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Can Thrombolysis Prevent Ischemic Heart Failure?

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Abstract. In the present era of thrombolysis, congestive heart failure secondary to (sub)acute coronary artery obstruction can be reduced to a considerable extent or even avoided altogether. Evidence from several recent trials in humans, aimed at restoring perfusion of the jeopardized myocardium – and thus preserving normal ventricular function – is presented. It is clear that thrombolysis, provided it is instituted within 4 h of onset of symptoms in patients with a large area of the myocardium at risk, can prevent ischemic heart failure.

Introduction

Pump failure, whether early and severe such as in acute cardiogenic shock, or insidious and late by congestion of upstream organs, is now the leading cause of cardiac death. Efforts at temporary mechanical or pharmacologic support of the heart have been largely unsuccessful so that attention is now more and more directed toward *prevention* of ventricular failure. When ischemic heart disease as a consequence of coronary artery obstruction(s) is the cause, limitation of the initial myocardial infarct size or even outright prevention of infarction itself appears to be the best approach, now that early reperfusion efforts with thrombolytic agents have proven to be very successful in this regard.

The dramatic effects of early thrombolysis in acute myocardial infarction (AMI) on enzymatic infarct size, left ventricular function and early mortality have been demonstrated in relatively few patients in comparison with the many large-scale trials with β blockade. Although experimental data with a variety of these pharmacologic agents seemed promising, in recent large-scale clinical trials in which early administration of β-adrenergic blockers was part of the procedure, such as the MIAMI trial [1] and also the ISIS-I trial [2], neither these agents nor the various calcium antagonists [3–6] have shown a reduction in mortality even approaching that achieved by early thrombolysis. Thus the efficacy of early reperfusion is now generally being recognized and implemented.

The randomized trial from the Netherlands Interuniversity Cardiology Institute is a good example of these observations [7]. It demonstrated that early thrombolytic (within 4 h) therapy with intracoronary streptokinase (152 patients) or with intracoronary streptokinase preceded by still earlier intravenous streptokinase (117 patients) when compared to conventional treatment in 264 patients (consisting of bed rest, sedatives, antiarrhythmics and/or antihypertensive drugs, whenever the hemodynamic state of the patient required this), patency of the infarct-related artery was demonstrated in patients (85%). Enzymatic infarct size, measured from cumulative α-hydroxybutyrate dehydrogenase (α-HBDH) release, was a median of 760 U/l in patients allocated to thrombolytic therapy versus 1,179 U/l in control subjects ($p = 0.0001$). This reflected a limitation of infarct size of approximately 30%. Left ventricular ejection fraction measured by radionuclide angiography before discharge was higher after thrombolytic therapy (median 50% versus 43% in control subjects, $p = 0.0001$). In later evaluations with contrast angiography at 4–6 weeks after AMI, these differences were even more striking. While there was a statistically not significant difference in terms of early cardiac failure in favor of lytic therapy early on, 1 year follow-up showed a highly significant reduction of 37 versus 53 deaths in patients conventionally treated ($p < 0.05$) (tables I–V). For all of these reasons, 12-month mortality at 8% was much lower in patients allocated to thrombolytic therapy versus 16% in the control group ($p < 0.01$) at 3 months ($p < 0.03$). Recently, Gotsman and Weiss [8] have shown that treatment beginning within <60 min after onset of symptoms in a mobile coronary care system results in even better preservation of cardiac function.

In the last two decades, coronary care units have made it possible to recognize and treat in time, previously fatal, arrhythmias during the acute stage of myocardial infarc-

Table I. Data from the Netherlands Interuniversity Cardiology Institute Trial [7].

Clinical course in hospital	Controls	Thrombolysis	p
Number of patients	264	269	
Hospital mortality (14 days)	26	14	0.05
Recurrent infarction (14 days)	9	12	
Angina pectoris	55	57	
Heart failure coronary care unit			
Mild	55	54	
Severe	12	10	
Shock	24	13	
Dopamine/dobutamine treatment	42	26	0.03
Respiratory support	11	6	
Intra-aortic balloon pump	10	16	
Heart failure reconvalescence	53	37	0.05
Ventricular fibrillation	61	38	0.01
Pericarditis	46	19	0.0004
Bleeding	7	53	0.0001
PTCA	9	59*	
Bypass surgery	16	29	

Modified after the data from the Netherlands ICIN study [7]. Summary of the clinical course in hospital in the two groups of patients. PTCA was performed more frequently in the thrombolysis group, when the 46 PTCA immediately after thrombolysis are included (*). Only p values <0.05 are reported.

tion. This has reduced, at least the in-hospital, mortality from 30% to <15%. Now the emphasis is on early reperfusion which can restore potentially jeopardized tissue to a 'life-sustainable' level. This in turn results in a reduction of later congestive heart failure. Indeed all our attention must now be directed towards limitation of myocardial infarct size or even outright prevention of the infarction itself in order to reach a further significant reduction in hospital mortality to less than 5%.

