European Heart Journal (1999) **20,** 819–826
Article No. euhj.1998.1443, available online at http://www.idealibrary.com on IDEAL®

Sustained benefit at 10–14 years follow-up after thrombolytic therapy in myocardial infarction

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Aims To investigate whether the benefit of thrombolytic therapy was sustained beyond the first decade. We report the 10–14 year outcome of 533 patients who were randomized to treatment with intracoronary streptokinase or to conventional therapy during the years 1980–1985.

Methods and Results Details of survival and cardiac events were obtained from the civil registry, from medical records or from the patient's physician. At follow-up, 158 (59%) of the 269 patients allocated to thrombolytic treatment and only 129 (49%) of the 264 conventionally treated patients were alive. The cumulative 1-, 5- and 10-year survival rates were 91%, 81% and 69% in patients treated with streptokinase and 84%, 71% and 59% in the control group, respectively ($P=0{\cdot}02$). Reinfarction during 10 years of follow-up was more frequent after thrombolytic therapy, particularly during the first year. Coronary bypass surgery and coronary angioplasty were more frequently performed after thrombolytic therapy. At 10 years approximately 30% of the patients were free from subsequent cardiac events.

Independent determinants of mortality were old age, indicators of impaired residual left ventricular function, multivessel disease and an inability to perform an exercise test at the time of hospital discharge.

Conclusion Improved survival after thrombolytic therapy is maintained beyond the first decade. Age, left ventricular function, multivessel disease and an inability to perform an exercise test were independent predictors for long-term mortality, as they are predictors for early mortality.
(Eur Heart J 1999; 20: 819–826)

Key Words: Myocardial infarction, thrombolysis, follow-up studies, risk factors, survival.

See page 785 for the Editorial comment on this article

Introduction

The introduction of reperfusion therapy has improved the outcome of patients with evolving myocardial infarction[1–9]. Hospital survival is improved, and this survival benefit is maintained during follow-up, reported up to 5 years after admission[10–14]. However, final assessment of the value of such therapy requires understanding of the true long-term effects, at least through the first decade. Such data are also required to analyse the cost effectiveness of this therapy[15]. The study organized by the Interuniversity Cardiology Institute of The Netherlands consistently showed improved coronary patency, limitation of infarct size, preservation of myocardial function and improved 5-year survival after reperfusion therapy with intracoronary streptokinase and, in some patients, immediate percutaneous transluminal coronary angioplasty[10]. In this 10–14-year follow-up report the long-term effects of reperfusion therapy are described. Patient characteristics associated with survival and mortality are reported. The data confirm that the salutary effects of early reperfusion therapy are maintained for at least a decade, and that the assumptions in previous cost–effect analyses were indeed valid[15].

Methods

From May 1981 to March 1985, 533 patients in five participating hospitals were randomized to treatment with intracoronary streptokinase (n=269) or to conventional therapy (n=264). The study design, patient characteristics and initial results have been reported

Revision submitted 8 December 1998, and accepted 9 December 1998.

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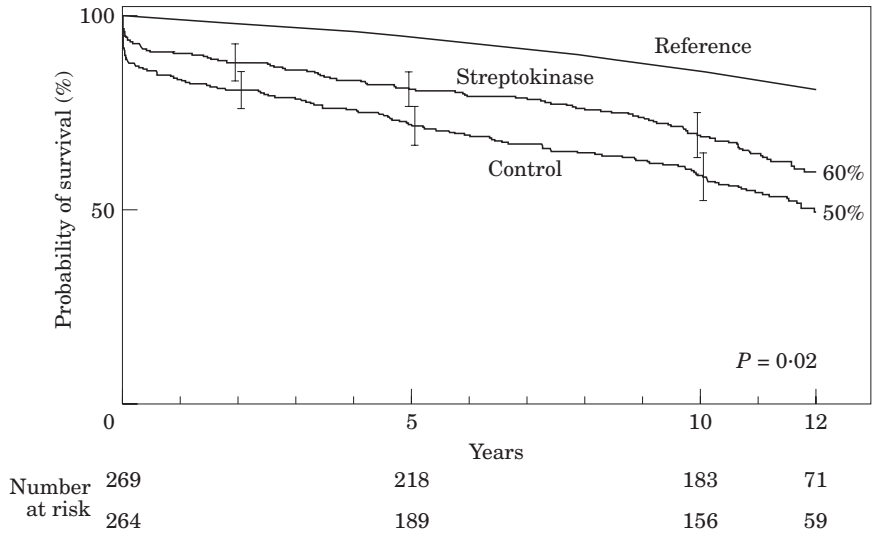

