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Clinical course after attempted thrombolysis in myocardial infarction

Results of pilot studies and preliminary data from a randomized trial

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Immediate results and follow-up are reported on 118 patients with a diagnosis of myocardial infarction who were included in studies on intracoronary thrombolysis at the Thoraxcenter. Pilot studies included 37 patients treated with streptokinase, nine with urokinase and six with nitroglycerine and nifedipine. First results of the present on-going randomized trial are described from 34 patients allocated to streptokinase therapy and 32 allocated to conventional therapy in the coronary care unit. Urokinase, nitroglycerine and nifedipine were not effective for recanalization. Streptokinase resulted in recanalization of 22 out of 29 occluded arteries in the pilot studies (71%), as well as 19 out of 23 occluded arteries in the randomized trial (83%). Five patients died during angiography and attempted recanalization. In the pilot studies, four patients died during follow-up. In none of these had recanalization been achieved. On the other hand, angina and reinfarction were observed more frequently in patients after successful recanalization. In the randomized trial no differences were observed in mortality, reinfarction rate, angina or results of predischarge stress testing between patients allocated to streptokinase treatment or controls. However, cardiac failure during follow-up seemed to be more prominent in controls. These preliminary data indicate that the clinical course in patients after attempted thrombolysis is similar to the course of patients treated by conventional methods. Both should be monitored carefully for signs of cardiac failure and episodes of myocardial ischemia and appropriate measures, including surgery, should be considered if these appear. Further randomized trials are warranted to determine whether patients after thrombolytic therapy have a better survival and fewer complications than patients treated conventionally.

Total occlusion of the corresponding coronary artery in patients with acute myocardial infarction has been documented by coronary arteriography within 6 h after the onset of symptoms[1]. Usually this occlusion is caused by a combination of a sclerotic plaque and a fresh thrombus. Recently it has been shown that this thrombus can be dissolved by selective intracoronary infusion of a thrombolytic agent[2–5]. In a smaller fraction of patients thrombolysis can be achieved with intravenous (systemic) administration of streptokinase[6]. Reports which have been published so far focus on the technical aspects and immediate results of intervention with intracoronary thrombolytic agents: streptokinase or urokinase alone or in combination with plasminogen. It appears that thrombolysis can be achieved in 80–90% of patients within the first hours after the onset of symptoms. However, the benefit to the patient of this invasive, expensive and potentially dangerous procedure remains uncertain. In particular, little information is available on the subsequent clinical course of patients in whom intracoronary thrombolysis has been attempted, in comparison with patients treated by conventional methods in the coronary care unit. Thus it remains uncertain whether these patients require urgent bypass surgery or long-term treatment with anticoagulants, antiplatelet drugs, β-blockers or other therapy.

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The present report describes the immediate results as well as follow-up data in 118 out of 129 patients who were admitted to the coronary care unit of the Thoraxcenter with an acute myocardial infarction and were included in studies on intracoronary thrombolysis during the period from September 1980 until February 1982. The incidence of angina, cardiac failure, new infarcts or death is reported during a follow-up period up to 18 months.

Patient selection and methods

Between September 1980 and February 1982, 461 patients were admitted to the coronary care unit of the Thoraxcenter with the diagnosis of acute myocardial infarction. One hundred and twenty-nine were included in the studies on intracoronary thrombolysis, based on the following criteria: males or females below 66 years of age with onset of typical symptoms of myocardial infarction within 4 h before admission. In the first 19 patients a maximum delay of 6 h between onset of symptoms and admission was accepted. Chest pain and typical ECG changes (ST elevation $> 0{\cdot}2$ mV in chest leads or $> 0{\cdot}1$ mV in standard leads) persisted in spite of treatment with oral nitroglycerine or nifedipine. Exclusion criteria were: history of gastrointestinal bleeding, cerebrovascular accident, hemorrhagic diathesis or menstrual bleeding. The procedure and possible benefits were explained to each patient as well as his/her relatives when present. In the pilot studies, 52 patients who met these criteria were submitted for coronary angiography and thrombolysis was attempted following the protocols 1–3 described below. Four other patients refused the interventions while seven were assigned to conventional therapy (see section 2 below). In the ongoing randomized trial 66 patients were assigned either to intracoronary streptokinase or conventional treatment.

A detailed description of the catheterization procedures and complications is presented in this issue of the *European Heart Journal* by Serruys *et al.*[7]. In short the following groups of patients were studied:

(1) In an initial series of 19 patients, treatment with intracoronary streptokinase was attempted (2000 U/min up to 250 000 U). One patient died from shock before streptokinase was administered[7]. In four other patients urokinase was employed in the same dosage.