Table II. Data from the GISSI trial [14] rearranged to demonstrate that patients treated early on show the best outcome and that those treated (too) late in fact show a higher mortality; note the near halving of the death rate in patients receiving thrombolysis within 1 h after onset of symptoms

Hours	SK, % (deaths/n)	C, % (deaths/n)	p	RR 95% (CI)	Total, % (deaths/n)
<3	9.2 (278/3,016)	12.0 (369/3,078)	0.0005	0.74 (0.63–0.87)	10.6 (647/6,094)
>3–6	11.7 (217/1,849)	14.1 (254/1,800)	0.03	0.80 (0.66–0.98)	12.9 (471/3,649)
>6–9	12.6 (87/693)	14.1 (93/659)	NS	0.87 (0.64–1.19)	13.3 (180/1,352)
>9–12	15.8 (46/292)	13.6 (41/302)	NS	1.19 (0.75–1.87)	14.6 (87/594)
<1	8.2 (52/635)	15.4 (99/642)	0.0001	0.49 (0.34–0.69)	11.8 (151/1,277)

n = Number of patients; NS = not significant; SK = streptokinase; C = controls; RR = risk ratio; CI = confidence interval.

Table III. A comparison between the data (in %) from the GISSI [14], ISAM [35], the Netherlands [7] and Western Washington [15] trials shows great similarity in beneficial outcome when the analysis is restricted to those treated within the first 4 h

	IV-SK (0–3 h) GISSI + ISAM		IC-SK (0–4 h) NL – ICI		IV-SK (0–4 h) W, Washington	
	control	lysis	control	lysis	control	lysis
Patency	± 20	± 50	± 20	85		
Infarct size		–15		–30		–10.3
LVEF	54	57	48	54	47	51
Mortality (3–4 weeks)						
ISAM	7	5	12	6		
GISSI	12	9				
Mortality (1 year)			18	9	30	17

Role of Coronary Thrombosis in Myocardial Infarction

The causal role of thrombosis in AMI has for a long time been a matter of debate. Although since Herrick's days it had been assumed that thrombosis was always the cause of an infarction, careful postmortem studies in the 1960s cast doubt on this theory because many patients showed infarction without complete coronary obstruction. Some researchers postulated, therefore, that thrombosis was the sequel of infarction. Such theories, based on postmortem examinations, were corrected through the detailed anatomic studies of Fulton et al. [9] and corroborated by DeWood et al. [10], whose coronary arteriographic studies in the first few hours after myocardial infarction showed that thrombosis was present in 86% of 517 patients within 4 h after onset of symptoms. These data were similar to those from the Netherlands Interuniversity Cardiological Institute [7] which indicated complete obstruction in 84% of the patients who were randomized to early angiography and intracoronary thrombolysis (table I). Thus, provided patients are studied early enough, most authors confirm that in acute infarction, thrombotic obstruction is the most frequent cause.

Recently, Falk [11] identified a ruptured atheromatous plaque to be the cause of 40 of 51 recent coronary artery thrombosis. This points to the significance of a sudden rupture of an atherosclerotic plaque in the genesis of coronary artery obstruction, either by hemorrhage into an expanding plaque or by serving as a nidus for rapid intraluminal platelet aggregation. Davies and Thomas [12] found that the same mechanism was operative regardless whether the ultimate clinical outcome was unstable angina, myocardial infarction or sudden death.

