise compared with those without ischemia (26 versus 33%). These differences were not statistically significant.

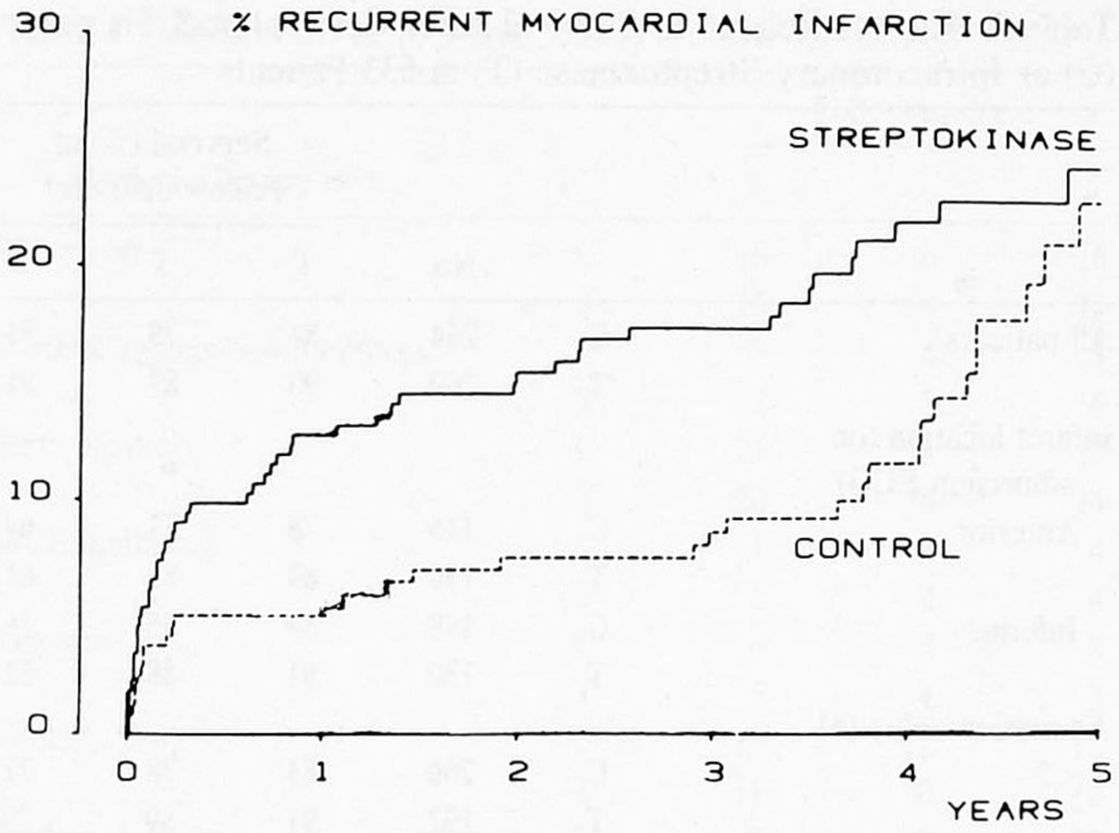


Figure 3. Cumulative rate (%) of first reinfarction observed in surviving patients with a 3 to 5 year follow-up period.

Revascularization procedures (Fig. 2). Coronary angioplasty and bypass surgery for postinfarction angina were more frequent in the first 3 years after thrombolytic therapy. A revascularization procedure was required in 35% of patients treated with thrombolytic therapy and in 27% treated with conventional therapy. In both groups, the event-free survival rate without reinfarction, angioplasty or bypass surgery was similar. More than half of the patients had an event-free 3 year survival and approximately 40% survived more than 5 years without reinfarction or an additional revascularization procedure.

