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Cost benefit analysis of early thrombolytic treatment with intracoronary streptokinase

Twelve month follow up report of the randomised multicentre trial conducted by the Interuniversity Cardiology Institute of The Netherlands

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SUMMARY The costs and benefits of early thrombolytic treatment with intracoronary streptokinase in acute myocardial infarction were compared in a randomised trial. All hospital admissions were recorded and the functional class was assessed at visits to the outpatient clinic during a 12 month follow up of 269 patients allocated to thrombolytic treatment and of 264 allocated to conventional treatment. Mean survival during the first year was calculated for patients with inferior and with anterior infarction and adjusted for impaired quality of life in cases where there were symptoms or hospital admission. In patients with inferior infarction mean survival was 337 days (out of a total follow up of 365 days) for patients allocated to thrombolytic treatment and 327 days for controls. Quality adjusted survival was seven days longer in the thrombolysis group (307 *vs* 300 days in controls). In patients with anterior infarction mean survival was significantly longer (35 days) in the thrombolysis group than in the control group as was quality adjusted survival (38 days) (304 *vs* 266 days in controls). The gain in life expectancy with thrombolytic treatment was 0·7 years for patients with inferior infarction, 2·4 years for patients with anterior infarction, and 3·6 years for the subset of patients with large anterior infarction who were admitted within two hours of the onset of symptoms. The costs of medical treatment, including medication, hospital stay, cardiac catheterisation, coronary angioplasty, and bypass surgery, in the first year follow up were higher in patients allocated to thrombolytic treatment (an additional cost of Dfl 7000 in inferior and Dfl 9000 in anterior infarction (£1 ≃ Dfl 3·3)) than in conventionally treated patients. The additional costs per year of life gained were Dfl 10 000 in inferior infarction, Dfl 3 800 in anterior infarction, and only Dfl 1 900 in patients with large anterior infarction admitted within two hours of onset of symptoms.

Intracoronary thrombolysis can be recommended as a cost effective treatment in patients with extensive anteroseptal infarction.

In the randomised trial conducted by the Netherlands Interuniversity Cardiology Institute, patency of the infarct related coronary artery was achieved in 85% of the patients treated with intracoronary streptokinase. This result was associated with limitation of enzymatic infarct size, improvement of global and regional left ventricular function, and improved survival.[1–6] Non-fatal reinfarction, however, occurred more frequently and percutaneous transluminal coronary angioplasty or coronary artery bypass grafting were required more

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often in patients allocated to thrombolytic treatment than in the control group.[1 2] The improved survival after early thrombolytic treatment on one hand and the higher incidence of non-fatal complications in these patients make it difficult to assess the true value of thrombolytic treatment in acute myocardial infarction. To obtain a complete picture of total mortality and morbidity the functional status of each patient was recorded at regular intervals during one year follow up. Also the total medical costs were recorded for each patient. From these data mean survival was calculated and adjusted for impaired quality of life when there were symptoms or hospital admission. The additional costs of thrombolytic treatment per year of life gained were also calculated.

Patients and methods

Five hundred and thirty three patients entered the trial as described in an earlier report.[1] Patients were eligible for the trial if they were admitted to one of the five participating coronary care units within four hours of the onset of chest pain with electrocardiographic signs that were typical of myocardial infarction. Two hundred and sixty four patients were allocated to conventional treatment and 269 to thrombolytic treatment. Of the latter patients, 152 were allocated to intracoronary streptokinase and 117 to intracoronary streptokinase preceded by intravenous streptokinase. Patients allocated to thrombolytic treatment were asked for their informed consent. Patients who refused consent or patients in whom thrombolytic treatment was withheld for other reasons received conventional treatment, but were included in the analysis on the basis of the intention to treat.[7] Acute coronary angiography was performed in 234 patients allocated to thrombolytic treatment. If the infarct related coronary artery appeared to be occluded, intracoronary streptokinase (usually 250 000 U) was given. In the second part of the study intravenous streptokinase (500 000 U) was given before angiography to reduce treatment delay. In 46 patients with severe residual stenosis of the infarct related coronary artery, coronary angioplasty was attempted as part of the recanalisation procedure. After catheterisation patients allocated to thrombolytic treatment had the same treatment protocol as the control group.[1] The location of the infarct was defined as anterior if there was ST segment elevation in leads V1 to V4 and as inferior if there was ST segment elevation in leads II, III, and aVF. When there was ST segment elevation in leads I, aVL, V5 and V6, the infarct was defined as anterior, unless ST segment elevation was also present in leads II, III, and aVF or ST segment depression was present in leads V1 to V4. In the latter case the infarct was defined as inferior. The ΣST on the electrocardiogram was defined for anterior infarcts as the sum of ST segment elevation in leads I, aVL, and V1 to V6 and that for inferior infarcts was defined as the sum of ST segment elevation in leads I, II, III, aVL, aVF, V5 and V6, and ST segment depression in leads V1 to V4.[6]