Figure 1 **Kaplan–Meier cumulative curves: comparison of reference Dutch population (matched on age 55 years and gender); 269 patients treated with streptokinase and 264 conventionally treated patients. The number of patients at risk during various follow-up intervals is presented under the x-axis. Vertical lines represent the 95% confidence intervals.**

previously[2,16,17]. Ninety-eight patients received intravenous streptokinase (250 000 U in 1 h) preceding angiography followed by treatment with intracoronary streptokinase. Forty-six patients underwent immediate coronary angioplasty after thrombolytic therapy. Data analysis was performed according to the 'intention to treat' principle.

Data collection and follow-up

Survival status was assessed from written replies to inquiries to the Municipal Civil Registration Service. Follow-up data concerning hospital admissions, recurrent myocardial infarctions and revascularization procedures were obtained by review of hospital records and from general practitioners. The definition of recurrent myocardial infarction was based upon the diagnosis of the treating physician. Some patients were contacted by telephone. Their information concerning hospital admissions was checked at the hospital involved.

Assessment of survival status was 99% complete. Median follow-up time from randomization was 12 years (range 3–14 years). In four patients who had moved abroad, survival status could not be retrieved and the last available follow-up data were used, obtained at 3–6 years (two patients allocated to reperfusion therapy and two to conventional therapy).

Survival analysis

Cumulative reinfarction and mortality rates for the two treatment groups were calculated according to the Kaplan–Meier method. The logrank test was used to compare survival and event-free survival among different patient groups. Using age- and gender-specific mortality data from The Netherlands in 1983, the expected survival in a reference population was calculated and compared with the survival in patients after myocardial infarction, with and without streptokinase therapy. Mortality risks were weighted according to the sex distribution of the trial population. The standardized mortality ratio, representing the observed mortality/expected mortality, was calculated for the two treatment groups. The loss in life expectancy was computed from conventional therapy compared with the reference population and the gain in life expectancy of early thrombolytic therapy[18].

Statistical analysis

Continuous variables were compared by Student's t-test and categorical variables by chi-squared tests. Patient characteristics were grouped into four categories. Clinical variables represented in the first category (I) were: age, sex, previous myocardial infarction, infarction site, Killip class at admission, time from symptom onset to treatment allocation, sum of ST elevation at admission, atrial fibrillation and ventricular fibrillation/flutter. In the second category (II) infarct size, as assessed from cardiac enzyme release, was added to the first category of clinical variables and in the third model (III) the (in)ability to exercise was added. The fourth category (IV) contained variables derived from coronary angiography and left ventriculography as well as variables from the previous categories: these additional variables