(2) Subsequently in 11 patients, recanalization was attempted with urokinase (five patients) or intravenous nifedipine and intracoronary nitroglycerine (six patients). Assignment of the intervention to these 11 patients was random, while seven patients were assigned to conventional therapy. This study was discontinued since recanalization with urokinase was achieved in only one patient.

(3) Based on the experience from these studies, a new pilot study was initiated, in which a percutaneous approach from the femoral artery was employed. After angiography of the infarct-related artery, streptokinase infusion was started immediately at a rate of 4000 U/min. If thrombolysis was not achieved after 30 min, 'superselective' catheterization of the occluded branch of a left coronary artery was performed with superselective streptokinase infusion. Eighteen patients were enrolled in this study.

(4) In June 1981 the current ongoing randomized trial was started. After admission, patients were randomized to conventional treatment in the coronary care unit aided by hemodynamic monitoring with a Swan Ganz thermodilution catheter or to coronary arteriography followed by intracoronary streptokinase. Informed consent was asked only after random assignment to streptokinase treatment. The flowchart of this study is illustrated in Fig. 1. Thirty-two patients were assigned to conventional therapy and 34 to an attempt at thrombolysis with intracoronary streptokinase. All patients received heparin (20 000 U/24 h) followed by oral coumarin until discharge from the hospital. Anticoagulants were continued after discharge in patients with left ventricular aneurysm or recognized mural thrombus in the left ventricle. In addition, nifedipine 10 mg every 4 h was given for two days in patients treated with streptokinase. All other medication such as antiarrhythmic drugs, diuretics or β-blockers were given when symptoms in the acute phase or during recovery from the infarct indicated their use.

In this report the data from the pilot studies (1, 2 and 3) have been combined. Data from the four patients who refused intervention as well as the seven patients assigned to conventional therapy are not presented since these groups are too small. Data from the ongoing randomized trial are presented according to the 'intention to treat' principle.