All patients were followed at the outpatient clinic for at least a year after admission. The following data were recorded:

(*a*) functional class (New York Heart Association) on the day of each visit to the outpatient clinic[8];

(*b*) all hospital admissions, including day of admission, day of discharge, and reason for admission;

(*c*) functional class before hospital admission and functional class at discharge; and

(*d*) day and cause of death and functional class before death (if a patient died).

From these data the functional state of each patient was defined every week as the lowest of mutually exclusive classifications: class I (New York Heart Association criteria), not in hospital; class II, not in hospital; class III, not in hospital; class IV, not in hospital; in hospital; or dead.

Functional class was assumed to have changed halfway between two subsequent visits to the outpatient clinic unless known otherwise. The mean number of days spent in each category was calculated for all patients. Mean survival was calculated for each group of patients as the mean time between admission to the study and death or the end of follow up (one year). Survival was adjusted for impaired quality of life according to the number of days spent in class II–IV or in hospital, as described in the results.[9] Life expectancy was estimated by the "DEALE" method.[10 11] The mortality rate was assumed to be 6% per year for patients alive at the end of follow up. Mean life expectancy was calculated for subsets of patients in both treatment groups as the interval from admission to the study to death for those who died during follow up and as 16·7 years (mean survival at a mortality rate of 6% per year) plus the duration of follow up for those who were alive at the end of follow up.

The costs of medical treatment the first year after acute myocardial infarction were calculated, taking into account the number of days in hospital, the increased costs for stay in a coronary care unit or surgical intensive care unit, costs of acute coronary angiography including thrombolytic treatment with or without coronary angioplasty, costs of elective coronary angiography, elective coronary angioplasty, bypass surgery, and medication as prescribed at discharge or at the outpatient clinic. The costs of medication were based on average dosages of antiarrhythmic drugs, platelet inhibitors, β blockers, cal-

Table 1 *Baseline and follow up data in a trial of intracoronary streptokinase*

	All patients			*Inferior MI*			*Anterior MI*		
	C	*T*	*p**	*C*	*T*	*p**	*C*	*T*	*p**
Number of patients	264	269		148	139		116	130	
Men	224	217		123	110		101	107	
Age (median)	56	57		57	58		55	56	
Previous myocardial infarction	60	56		31	28		29	28	
Median admission delay (min)	90	90		90	90		90	90	
Median cumulative HBDH release (U/l)	1100	770	0·0001	970	670	0·007	1280	840	0·005
Mean angiographic LVEF (day 10–40 (%))	47	53	0·0001	49	57	0·0001	43	50	0·002
Total one year mortality	43	26	0·03	17	12	0·4	26	14	0·01
Recurrent myocardial infarction	14	36	0·001	9	26	0·001	5	10	0·3

MI, myocardial infarction; C, control group; T, thrombolysis group; HBDH, α hydroxybutyrate dehydrogenase; LVEF, left ventricular ejection fraction. *Two tailed p values (Mann-Whitney's rank sum test or Fisher's exact text).

cium antagonists, digoxin, diuretics, nitrates, other vasodilators, and the costs of anticoagulation treatment including regular coagulation tests.

Differences between groups were tested by Fisher's exact test, Mann-Whitney's rank sum test, or Student's *t* test when appropriate. Two tailed p values are reported.

