PAPERS AND ORIGINALS

Streptokinase in Recent Myocardial Infarction: A Controlled Multicentre Trial

EUROPEAN WORKING PARTY

British Medical Journal, 1971, 3, 325-331

Summary

In this controlled multicentre trial treatment with either streptokinase or heparin was allocated at random to patients suffering from myocardial infarction of less than 24 hours' duration. Treatment with either drug was standardized and lasted for 24 hours. A total of 764 patients entered the trial; 34 patient charts were rejected (including all 28 charts from one centre) because of data failure. On retrospective analysis of the 730 remaining patients the two groups were found to have been comparable at the start.

The total hospital mortality was 18.5% of 373 patients allotted to streptokinase treatment and 26.3% of 357 given heparin. The mortality after infusion (24 hours) was 10.6% of 340 patients treated with streptokinase and 17.8% of 320 given heparin ($P=0.011$). Reinfarction in hospital after the 24-hour period of infusion occurred significantly less often in patients treated with streptokinase ($P=0.036$). Bleeding from puncture sites and pyrexia occurred more frequently during streptokinase treatment.

After exclusion of those patients whose diagnosis was unconfirmed on retrospective assessment, the total

hospital mortality rate was 19.0% of 357 patients treated with streptokinase and 27.4% of 339 treated with heparin ($P=0.011$). These results indicate that in recent myocardial infarction streptokinase was superior to heparin in reducing mortality and reinfarction rate during an average period of six weeks in hospital.

Introduction

Several studies on the use of urokinase, streptokinase, or plasma activated by streptokinase or urokinase in the treatment of recent myocardial infarction have been reported (Amery *et al.*, 1969). Only two multicentre controlled trials of streptokinase in recent myocardial infarction have been published. In one (Schmutzler *et al.*, 1966) 297 patients were treated with streptokinase for 18 hours followed by coumarin for 18 hours and 261 control patients were treated only with heparin followed by coumarin drugs; in all patients the interval between the onset of clinical symptoms and starting treatment was less than 12 hours. The overall mortality over the first 40 days in the two groups was 14.1% and 21% respectively ($\chi^2=4.64$, $P=0.031$). Excluding the first 24 hours in hospital, the mortality in the streptokinase series was 8.7% compared with 16.1% for the control group ($\chi^2=6.37$, $P=0.012$). In another European multicentre trial 84 patients whose myocardial infarction had occurred less than 72 hours before were treated with a standard dose of streptokinase (1,200,000 IU initially and then 100,000 IU hourly for 72 hours followed by coumarin) and 83 patients were given only anticoagulants (heparin for 72 hours followed by coumarin). No significant difference in mortality in hospital could be found between the two groups (Amery *et al.*, 1969).

In the multicentre trial reported here a lower initial dose of streptokinase (250,000 IU) and a maintenance dose of 100,000 IU hourly for 24 hours were given. The aim was to study the effect of streptokinase treatment on mortality in patients with a myocardial infarction of less than 24 hours' duration. Admission to the trial was according to a strict randomization schedule.

The following centres participated:

Städtische Krankenanstalten, Goslar, Medizinische Abteilung, Germany (Dr. F. Lewien); Allgemeines Krankenhaus Altona, Hamburg, I. Medizinische Abteilung, Germany (Dr. P. Lübcke, Dr. O. Müller-Plathe); Kreiskrankenhaus Herford, Medizinische Klinik, Herford, Germany (Professor Dr. E. F. Gersmeyer, Dr. G. Musche, Dr. H. Kortemeier); Medizinische Universitätsklinik, Innsbruck, Austria (Professor Dr. H. Braunsteiner, Dozent Dr. F. Holzknacht, Dr. F. Spöttl); Städtisches Krankenhaus München-Schwabing, I. Medizinische Abteilung, Germany (Professor Dr. H. Begemann, Dr. G. Roeber, Professor Dr. E. König); Städtische Krankenanstalten, Remscheid, Germany (Professor Dr. J. Hamm, Dr. C. Schultz); Bergwegziekenhuis, Rotterdam, Netherlands (Dr. S. A. ten Bokkel Huinink, Dr. H. J. Vermeulen); Städtische Krankenanstalten Solingen, Medizinische Klinik 1, Germany (Dr. J. Bredt, Dr. K. Schweikart, Dr. F. Pfeiffer); Städtische Krankenanstalten Solingen, Medizinische Klinik 2, Germany (Professor Dr. U. Kanzow, Dr. S. Haastert, Dr. J. Hoppe).