These observations therefore bring several fundamental concepts into focus: (1) angiography can be carried out in AMI without major risks to establish whether obstruction is the cause of ischemia; (2) thrombosis is present in the majority of cases when studied within the first few hours after symptoms; (3) such an obstructing thrombus can be resolved in the majority of cases by immediate thrombolytic therapy for which a multitude of agents now present themselves; (4) although the prevalence of complete obstruction de-

Table IV. Detailed analysis of the incidence of ventricular fibrillation (VF) as a sign of ventricular dysfunction, from the Netherlands study [7]; note the marked reduction in shock and VF

	Controls (n = 264)		Thrombolysis (n = 269)	
	n	%	n	%
Total VF	60	23	36	13
Primary VF (< 48 h)*	24	9	13	5
Catheter-induced VF	9	3	15	5
Late VF (> 48 h)	10	4	2	1
Shock + VF	17	7	6	2
* Median delay after symptoms:	3 h		2 h	

Table V. Effect of intracoronary thrombolytic therapy on enzyme infarct size, global left ventricular function and 3-month mortality in patients[1]

Interval (h) symptoms – admission	< 2		2–4		< 2		2–4	
Sum ST elevation, mV	> 1.2		> 1.2		< 1.2		< 1.2	
	C	SK	C	SK	C	SK	C	SK
Number of patients	112	92	35	372	72	81	24	35
α-HBDH release, U/l	1,440**	820	1,640*	1,180	800*	500	680	660
LVEF, %	40**	48	44	46	44**	57	52	47
Mortality, %	16*	7	17	8	10	4	8	9

C = Conventional treatment; SK = intracoronary streptokinase. * $p < 0.05$; ** $p < 0.0005$; C vs. SK.

[1] Data from the Netherlands study [7, 34, 43] rearranged into 'early' (< 2 h), 'late' (2–4 h) and large (sum of ST segment elevations > 1.2 mV) or small (sum ST < 1.2 mV) subgroups. It is evident that the greatest benefit in terms of maintained ventricular function is found in those treated early or with the larger infarcts.

clines as the time after the onset of symptoms lengthens, myocardial loss is permanent after the first few hours; (5) while residual obstruction in and around the plaque remains a major problem even after successful lysis efforts at early reperfusion will salvage tissue and preserve myocardial function particularly when followed by more permanent revascularization efforts such as percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft surgery on a semiurgent but elective basis.

It is therefore likely that limitation of infarct size and avoidance of later congestive heart failure will be successful only in those patients who present themselves for therapy within hours after onset of symptoms of AMI. This is evident from the data in tables II, III and V. Indeed, the experimental evidence of Sobel et al. [13] demonstrated that only reperfusion within 4 h will limit the ultimate infarct size and achieve return towards normal cardiac function and metabolism. By now, overwhelming clinical evidence [7, 8, 14–16] has accrued, which confirms the efficacy of reperfusion in the first 0–4 h, with the greatest reductions in mortality and limitation of infarct size being achieved in those patients in whom lysis could be achieved within 2 h or less.

In an Editorial in 1982, in which the published data up to that year were reviewed, Rentrop and Hugenholtz [17] voiced various notes of caution against excessive early enthusiasm for thrombolytic therapy. They pointed to the many factors which could positively or negatively influence the ultimate outcome. These included the need to know the time interval between the onset of symptoms and reperfusion, the extent of restoration of myocardial function in the region perfused by the infarct-related artery, the functional availability of collateral flow, the best route and optimal dose of the thrombolytic agents, the best agent and its side effects, and the degree to which the usual sequelae of myocardial infarction, such as subsequent angina, reinfarction, *congestive*

heart failure and death, could be reduced in the treatment group when compared to a control group, randomly assigned to conventional treatment. Now, in 1988, that evidence is available and it can be stated without ambiguity that the most effective manner to reduce the incidence of (or avoid altogether) subsequent congestive heart failure in ischemic heart disease is early restoration of blood flow to the area affected by obstruction to coronary flow.

Which Proof Is Available: Intravenous and Intracoronary Studies in Humans

Early Reperfusion Studies.

The feasibility of rapid dissolution of intracoronary thrombi by systemic or selective infusion of thrombolytic substances has been convincingly demonstrated in experimental series and in clinical pilot studies as long as 30 years ago. However, because of lack of proper study design, the older experience should be eliminated from current considerations, although Yusuf et al. [18] concluded from a pooled analysis of some 6,000 patients in 24 randomized trials with intravenous streptokinase between 1950 and 1980 that a reduction in the odds of death by 22 ± 5% could be deduced. This, despite the fact that nonsignificant results were achieved in most individual studies.

