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Cost-utility analysis of thrombolytic therapy

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An analysis of the cost-effectiveness of thrombolytic therapy was performed, based on 3- to 5-year follow-up data, from 533 patients randomized to receive conventional therapy or intracoronary streptokinase. At the 3-year follow-up, mortality was 22% in the former group and 14% after thrombolysis. The estimated average gain in life years by thrombolytic therapy was 3·4, whereas this figure was only 1·6 years in patients with inferior wall infarction, and 5·1 years in patients with anterior wall infarction. The lifetime costs for conventional therapy, estimated as ECU 15 110, were increased by ECU 5530 when thrombolytic therapy was applied, including direct treatment costs and the additional costs of extra coronary bypass surgery and PTCA.

After correction for quality of life, and discounting future costs and future events at 5% year^{-1}, the additional costs for each life year were ECU 2940 for all patients treated. This was broken down into ECU 7030 and ECU 2000 for patients with inferior and anterior wall infarction respectively. These figures compare favourably with other modes of cardiovascular therapy.

Thrombolytic therapy does not substantially increase the need for bypass surgery or PTCA. It is very cost-effective, and its application should not be limited by economic resources.

Introduction

Thrombolytic therapy improves survival of selected patients with myocardial infarction[1–6], but also increases the need for additional revascularization procedures. Furthermore, in some studies re-infarction occurs more frequently after thrombolytic therapy compared with conventional treatment[1,6]. In order to assess the cost-effectiveness of thrombolytic therapy, treatment costs, as well as both additional costs during follow-up and the predicted future costs should be taken into account. Earlier cost-effectiveness and cost-utility studies were based on a theoretical model with data obtained from literature[7], or on one-year follow-up data from the trial conducted by the Inter-university Cardiology Institute of The Netherlands[8]. In the latter analysis it was presumed that more than one year after thrombolytic therapy patients would follow a similar course to those conventionally treated. However, the recently completed 3- to 5-year follow-up data indicate that later mortality rates are also reduced by thrombolytic therapy[9]. Since this may considerably influence the cost-effectiveness and cost-utility of therapy, a new analysis was performed, accounting for all observed events during 3-year follow-up. Thrombolytic therapy in this trial consisted of intracoronary administration of streptokinase in some of the patients, preceded by intravenous streptokinase. Since long-term prognosis appeared to be mainly related to left ventricular function and coronary anatomy at the time of hospital discharge[9], it is likely that the conclusions can be extrapolated to other forms of thrombolytic therapy, including intravenous administration of streptokinase, anistreplase (APSAC) and alteplase (rt-PA).

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Patient selection and methods

In five participating hospitals, 533 patients with electrocardiographic evidence of myocardial infarction[6,8] and a duration of symptoms not exceeding 4 h, were randomly allocated to conventional therapy (n=264), or to thrombolytic therapy with intracoronary streptokinase (n=269). Thirty-five of the latter patients refused consent, but were included in the analysis according to treatment allocation (intention-to-treat principle). Intracoronary streptokinase (250 000 units in one hour in most patients) was administered in 234 patients, 46 of whom also underwent percutaneous transluminal coronary angioplasty (PTCA) as part of the reperfusion procedure[6]. Streptokinase was given intravenously, preceding angiography in 98 patients (500 000 units in approximately 30 min). Additional details of patient selection and study procedures have been published earlier[6,8,9].

THE COST-EFFECTIVENESS MODEL

The model used in this study is based on the observed patterns of survival, days in hospital, reinfarction, PTCA, coronary bypass surgery (CABG), and use of medication during 3 years follow-up[10]. Late survival was estimated from 3-year survival combined with the standard mortality rates in the age-matched population, with an additional factor for increased mortality in patients with coronary disease. The pattern of morbidity (re-infarction, hospital admission, PTCA, CABG, NYHA function class and use of medication) during life-long follow-up was assumed to be equal to the observed 2- and 3-year pattern.