Co-ordinating centre, Academisch Ziekenhuis, Leuven, Belgium (Professor Dr. M. Verstraete, Dr. A. Amery, Dr. J. Vermeylen).

Design and Method

The trial was carried out between September 1967 and May 1970. The main criterion for inclusion was a clinical diagnosis of a myocardial infarction that had occurred less than 24 hours before. At the conclusion of the trial the electrocardiographic evidence of recent infarction was examined by an independent expert, who read the serial electrocardiograms for each patient without knowing what treatment had been given (see Appendix).

Patients who had a history of a bleeding diathesis, a potential bleeding site (active peptic ulcer, recent major surgery), seriously impaired renal or liver function, or a serious allergy were excluded from the trial. Those with a significant hypertension (diastolic pressure more than 100 mm Hg) on admission or at any time before the start of treatment, or with a retinopathy of more than grade II (Keith-Wagener-Barker), were also excluded. No exclusions were made on the grounds of age, sex, previous myocardial infarction, cerebrovascular accident, or the presence of diabetes.

A special, numbered patient chart was designed for the trial.* It provided for a record of the identity by code of the treatment centre and the patient, general information and previous medical history, state of patient on admission, and investigations before and during treatment. There were also sections for recording clinical details of the infusion period and for a final evaluation of the case on discharge. All questions were numbered and most could be answered by "yes" or "no." The data were then summarized and analysed by computer.

Details of the electrocardiographic studies are given in the Appendix.

Treatment

Treatment started with either 250,000 IU of streptokinase in 50 ml of glucose 5% or 100 mg of heparin in 50 ml of glucose 5% administered over a 20-minute period. Coumarin was given in both groups immediately. The maintenance dose of streptokinase was 100,000 IU hourly for 24 hours (1,200,000 IU of streptokinase dissolved in 50 ml of glucose 5% over 12 hours followed by the same dose over the next 12-hour period). The maintenance dose of heparin was 150 mg dissolved in 50 ml of glucose 5% administered over 12 hours followed by the same dose during the next 12 hours.

For both groups special attention was paid to the transition period between the infusion and the effect of the coumarin treatment. When necoumalone (acenocoumarol) or ethyl biscoumacetate was used no special precautions had to be taken. When phenprocoumon was used it was necessary to give some intravenous heparin injections after the infusion period—that is, 10,000 IU (100 mg) of sodium heparin intravenously 28, 32, and 36 hours after the beginning of treatment. It was recommended that heparin should be given until the prothrombin decreased to the desired level. Treatment with oral anticoagulants was continued routinely in all patients at least until discharge from hospital. The coumarin used and the dosage was decided by each centre.

Apart from the trial drugs, the treatment given for myocardial infarction, shock, or arrhythmia in both groups was at the discretion of the clinician in charge.

Statistical Procedure

For each set of 20 serially numbered patient charts assigned to a participating centre an equal number of "streptokinase" or "heparin" cards were allotted in a random order by the co-ordinating centre. The distribution was designed so that

at the end of the trial each centre would have treated equal numbers of patients with streptokinase or heparin, thus permitting a separate evaluation of the results for each centre as well as allowing for comparison of the results among the participating centres. When each patient's chart and blood samples were returned to the co-ordinating centre they were checked to make sure the scheduled treatment had been given.