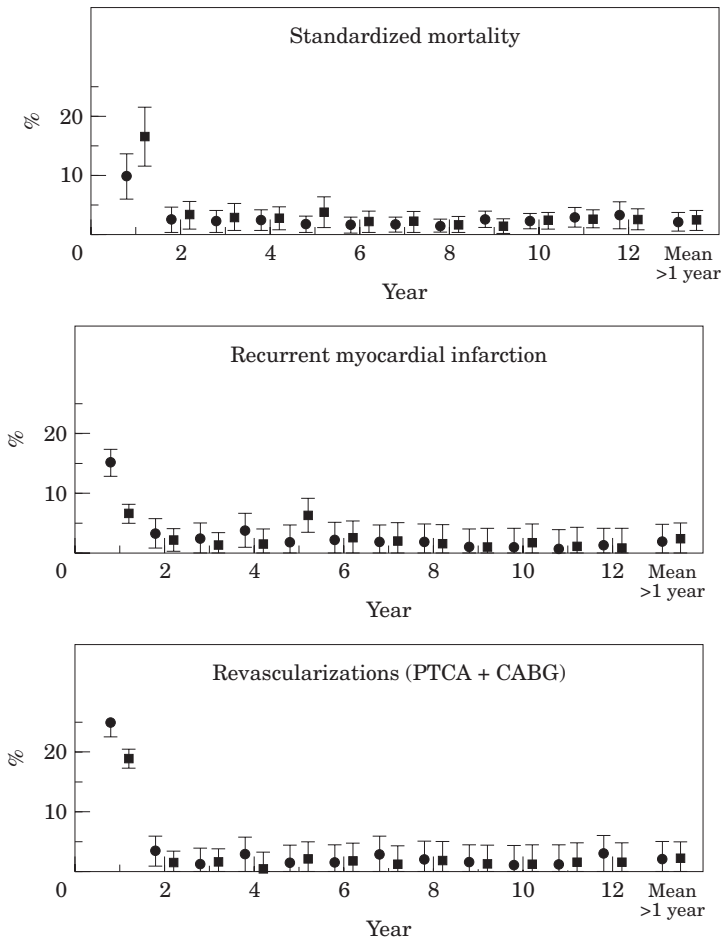

Figure 2 **Annual standardized mortality ratio: ratio of the observed mortality and expected mortality of age and gender matched subgroups of the reference Dutch population with 95% confidence intervals in patients treated with streptokinase (●) and patients treated with conventional therapy (■). Recurrent myocardial infarction rates and revascularization rates, corrected for the patients at risk during follow-up.**

were the extent and severity of coronary artery disease and left ventricular ejection fraction as measured by contrast angiography or by radionuclide angiography. The Cox proportional hazards model was used to identify independent risk factors for mortality and their relative risk estimates.

Results

A total of 533 patients were enrolled in this study. Baseline characteristics have been described in detail elsewhere[9]. The mean age was 56 years (range 28–71 years), 18% were female, 22% had a previous infarction and 46% were admitted with an anterior infarction. At final follow-up, 158 (60%) of the 269 patients allocated to thrombolytic treatment were alive and only 129 (50%) of the 264 patients with conventional therapy. The cumulative 1-, 5- and 10-year survival rates were 91%, 81% and 69% in patients treated with streptokinase and 84%, 71% and 59% in the control group, respectively. The gain in survival by early reperfusion therapy was highly significant ($P=0{\cdot}02$) by logrank analysis. The corresponding expected survival of the reference population was 99%, 95% and 86%, respectively (Fig. 1). The loss of life-years for myocardial infarction can be computed as the area between the survival curve of patients receiving conventional therapy and the reference population. The loss corresponded to 28 months at 12 years of follow-up. Extrapolating this would amount to a loss in life expectancy of 65 months. By using early reperfusion therapy 32% of the loss in average life expectancy was regained. In patients allocated to reperfusion therapy, the loss at 12 years follow-up was 17 months and the loss in life expectancy 44 months. The standardized mortality ratios up to 10 years of follow-up are shown in Fig. 2. The mean standardized mortality in years 2–10 was 2·1% in