Cost figures for events and procedures were based on the actual 1988 costs in the University Hospital Dijkzigt, Rotterdam[8]. Future costs and benefits have been discounted at 5% per year, as is usual in economic evaluations of health care programmes in The Netherlands[11]. The effect of model parameters on the results was illustrated by sensitivity analysis.

SURVIVAL

Survival status was obtained in all patients (except two who live abroad) through the municipal registries in May 1988. Data regarding hospital admissions, additional procedures, functional classification (NYHA) at yearly intervals, as well as prescribed medication, were collected through the cardiologists who were treating the patients. Five-year survival data were available from some of the patients. Nevertheless, the computations in this report were based on completed 3-year follow-up data[9]. For the purpose of cost-effectiveness analysis, prediction of long-term survival was based on the standard mortality rates for an age-matched male population in The Netherlands[12]. The yearly mortality rates in patients after myocardial infarction were estimated at between 0·6 and 3·4% higher than in the reference population, dependent on treatment and infarct localization.

RE-INFARCTION, PTCA AND BYPASS SURGERY (CABG)

During the first year re-infarction, PTCA and CABG occurred at higher rates after thrombolysis than after conventional therapy. In subsequent years the rates of re-infarction, PTCA and CABG were much lower, and not essentially different between the two groups[9]. In the model it was assumed that the rates of PTCA and CABG after the third year would be the same as the observed rates in the second and third years.

QUALITY OF LIFE, UTILITIES

The level of cardiovascular symptoms, as expressed in the functional classification by the New York Heart Association, was considered to express quality of life after myocardial infarction[8]. In the model, it was presumed that the observed patterns of NYHA functional class and hospital admissions during years 2 and 3 would continue during later follow-up. The utilities assigned to patients in class I, II, III/IV and to patients admitted to hospital were respectively 100%, 70%, 50% and 33%[13].

COSTS

The costs of various procedures were: Coronary Care Unit per day, ECU 650; Medium Care Unit or cardiology ward, ECU 260 per day; elective coronary angiography, ECU 1130; emergency angiography with intracoronary streptokinase, ECU 3000; PTCA, ECU 4350; CABG including Intensive Care Unit, ECU 8260. The costs assigned to reinfarction included 3 days CCU and 6 days medium care amounting to Dfl 10.000. For comparison, 1 ECU is approximately equal to 2·5 Dfl, 2·0 DM, 1·1 US $ and £0·7. Costs of medication were based on the observed use of medication during follow-up. Again, it was assumed that the observed use of medication in both groups would continue life-long.

Table 1 Cumulative incidences (%) of mortality, recurrent infarction, coronary bypass surgery (CABG) and coronary angioplasty (PTCA) after conventional therapy (C) or thrombolysis (T). Three year follow-up was complete

Years		1	2	3	5
Mortality					
All patients	C	15·9	18·7	22·2	29·1
	T	10·0	11·8	14·1	18·8
Inferior MI	C	11·4	13·4	15·3	23·7
	T	8·7	10·3	11·8	18·5
Anterior MI	C	21·7	25·5	28·7	36·2
	T	11·1	13·2	15·0	19·5
Recurrent infarction					
All patients	C	5·0	7·4	8·4	22·5
	T	13·1	15·7	17·5	25·7
Inferior MI	C	5·1	8·2	9·1	24·4
	T	17·5	20·0	21·7	30·2
Anterior MI	C	5·0	6·1	7·5	18·9
	T	8·3	11·0	12·9	20·6
CABG					
All patients	C	12·7	14·1	16·1	16·1
	T	17·6	19·7	20·1	24·4
Inferior MI	C	13·8	16·1	17·8	17·8
	T	16·4	19·7	19·7	20·8
Anterior MI	C	11·1	11·1	13·7	13·7
	T	18·7	19·6	20·6	27·8
PTCA					
All patients	C	5·9	5·9	6·4	9·3
	T	7·1	8·8	9·3	12·1
Inferior MI	C	5·8	5·8	6·7	8·2
	T	6·1	7·7	8·6	11·2
Anterior MI	C	5·9	5·9	6·4	9·3
	T	7·1	8·8	9·3	12·1