Since at the start of the trial it was unknown how streptokinase would compare with heparin in the treatment of myocardial infarction it was considered that two-tailed alternatives had to be used in testing for significance. When using χ^2 this involves comparing the calculated χ^2 value with its one-tail upper critical value (Bailey, 1959) and quoting the tabular P value as the significant level. In order to provide clear-cut information the true level of significance was determined by using a table giving exact P values for each calculated χ^2 (Kendall and Stuart, 1963) rather than the nominal conventional significance level. In borderline cases the χ^2 values both with and without correction for continuity are quoted, otherwise the corrected χ^2 values are stated.

For 2×2 tables where unknowns were left out (see, for example, Table I) the corresponding χ^2 values were recomputed as χ^2 components of the complete 3×2 table χ^2 values. Nowhere did this lead to significant changes. This check was made because it was thought that comparisons should be made systematically on the basis of the total numbers of patients at risk. Indeed, only the entire treatment groups have been made comparable by the randomization procedure. For the same reason comparisons between treatments only within the group of survivors or only the group of non-survivors should be regarded with caution, and they have been supplemented with comparisons based on the total numbers of patients. However, when groups are defined with reference to factors possibly influencing treatment and not according to categories of responses to treatment (Bhappkar and Koch, 1968) separate "marginal" χ^2 have been used.

Results

Though it was intended that streptokinase or heparin treatment should begin within 24 hours of onset of symptoms it was begun in 15 patients between 24 and 48 hours after. Nevertheless, it was decided to include these 15 patients in the first analysis.

Once the envelope of a patient chart had been opened the patient was considered to have been admitted to the trial. Eight patients died after admission but before the infusion had been started; all were in the heparin-treated group. They also have been included in the first analysis, since it is important to compare mortality in terms of the original intentions about treatment without regard to changes which might be made later. In fact, exclusion of these patients from the analysis of the results might vitiate the comparison of the effects of treatment. Randomization is used to obtain the same "baseline" mortality risk for both treatment groups, and the relative merits of the treatments are evaluated against this common baseline. To exclude results on the sole basis of the time of death would raise the baseline for the heparin group and correspondingly lead to an underestimation of its treatment mortality.

Thirty-three patients treated with streptokinase and 29 treated with heparin died during the infusion period. The infusion was stopped or the rate changed in 13 in the streptokinase group and in nine in the heparin group. Bleeding was the reason for stopping in seven streptokinase-treated and two heparin-treated patients, and in four and three patients respectively it was because the diagnosis of recent myocardial infarction appeared to be wrong.

Out of 764 patients entered in the study 28 from one centre were excluded from the analysis because they were not treated

* A copy of the chart can be obtained from the co-ordinating centre. Requests should be addressed to Professor M. Verstraete, Department of Medicine, Academische Ziekenhuis, 3000 Leuven, Belgium.