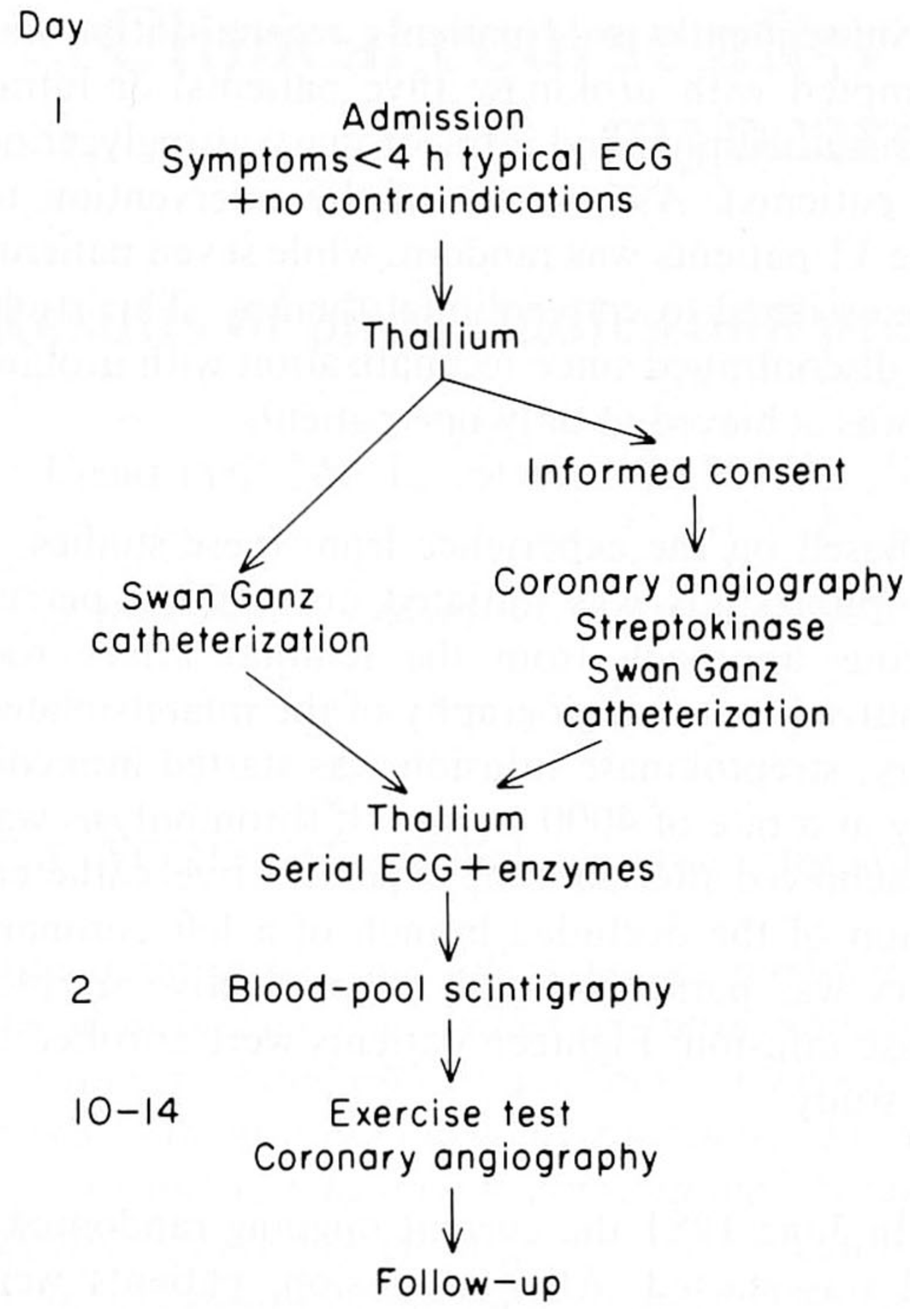

Figure 1 Flow chart of the procedures in the current randomized trial at the Thoraxcenter.