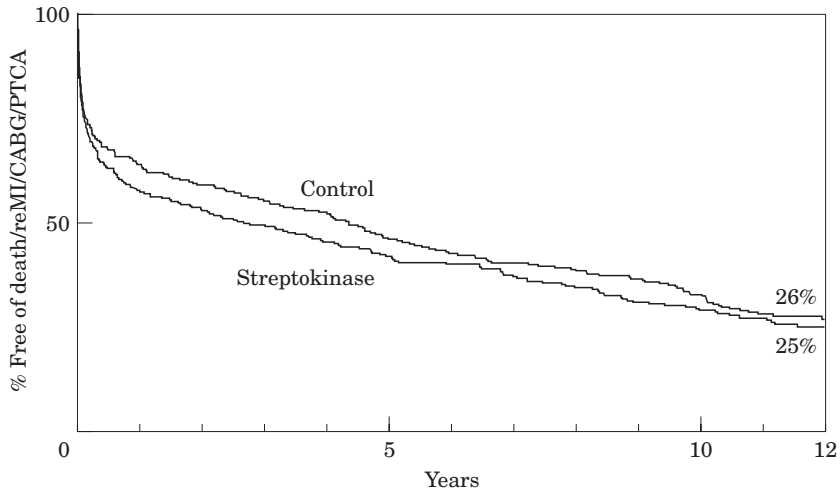

Figure 3 **Ten-year freedom from death, recurrent myocardial infarction, coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA) in 269 patients treated with streptokinase and 264 conventionally treated patients.**

patients allocated to streptokinase and 2·4% in patients receiving conventional therapy. This difference is not statistically significant.

Reinfarction

Recurrent infarction occurred more frequently in patients who received thrombolytic treatment than in conventionally treated patients ($P=0·03$). In particular, early reinfarction, within the first year, was more frequent after reperfusion therapy, while subsequent reinfarction rates, after the first year, were low in both groups, averaging 2% per year (Fig. 2). Eighty-six (32%) patients treated with streptokinase had at least one recurrent myocardial infarction at a mean follow-up time of 3·5 years; 39 of these patients had a first reinfarction within 1 year after randomization. Fifteen patients had a second reinfarction, which was followed by a third reinfarction in three patients and a forth and fifth in one patient. Of the conventionally treated patients, 62 (23%) had a recurrent myocardial infarction after a mean of 3·5 years, of which 16 occurred within the first year. A second reinfarction was reported in nine patients and was followed by a third reinfarction in two patients.

Revascularization

Forty-three (16%) of the patients treated with streptokinase underwent coronary angioplasty and 77 (29%) underwent coronary bypass surgery. In conventionally treated patients the intervention rate was lower ($P<0·001$): only 26 patients (10%) underwent coronary angioplasty and 55 patients (21%) coronary bypass surgery. Revascularization procedures were performed predominantly in the first year; after the first year these were infrequent and not statistically significant between treatment groups, averaging 1·9% and 1·5% per year (Fig. 2).

Event free survival

At 1 year, freedom from death, recurrent myocardial infarction, bypass surgery and angioplasty was 57% in patients treated with streptokinase and 64% in conventionally treated patients. Freedom from cardiac events was 42% and 46% at 5 years and 29% and 32% at 10 years, respectively (Fig. 3). The probability of a difference from the control group was not significant.

Risk assessment

Univariable predictors for increased mortality were: the clinical parameters, age ($\geq$55 years), Killip class III or IV, extensive infarction identified by total ST elevation of more than 1·2 mV on the admission ECG; parameters representing residual left ventricular function, enzymatic infarct size, the inability to perform an exercise test and an ejection fraction of less than 40%; and parameters reflecting the extent of coronary artery disease, previous myocardial infarction and the presence of multivessel disease (Table 1). After multivariable analysis of clinical admission data (model I), five parameters were retained: Killip class III or IV, age ($\geq$55 years), total ST elevation >1·2 mV, previous infarction and an anterior infarction location. When all data available at discharge were added in the multivariable model, age ($\geq$55 years) was retained as a clinical predictor, together with parameters representing left ventricular function and extent of coronary disease. Cumulative survival in patients with