Results

Five hundred thirty-three patients were entered in the trial, randomized to conventional therapy (n = 264) or thrombolytic therapy with intracoronary streptokinase (n = 269). The mean age was 55 years, 83% were male and 22% had had a previous myocardial infarction. At hospital admission, 15% suffered from mild heart failure and 4% were in severe heart failure or cardiogenic shock. These and other baseline characteristics were similarly distributed between both treatment groups[6]. The observed mortality after one year was 16% in the conventional therapy group and 10% in the streptokinase group; 3-year mortality figures were 22% and 14% respectively (Table 1). The yearly mortality rate during years 2 and 3 after conventional therapy was 3·8%, and after thrombolytic therapy 2·3%. In the sub-group of patients with inferior infarction (148 patients allocated to conventional therapy and 130 patients to thrombolysis) 3-year mortality rates were 15 and 12%, respectively. A larger difference was apparent after anterior infarction (116 patients undergoing conventional therapy and 130 patients allocated to thrombolysis) with 3-year mortality rates of 29 and 15%.

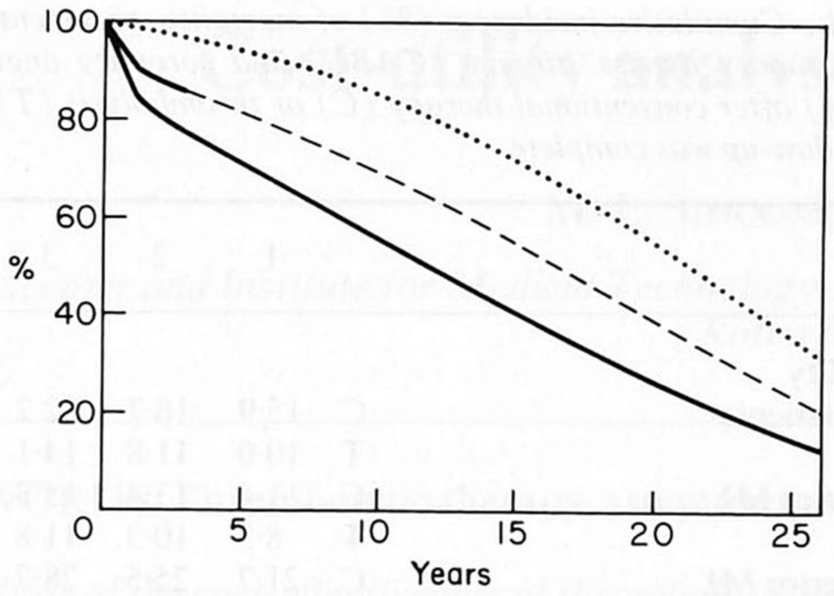

Figure 1 Standard survival curve for males, aged 55 years, in The Netherlands, and the observed (1–3 years), and predicted survival curves after myocardial infarction, treated conventionally or by intracoronary streptokinase. The model, as shown in the figure, is based on the assumption that yearly mortality rates in conventionally treated patients (————) will be 2·7% higher than in the reference population (· · · ·), and after thrombolytic therapy (– – – –) 1·2% higher (see Table 2).