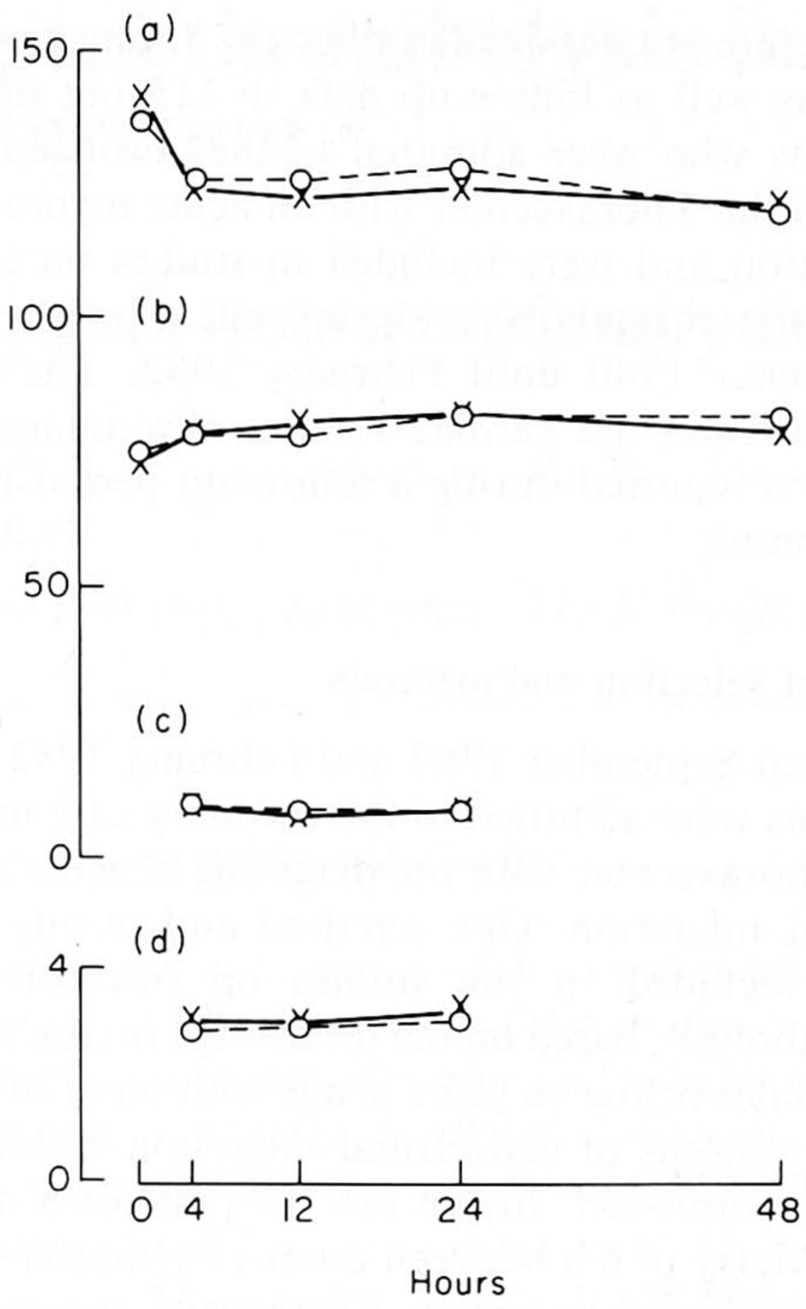

Figure 2 Hemodynamic data measured at the coronary care unit in 62 patients allocated to either conventional therapy (○) or intracoronary streptokinase (X). The mean values are plotted. No differences were apparent in any measure variable: (a) systolic blood pressure, mean arterial pressure (not shown), (b) heart rate, pulmonary artery pressure (not shown) or (c) pulmonary capillary wedge pressure and (d) cardiac index.