Table 1 Univariable analysis of predictors for long-term outcome

Variable	Placebo	Streptokinase	Overall	Relative risk	95% Confidence interval
Clinical data					
Age, year					
<55	47/112	30/111	77/223		
>55	85/150	79/156	164/306	1·55	1·26–1·91
Gender					
Male	110/220	88/215	198/435		
Female	22/42	21/52	43/94	1·00	0·78–1·27
Previous MI					
No	96/202	78/211	174/413		
Yes	36/60	31/56	67/116	1·37	1·13–1·66
ST-elevation					
>1·2 mV	42/95	35/114	77/209		
<1·2 mV	76/146	64/129	140/275	1·38	1·12–1·71
Killip class III/IV					
No	124/251	100/254	224/505		
Yes	8/11	9/12	17/23	1·67	1·28–2·17
Anterior MI					
No	66/147	53/139	119/286		
Yes	66/115	56/128	112/243	1·21	1·00–1·45
VT/VF					
No	77/158	51/147	128/305		
Yes	55/104	58/120	113/224	1·20	1·00–1·45
Hx of angina					
No	93/188	75/198	168/386		
Yes	39/74	34/69	73/143	1·17	0·96–1·43
Systolic BP					
>90 mmHg	127/252	98/252	225/504		
<90 mmHg	5/10	11/15	16/25	1·43	1·05–1·95
Atrial fibrillation					
No	123/242	99/249	222/491		
Yes	9/20	10/18	19/38	1·11	0·79–1·54
Time to treatment					
<2 h	98/199	77/191	175/390		
>2 h	34/63	32/76	66/139	0·95	0·77–1·16
Treatment					
CT	132/262		132/262		
Sk i.v.		17/37	17/37	0·91	0·63–1·32
Sk i.c.		42/104	42/104	0·80	0·62–1·05
Sk i.v.+i.c.		33/81	33/81	0·81	0·61–1·08
Sk i.c.+PTCA		17/46	17/46	0·73	0·49–1·09
Enzymes					
Infarct size (HBDH)					
<1100	47/115	52/158	99/273		
>1100	53/101	39/70	92/171	1·48	1·20–1·83
Exercise results					
Inability XECG					
No	82/193	66/197	148/390		
Yes	50/68	42/69	92/137	1·77	1·49–2·10
Angiography					
Vessel disease					
Single	28/83	35/129	63/212		
Multi-	61/113	50/104	111/217	1·72	1·35–2·20
Stenosis IRV					
<90%	31/60	44/139	75/199		
>90%	60/143	50/107	110/250	1·17	0·93–1·47
LVEF					
>40%	64/163	57/198	121/361		
<40%	47/77	43/56	90/133	2·02	1·67–2·44

CT=conventional treatment; MI=myocardial infarction; VTVF=ventricular fibrillation/flutter; BP=blood pressure; IV=intravenous; IC=intracoronary; IRV=infarct related vessel; LVEF=left ventricular ejection fraction; XECG=exercise test.