Table 2 Predicted life expectancy (mean, years) in the same patient groups as shown in Table 1, using five different models for late mortality. R = the same mortality as in the normal reference population; R + 1·2 = mortality rate 1·2% higher than the reference population, etc. For all models life expectancy after thrombolytic therapy (T) is compared with conventional therapy (C), and the difference T-C is presented. The difference T-C represent the average gain in life years by thrombolytic therapy. Further computations in Tables 3–5 are based on the second model: mortality after conventional therapy 2·7% higher, and after thrombolysis 1·2% higher than in the normal reference population (R + 2·7, R + 1·2)

Mortality						
	C	R	R+2·7	R+2·7	R+3·7	R+3·7
	T	R	R+1·2	R+2·7	R+2·7	R+3·7
All patients						
	C	17·0	13·2	13·2	12·2	12·2
	T	18·7	16·6	14·5	14·5	13·4
	T-C	1·7	3·4	1·3	2·3	1·2

Table 3 Predicted life expectancy, using the third model from Table 2 and the effects of quality adjustment and discounting as explained in the text. See legend Table 2

Life expectancy	+	+	+	+
Quality-adjusted			+	+
Discounted		+		+
All patients				
C	13·2	8·7	11·8	7·7
T	16·6	10·4	14·8	9·3
T-C	3·4	1·7	3·1	1·6
Interior MI				
C	16·5	10·3	14·9	9·3
T	18·1	11·1	16·0	9·8
T-C	1·6	0·8	1·1	0·5
Anterior MI				
C	11·5	7·7	10·1	6·8
T	16·6	10·3	15·2	9·4
T-C	5·1	2·6	5·1	2·6

Table 4 Observed 3-year and estimated 'lifetime' costs per patient for conventional therapy (C) and thrombolysis (T), with intra-coronary streptokinase. Costs are presented in ECU. The extra costs due to thrombolytic therapy, labelled T-C, for patients with anterior infarction are greater than for patients with inferior infarction

All patients	Observed costs in first 3 years	Annual costs after 3 years	Lifetime cost
All patients			
C	9·300	430	15·100
T	13·000	430	20·640
T-C	3·700		5·530
Inferior infarction			
C	9·570	430	17·500
T	12·650	610	21·900
T-C	3·080		4·400
Anterior infarction			
C	8·870	390	12·970
T	12·870	430	19·390
T-C	4·000		6·420

Fig. 1 shows the survival curve in 55-year-old males in The Netherlands, as well as the observed and predicted curves after myocardial infarction, treated conventionally or with intracoronary streptokinase. Mean life expectancy for 55-year-old males in The Netherlands is 21·0 years. In Table 2, life expectancy after myocardial infarction is presented using various estimates of mortality after the observed follow-up period. If the observed differences, in mortality rate between the reference population and the patients in both treatment groups are maintained, the average gain in life years by thrombolytic therapy is 3·4 years, as shown in the second column in Table 2. Further computations will be based on this model. The average gain in life years would be reduced to 1·3 or 1·2 years, if mortality rates after the third year were the same in both treatment groups (third and fifth columns in Table 2). The estimated gain is 5·1 life years in patients with anterior wall infarction (Table 3) and only 1·6 years in patients with inferior wall infarction. In the latter group of patients quality-adjusted gain in life years by thrombolytic therapy is lower, 1·1 years only, after adjustment for quality of life based on New York Heart Association function classes. On the other hand, quality adjustment does not affect the estimated gain in life years after thrombolytic therapy for anterior infarction. Discounting future life years at an annual rate of 5% approximately halves estimated gain in life years. Discounted, quality-adjusted gain in life expectancy is 1·6 years for all patients treated, 0.5 years for patients with inferior infarction and 2·6 years for patients with anterior infarction.

The costs of treatment, including the observed costs between hospital admission and 3-years follow-up and the predicted costs for later admissions and procedures, are presented in Table 4. The additional costs of thrombolytic therapy with intracoronary streptokinase during the first 3 years are approximately ECU 3700. This difference increases to ECU 5530 when the additional costs during

Table 5 Estimated costs (ECU) for each year of life gained by thrombolytic therapy with intracoronary streptokinase. See also Tables 1–4