Results

One year follow up was complete in all 533 patients admitted to the trial, and the duration of follow up ranged from one to four years (mean two years). Baseline characteristics were distributed evenly between both treatment groups (table 1). Patients allocated to thrombolytic treatment showed a 30% limitation of infarct size estimated enzymatically (median hydroxybutyrate dehydrogenase release 770 U/l *vs* 1100 U/l in controls, p = 0·0001), higher left ventricular ejection fraction by contrast angiography (53% *vs* 47%, p = 0·0001), improved one year survival (90% *vs* 84%, p = 0·03), and a higher incidence of non-fatal reinfarction (13% *vs* 5%, p = 0·001). Mean hospital stay during the first year was similar in both treatment groups, although coronary angioplasty and bypass surgery were performed more frequently in the thrombolysis group (table 2).

Figure 1 shows the proportion of patients in each functional class at weekly intervals during one year follow up. The survival of patients allocated to thrombolytic treatment was greater than that of the control group as is evident by the larger area occupied by the survivors. The mean survival and average number of days spend in each category were calculated (table 3). In the thrombolysis group more days were spent without symptoms (232 *vs* 210 days in controls, p = 0·08), as illustrated by the larger area of class I after thrombolysis in fig 1. There were

Table 2 *Hospital admissions, hospital stay, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, and cardiac catheterisations in all patients, in patients with inferior and anterior infarction, and in the subgroup of patients with anterior infarction and extensive myocardial ischaemia admitted to the hospital within two hours of the onset of symptoms (see results)*

	All patients		*Inferior MI*		*Anterior MI*		*Anterior infarction ∑ ST ⩾ 1·2 mV admitted within 2 h*	
	C	*T*	*C*	*T*	*C*	*T*	*C*	*T*
Number of patients	264	269	148	139	116	130	50	45
Catheterisation + Sk		195		107		88		29
Catheterisation + Sk + PTCA		46		17		29		12
Elective catheterisation	205	199	120	99	85	100	35	38
Recurrent MI	14	36	9	26	5	10	2	4
Late PTCA	13	23	7	9	6	14	2	8
CABG	32	44	21	22	11	22	1	4
Other hospital admissions	74	75	41	39	33	36	18	16
Days in hospital (general ward)	4562	4500	2521	2310	2041	2190	791	689
Days in CCU	858	979	491	523	367	456	164	133
Days in surgical ICU	64	88	42	44	22	44	2	8

Sk, streptokinase; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; CCU, coronary care unit; ICU, intensive care unit; ∑ ST: total ST segment elevation on the electrocardiogram made at admission to the trial.