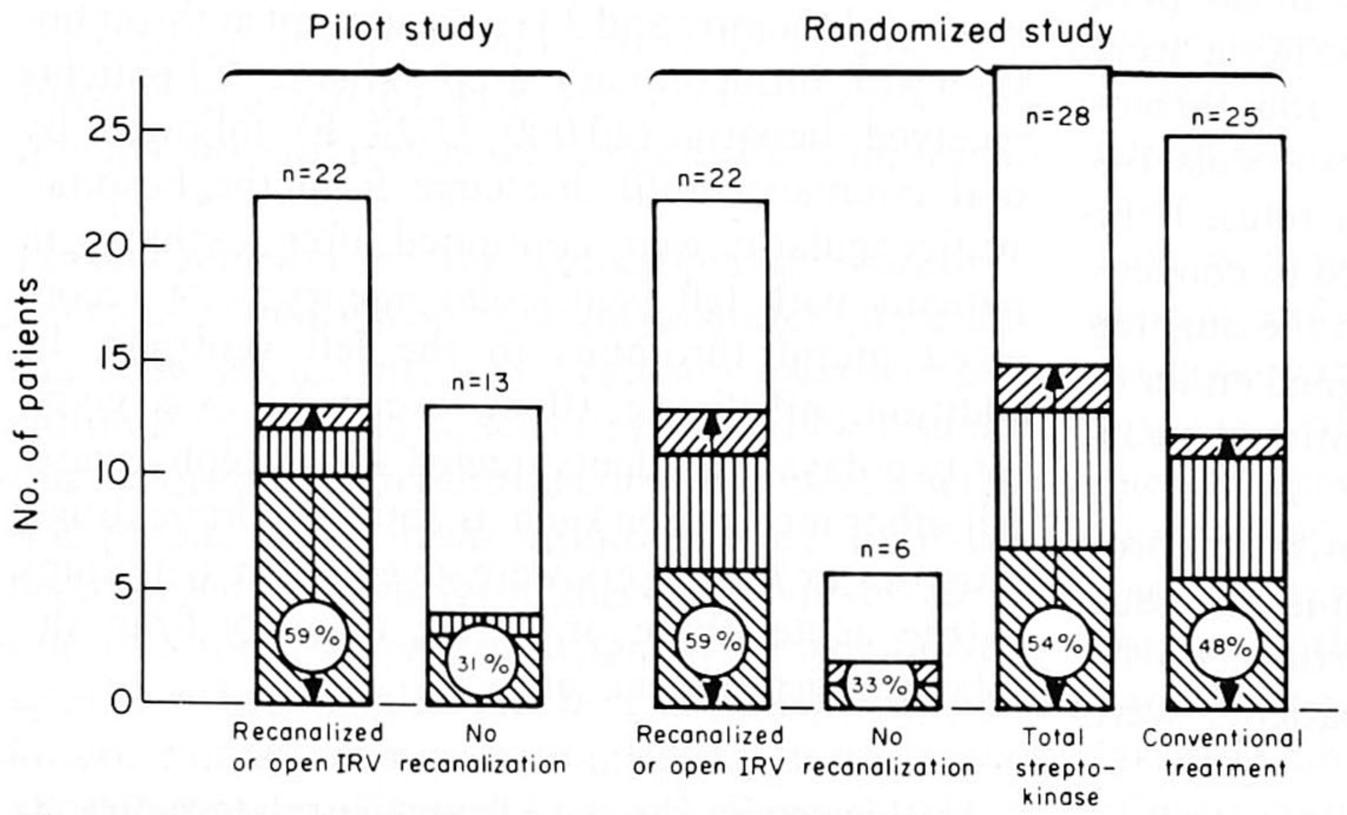

Figure 3 Exercise-induced myocardial ischemia during symptom limited pre-discharge stress testing on a bicycle ergometer. In the pilot studies ST segment depression was more frequent in patients with recanalized or open infarct related vessels when compared with patients in whom recanalization was not achieved ($P<0{\cdot}05$, Student's t-test). No significant differences are apparent in patients allocated to streptokinase intervention or conventional treatment in the randomized study. ▨ = ST depression; ▨ = angina pectoris; □ = no ST ↓ or angina; ▥ ST ↓ and angina.

Table 1 Clinical follow up in 52 patients who underwent cardiac catheterization during acute myocardial infarction in the pilot studies. Total mortality was eight out of 52 patients, four deaths occurred during the procedure while four other patients died during follow up. Reinfarction, angina and exercise-induced ischemia seemed to be more frequent in patients with open arteries after the intervention while late death was observed only in patients in whom the artery remained occluded

	Intervention					
	Streptokinase (n=37)		Urokinase nitroglycerine, nifedipine (n=15)		Total series pilot study (n=52)	
Result of intervention	Open or recanalization	Occluded	Open or recanalization	Occluded	Open or recanalization	Occluded
n	25	8	5	10	30	18
Death during procedure	4		—		4	
Late death	—	2	—	2	—	4
Hospital reinfarction	4(1†)	1	—	—	4(1†)	1
Late reinfarction	2	—	—	1	2	1
Cardiac failure	5	3	—	3	5	6
Angina	15	3	1	3	16	6
CABG/PTCA	9	—	—	—	9	—
Exercise test ST/angina	10/17	2/5	3/5	2/8	13/22	4/13
Survivors without angina, infarct or cardiac failure	5	2	4	3	9	5
Follow-up (patient years)	27		14		41	

CABG = Coronary artery bypass grafting; PTCA = Percutaneous transluminal coronary angioplasty.

Results

ANGIOGRAPHIC DATA

Intracoronary nitroglycerine and intravenous nifedipine as well as intracoronary urokinase in the utilized dosage had little effect on coronary occlusion in the pilot studies. Recanalization was achieved in two out of eight patients after urokinase and in one out of five patients after nitroglycerine and nifedipine.

Intracoronary administration of streptokinase resulted in recanalization of 19 out of 26 arteries in patients with acute infarcts. In seven patients the artery remained occluded. In one other patient streptokinase was not administered since the occluded postero-lateral branch was not recognized during angiography. In six patients the infarct-related vessel was not occluded at angiography. In fact, two of these patients had complete normalization of the ECG after the procedure, without elevated CK levels. These two patients suffered from severe unstable angina and were successfully operated shortly afterwards. Four patients died during the catheterization procedure; three before thrombolysis was attempted and one during streptokinase infusion. A detailed description of these fatal complications is given in the report by Serruys *et al.*[7].

In five out of 66 patients in the randomized study sequential ECGs and enzyme analysis showed no infarct. The discharge diagnosis in three of these patients was unstable angina, and pericarditis in the other two. Three of these five patients were assigned to conventional treatment, one refused angiography and one had normal coronary arteries. Out of 23 patients with an occluded infarct-related artery, recanalization was achieved in 19. One patient died suddenly 30 min after opening of an occluded right coronary artery[7].

Table 2 Details on mortality during and after attempted thrombolysis, and in randomized controls

	Sex/age	Previous infarct	Index infarct	Angio	Result of intervention	Cause of death	Interval after infarct
Pilot studies	m 45	—	ant.	1 V	LAD+LCX occl.	Shock during procedure	4 h
	m 49	inf.	ant.	?	LAD+LCX occl.	Shock during procedure	4 h
	m 58	—	ant.	?	—	Shock during procedure	5 h
	m 42	ant.	inf.	?	—	Shock during procedure	6 h
	m 52	—	ant.	2 V	LAD occl.	VF	1 day
	m 52	ant.	inf.	1 V+	RCA occl.	Reinfarction	4 days
	m 58	?	ant.	2 V	LAD occl.	Operation (aneurysm)	6 months
	m 52	inf.	ant.	1 V+	LAD occl.	Sudden	11 months
Random							
Streptokinase	m 58	?	int.	1 V+	RCA opened	Sudden during procedure	2 h
	m 50	—	ant.	?	Refused	Reinfarction	17 days
	m 61	—	ant.	3 V	Open LAD no streptokinase	Operation (bypass)	1 month
Random							
Control	m 58	inf.	ant.	2 V	—	VF	2 h
	m 67	—	ant.	3 V	—	Reinfarction with shock	2 months
	m 54	ant.	—	1 V	—*	Congestive heartfailure	4 months