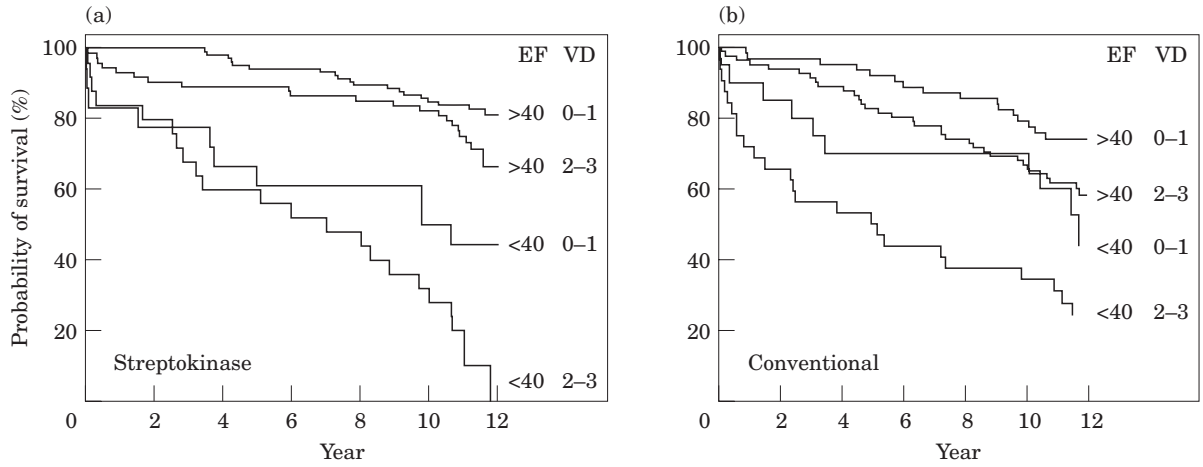

Figure 4 **Survival curves after hospital discharge stratified for patients with left ventricular ejection fraction (EF) of 40% or greater or below 40% combined with none or one diseased vessel versus more than one diseased vessel (coronary artery disease 0 to 1 or 2–3). No differences were found between patients treated with streptokinase (a) and conventionally treated patients (b).**

multivessel disease and impaired left ventricular function at 1, 5 and 10 year intervals was only 77%, 54% and 33%, respectively, as compared with 99%, 94% and 83% in patients with single vessel coronary artery disease and a well-preserved left ventricle (Fig. 4). Allocation to streptokinase was a predictor of survival at the time of hospital admission (model I). However, this was no longer apparent when estimates of residual left ventricular function of discharge were included in the analysis (models II, III, IV) (Table 2). This supports the concepts that early reperfusion therapy salvages myocardial tissue which contributes to subsequent survival.

Discussion

Since 1985 a few key papers have shown persistent benefit of fibrinolytic therapy[1–9]. As a result, the use of such treatment has increased rapidly. The results described in the present study show that improved survival in patients treated with early thrombolytic therapy is maintained beyond the first decade. The difference in survival, favouring thrombolytic therapy, was 6% at hospital discharge, 10% at 1 year and remained at 10% at 10 years of follow-up. Mortality was high in the first year, particularly in the control group, but subsequently the annual standardized mortality ratio remained stable over the years and did not differ significantly between groups. This is in agreement with reports from other series[11–14], which also show sustained, unchanged benefit during long-term follow-up. An important finding is that the absolute difference in survival of 10% observed at 1 year is maintained throughout 10 years, which means a relative improvement of survival in the thrombolytic group. Our analysis shows that an annual mortality rate of about 2·6–3·3% can be anticipated in patients surviving their first myocardial infarction for 1 year. This annual mortality rate continues to be about twice as high as the reference population throughout 10 years, which is in agreement with another study[19].

When the parameters of infarct size or residual left ventricular function were included in the model, multivariate analysis did not indicate any contribution of thrombolytic therapy. This supports the notion that survival benefit is established within the initial period through myocardial salvage and preservation of left ventricular function. The proposed mechanism of improved survival after thrombolytic therapy, through salvation of myocardial tissue and preservation of left ventricular function, implies that factors determining early survival will also influence long-term survival. Indeed, besides age, left ventricular ejection fraction at the time of discharge and the extent of coronary artery disease appeared to be the main predictive variables influencing short- and long-term mortality.

Two phases can be distinguished in the clinical course of the patients in this study. During the first year events are frequent and include reinfarction (15% streptokinase and 6% in controls) and revascularization procedures (21% and 16% respectively). The course stabilizes after the first year with mortality rates of about 3%, reinfarction rates of 3% and revascularization rates of 3%, which were not different among the two treatment groups. The continued instability during the first months after myocardial infarction is in agreement with a recent report indicating rapid progression of coronary artery lesions at different sites shortly after infarction[20]. This is compatible with the suggestion that, at least in some patients, an infectious component may lead to or facilitate a period of instability in patients with coronary artery disease[21,22].