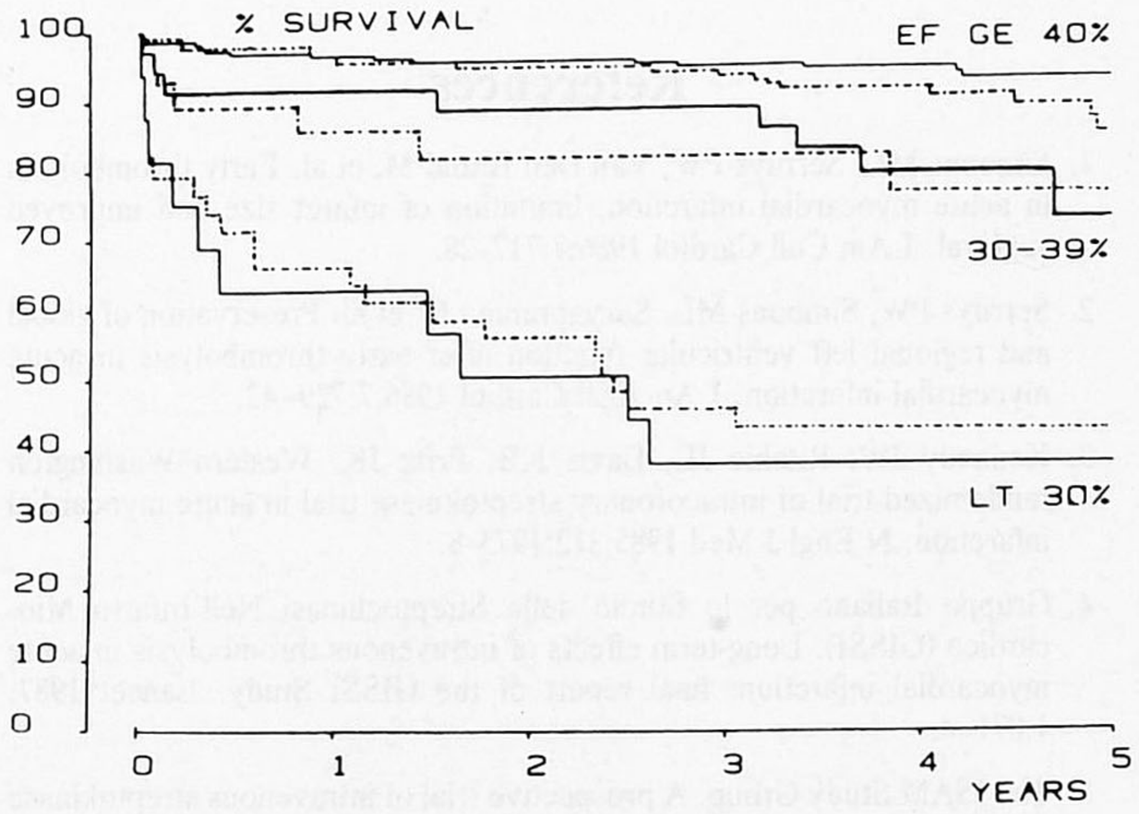
Predictors of survival and reinfarction (Table 4). To assess which factors determine long-term survival after thrombolytic therapy, data were analyzed in the 422 hospital survivors with complete angiographic data. Cox regression analysis revealed that left ventricular ejection fraction between days 10 and 40 was the best predictor of long-term survival in both patient groups. Other predictors were the severity of the stenosis of the infarct-related coronary artery and either the extent of coronary disease or age and a history of previous infarction. It should be noted that the original allocation to thrombolytic or conventional therapy carried no predictive value in addition to the factors mentioned. For example, the survival curves of patients in both groups with a similar left ventricular ejection fraction at angiography between days 10 and 40 virtually overlap (Fig. 4). Thus, the long-term benefit of thrombolytic therapy could be explained by the better left ventricular function and the lower number of patients with an occluded vessel. Patients who were discharged with preserved left ventricular function and no remaining stenosis >50% had a 95% chance of 5 year survival (Fig. 5). This group included 97 (23%) of the 422 patients with complete data. In contrast, the estimated 5 year survival rate was only 55% in 76 patients discharged with impaired ventricular function and either a severe resid-

Table 4. Observed (1 to 3 year) and Estimated (5 year) Survival Rates in 422 Patients With Angiography Between Days 10 and 40

Angiography		No.	Follow-up Year 1	3	5
Left ventricular ejection fraction (%)					
>40	C	145	96	94	86
	T	184	98	97	83
<40	C	49	87	72	57
	T	44	90	78	65
Infarct-related vessel stenosis (%)					
<90	C	55	97	93	80
	T	132	99	98	94
>90	C	139	92	86	78
	T	96	92	86	78
Vessels with stenosis >50%					
0 to 1	C	84	98	95	79
	T	124	99	98	92
2 to 3	C	110	91	83	77
	T	104	93	86	81
Age (yr)					
<55	C	88	95	91	83
	T	96	99	97	95
>55	C	106	93	87	76
	T	132	94	89	81
Previous infarction					
No	C	154	95	91	84
	T	184	98	96	92
Yes	C	40	88	78	62
	T	43	88	79	62

C = conventional therapy; T = thrombolysis.