	Life expectancy (years)	Lifetime costs (ECU)	Costs for each life year		
			Crude	Discounted	Discounted, quality adjusted
All patients					
C	13·2	15·110			
T	16·6	20·640			
T-C	3·4	5·530	1·630	2·690	2·940
Inferior infarction					
C	16·5	17·500			
T	18·1	21·900			
T-C	1·6	4·400	2·750	4·730	7·030
Anterior infarction					
C	11·5	12·970			
T	16·6	19·390			
T-C	5·1	6·420	1·260	2·020	2·000

Table 6 Sensitivity analysis: comparison of the effect of four different models on the estimated life expectancy (see also Tables 1 and 3), total costs (see also Table 5) and extra costs for thrombolytic therapy without (crude) and after quality adjustment and discounting of future costs and future life years. Discount rate = 5% year^{-1}

Model assumptions	Life expectancy (years)			Total costs (ECU)			Extra costs year^{-1} (ECU)	
	C	T	T-C	C	T	C-T	Crude	Quality adjusted discounted
A. Measured mortality rates C = reference population + 2·7% T = reference population + 1·2%	13·2	16·6	3·4	15·110	20·640	5·530	1·630	2·940
B. Mortality rates as in A Rates of re-infarction, CABG and PTCA twice as high in C and T	13·2	16·6	3·4	18·450	25·480	7·030	2·070	3·470
C. Mortality rates as in A Rates of re-infarction, CABG and PTCA twice as high in T only	13·2	16·6	3·4	15·110	25·480	10·370	3·050	4·890
D. Mortality rate the same in C and T C = reference population + 2·7% T = reference population + 2·7%	13·2	14·5	1·3	15·110	19·630	4·520	3·480	5·540

future life years are added. Additional costs in patients with inferior infarction were somewhat lower than in patients with anterior infarction.

From these data, the additional costs for each life year gained by thrombolytic therapy can be computed, as shown in Table 5. In the whole study population the crude, undiscounted, costs per year of life gained by thrombolytic therapy are ECU 1630. After discounting future costs at 5%, the additional costs are ECU 2690, while these are ECU 2940 when the correction for quality of life (utility) is also applied. These figures are more favourable in patients with anterior infarction, and less favourable in patients admitted with inferior wall infarction. Discounted quality-adjusted costs per life year where only ECU 2000 in patients with anterior infarction and were ECU 7030 in patients with inferior infarction treated by intracoronary streptokinase.

In the computations it was assumed that the trends in mortality, re-infarction, CABG and PTCA, as observed in the second and third year, would continue life long. In order to assess the sensitivity of the computed costs per life year for these assumptions, three alternative models were analysed. Data in Table 6 indicate that doubling the event rates in both treatment groups causes only a small increase in costs per life year (Model B), while these costs would almost double if the event rates increased twofold after thrombolytic therapy only (Model C). Costs per year of life also double when it is assumed that mortality rates after the third year would be the same in both treatment groups (Table 6, Model D). Similar changes in costs per life year were computed using the alternative assumptions in patients with inferior or anterior infarction.

Discussion

The introduction of thrombolytic therapy has improved patient survival and quality of life during the first years after myocardial infarction[1–6,9]. However,

there is some concern that thrombolytic therapy would increase the need for other procedures, particularly coronary bypass surgery and coronary angioplasty, and that the total costs of thrombolytic therapy would require a substantial part of the health care budget. The present analysis demonstrates that such concern is not warranted, and that thrombolytic therapy is a relatively cost-effective health care provision.