TABLE 1—Characterization of Both Groups on Admission

	Strepto- kinase	Heparin	χ^2	P†
Total No. of cases	373	357		
Identification:				
Mean age (years)	59.0	60.1		
Sex { Male	304	293		
Female	69	64		
Obesity index { Mean	103.6	103.6		
S.D.	9.4	9.1		
No.	394	305		
History:				
Cerebrovascular accident { Yes	16	10	0.726	0.394
before present infarction { No	347	333	1.107	0.292
Unknown	10	14		
Atherosclerotic disease { Yes	57	42	1.447	0.229
of peripheral arteries { No	288	283	1.720	0.190
Unknown	28	32		
Diabetes mellitus { Yes	39	50	1.923	0.166
{ No	313	285	2.251	0.134
Unknown	21	22		
History of previous { Yes	32	41	1.491	0.222
episode of heart failure { No	328	301	1.808	0.181
Unknown	13	15		
History of { Yes	57	55	0.0008	—
previous hypertension { No	294	282	0.0008	—
Unknown	22	20		
History of previous { Yes	35	44	1.368	0.242
myocardial infarction { No	325	300	1.662	0.198
Unknown	13	13		
History of angina { Yes	219	197	0.949	0.329
before present infarction { No	148	156	1.102	0.317
Unknown	6	4		
Non-atherosclerotic { Yes	6	9		
heart disease { No	357	338		
Unknown	10	10		
Time interval between { Mean	8.9	9.1		
onset of pain and { S.D.	10.5	9.1		
start of treatment in { No	371	344		
hospital (hours) { Unknown	2	13		
Clinical findings on admission:				
Heart failure on admission { Yes	55	58	0.259	0.611
{ No	316	294	—	—
Unknown	2	5		
Shock on admission { Yes	59	72	2.010	0.156
{ No	313	285	—	—
Unknown	1	0		
Arrhythmia on admission { Yes	101	77	2.710	0.100
{ No	270	278	—	—
Unknown	2	2		
Friction rub on admission { Yes	6	9	0.702	0.402
{ No	354	341	0.703	0.402
Unknown	13	7		
Retrosternal pain { Yes	314	288	1.161	0.205
on admission { No	57	66	1.383	0.240
Unknown	2	3		
Recent embolus { Yes	1	1	—	—
{ No	363	343	0.002	—
Unknown	9	13		
Systolic blood pressure { Mean	135.6	133.9		
on admission (mm Hg) { S.D.	29.6	31.7		
Unknown	5	7		
Diastolic blood pressure { Mean	86.9	85.8		
on admission (mm Hg) { S.D.	16.2	17.5		
Unknown	13	11		
Pulse rate (beats per minute) { Mean	82.3	84.1		
{ S.D.	18.4	17.6		
Unknown	8	9		
Prognostic estimate { Bad	82	75	0.062	0.802
{ Good	290	282	0.115	0.735
Unknown	1	0		
Temperature (°C) { Mean	37.0	36.9		
{ S.D.	0.6	0.5		
Unknown	358	346		
Anticoagulants { Yes	3	3		
administered before { No	369	353		
admission { Unknown	1	1		
Laboratory findings on admission:				
Serum G.O.T. { Mean	1.348	1.321		
(in log ₁₀ mmol/ml) { S.D.	0.397	0.361		
Creatine phosphokinase { Mean	3.46	4.09		
(μmol/l. serum/hr) { S.D.	4.40	5.83		
Haemoglobin (g/100 ml) { Mean	15.09	15.08		
{ S.D.	1.60	1.82		
Leucocyte count/mm ³ { Mean	11,140	11,260		
{ S.D.	4.72	4.82		
Erythrocyte sedimentation { Mean	0.829	0.956		
rate (log ₁₀ mm after 1 hr) { S.D.	0.418	0.421		
Fibrinogen level { Mean	324.1	337.1		
(log ₁₀ mg/100 ml) { S.D.	132.6	122.5		
Serum cholesterol { Mean	271.9	275.4		
(mg/100 ml) { S.D.	64.9	67.2		

*First figure: χ^2 corrected for continuity, based on known cases only. Second figure: χ^2 not corrected for continuity, based on all cases, for 2×2 subtable from 3×2 table.
†Upper-tail P value for testing against two-tailed alternatives.

in accordance with the system of serially numbered envelopes. Moreover, plasma samples which should have been taken at the end of the heparin or streptokinase infusions were sent only infrequently to the co-ordinating centre. Six other patients also had to be excluded as in four the charts were lost and in two the treatment code was not followed. Thus 730 patients were included in the first analysis—373 treated with streptokinase and 357 with heparin. Eight centres co-operated in the trial. About one-third of the patients were treated in a coronary care unit.

The cases in the two groups did not differ appreciably in those factors which are considered to influence the risks associated with myocardial infarction, nor in several other ways (Table I). The number of patients who had already suffered two or more myocardial infarctions was slightly higher in the heparin-treated group (44 out of 344) than in the streptokinase-treated group (35 out of 355). This difference is not significant ($P > 0.1$), nor is the higher incidence of arrhythmia on admission in patients treated with streptokinase ($P = 0.10$).