Figure 4. Survival of patients with left ventricular ejection fraction (EF) ≥40% (GE), 30 to 39% and <30% (LT) as measured by contrast angiography between days 10 and 40. No difference was observed between patients treated with streptokinase (**continuous lines**) or conventional therapy (**dotted lines**) within a given range of ejection fraction.



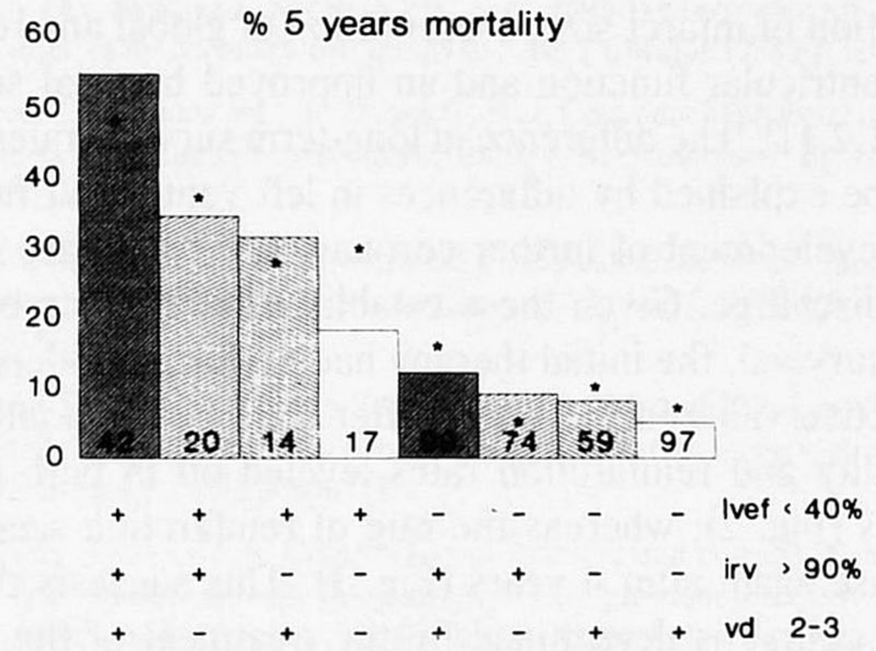


Figure 5. Prediction of the 5 year mortality rate (%) by Cox regression analysis based on left ventricular ejection fraction (lvef), the extent of coronary artery disease and the status of the infarct-related vessel (irv) (>90% stenosis) as assessed at hospital discharge. The **height of each bar** corresponds with the predicted mortality rate, and the **number in each bar** indicates the number of patients in that particular subgroup. The **asterisks** indicate the actually observed 5 year mortality rate in each subgroup. This analysis was performed in 422 patients with angiography between days 10 and 40. vd 2-3 = patients with double or triple vessel coronary artery disease.

ual stenosis of the infarct-related vessel or double or triple vessel narrowing, or both.

Predictors of reinfarction by multivariate analysis were initial therapy with streptokinase, inferior location of the infarction and a residual stenosis >90% in the infarct-related vessel. Predictors of the combined end point of death or reinfarction were left ventricular ejection fraction, ≥90% stenosis of the infarct-related vessel and a history of previous infarction.

Discussion

Role of thrombolytic therapy in long-term survival. The present data demonstrate, for the first time, the sustained benefits of thrombolytic therapy up to 5 years after randomization. Earlier reports were confined to a 1 year follow-up period (1,6,7) or to a comparison of so-called "successful" and "nonsuccessful" thrombolysis (16). The long-term follow-up data confirm our earlier report (13) that the gain in survival was greatest in patients with impaired left ventricular function on admission and a large anterior infarction treated early after the onset of symptoms. Nevertheless, thrombolytic therapy was also effective in patients with inferior wall infarction. The decision whether thrombolytic therapy is warranted in a given patient should be based on a cost-effect analysis of data from this and other studies (17,18).