Systematic efforts at restoration of anterograde flow after intracoronary administration were not introduced into clinical practice until 1979 by Rentrop et al. [19, 20] in Germany. Since then, we have witnessed a dramatic increase in the number of patients with acute ischemic cardiac disorders who have been treated by intracoronary streptokinase infusion [21–23]. The advantages of early intravenous administration combined with intracoronary lysis and aggressive follow-up treatment of residual coronary artery obstruction with coronary angioplasty or bypass surgery to optimize coronary blood flow have recently been adequately investigated [17, 24, 25]. These striking benefits are entirely consistent with experimental evidence. Thus, most advanced cardiac centers now favour immediate and optimal reperfusion. An example of its significant influence on ventricular fibrillation is given in table IV.

Furthermore, our concepts regarding the time course of ischemia evolve, particularly for the role of the available collateral supply and the load existing on the heart at the time of onset of coronary obstruction (hypertension, tachycardia, etc.). Thus, supportive pharmacologic therapy or interventions for specific additional derangements will play an increasing role. Examples are, β-receptor blockers when excessive tachycardia or elevated blood pressure exist, calcium entry blockers when ischemia and spasm are still predominating, 'inodilators' such as the compound under discussion today when hypotension and peripheral vasodilation are desired, or 'scavengers' of unwanted metabolites, such as oxygen radicals released during the reperfusion phase. In fact, they may play a major role in treatment because reperfusion, particularly when carried out late, could induce additional myocardial damage which under certain circumstances such as a large area at risk might be as great as the ischemia-related necrosis in the first place. Obviously this is an area ripe for research.

More Recent Studies in Thrombolysis

Returning to the editorial question posed in our Editorial [17]: What *have* we learned from the experience in the years since 1980?

Most importantly, early recanalization, whether by guidewire alone [19] or by clot lysis with urokinase [27] or recombinant tissue plasminogen activator [28–30], with or without PTCA [31] have all been shown to limit infarct size [7, 8, 32], preserve cardiac function [7, 8, 33] and reduce early as well as late mortality [7, 8, 14, 15]. Thus the earlier requirements to demonstrate efficacy have largely been met and it is now more a matter of implementation of this strategy than of finding the optimal agent or technique.

Which Patients Should We Select?

Here I cite from a recent study from our Institute [34]: 'In the present study the beneficial effects of streptokinase in patients admitted between 2 and 4 h after onset of chest pain were observed only in those with extensive myocardial ischemia, as reflected by a high Σ ST[1], and in patients in Killip class III or IV at admission. Although recanalization was also observed in a high percentage (68%) of patients with low Σ ST, this did not lead to limitation of enzymatic infarct size, improvement in LVEF, or reduction in mortality (table V). In the Western Washington trial [15], mean time to initiation of streptokinase infusion was 276 min, and patients with newly formed Q waves or receiving maintenance therapy for congestive heart failure were excluded. A significant reduction in early mortality was reported, although no beneficial effect on infarct size by thallium imaging or on left ventricular function was observed. Apparently this study included many patients who could not benefit from thrombolytic therapy according to our analysis, while patients with extensive ischemia leading to left ventricular failure, who might have benefitted from thrombolytic therapy, were excluded. In two other studies, the infusion of streptokinase started on average more than 5 h after the onset of symptoms and patients with signs of cardiogenic shock were excluded. No improvement in left ventricular function or reduction in mortality was observed, which is consistent with our observations. Among three relatively small studies, beneficial effects of thrombolytic therapy were observed in only one, in which the mean time between onset of symptoms and admission was 160 min [23]. In most of these studies patients with newly formed Q waves or signs of cardiogenic shock were excluded, and these groups of patients were shown to benefit greatly from thrombolytic therapy in the present trial' [7, 34]. This underlines once more that the interval of symptoms to onset of therapy may not exceed 4 h except when obvious signs of cardiac ischemia are still present.

Which Patients Benefit Most from Thrombolytic Therapy by Intracoronary Streptokinase?

'Thrombolytic therapy with intracoronary streptokinase led to significant limitation of infarct size, improvement in left ventricular function, and reduction in mortality in patients with extensive myocardial ischemia, that is in those patients with a high ST, in whom thrombolytic therapy was started in the first few hours after onset of symptoms. Data from the GISSI trial [14] and the ISAM [35] study also indicate that beneficial effects from intravenous streptokinase dominate in patients admitted within 3 h after onset of symptoms. Thus, it can now be recommended that thrombolytic therapy be of-

[1] ST = Sum of ST segment elevation in precordial leads.

