case ventilatory depression returns. The use of a larger dose of naloxone, given either intravenously or intramuscularly, is being investigated to determine whether the action of naloxone can be usefully prolonged.

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Streptokinase in acute myocardial infarction: a controlled multicentre study in the United Kingdom

C P ABER, N M BASS, C L BERRY, P H M CARSON, R J DOBBS, K M FOX, J J HAMBLIN, S P HAYDU, G HOWITT, J E MACIVER, R W PORTAL, E B RAFTERY, R H ROUSELL, J P P STOCK

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Summary

In a multicentre trial of streptokinase in acute myocardial infarction 302 patients received an intravenous infusion of 2 500 000 IU of streptokinase over 24 hours, while 293 patients served as controls. Neither group received anticoagulants unless indicated by thromboembolic complications. No significant difference in mortality was evident during inpatient treatment nor at six-week or six-month follow-up. The inpatient death rate was 12.6% in the streptokinase group and 13.7% among controls.

There was no significant difference in the peak levels or pattern of enzyme increase. The incidence of cardiac failure and reinfarction was similar in the two groups, but major arrhythmias were less common in those on streptokinase ($P < 0.05$). In the streptokinase group there were 36 minor and six more serious haemorrhagic com-

plications. Gastrointestinal haemorrhage may have contributed to the death of one patient in each group. There were 18 thromboembolic complications in the streptokinase group and 38 among the controls. Pathological examination of the hearts of 25 patients who had taken streptokinase and 24 controls showed no striking differences between the groups, but haemorrhagic infarcts were found in three patients who had received streptokinase.

An infusion of streptokinase within 24 hours of the onset of acute myocardial infarction does not significantly affect the mortality or course of the illness up to six months.

Introduction

Since the introduction of streptokinase into clinical practice 17 years ago^{1 2} the therapeutic value of thrombolytic agents in acute myocardial infarction has remained in doubt. Only recently have a series of major controlled trials been undertaken (table I).³⁻⁷ No conclusive result in favour of streptokinase has emerged from these studies, in which the initial thrombolytic treatment followed by anticoagulation was compared with anticoagulant treatment alone. The trial reported here was started in the United Kingdom in August 1971 and ended in June 1974. Its object was to determine whether thrombolytic treatment influenced early or late mortality, the incidence of complications, and the pathological findings in the hearts of patients who died. Preliminary results have been briefly reported⁸; we present here the final results, concluding the study at six months' follow-up.

Design of trial

Criteria for admission—The trial was conducted in coronary care units in five different hospitals, the only requisite for entry being a diagnosis of myocardial infarction within the previous 24 hours. At the time of entry into the trial this rested necessarily on the clinical picture and the initial electrocardiogram (ECG). The ECG criteria for infarction used were those of the World Health Organisation,⁹ the diagnosis of acute infarction was not accepted unless there was a significant increase in either serum aspartate aminotransferase (SGOT) or lactate dehydrogenase (LDH) concentrations, or both. Both sexes were accepted and no upper age limit was prescribed.

Statistical design—The statistical design, described by Armitage,¹⁰ tested the null hypothesis that the death rates in the streptokinase and control groups were the same against a two-sided alternative

Kingston General Hospital, Kingston-upon-Hull

C P ABER, MD, FRCP, consultant cardiologist
K M FOX, MB, MRCP, registrar in cardiology
R W PORTAL, MD, FRCP, consultant cardiologist

Stoke-on-Trent

N M BASS, MB, MRCP, honorary senior registrar (present address: Cardiology Department, Green Lane Hospital, Auckland, New Zealand)
P H M CARSON, FRCP, FACC, consultant cardiologist
J P P STOCK, MD, FRCP, consultant cardiologist (Dr Stock died on 4 October 1973)

Guy's Hospital Medical School, London

C L BERRY, MD, MRCPATH, reader in pathology

Manchester Royal Infirmary, Manchester

R J DOBBS, MRCP, DHC, research fellow, cardiology department
G HOWITT, MD, FRCP, consultant cardiologist
J E MACIVER, MD, FRCPATH, consultant haematologist

Southend General Hospital, Westcliff-on-Sea, Essex

J J HAMBLIN, MB, MRCP, consultant physician
S P HAYDU, MB, MRCP, registrar

Northwick Park Hospital, Harrow, Middlesex

E B RAFTERY, MD, MRCP, consultant cardiologist

Hoechst Pharmaceuticals, Hounslow, Middlesex

R H ROUSELL, MSc, MB, head of medical services

TABLE I—Details of major controlled trials of streptokinase treatment in myocardial infarction