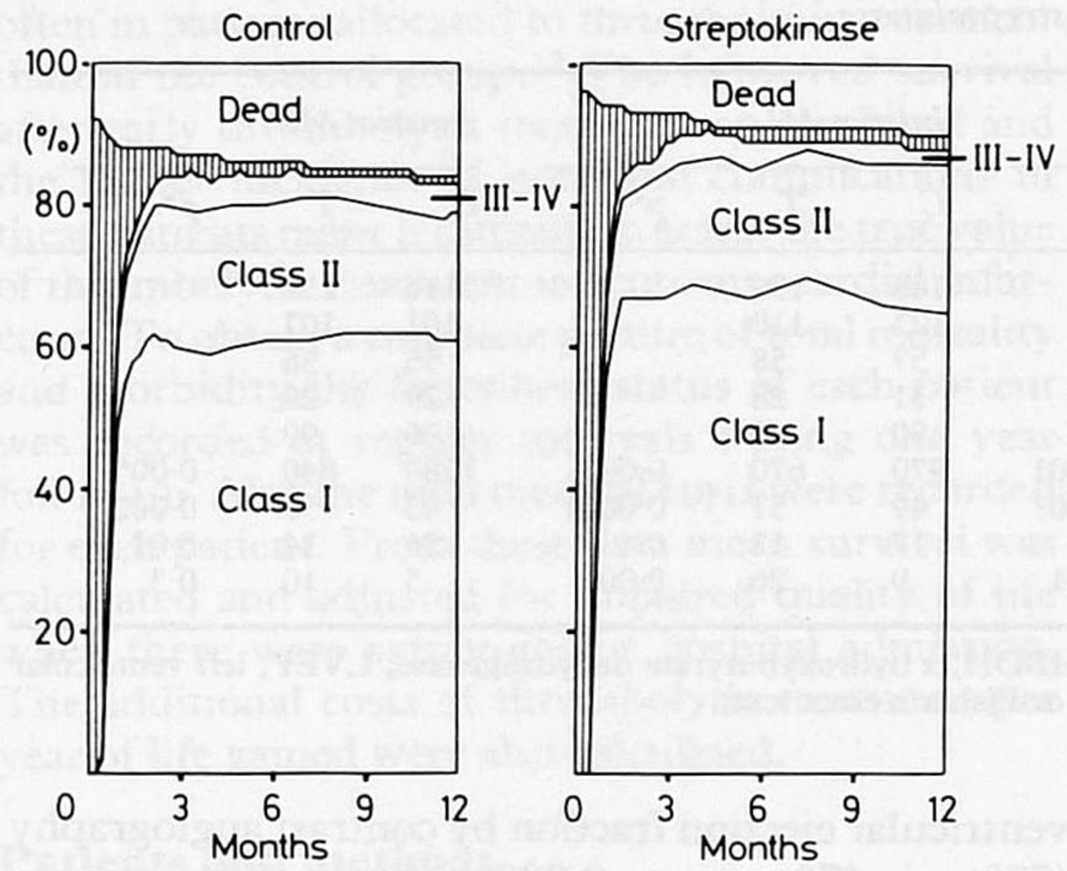

Fig 1 *Proportion of patients in each functional class during the first year after myocardial infarction. The shaded area represents admission to hospital. New York Heart Association classes III and IV are combined.*