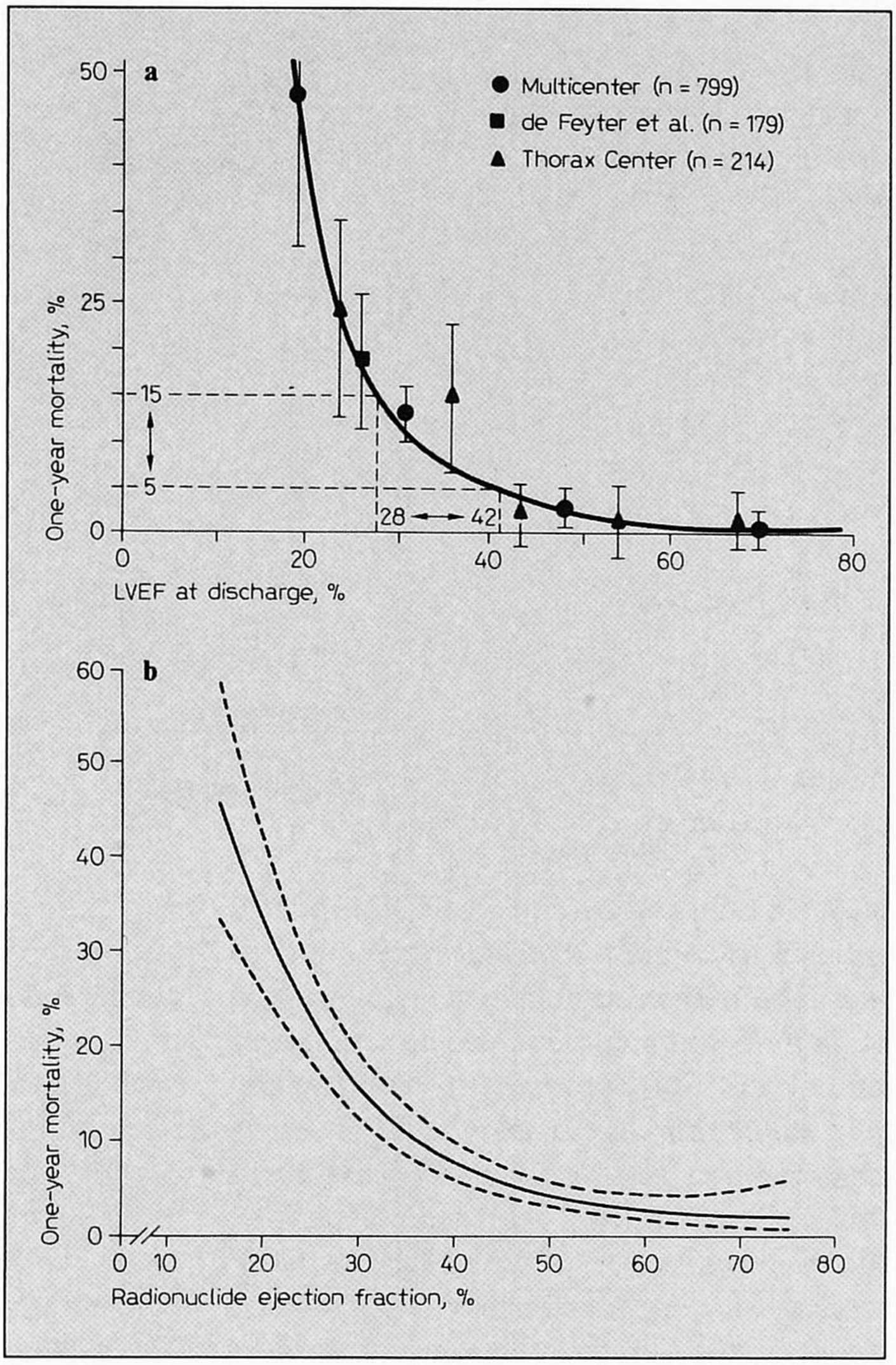

Fig. 1. a There is a curvilinear relationship between the resting left ventricular ejection fraction at discharge and first year mortality. This relationship has been found by many authors [38–40]. If one could move the immediate postinfarct ejection fraction from say 25 to 40%, the gains in 1 year survival (85–95%) appear to be impressive. LV = left ventricle. **b** Same data as in figure 1a [38–40], now depicted with 95% confidence limits for all 1,192 patients studied.

fered to patients admitted within the first few hours after the onset of symptoms, and only to those patients who show extensive ST segment elevation on the ECG.'