Trial	Year	No of patients	Anticoagulants used in control and streptokinase groups	Streptokinase dose (IU)		Duration of infusion (hours)	Interval between onset of symptoms and start of treatment (hours)	Mortality (%)			Significance (P)
				Loading	Hourly			Time period	On streptokinase	Controls	
German/Swiss I ¹	1966	558*	Yes	250 000	150 000	18	<12	Up to 40 days	14.1	21.7	<0.05
								≤24 hours	5.4	5.4	NS
German/Swiss II ²	1970	269*	Yes	250 000	100 000	18	<12	2-40 days	8.7	16.1	<0.02
								Up to 40 days	14.5	26.0	<0.03
								≤24 hours	2.2	10.7	<0.01
European Working Party ³	1971	730†	Yes	250 000	100 000	24	<24	2-40 days	12.3	15.3	NS
								Up to discharge‡	18.5	26.3	<0.02
								≤24 hours	8.8	10.4	NS
								2 days to discharge	10.6	17.8	<0.02
Italy ⁷	1971	321† (CCU)	Yes	250 000	150 000	12	<12	Up to 40 days	11.6	11.5	NS
								≤24 hours	1.8	2.6	NS
Australia ⁸	1973	517† (CCU)	Yes	250 000	100 000	17	<24	2-40 days	9.9	9.1	NS
								Before discharge§	6.4	8.7	NS
United Kingdom	1975	595* (CCU)	No	250 000	100 000	24	<24	At 3 months	9.8	12.6	NS
								Up to 42 days	14.2	15.0	NS
								≤24 hours	3.6	4.8	NS
								2-42 days	11.0	10.8	NS

*Patients with confirmed infarct only. †Includes patients in whom infarct was not confirmed. ‡Discharge at about 40 days. §Time of discharge not stated. CCU = Conducted entirely in coronary care units. NS = Not significant.

TABLE II—Prognostic Index (modified from Norris *et al*¹⁰) using patient's age and systolic blood pressure on admission

Score	Age (years)					Blood pressure (mm Hg)									
	<50	50-59	60-69	70-79	≥80	<55	55-64	65-74	75-84	85-94	95-104	105-114	115-124	≥125	
Score	1.0	1.5	2.5	3.0	4.0	10.0	7.0	6.5	5.0	4.0	3.0	2.0	1.0	0	

Subgroup 1—those with scores of ≤3 (461 patients). Subgroup 2—those with scores of 3.5-8.5 (125 patients). Subgroup 3—those with scores of ≥9 (9 patients).

hypothesis that one regimen would produce a higher death rate than the other. The chance of rejecting a true null hypothesis (type I error) was fixed at 0.025 and the chance of rejecting a true alternative hypothesis at 0.05. In other words, a two-sided significance level of 2½% with a power of 95% was used.

Exclusions—The chief reasons for exclusion from the trial were: known haemorrhagic disorder; gastrointestinal haemorrhage within the previous six months; history of peptic ulceration; recent surgery; an initial diastolic blood pressure over 120 mm Hg or definite history of hypertension; hepatic disease; previous streptokinase treatment or previous entry to the trial.

Allocation and subgrouping—A total of 660 patients were admitted to the trial. The numbers contributed by the five participating centres ranged from 69 to 204. After admission to the trial the patient was allocated to one of three subgroups (A, B, or C) according to a simple prognostic index modified from Norris *et al*¹¹ (table II). This index was based on the sum of scores allocated according to the patient's age and systolic blood pressure on admission. Group C contained patients thought to be at greatest risk by virtue of their greatest age and lowest blood pressure. This stratification into three prognostic subgroups was not part of the statistical design, but was done only to ensure that the rarer patients with an initially greater chance of dying as a result of their infarction were divided evenly between the streptokinase and control groups. Each patient was then randomly allocated to either the streptokinase (332) or control (328) group.

Treatment regimen—Streptokinase 250 000 IU was given in 25 ml of 5% dextrose by intravenous infusion over 30 minutes. In the succeeding seven and a half hours a continuous infusion of 750 000 units was given in a volume of 200 ml, followed by 750 000 IU in each of two further eight-hour periods. Thus a total of 2 500 000 IU was given in a volume of 625 ml over 24 hours. Neither those taking streptokinase nor the controls were given anticoagulant treatment unless this became clinically indicated by thromboembolic events. No corticosteroid was given during the streptokinase infusion unless it was required to control pyrexia or skin reaction. The management of both groups was similar as regards the speed of mobilisation and length of stay in hospital.