Mortality during and after attempted thrombolysis, and in randomized controls. m = male; inf. = inferior; ant. = anterior/anteroseptal; RCA = right coronary artery; LCX = left circumflex artery; LAD = left anterior descending artery; VF = ventricular fibrillation; angio = 1–3 vessel disease (+ indicates that not all arteries were visualized); * = anterior wall infarction was suspected from the ECG, however CK remained normal; ? = unknown.

Table 3 Recurrent myocardial infarction in patients after attempted thrombolysis and in controls. See legend to Table 5

	Sex/age	Index infarct	Recurrent infarct	Angio	Result of intervention	Interval recurrent infarct	Anti-coagulants
Pilot studies	m 51	inf.	inf. (†)		RCA 100%	4 days	+
	m 58	inf.	inf.		RCA 50%	4 days	+
	m 51	inf.	inf.		LCX 95%	5 days	+
	m 61	inf.	inf.		RCA 95%	20 days	−
	m 45	lat.	lat.		LCX 95%	21 days	−
	m 46	ant.	ant. (PTCA)		LAD 75%	21 days	+
	m 53	ant.	inf. (CABG)		LAD 95%	30 months	+
	m 55	inf.	inf.		LCX 100%	7 months	−
Random							
Streptokinase	m 53	inf.	inf.	1V+	RCA 95%	15 days	−
	m 50	ant.	inf. (†)	Refused	—	17 days	+
	m 31	inf.	inf.	1V+	RCA 75%	30 days	−
	m 59	inf.	inf.	1V+	RCA 95%	3 months	−
Random							
control	m 60	inf.	inf.	—	–	10 days	−
	m 27	ant.	ant.	—	LAD 0%	15 days	−
	m 64	ant.	ant.	—	LAD 75%	21 days	+

0–100% Denotes visual score of diameter narrowing in the infarct related coronary artery. lat. = Lateral infarction. For other abbreviations see Tables 1 and 2.

Table 4 Coronary bypass surgery or PTCA after attempted thrombolysis

	Sex/age	Index infarct	Angio	Result of intervention	Procedure	Interval	Complications
Pilot studies	f 54	ant.	1 V	LAD open	PTCA	1 day	—
	m 51	none	2 V	No occl.	CABG	1 day	—
	m 37	none	1 V	No occl.	CABG	7 days	—
	m 46	ant.	1 V	LAD open	PTCA	21 days	Subendocardial infarction
	m 42	ant.	2 V	LAD open	CABG	21 days	—
	m 53	ant.	2 V	LAD open	CABG	28 days	Inferior infarction
	m 61	ant.	1 V	LAD open	CABG	6 week	—
	f 45	lat.	3 V	LCX open	CABG	2 months	—
	m 36	ant.	2 V	LAD open	PTCA	15 months	—
Random Streptokinase	m 57	none	2 V	LAD open	PTCA CABG	1 day	—
	m 61	ant.	2 V	LAD open	CABG	21 days	Death
	f 61	ant.	2 V	LCX open	CABG	1 month	—
	m 49	ant.	3 V	LAD open	CABG	6 months	—
Random control	f 49	none	1 V	—	PTCA	1 day	—
	m 64	ant.	3 V	—	CABG	1 months	—

For abbreviations see legends to Tables 1, 2 and 3.

FOLLOW-UP DATA

The patients were followed at the outpatient clinic at regular intervals. Mean follow-up in the pilot studies was nine months and the longest follow-up was 18 months. The recorded cardiac events are summarized in Table 1. Four patients died during the catheterization procedure[7]. In the four late deaths thrombolysis had not been achieved. Details on the causes of death are presented in Table 2. Early and late reinfarctions occurred in six out of 30 (20%) patients with open infarct-related vessel and in two out of 18 (11%) of patients in whom the artery remained occluded (Table 1). In seven patients the recurrent infarct had the same location as the first infarct. In one other patient an inferior wall infarction developed during coronary bypass surgery while the first infarct was located in the anterior wall (Table 3). Five of these patients used anticoagulants at the time of reinfarction.