Quality of Life after Thrombolysis

In the cost-benefit analysis of the randomized trial conducted by the Netherlands Interuniversity Cardiology Institute [4, 34] we observed the following: 'all hospital admissions were recorded and functional class was defined for each patient at regular intervals during the first year after entry. The method proposed by Olsson et al. [36] allows the analysis of differences in the quality of life, morbidity and mortality between the two treatment groups. While the symptoms of angina pectoris or heart failure are

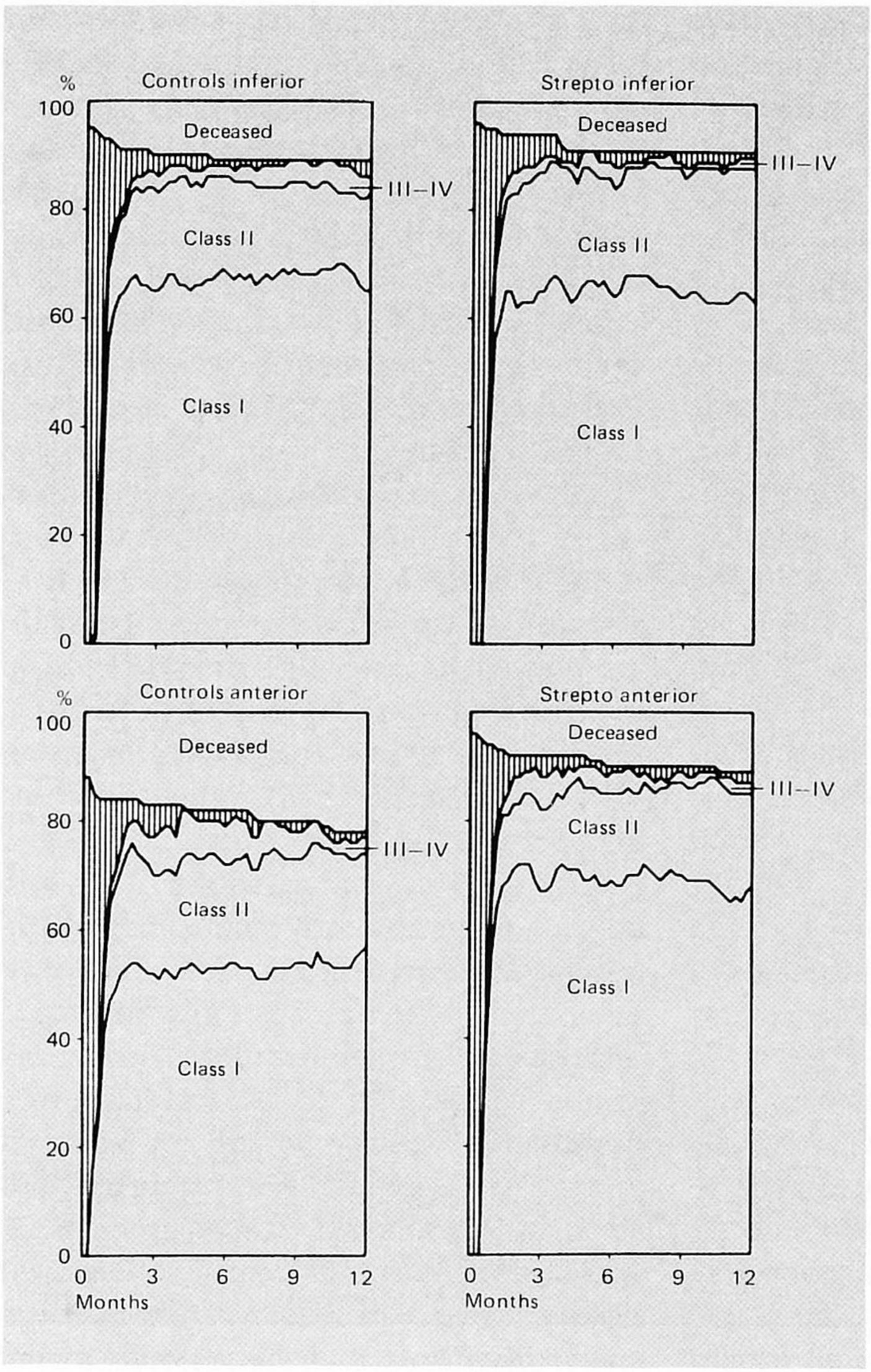

Fig. 2. A schematic overview of the symptomatic state during the first 12 months after onset of thrombolysis (Strepto) or start of conventional therapy (Controls). Class I reflects an asymptomatic course, class II occasional visits to the clinic for minor complications, class III–IV congestive heart failure or other signs of dysfunction or need for interventions. The hatched areas indicate hospitalization days. Data reproduced from Vermeer [43]. Horizontal axis: duration of observation in months. Vertical axis: percent of all patients in each subgroup divided over the various classes. It is evident that patients with anterior wall infarction treated by streptokinase show the greatest improvement in their quality of life.

dependent on the patient's opinion, quality of life can be measured in an objective manner from the ability to carry on normal activity [37] as estimated by the Karnofsky Performance Status Scale. As shown earlier in patients with anterior infarction, thrombolytic therapy improved life expectancy, while the analysis depicted in figures 1–3 also demonstrates a striking effect on quality of life. However, the salutary effects of thrombolytic therapy in inferior infarction remained small, while costs for intervening episodes and procedures were in fact higher. Although total duration of hospital stay appeared to be equal in both treatment groups, admissions in the thrombolysis group were