Investigations—Conventional 12-lead ECGs were recorded on admission and then daily. Blood for SGOT measurement was drawn on entry to the trial and at 12, 18, and 24 hours and for LDH at entry and daily for 10 days. Fibrin degradation products (FDP) and thrombin time were estimated in the streptokinase group at entry

and at 4, 24, and 48 hours. The FDP of all patients was measured in a single laboratory at one of the centres (JEM).

Necropsies were performed whenever possible in patients dying in hospital. The hearts were preserved with minimal dissection for later examination by the pathologist to the trial (CLB).

Follow-up—Patients were reassessed by means of clinical examination, chest x-ray examination, and ECG six weeks and six months after infarction.

Results

Sixty-one of the 600 patients admitted to the trial were excluded from the analysis because of failure to show recent myocardial infarction; four others were excluded because they departed from the protocol. Thus 595 patients (526 men and 69 women) were left for analysis. The numbers of patients contributed by the five centres for the final analysis are shown in table III. Although the numbers contributed by different centres varied widely all centres adhered to rigid inclusion and exclusion criteria during the study. Furthermore, patients were allocated to the streptokinase or control group according to a blind randomised code. There were 302 patients taking streptokinase and 293 controls. Prognostic subgroup A contained 234 on streptokinase and 227 controls, subgroup B 63 on streptokinase and 62 controls, and subgroup C five on streptokinase and four controls.

A detailed assessment of the comparability of the streptokinase and control groups as a whole and by subgroup is shown in table IV. There were significantly more controls with a history of angina. Otherwise, there were no major differences in sex, age, previous infarction, initial systolic blood pressure, and interval between infarct and admission (start of streptokinase treatment in the treated group).

TABLE III—Numbers of treated and control patients with proved infarction contributed by the five participating centres

Centre	1	2	3	4	5	Total
No on streptokinase	97	39	30	46	90	302
No of controls ..	94	40	30	45	84	293
Total	191	79	60	91	174	595

TABLE IV—Comparability of groups on admission to trial

	All groups			Prognostic group 1			Prognostic group 2			Prognostic group 3		
	Strepto-kinase group	Controls	Signifi- cance (P)	Strepto-kinase group	Controls	Signifi- cance (P)	Strepto-kinase group	Controls	Signifi- cance (P)	Strepto-kinase group	Controls	Signifi- cance (P)
Total No of men ..	272	254	NS	214	196	<0.1	53	54	NS	5	4	NS
Total No of women ..	30	39	NS	20	31	<0.1	10	8	NS			
Mean age (years) ..	55.9	57.1	NS	54.5	56.1	<0.15	60.1	60.6	NS	68.6	60.0	NS
History of angina ..	45.0	54.3	<0.025	45.3	56.8	<0.025	44.4	46.8	NS	25.0	40.0	NS
(% of patients)												
Previous infarction ..	19.2	18.4	NS	17.9	18.1	NS	23.8	21.0	NS	20.0	nil	NS
(% of patients)												
Infarct to admission ..	6.9	7.3	NS	6.5	7.6	NS	6.8	7.4	NS	9.0	4.6	NS
(hours)												
Systolic blood pressure ..	136.4	138.5	NS	146.5	149.7	NS	104.8	103.4	NS	59.0	50.0	NS
on admission (mm Hg)												

Apart from test used for comparing groups in time from admission to infarct, tests based on the assumption of a normal distribution were used. For testing the comparability in time from infarct to admission a Mann-Whitney U test was used.

Weights and heights were recorded in 183 patients on streptokinase and 189 controls. The mean height was 171 cm in each group and the mean weight less ideal weight 8.2 kg in those on streptokinase and 8.4 kg in the controls. The mean stay in hospital was 13.6 days in the streptokinase group and 13.9 days in the control group.

A further breakdown of the time from infarct to admission is given in table V. This confirms that there were no major differences in the time from infarct to admission between either the streptokinase or control group or the various prognostic subgroups. In all groups 25% of patients were admitted within three hours, 50% within five hours, and 75% within 12 hours.

All differences between the streptokinase and control groups tended to favour the streptokinase group slightly.