There were no differences in the clinical features between the two treatment groups at hospital admission (1). Thrombolytic therapy with intracoronary streptokinase resulted in

limitation of infarct size, preservation of global and regional left ventricular function and an improved hospital survival rate (1,2,11). The difference in long-term survival rates could fully be explained by differences in left ventricular function and development of further coronary artery disease at hospital discharge. Given these established predictors of long-term survival, the initial therapy had no further independent predictive value for survival. After the initial 3 months, the mortality and reinfarction rates leveled off in both patient groups (Fig. 2), whereas the rate of reinfarction seemed to increase again after 4 years (Fig. 3). This suggests that the initial course is determined by the treatment of the infarction, while long-term prognosis is related to the further development of coronary artery disease.

Role of coronary thrombolysis and angioplasty. It should be appreciated that this trial was performed during a period when the methods for thrombolytic therapy developed rapidly. Accordingly, the actual therapy given to patients allocated to thrombolysis differed (Table 2). Nevertheless, the principle was maintained to compare a strategy of thrombolytic therapy with conventional management of myocardial infarction, and the data were analyzed according to the "intention to treat" principle. In a selected subgroup of patients, immediate coronary angioplasty was performed as part of the reperfusion strategy. These patients fared better than the other patients after thrombolytic therapy. To account for differences in baseline characteristics of patients with and without immediate angioplasty, a matched pair analysis was performed (19), which demonstrated no effect on infarct size or left ventricular function after angioplasty, although recurrent ischemic episodes and reinfarction were reduced. Recently, the effects of systemic immediate or early coronary angioplasty were analyzed in three studies (20–22). Systematic angioplasty 18 to 48 h after thrombolysis in patients with suitable anatomy did not improve the 1 year survival rate, as recently reported by the Thrombolysis in Myocardial Infarction (TIMI) investigators (20), whereas immediate angioplasty in all patients (21) and patients with suitable anatomy (22) had no benefit in terms of infarct size, left ventricular function or survival compared with thrombolytic therapy with rt-PA without mechanical intervention.

Indications for an additional revascularization procedure. The improved long-term survival after thrombolytic therapy may be related in part to more frequent bypass surgery and coronary angioplasty in these patients. These additional revascularization procedures were performed only in patients with angina or otherwise documented myocardial ischemia. One might speculate whether the long-term prognosis after thrombolytic therapy, as presented in this report, could be further improved by more extensive revascularization in a greater number of patients. The data in Figure 5 indicate a good prognosis in all patients with preserved left ventricular function and only a small (7%) difference in the 5 year survival rate among the patients in this group with and without residual coronary artery disease. Thus, it can be predicted that the benefits of additional interventions in these patients will only be small, particularly when the risks of angioplasty or bypass surgery are taken into account. The potential benefits of additional revascularization appeared greater in patients with impaired left ventricular function (Fig. 5). This is in agreement with earlier observations that elective coronary bypass surgery in patients with mild angina has little or no effect on survival (23), except in those patients with markedly impaired left ventricular function (24). Our present clinical practice is still to follow-up patients after myocardial infarction closely and to perform angioplasty or surgery in patients with signs of recurrent myocardial ischemia. The presented data indicate that this policy should be the same whether or not thrombolytic therapy has been given as initial therapy.

Medical therapy after thrombolysis. In the present study, medical treatment was similar after thrombolysis or conventional therapy (Table 1). Beta-blockers were prescribed in 20% of the patients at 1 year, and anticoagulants were given to those patients with a severely damaged ventricle or mitral incompetence. Aspirin or other platelet aggregation inhibitors were infrequently used. On the basis of recent information, it seems likely that systematic treatment with aspirin and beta-blockers would further reduce the incidence of early reinfarction (6,25) and thereby further improve long-term survival (26).

Conclusion. In all patient groups, a consistent reduction in the mortality rate was observed at the 5 year follow-up evaluation after thrombolytic therapy with intracoronary streptokinase. Because long-term outcome was related to left ventricular function and the extent of coronary artery disease on discharge, and not to the therapy given on admission, it seems likely that other thrombolytic regimens will have similar results. Thus, it can be expected that the improved early and 1 year survival rates obtained with intravenous streptokinase (4–6), APSAC (7) and rt-PA (8–10) will also be maintained at longer follow-up intervals.

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