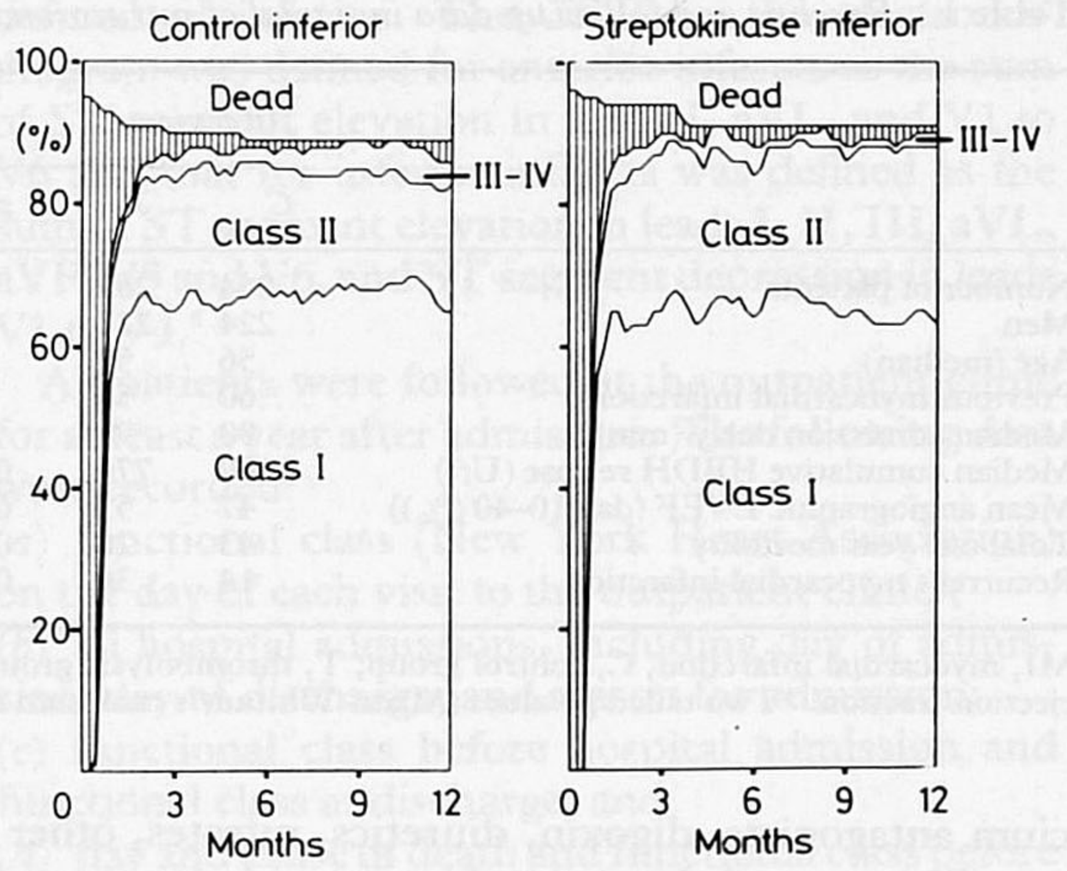

Fig 2 *Proportion of patients with inferior infarction in each functional class during the first year after myocardial infarction. See legend to fig 1.*

considerable differences in the efficacy of thrombolytic treatment between patients with anterior and those with inferior infarction. Mean survival at one year follow up after inferior infarction was 10 days longer in the thrombolysis group than in the control group ($p = 0{\cdot}4$), although those on thrombolysis spent fewer days without symptoms (225 *vs* 232 days in controls, fig 2). In patients with anterior infarction differences in survival between the two treatment groups were more pronounced than those in the group with inferior infarction (fig 3). Mean survival was 35 days longer in the thrombolysis group ($p = 0{\cdot}02$), and they had more days without symptoms (239 *vs* 183 days in controls, $p = 0{\cdot}002$).

To take account of the opposite trends in mortality and morbidity, especially in patients with inferior infarction, quality adjusted survival was calculated by estimating the impairment of the quality of life by symptoms or hospital admission. Quality of life without symptoms (class I) was scored as 100%. Quality of life in class II was estimated as 90%, in class III or IV as 70%, and in hospital as 30%.[9] So quality adjusted mean survival for patients with inferior infarction was 307 days (out of 365 days) in the thrombolysis group and 300 days in the control group (table 3). In patients with anterior infarction quality adjusted survival was 38 days longer in the thrombolysis group than in the controls ($p = 0{\cdot}008$).

The costs of medical treatment the first year after myocardial infarction were based on 1984 prices at the University Hospital Dijkzigt, Rotterdam. We included days spent in hospital (Dfl 600/day), days in a coronary care unit (Dfl 1500/day), days in a surgical intensive care unit (Dfl 2500/day), costs of acute cardiac catheterisation including thrombolytic treatment (Dfl 6200) or coronary angioplasty (Dfl 11 900), costs of elective catheterisation (Dfl 2600), elective coronary angioplasty (Dfl 8300), bypass surgery (Dfl

Table 3 *Mean number of days spent in the different functional classes or in hospital, quality adjustment for each situation (see results), and quality adjusted survival for all patients admitted to the trial and for patients with inferior or anterior infarction*

	All patients		*Inferior MI*		*Anterior MI*		*Quality adjusted data*						
	C	*T*	*C*	*T*	*C*	*T*	*Quality adjustment factor*	*All patients* C	*All patients* T	*Inferior MI* C	*Inferior MI* T	*Anterior MI* C	*Anterior MI* T
Class I	210	232	232	225	183	239	1·00	210	232	232	225	183	239
Class II	63	66	59	76	69	56	0·90	57	59	53	68	62	50
Class III-IV	14	9	10	8	19	10	0·70	10	7	7	6	13	7
In hospital	26	27	26	28	26	27	0·30	8	8	8	8	8	8
Mean survival (days)	313	334	327	337	297	332		285	306	300	307	266	304