The prognostic estimate was noted as "bad" when the clinician, before opening the envelope, judged from experience that the patient had a greater chance of dying than of surviving. It must not be confused with a coronary prognostic index constructed from numerical weightings given to measurable factors. The 112 cases with a history of previous hypertension (diastolic pressure < 100 mm Hg) are evenly spread over both treatment groups (3×2 table: $\chi^2 = 0.03$, $P = 0.86$). Of course, only marginal comparisons could be made in this way—that is, comparisons for the categories (yes, no, unknown) in only one classification at a time.

Checks on Treatment

That the treatment given in the different centres accorded with the directives of the programme could to a large extent be confirmed from analysis of plasma samples sent to the co-ordinating centre. The plasminogen values in the streptokinase-treated patients were determined in frozen plasma samples obtained from blood withdrawn at the end of the infusion of the initial dose and 24 hours later—that is, just before the end of the streptokinase infusion. Since the values are lacking for only 6.7% of the patients who survived the infusion period the data are likely to represent the total population. In 67.4% of the patients the plasma plasminogen was below 200 U/ml (below 4% of the normal value) at the end of the infusion period. Unfortunately it was impossible to rely on measurements of labile factors such as plasminogen activator in the frozen blood samples to express the degree of activation of the fibrinolytic system, since their assessed levels are unreliable following deep-freezing and storage during transport. The thrombin time was used as a measure of anti-coagulant action in the heparin group. Results were available in 90% of patients who survived the infusion period, and the thrombin time was three times or more the normal value in 70.3% after the initial dose and in 54.3% at the end of the 24-hour infusion.

It was difficult to know what ancillary treatment was given, but there was no evidence that there were appreciable differences between the two groups in each centre in the use of other drugs, though antiarrhythmic drugs were used more often during the latter years of the trial.

Mortality

Ideally comparisons should be stated as differences in survival rate expressed in numbers of patient-days. A long-term follow-up analysis must await time, and this study reports only hospital mortality. Since the duration of stay in hospital averaged 44.2 days (S.D. 13.9) for 373 patients treated with streptokinase and 42.7 days (S.D. 11.6) for 357 treated with heparin, hospital mortality is expressed in numbers of patients.

The mortality rates at different centres are shown in Table II. The considerable variation between the centres is not surprising, since many factors influence the type of patient treated and clinicians may adopt different criteria in diagnosing myocardial infarction. It is also striking that the two centres (A and B) where no patients were admitted to an intensive care unit

had a higher mortality rate in the streptokinase-treated patients than in the heparin-treated patients.

Table III shows the distribution of times of death. The

TABLE II—Hospital Mortality of Patients with Myocardial Infarction with Respect to Treatment and Trial Centre

Trial Centre	Total		Streptokinase Group		Heparin Group		χ^2	P
	No.	%	No.	%	No.	%		
A ..	17/66	25.8	9/34	26.5	8/32	25.0	0.021	0.885
B ..	13/58	22.4	7/29	24.1	6/29	20.7	—	—
C ..	41/168	24.4	14/82	17.1	27/86	31.4	3.923	0.048
D ..	11/60	18.3	4/30	13.3	7/30	23.1	0.445	0.505
E ..	9/77	11.7	5/44	11.4	4/33	12.1	0.065	0.805
F ..	30/151	19.9	12/77	15.6	18/74	24.3	1.303	0.254
G ..	37/116	31.9	16/59	27.1	21/57	36.8	0.854	0.356
H ..	5/34	14.7	2/18	11.1	3/16	18.8	0.020	0.880
Total	163/730	22.3	69/373	18.5	94/357	26.3	6.007	0.014