Mortality—The inpatient crude death rate in the streptokinase (38 deaths) and control groups (40 deaths) was similar (table VI). The death rates relative to the time of infarction and the cumulative death rates at seven days, six weeks, and six months are shown in table VII. Again no significant difference was evident, although that most nearly approaching significance was the difference between the two groups at 12 to 24 hours after the onset of symptoms ($P=0.07$).

TABLE V—Quartiles of distribution of times from infarct to admission (hours)

	Streptokinase group			Controls		
	Lower	Median	Upper	Lower	Median	Upper
Prognostic group 1 ..	3	5	10	3	5	11
Prognostic group 2 ..	3	4	9	3	4	12
Prognostic group 3 ..	3	5	6	1	2	12
All groups ..	3	5	10	3	5	12

TABLE VI—Inpatient mortality (%) in streptokinase and control groups. Actual numbers of inpatient deaths are given in parentheses

	Streptokinase group	Controls	Total
<i>Centres</i>			
1	12.4 (12)	9.6 (9)	11.0 (21)
2	7.7 (3)	15.0 (6)	11.4 (9)
3	20.0 (6)	13.3 (4)	16.7 (10)
4	8.7 (4)	15.6 (7)	12.1 (11)
5	14.4 (13)	16.7 (14)	15.5 (27)
<i>Prognostic groups</i>			
A	9.0 (21)	9.7 (22)	9.3 (43)
B	23.8 (15)	22.6 (14)	23.2 (29)
C	40.0 (2)	100.0 (4)	66.7 (6)
Total	12.6 (38)	13.7 (40)	13.1 (78)

TABLE VII—Overall mortality (%) at intervals after infarction and overall rate at six weeks' and six months' follow-up

	<12h	-24h	-48h	-7 days	Total at 7 days	-6 weeks	Total at 6 weeks	-6 months	Total at 6 months
Streptokinase group	2.7	1.0	2.1	5.6	10.9	3.7	14.2	1.9	15.9
Controls ..	1.8	3.1	1.8	4.7	10.9	4.6	15.0	3.2	17.8

TABLE VIII—Mortality in relation to site of infarct in streptokinase and control groups. Actual numbers of deaths are given in parentheses

Site of infarct	Total No of patients	Mortality (%)	
		Streptokinase group	Controls
Anterior, anterolateral and lateral ..	282	21 (31)	25 (33)
Interior and inferolateral ..	258	7 (9)	8 (11)
Anterior and inferior ..	16	43 (3)	33 (3)
ECG non-localising (enzymes positive) ..	39	25 (5)	26 (5)

TABLE IX—Incidence of cardiac failure, reinfarction, and arrhythmias (% of patients) in streptokinase and control groups

	Streptokinase group	Controls	Significance (P)
Cardiac failure:			
On admission ..	23.8	21.8	NS
From 24 hours to discharge (or death) ..	13.5	14.0	NS
Reinfarction:			
Before discharge (or death) ..	3.6	4.1	NS
All arrhythmias ..	53	59	NS
Major arrhythmias* ..	23	30	<0.05

*See text.

There was no relationship between mortality and site of infarction (table VIII).

Incidence of cardiac failure, reinfarction, and arrhythmias—Cardiac failure was diagnosed on conventional clinical grounds, while the same diagnostic criteria were applied to reinfarction as were used for the original infarct.⁹ ECG tracings were used to define the nature and incidence of arrhythmias and other disorders of conduction. We thought that in the interest of brevity these could be grouped under a single heading of "major" arrhythmias, which included atrial fibrillation, supraventricular tachycardia, left or right bundle-branch block, heart block (grades 1, 2, and 3), ventricular tachycardia, and fibrillation and asystole. The incidences of cardiac failure, reinfarction, and major arrhythmias is shown in table IX. The control group showed a significantly greater incidence of major arrhythmias.

Enzyme levels—The enzyme peaks were of comparable magnitude and occurred at much the same interval after infarction in both groups (tables X and XI). SGOT levels were measured only during the first 24 hours after admission to the study, while LDH was estimated daily for 10 days. As expected the peak levels were significantly higher in those patients who died.