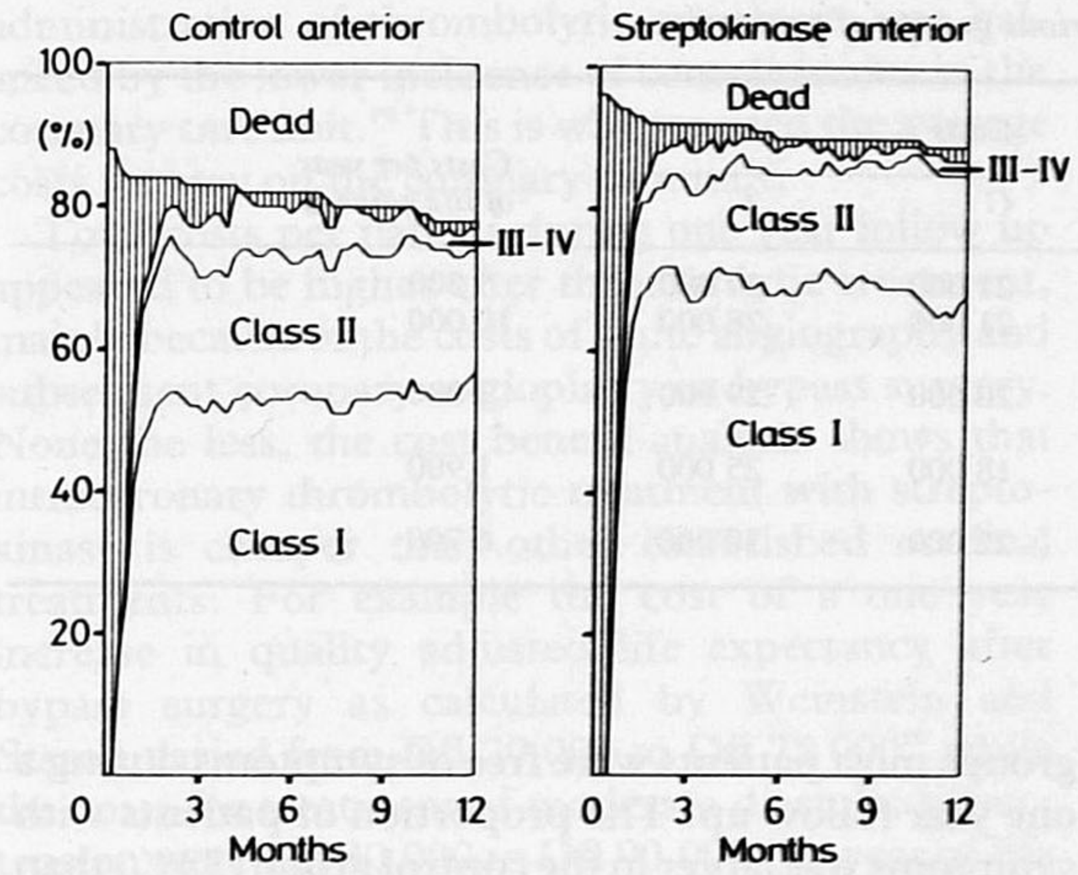

Fig 3 *Proportion of patients with anterior infarction in each functional class during the first year after myocardial infarction. See legend to fig 1.*

14 000), and medication prescribed during one year follow up (£1 ≃ Dfl 3·3). Total costs of medical treatment the first year after myocardial infarction averaged Dfl 21 000 for inferior infarction and Dfl 20 000 for anterior infarction in the control group, and Dfl 28 000 for inferior infarction and Dfl 29 000 for anterior infarction in patients allocated to thrombolytic treatment. The higher costs of patients allocated to thrombolytic treatment were mainly the result of acute catheterisation (table 4).

Life expectancy was calculated by the DEALE method.[10,11] A mortality rate of 6% per year was assumed for patients who were alive at the end of follow up. This assumption was based on long term prognosis after myocardial infarction seen in several large studies.[12–15] Thrombolytic treatment increased life expectancy (table 5), particularly in patients with anterior infarction (2·4 years). Additional costs per year of life gained were Dfl 3800 in patients with anterior infarction and Dfl 10 000 in inferior infarction.

Subgroup analysis showed the largest limitation of enzymatic infarct size and greatest reduction in three month mortality by thrombolytic treatment in patients with high total ST segment elevation (ΣST ⩾ 1·2 mV) admitted to the hospital within two hours of the onset of chest pain.[6] When this analysis was applied to life expectancy after myocardial infarction the effects of thrombolytic treatment were only apparent in patients with anterior infarction. Again, the greatest benefit was seen in patients with extensive myocardial ischaemia (ΣST ⩾ 1·2 mV), admitted to the hospital within two hours of the onset of symptoms. In this subgroup mean quality adjusted survival in the first year was 69 days longer in the thrombolysis group (310 *vs* 241 days in controls, p = 0·006) and life expectancy was 3·6 years longer (table 5). Total costs of medical treatment in this subgroup were lower because there were fewer hospital admissions (table 2). Net costs per year of life gained by thrombolytic treatment were only Dfl 1900 in patients with large anterior infarctions who were admitted within two hours of the onset of symptoms.