Postinfarct angina occurred in 16 out of 30 patients (53%) with open infarct-related vessels and only in six out of 18 patients (33%) in whom the artery remained occluded. Nine patients developed angina which was insufficiently controlled by medication and required percutaneous transluminal coronary angioplasty or coronary bypass surgery. These nine were all in the group with open or recanalized infarct-related coronary arteries (Table 4). In the recovery phase after the infarction and in the outpatient clinic, clinical signs of cardiac failure: dyspnea, rales, gallop rhythm, or radiological signs of left ventricular failure were seen twice as often in patients with occluded vessels (6/18 = 33%) as in patients with open arteries (5/30 = 17%).

Clinical data from the first 66 patients in the current randomized study are presented in Table 5. All patients were classified according to the initial random assignment. Three patients died in each group (Table 2). Hemodynamic monitoring with a Swan Ganz thermodilution catheter was performed in 62 patients (Fig. 2). The catheter was removed after 24 h unless the hemodynamic status of the patient remained unstable. No differences could be demonstrated between the two groups in any measured variable: heart rate, systolic blood pressure, pulmonary artery pressure, pulmonary capillary wedge pressure or cardiac index. The medication during the first two days in the coronary care unit was also similar except for systematic differences related to the protocol. On the other hand, clinical signs of cardiac failure after the acute episode were more frequent in the group assigned to conventional

Table 5 Clinical follow-up in 66 patients in the present ongoing randomized trial. Mortality, reinfarction rate, angina and the results of stress testing are similar in both groups. Clinically recognized cardiac failure was more frequent in patients allocated to conventional treatment

	Assignment	
	Catheterization + thrombolysis (n = 34)	Conventional treatment (n = 32)
Death during procedure	1	—
Late death	2	3
Hospital reinfarction	3(1†)	2
Late reinfarction	1	1
Cardiac failure	2	8
Angina	14	11
CABG/PTCA	4	2
Exercise test ST/angina	15/28	12/25
Survivors without angina, reinfarction or cardiac failure	18	14
Follow-up (patient years)	8	9

treatment. Again reinfarctions occurred in the same region as the first infarct in six out of seven cases (Table 3).

Exercise tests were performed before discharge from the hospital in 35 patients in the pilot studies. The test was not done for various reasons in 17 patients: six patients died in the hospital, one developed recurrent infarction, four patients with successful thrombolysis had unstable angina, four were in cardiac failure while two patients had severe chronic pulmonary disease. Myocardial ischemia judged from exercise-induced angina and/or ST segment depression was observed in 13 out of 22 patients with open or recanalized arteries at admission (59%) and in four out of 13 patients with occluded vessels (31%). The exercise capacity at the time of discharge was similar in both groups (Table 6). In the randomized trial, exercise tests were done in 53 out of the 66 patients. Five patients died in hospital, four others had recurrent infarction, one refused the test, one patient suffered from muscular dystrophy, one patient was transferred to another hospital and one test could not be performed because of technical problems with the equipment. No significant differences were observed between the two treatment groups. However, the same trends could be recognized as in the pilot study. Angina or exercise-induced myocardial ischemia were more frequent in the patients assigned to thrombolytic therapy than in the controls (Table 6, Fig. 3).

Discussion

The efficacy of intracoronary streptokinase in terms of recanalization of an occluded coronary artery in patients with myocardial infarction is similar to that reported by others[3–5, 8]. Urokinase in a similar dosage was not effective and therefore abandoned. It is possible that higher dosages of urokinase would have been as effective as streptokinase since both preparations have been successful in the treatment of massive pulmonary embolism[9]. The high rate of recanalization• by streptokinase supports the concept that thrombus formation plays a major role in acute myocardial infarction[1,10,11]. From our experience it seems that drugs which can abolish coronary spasm such as nitroglycerine and nifedipine seldom result in recanalization[12,13], which makes spasm as a major cause of infarction unlikely. Opinions differ on the optimal drug treatment after attempted thrombolysis. Long-term administration of coumarin anticoagulants is proposed as well as antiplatelet therapy with acetylsalicylic acid or dipyridamole[13]. In our studies heparin was followed by coumarin. This was discontinued at discharge, unless there was a specific indication for long-term anticoagulation such as left ventricular

Table 6 Exercise tolerance, expressed as a percentage of predicted normal working capacity and incidence of exercise-induced myocardial ischemia during symptom limited pre-discharge exercise test in the pilot studies and in the randomized trial. Exercise tolerance is similar in all groups. In the pilot studies myocardial ischemia was apparent more frequently in patients with successful recanalization or open infarct-related vessels at angiography (see also Fig. 3)