TABLE X—Peak SGOT levels in streptokinase and control groups

SGOT levels	Streptokinase group		Controls	
	No of patients	Mean peak (IU/l)	No of patients	Mean peak (IU/l)
At admission	23	156.47	28	179.10
12 hours	82	299.30	43	201.62
18 hours	85	319.58	83	231.15
24 hours	101	317.18	122	287.63
Total recorded	291	300.14	276	246.23
Number dead	44	439.88	41	335.00
Number alive	247	275.25	235	230.75
Not recorded	11		17	

TABLE XI—Peak LDH levels in streptokinase and control groups

LDH levels	Streptokinase group		Control	
	No of patients	Mean peak (IU/l)	No of patients	Mean peak (IU/l)
At admission	16	601.56	24	661.16
24 hours	158	1425.84	113	1301.42
48 hours	68	1333.61	99	1566.81
3 days	28	1201.39	19	1255.00
4 days	6	742.50	9	622.77
5 days	1	580.00	2	947.50
6 days	2	470.00	1	860.00
7 days			3	370.00
8 days	1	295.00	2	515.00
9 days				
10 days	1	1680.00		
Total recorded	281	1306.70	272	1293.45
Number dead	40	1806.40	41	1554.87
Number alive	241	1223.76	231	1247.05
Not recorded	21		21	

TABLE XII—Fibrinolytic degradation products at four hours in streptokinase and control groups

FDP titre	Streptokinase group		Controls	
	All patients	Patients who died	All patients	Patients who died
1/2	18	2	155	21
1/4	11	2	37	8
1/8	6		7	1
1/16	5		2	
1/32	10		1	1
1/64	6	1		
1/128	11			
1/256	22	10		
1/512	30	6	1	1
1/1024	52	9	3	
1/2048	18	1		
1/4096	19	1		
1/8192	9	1		
Total recorded	217	33	206	32
Not recorded	85	15	87	20
Total	302	48	293	52

Fever—Inspection of the patients' temperature records showed no significant difference in pattern between the two groups. Febrile reactions attributed to streptokinase were few, but 13 patients were given corticosteroids, and five of these showed fever disproportionate to the infarct. Steroids were also given to six patients in the control group for conditions unrelated to the infarction.

Fibrinolytic activity—As a measure of the effectiveness of streptokinase treatment fibrinolytic activity was assessed by measuring the level of FDP in the serum by the tanned red cell haemagglutination-inhibition immunoassay.¹² The FDP levels at four hours in the treated and control groups are given in table XII. A titre of less than 1/8 may be regarded as normal by this method. A significantly raised FDP concentration was found in 188 out of 217 cases (87%) in the treated group, with titres of 1/256 or more being seen in 150 cases (69%). Thrombin times (table XIII) closely paralleled the FDP levels. In practice, these results were seldom available before the

end of streptokinase infusion and did not therefore influence dosage or management.

Haemorrhagic complications—The incidence of bruising, epistaxis, haematuria and gastrointestinal bleeding is shown in table XIV. In the main these episodes were not severe, but in six patients in the streptokinase group the haemorrhage was severe enough to necessitate stopping treatment and reversing the fibrinolysis. In one patient on streptokinase and one control a gastrointestinal bleed may have contributed to death. Neither patient was receiving anticoagulant treatment. The haemorrhages in the streptokinase group were not predictable by excessively prolonged thrombin times.

Thromboembolic complications—Clinically diagnosed venous thrombosis, pulmonary embolism, and systemic embolism occurred more often in the control group. The incidence of stroke was similar in both groups (table XV).

Pathology—Fifty-three hearts were available for pathological examination, 27 from the streptokinase group and 26 from the control group. Two hearts from the streptokinase group were excluded from the study when it was found that no streptokinase had been administered before death, and two control hearts were excluded because of

TABLE XIII—Thrombin times at admission and at four hours in streptokinase and control groups

Ratio of thrombin time at 4 h to admission value*	0	1	2	3	4	5	Not recorded	Total
No of patients: Streptokinase group ..	10	94	83	36	17	21	41	302
Controls ..	73	158					62	293

*Lower limit of interval.

The desired thrombin time range is two to four times the control value (admission). As expected thrombin times at four hours were not raised in the controls.

TABLE XIV—Haemorrhagic complications in hospital in streptokinase and control groups. Figures in parentheses indicate number of patients in whom streptokinase treatment was stopped

	Bruising	Epistaxis	Haematuria	Gastrointestinal bleeding	Other
No in streptokinase group	26	6 (1)	5 (2)	4 (3)	1
No of controls ..	1	1		2	

Figures indicate numbers of patients. Brackets show those in whom SK therapy was terminated.