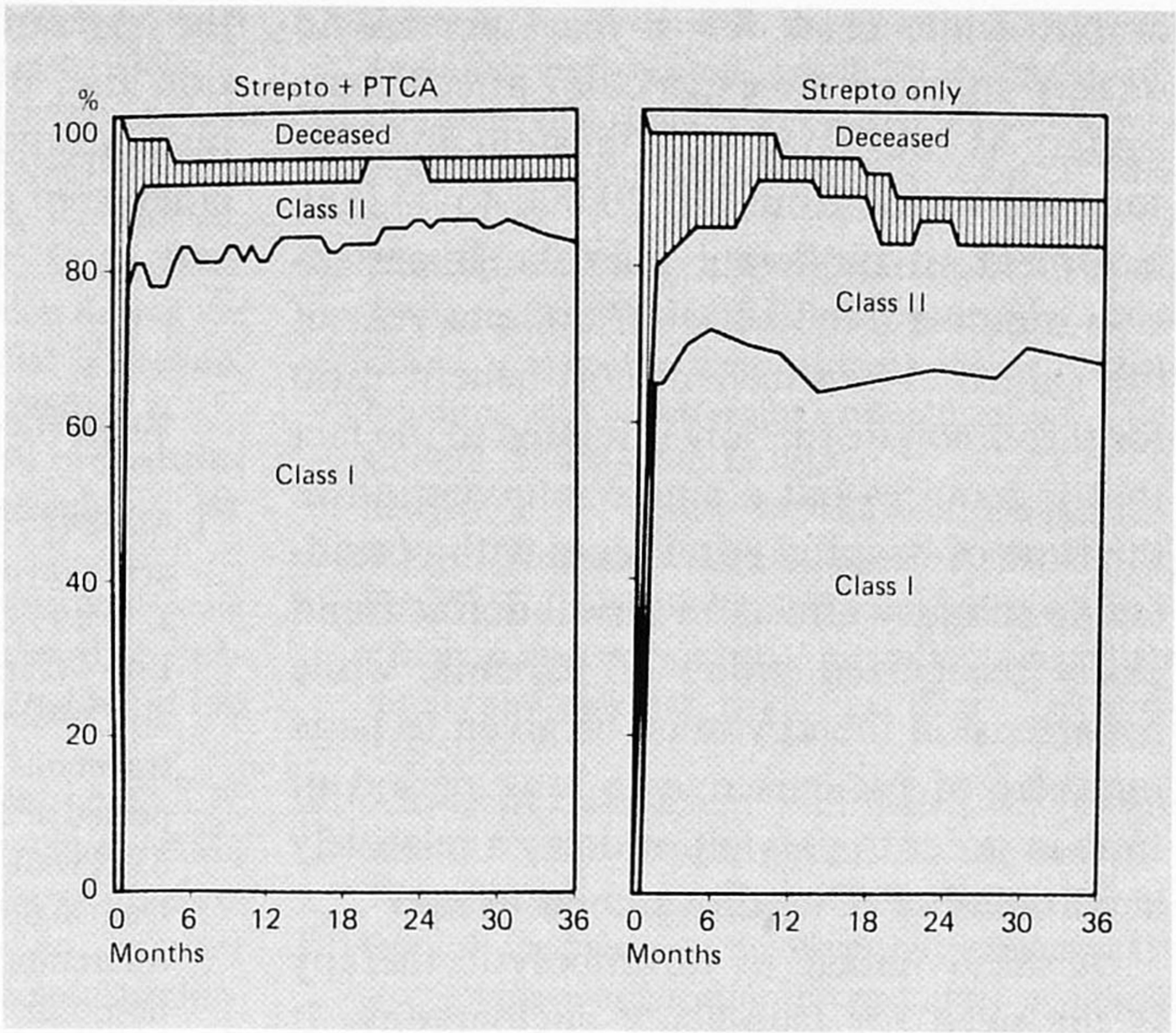

Fig. 3. It is evident that the group treated with streptokinase and PTCA experiences the greatest benefit. See figure 2 for details.

more often related to ischemia (reinfarction and additional revascularization procedures as coronary angioplasty or bypass surgery). In the control group more admissions were due to symptoms and signs of *heart failure.* This confirms the more severe impairment of left ventricular function in conventionally treated patients over the first year of follow-up.

The true 'costs' of thrombolytic therapy include the acute intervention as well as the higher incidence of reinfarction and additional revascularization procedures. It should be noted that the number of days 'in hospital' was based on a weekly assessment of functional status. It was 21 days in both treatment groups.'

Recently some have advocated even earlier release from hospital after successful lysis. Our calculation of total costs was based on actual hospital stay, catheterizations, coronary angioplasty, and bypass surgery during follow-up. The increased workload due to the administration of thrombolytic therapy was balanced by the lower incidence of complications in the coronary care unit as thrombolytic therapy reduced the occurrence of ventricular fibrillation (table IV), cardiogenic shock, and heart failure, workload on the coronary care unit was not affected (41). Therefore the average costs for stay on the coronary care unit were used. Medication was not taken into account since this did not differ between the two treatment groups.

Total costs per patient during the first year of follow-up were higher after thrombolytic therapy. This was mainly due to the costs of acute angiography and subsequent coronary angioplasty or bypass surgery. Even so, the cost-benefit analysis of intracoronary thrombolytic therapy with streptokinase is very favorable when compared with other established medical therapies. For ex-