Thrombolytic therapy with intracoronary streptokinase results in a substantial reduction in mortality from myocardial infarction, and in an average increase of life expectancy of 3·4 years (Table 2). In the first year 18% of the patients underwent coronary bypass surgery and 7% underwent PTCA, while these figures were 13% and 6% respectively after conventional therapy. Thus the additional requirements for bypass surgery and PTCA were approximately 50 and 10 procedures in the first year for every 1000 patients with myocardial infarction treated with thrombolysis, and approximately 80 and 30 additional procedures during 5-year follow-up. The current data were based on a study with intracoronary streptokinase, conducted in five referral hospitals for revascularization therapy. Recent studies with intravenous streptokinase, alteplase (rt-PA) and anistreplase (APSAC), which included many patients from primary care hospitals, have also shown that thrombolytic therapy improves survival, without or with only few increases in additional revascularization procedures[1–5]. In The Netherlands, with a population of 15 million, approximately 35 000 patients suffer from myocardial infarction each year. If the current indications for thrombolytic therapy are applied, at most 6000 of these patients will receive thrombolytic therapy, or 400 patients per million inhabitants per year. The present investigation shows that the introduction of thrombolytic therapy will not increase hospital admission time, although it may require a small increase in coronary bypass operations and angioplasties.

The extra costs of thrombolytic therapy appear to be largely due to the direct costs of the intervention. The total extra costs during the lifetime of the patient were estimated at ECU 5530. Approximately half of this sum (ECU 3000) was needed for emergency catheterization and intracoronary administration of streptokinase. Other thrombolytic regimens, including intravenous streptokinase, alteplase and anistreplase are considerably less expensive than intracoronary therapy; thus it can be predicted that the total cost of such therapeutic regimens will be considerably lower than the estimates presented in this analysis. On the other hand, in most randomized trials with other thrombolytic regimens the difference in survival after 1 year was smaller than the 6% difference observed in this study[1–5]. However, it is likely that the costs per life year will be in the same range as, or lower than, in the present study, when lower treatment costs are combined with lower 1-year survival differences. A precise comparison of the cost-effectiveness of different thrombolytic regimes cannot yet be performed.

The cost-effectiveness of thrombolytic therapy in a given patient will depend on the mortality risk and the potential benefits of the therapy. For example, in a patient with anterior infarction the mortality risk is higher and the gain in life expectancy by thrombolytic therapy is 5 times greater than in a patient with inferior infarction (Table 3). Similarly, the cost-effectiveness of thrombolytic therapy is greater in patients treated early than in those treated later after the onset of symptoms. Nevertheless, the discounted quality-adjusted costs per life year of patients with inferior infarction in the present study compares favourably with, for example, the cost-effectiveness of treatment of mild hypercholesterolemia which amounts to ECU 22 000–48 000 per life year[11].

The model used for this analysis is based on the measured survival in the reference population, corrected for the expected increased mortality due to coronary disease. Long-term prediction of need for hospital admission, revascularization procedures and medication was based on the observed patterns during 3-year follow-up of the patients under investigation. These assumptions may be questioned. However, the sensitivity analysis indicates that the conclusions would remain essentially unchanged, should other assumptions be made (Table 6). This is largely due to the observation that the additional events and procedures related to thrombolytic therapy, and the extra costs incurred, occurred almost exclusively within the first few months or first year after the initial event.

Survivors of myocardial infarction may suffer from angina or from heart failure. These symptoms reduce the quality of life, as does hospitalization for PTCA, bypass surgery or other therapy. In the present study, as well as in a previous report, the functional class was used as a measure of quality of life[8]. In the previous report, the utilities for each functional class were derived from the Karnofsky Index[14]. The utilities proposed by Torrance[13] have been derived from interviews with patients and physicians, and are thus more appropriate. Since the distribution of functional state does not differ greatly between survivors after conventional or thrombolytic therapy, the discounted quality-adjusted costs per life year hardly change, if one set of utilities[13] could be replaced by another set[14].

From the present analysis it can be concluded that the introduction of thrombolytic therapy does not substantially increase the need for bypass surgery or angioplasty. Thrombolytic therapy does, however, significantly improve the life-expectancy of patients with evolving myocardial infarction; it improves the quality of life of surviving patients[9] and is an extremely cost-effective health care provision (relative to primary prevention programs). These data support the widespread use of thrombolytic therapy in selected patients with evolving myocardial infarction, which should not be limited by economic resources.

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