TABLE XV—Thromboembolic complications in hospital in streptokinase and control groups

	Venous thrombosis	Pulmonary embolism	System embolism	Stroke
No on streptokinase group	8	5		5
No of controls ..	17	13	3	5
Significance (P) ..	<0.1	<0.1		

TABLE XVI—Pathological findings in 49 hearts from patients in streptokinase and control groups

	Streptokinase group	Controls
No of hearts examined	25	24
Nature of occluding lesion:		
Thrombus	11	10
Haemorrhage in plaque	3	6
Stenosis only	3	3
Previous occlusion	8	6
Endocardial thrombus	11	10
Myocardial tears	5	4
Evidence of previous ischaemia	11	12
Extension of infarct	2	3
Haemorrhagic infarcts	3	

extensive dissection before examination by the trial pathologist. At the time of examination the group to which each heart belonged was not known. The findings in the remaining 49 hearts are summarised in table XVI. Full information on macroscopic examination and microscopy has been published elsewhere.¹³

Discussion

The rationale of streptokinase treatment in acute myocardial infarction has never rested on the sanguine expectation that lysis of newly formed thrombus would protect the threatened myocardium from necrosis. It seemed possible, however, that the size of the infarct might be reduced by preventing extending thrombosis in the affected or neighbouring arteries or in small vessels at the periphery of the infarct. If this were so a fall in mortality or in early complications might be apparent. The results of our own and other studies conducted entirely in coronary care units have failed to confirm this hypothesis, however. Details of the earlier major trials of streptokinase in acute infarction are summarised in table I together with those of our study. The dose and duration of streptokinase treatment are broadly comparable and in all trials the treatment was started within 24 hours of the onset of symptoms. Like ours, patients in the Italian and Australian studies were all treated in coronary care units. Our trial differed chiefly in that anticoagulant treatment was given to neither those receiving streptokinase nor controls unless indicated by the development of thromboembolic complications.

On the basis of the simple prognostic index only nine patients fell into subgroup C. Admission of patients to the trial at the five participating centres was neither universal nor consecutive but was governed by administrative and staffing considerations. There were understandable problems in entering a patient whose clinical condition was already absorbing the efforts of the staff in supportive or resuscitative measures. The small number of patients in this group precludes meaningful analysis and leaves open the question whether such patients might benefit from streptokinase. Once admitted to the trial, however, allocation of the patient to either the streptokinase or control group was according to strict blind random chart.

No significant difference in overall mortality emerges from analysis of prognostic subgroups A and B, but there was a wide and unexplained variation between the mortality rates at different centres (table VI). This has also been seen in other studies.⁵ Two patients in the streptokinase and three in the control group died within six hours of infarction.

The largest difference in the hospital death rates between those on streptokinase and controls occurred 12-24 hours after infarction. Though fibrinolytic activity should be maximal at this time the difference was still not significant ($P=0.07$), and there are no data to suggest that this slightly favourable trend would have continued had anticoagulants been used after the streptokinase infusion. The analysis shows no evidence that any particular feature such as age, early treatment, or site of infarct influenced the outcome in the two groups. Nor does a comparison of the peak values of SGOT or LDH suggest that streptokinase limits the extent of myocardial necrosis. It was not unexpected

that the mean peaks in the 85 patients who died exceeded those of the survivors, for it is now established that the magnitude of the enzyme rise reflects the size of the infarct.

The incidence of cardiac failure and reinfarction in hospital was similar in the two groups. Although the incidence of major arrhythmias was less in the streptokinase group this had no bearing on the ultimate mortality.

Though the incidence of haemorrhagic manifestations in the streptokinase group cannot be ignored it was not prohibitive, being a possible contributory cause of death in only one patient. Allergic reactions to streptokinase did not constitute a problem despite the absence of routine corticosteroid cover. The difference in thromboembolic complications in the two groups was favourable to streptokinase and may reasonably be attributed to the drug's thrombolytic action at a time when immobility and reduced cardiac output were conducive to stasis.

Pathological examination of hearts showed that the only difference between the groups that might be significant was the finding of haemorrhagic infarcts in three patients given streptokinase, a change that has been commented on.¹⁴ The rather high incidence of myocardial rupture in both groups was probably related to external cardiac massage during attempted resuscitation.

Our trial, like the Italian and Australian ones, has failed to provide support for the routine use of streptokinase in acute myocardial infarction. Its prophylactic value in crescendo angina has yet to be assessed by a controlled study.

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