ample, while costs for 1 year increase in quality-adjusted life expectancy after bypass surgery as calculated by Weinstein and Stason [42] varied from Dfl 20,000 to 75,000, treatment of moderate diastolic hypertension requires Dfl 30,000–90,000 per year of life gained. The excellent cost-benefit ratio for thrombolytic therapy is related to the fact that it requires but a single intervention at the time of hospital admission, with considerable salutary effects in a well-defined and easily recognized group of patients, while hypertension therapy must be given to large numbers of patients over a long period of time in order to prevent or delay a relatively small number of cardiovascular events.

A disadvantage of thrombolytic therapy is the need for (sub)acute angiography. It should be noted however, that the costs of equipment and personnel for 24 h angiography service were included in the analysis. It is as yet unknown how the cost-benefit ratio of intracoronary thrombolysis relates to intravenous thrombolysis. Intravenous administration of streptokinase is initially less expensive, but also considerably less effective than intracoronary treatment both in achieving patency, in terms of salvage of myocardial function and mortality reduction. Careful analysis of follow-up data of ongoing trials with intravenous streptokinase, intravenous tissue plasminogen activator and intracoronary treatment with or without immediate coronary angioplasty should enable physicians and health authorities to decide upon the most cost-effective method for thrombolytic treatment. From presently available data, thrombolysis (preferably begun by intravenous lytic therapy) can be recommended as a cost-effective therapy in patients with extensive anterior myocardial ischemia provided therapy begins early after the onset of symptoms of myocardial infarction (i.e. 0–4 h). The result will be better residual ventricular function and reduced incidence of congestive heart failure.

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