Discussion

The randomised trial conducted by the Interuniversity Cardiology Institute of The Netherlands showed that early thrombolytic treatment can limit infarct size, improve left ventricular function, and reduce mortality. Improved survival after thrombolytic treatment was also reported by the Western Washington Trial[16] and to a lesser extent after intravenous streptokinase in the GISSI trial.[17] The present analysis indicates that this improved survival after thrombolytic treatment is accompanied by improved quality of life at an acceptably low cost.

Table 4 *Costs (Dfl)* of medical treatment in the first year after myocardial infarction.*

	All patients		*Inferior infarction*		*Anterior infarction*	
	C	*T*	*C*	*T*	*C*	*T*
Number of patients	264	269	148	139	116	130
Cost of:						
Catheterisation + Sk		1 209 000		663 000		546 000
Catheterisation + Sk + PTCA		547 000		202 000		345 000
Elective catheterisation	533 000	517 000	312 000	257 000	221 000	260 000
Late PTCA	208 000	191 000	58 000	75 000	50 000	116 000
Days in hospital (general ward)	2 738 000	2 700 000	1 513 000	1 386 000	1 225 000	1 314 000
Days in CCU	1 286 000	1 468 000	736 000	784 000	550 000	684 000
CABG + 2 days surgical ICU	608 000	836 000	399 000	418 000	209 000	418 000
Medication costs	198 000	204 000	106 000	102 000	92 000	102 000
Total	5 471 000	7 690 000	3 124 000	3 887 000	2 347 000	3 785 000
Average costs per patient	21 000	29 000	21 000	28 000	20 000	29 000

*Costs (Dfl) per patient for each item were respectively 6 200, 11 900, 2 600, 8 300, 600, 1 500, and 19 000 (£1 ≃ Dfl 3·3). Medication costs were based on standard dosages of prescribed cardiovascular drugs. See table 2 for abbreviations.

Table 5 *Calculation of costs (Dfl) per year of life gained in various groups of patients.*

	Mean life expectancy (yr)		*Costs*		*Costs per year of life gained*
	C	*T*	*C*	*T*	
All patients	15·3	16·8	21 000	29 000	5 300
Inferior infarction	16·3	17·0	21 000	28 000	10 000
Anterior infarction (all patients)	14·1	16·5	20 000	29 000	3 800
Anterior infarction (admission $\leqslant$2 h and $\sum$ ST $\geqslant$ 1·2 mV)	12·7	16·3	18 000	25 000	1 900
Anterior infarction (admission 2–4 h or $\sum$ ST < 1·2 mV)	15·1	16·6	22 000	32 000	6 700

See footnotes to tables 1 and 2.

The benefits of thrombolytic treatment were most clear cut in patients with anterior infarction—an observation that accords with the results of the GISSI trial.[17] The site of the infarct was based on electrocardiographic criteria, which were available shortly after hospital admission. Angiographic data were not used to determine the location of the infarction. Patients in the thrombolysis group in whom the infarct related obstruction was in the circumflex artery (as assessed by acute angiography) had electrocardiographic signs of anterior infarction in approximately 40% of the cases and of inferior infarction in 60%.