In the present study, between 1981 and 1985, revascularization procedures were performed in patients with repetitive recurrent ischaemia after the initial infarct. A

Table 2 Multivariate analysis and relative risks

Model	I	II	III	IV
Clinical data	+	+	+	+
Infarct size		+	+	+
Inability XECG			+	+
Angiogram				+
Age (years)				
<55 (42·1%)				
>55 (57·9%)	1·90 (1·43–2·55)	1·82 (1·32–2·50)	1·79 (1·29–2·48)	1·62 (1·13–2·33)
Hx infarction				
No (79·5%)				
Yes (20·5%)	1·66 (1·22–2·26)	1·65 (1·15–2·36)		
Anterior infarction				
No (54·8%)				
Yes (45·2%)	1·44 (1·10–1·89)			
Killip class III/IV				
No (95·7%)				
Yes (4·3%)	2·44 (1·43–4·17)			
ST-elevation (mV)				
<1·2 (43·2%)				
>1·2 (56·8%)	1·70 (1·28–2·27)	1·43 (1·04–1·97)	1·43 (1·03–1·97)	
Infarct size				
<1100 (60·5%)				
>1100 (39·5%)		1·83 (1·34–2·50)	1·67 (1·23–2·28)	
Inability XECG				
No (75·3%)				
Yes (24·7%)			2·28 (1·63–3·18)	1·83 (1·24–2·70)
LVEF				
>40 (73·6%)				
<40 (26·4%)				2·94 (2·10–4·13)
Vessel disease				
Single (50·6%)				
Multi- (49·4%)				1·57 (1·11–2·22)
Treatment				
CT (49·8%)				
SK (50·2%)	0·76 (0·58–1·00)	0·99 (0·73–1·34)	0·96 (0·70–1·30)	1·04 (0·74–1·46)

XECG = exercise test; Hx = history; LVEF = left ventricular ejection; CT = conventional (treatment); SK = streptokinase (treatment).
Treatment was forced into the models; 95% confidence intervals for the models are represented between brackets.

recent study[23] has shown that extensive use of revascularization procedures in patients with symptomatic or silent post-infarct ischaemia, may reduce the incidence of early infarction. Thus, a more aggressive intervention regimen might help to avoid part of the excess reinfarction that was observed in the first year after reperfusion therapy.

In the study period, as mentioned above, patients were treated predominantly with aspirin or coumadin and with beta-blockers (37%) after myocardial infarction. More recently, it has been shown that systematic treatment with cholesterol-lowering HMG-CoA reductase inhibitors[24–26] and treatment with ACE inhibitors[27,28] reduce the incidence of reinfarction. Thus, an improved prognosis with lower myocardial reinfarction rate and lower subsequent mortality may be expected using modern multidrug regimens.

Since prognosis in patients in the current study was related predominantly to the left ventricular function and extent of coronary artery disease, at the time of discharge, the same approach for medical and revascularization therapy should be followed for patients who did and those who did not initially receive reperfusion therapy.

Limitations

The treatment that was given for acute myocardial infarction between 1980 and 1985 is no longer current. Intra-coronary streptokinase is no longer given and the dose of intravenous streptokinase is now different from that used in those earlier years. This is inevitable when reporting long-term survival and event-free survival results as treatment evolves with the passage of time. Nevertheless, our main point that re-establishment of coronary patency improves survival, is not invalidated.

Conclusion

This study has provided unique data about the long-term outcome after thrombolytic treatment. For the first time, improved survival after thrombolytic therapy has been shown to be maintained beyond a decade. Predictors for early and late mortality were the same. Long-term outcome was related to age, parameters of left ventricular function and to the extent of coronary artery disease.

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