	ST and/or angina		% Maximal working capacity	
	No. of patients (%)		Mean (range)	
Pilot studies				
Successful recanalization or open IRV (n = 22)	13	(59%)	78	(47–100)
Not successful (n = 13)	4	(31%)	82	(48–113)
Randomized trial				
Catheterization group: successful or open IRV (n = 22)	13	(59%)	81	(43–105)
Not successful (n = 3)	1		85	(60–114)
Refusers (n = 3)	1		90	(69–113)
Total (n = 28)	15	(54%)	82	(43–114)
Conventional treatment (n = 25)	12	(48%)	78	(52–120)

IRV = infarct related vessels.

aneurysm or intraventricular thrombus. Since seven out of 15 patients used anticoagulants at the time of recurrent infarction (Table 3), the optimal mode of therapy after thrombolysis should be the subject of further investigation.

Contrary to the statements in a recent editorial[14] the procedure is certainly not without risk. We observed five deaths in a total of 82 patients during attempts at thrombolysis. In the proceedings of the symposium which initiated the editorial[14], data from a cooperative German study were reported which included seven deaths in 232 patients[13]. It is difficult to assess the risk of angiography and thrombolysis in a given patient. However, this risk is most likely related to the condition of the patient when the procedure is initiated. Current experience indicates that the safety of the procedure can be improved if patients with severe cardiac failure or shock are excluded until their hemodynamic state has been stabilized. However, it is possible that patients who carry the greatest risk may benefit the most when the procedure is successful[5]. This dilemma can only be solved by larger prospective randomized trials.

It has been postulated that patients after thrombolysis in acute myocardial infarction remain at risk of reinfarction by reocclusion of the same artery[15]. These authors[15], as well as others[12], propose early coronary bypass surgery or percutaneous coronary angioplasty. In our pilot studies reinfarction was indeed more frequent after successful thrombolysis, however, in the randomized trial so far no differences were observed. Thus coronary bypass surgery is not obligatory after successful thrombolysis. In our series surgery was recommended only in patients with postinfarction angina. Reinfarction occurred mostly in the same region as the first infarct. This was true both in patients with successful thrombolysis, and in patients with persistent occlusion as well as in controls.

Exercise-induced angina and ST segment depression were more frequent in patients after successful thrombolysis. This increased incidence of angina can possibly be prevented if thrombolysis is immediately followed by transluminal angioplasty in patients with a severe residual stenosis.

No differences were found in the hemodynamic profile of treated patients and the control group during the first two days in the coronary care unit. However, in the convalescent period, clinically recognized cardiac failure was more frequent in controls and in patients with occluded arteries than

in patients after successful thrombolysis. If this is confirmed by subsequent studies, it could provide an indication that myocardial damage can be reduced by early thrombolysis.

The ultimate benefits of intracoronary thrombolysis in acute myocardial infarction remain uncertain. Data published so far, indicate that some improvement of left ventricular function as assessed by contrast ventriculography or gated blood-pool scintigraphy may be obtained after successful thrombolysis compared with patients whose arteries remain occluded[12,16–19]. However, the differences are small. Also considerable overlap was observed between thallium redistribution patterns after successful and unsuccessful thrombolysis. Details on these studies appear elsewhere in this issue of the *Journal*[19].

As in other series, some patients show no rise of serum enzymes in spite of the initial clinical diagnosis of myocardial infarction. This is unavoidable since if thrombolysis is to be attempted it should be carried out as soon as feasible after admission and often before the diagnostic work-up has been completed. In our series seven patients were ultimately classified as having unstable angina while two appeared to have pericarditis which simulated ECG signs of early myocardial infarction.

In conclusion, the presently available data have not shown that the theoretical benefits of intracoronary thrombolysis can be readily demonstrated in practice. The procedure is expensive, time consuming and not without risk to the patient. On the other hand there are indications that some myocardial salvage can be achieved in some of the patients. Thus further studies comparing intracoronary thrombolysis with conventional treatment should be undertaken. Especially, it is mandatory that those groups of patients who may benefit most from the procedure be better defined. Such studies might also reinvestigate the value of intravenous administration of streptokinase or other thrombolytic drugs[6,20]. Finally this intervention should ultimately be compared with other therapeutic modalities such as β-blockers in acute myocardial infarction[21].

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