In this analysis all hospitals admissions were recorded and functional class was defined for each patient at regular intervals during one year follow up according to the method proposed by Olsson *et al.*[18] This enabled us to compare differences in mortality and morbidity between the two treatment groups. Although the assessment of impairment in the quality of life when angina pectoris or heart failure occur is dependent on the patient's opinion, the quality of life can be measured objectively by the patient's ability to carry on normal activity[9] as estimated by the Karnofsky Performance Status Scale. It is evident that in patients with anterior infarction thrombolytic treatment improved both life expectancy and quality of life, while the beneficial effects of thrombolytic treatment in inferior infarction remained small. These conclusions are independent of the method of quality adjustment, and remain unchanged when other quality adjustment factors are used. The total duration of hospital stay was the same in both treatment groups. However, admissions in the thrombolysis group were more often related to ischaemia (because of reinfarction and for additional revascularisation procedures such as coronary angioplasty or bypass surgery), whereas in the control group more admissions were the result of heart failure. This confirms that left ventricular function was more impaired in conventionally treated patients. The data shows that in both treatment groups most patients were free of symptoms during a one year follow up. The proportion of patients with symptoms was larger in the control group (33%) than in the thrombolysis group (22%) for patients with anterior infarction. Thus thrombolytic treatment improved survival and the quality of life in this group of patients. It is not clear why thrombolytic treatment was less effective in patients with inferior infarction. A possible explanation could be the higher reinfarction rate seen in these patients which abolishes the initially beneficial effects of thrombolytic treatment (table 1).

In the calculation of mean life expectancy a mortality rate of 6% per year was assumed for patients in both treatment groups. Sensitivity analysis indicated that the differences in mean life expectancy between the two treatment groups (table 5) persisted when a mortality rate of 5% or 7% was assumed for patients in both treatment groups. Long term prognosis depends on left ventricular function at discharge.[3] Since patients in the thrombolysis group had better left ventricular function than the control group,[3 5 6] the differences in mean life expectancy between the two treatment groups might even be underestimated, and the actual improvement of life expectancy by thrombolytic treatment might be greater than the data shown in table 5.

The true costs of thrombolytic treatment include the acute intervention as well as the higher incidence of reinfarction and additional revascularisation procedures. This is why we calculated total costs in the first year. We based the number of days in hospital (table 3) on a weekly assessment of functional state. This overestimated actual hospital stay which was 21 days in both treatment groups. Calculation of total costs was based on actual hospital stay, catheterisations, coronary angioplasty, and bypass surgery during follow up. Although thrombolytic treatment reduced the occurrence of ventricular fibrillation, cardiogenic shock, and heart failure,[1] the workload in the coronary care unit was not affected. The increased workload caused by the

administration of thrombolytic treatment was balanced by the lower incidence of complications in the coronary care unit.[19] This is why we used the average costs for stay on the coronary care unit.

Total costs per patient during one year follow up appeared to be higher after thrombolytic treatment, mainly because of the costs of acute angiography and subsequent coronary angioplasty or bypass surgery. None the less, the cost benefit analysis shows that intracoronary thrombolytic treatment with streptokinase is cheaper than other established medical treatments. For example the cost of a one year increase in quality adjusted life expectancy after bypass surgery as calculated by Weinstein and Stason varied from Dfl 20 000 to Dfl 75 000[20] while the costs for treatment of moderate diastolic hypertension were Dfl 30 000 to Dfl 90 000 per year of life gained (£1 ≃ Dfl 3·3).[21] The cost benefit ratio of thrombolytic treatment is good because it requires only one intervention during hospital admission and has considerable beneficial effects, especially in patients with a larger anterior infarction. The treatment can thus be limited to a well defined and easily recognised group of patients, while hypertension treatment must be given to large numbers of patients for a long time in order to prevent or delay quite a small number of cardiovascular events.

A disadvantage of intracoronary thrombolytic treatment is the need for angiography during the acute stage. We included the costs of equipment and staff for a 24 hour angiography service in the analysis. We do not know how the cost benefit ratios of intracoronary thrombolysis and intravenous thrombolysis compare. Intravenous administration of streptokinase is initially less expensive, but also considerably less effective than intracoronary treatment in achieving patency, in salvage of myocardial function,[22] and in reducing mortality.[17] Careful analysis of follow up data of trials of intravenous streptokinase,[17 22] intravenous tissue plasminogen activator,[23–25] and intracoronary treatment (with or without immediate coronary angioplasty) should enable physicians and health authorities to decide upon the most cost effective method of thrombolytic treatment. Current data on intracoronary thrombolysis indicate that it is a cost effective treatment for patients with extensive anterior myocardial ischaemia[6 26] admitted early after the onset of symptoms of myocardial infarction.

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