TABLE III—Mortality with Respect to Treatment and Time of Death

Time of Death	Total	Streptokinase Group		Heparin Group		χ^2	P
		No.	%	No.	%		
(1) Before infusion	8/730	0/373	—	8/357	2.2	6.51*	0.011†
(2) During infusion	62/722	33/373	8.8	29/349	8.3	0.016	—
(3) (1)+(2)	70/730	33/373	8.8	37/357	10.4	0.325	—
(4) During 2nd or 3rd day	37/660	15/340	4.4	22/320	6.8	1.453	0.228
(5) After 3rd day	56/623	21/325	6.4	35/298	11.8	5.039	0.025
(6) After infusion = (4)+(5)	93/660	36/340	10.6	57/320	17.8	6.523	0.011
(7) Total	163/730	69/373	18.5	94/357	26.3	6.007	0.014
Survivors	567/730	304/373	81.5	263/357	73.7	—	—

*Marginal χ^2 values corrected for continuity, all based on one degree of freedom.
†If not corrected for continuity: $\chi^2=8.45$, $P=0.0036$; exact Fisher $P=0.0031$.

differences between both frequency distributions were analysed in a 5×2 table yielding a total of $\chi^2 15.7$ ($f=4$, $P=0.005$). The differences may be pinpointed down to mortality differences in the postinfusion period.

Clinically the time of death is not an additional index of effectiveness of treatment unless long periods—not days—are considered. We may therefore disregard the differences in time of death and note only differences due to treatment. From these it seems proved that there is no difference between the groups in the period before and during infusion (in which, in fact, no difference was to be expected) and that there is a clear difference in favour of streptokinase in the postinfusion period, in which a difference due to the treatment might be expected. Our findings agree with those of Schmutzler *et al.* (1966).

Among the causes of death, based on clinical criteria and not postmortem data, the only one that showed a significant difference between the groups was heart failure, whether considered in the group of patients who died (23.1% and 40.4% respectively; $\chi^2=4.587$, $P=0.032$) or related to the total number of patients at risk (4.3% and 10.6% respectively, $\chi^2=10.754$, $P=0.001$). This unexplained difference showed a similar pattern in 10 patients with multiple infarctions who died because of heart failure—two were treated with streptokinase and eight with heparin.

The patients were retrospectively grouped according to the interval between the onset of acute symptoms and the start of streptokinase or heparin therapy (Table IV). The mean time interval was 8.9 hours for 371 streptokinase-treated patients and 9.1 hours for 344 heparin-treated patients. In the 15 patients whose treatment began 48 hours after the first symptoms, contrary to the intention of the trial, six were treated with streptokinase and all survived and nine were treated with heparin and three died after infusion.

Taking into account patients treated within the first 12 hours, the mortality in the streptokinase group was 17.1% compared with 20.2% in the heparin-treated group. The corresponding figures for patients treated 12 hours or more after the acute onset of symptoms were 22.7% (streptokinase group) and 29.1% (heparin group).

Influence of Age and Sex

In men, all age groups combined, the difference between the treatment groups is significant ($\chi^2=5.34$ (corrected) or 5.81 (uncorrected); $P=0.021$ or 0.016 respectively) (Table V). In women, because of their smaller number, the lower mortality in the streptokinase group cannot be proved to be significant. However, the difference in mortality among men in the two groups (26.2%–18.1%=8.1%) is not significantly different from the corresponding difference among women (26.6%–20.3%=6.3%) (interaction $\chi^2=0.06$, $f=1$). In the age group below 60, both sexes combined, as well as in the age group above 70, both sexes combined, the difference between the treatment groups is evident ($\chi^2=4.49$ or 5.21, $P=0.034$ or 0.022, and $\chi^2=4.72$ or 5.52, $P=0.030$ or 0.019 respectively, the first figures referring to corrected χ^2 values). Again the difference among patients below 60 years is not different from the corresponding difference in the age group above 60 (interaction $\chi^2=0.03$, $f=1$). This shows that streptokinase is better, irrespective of age.

The mortality rate for patients who had one or more previous infarctions was calculated separately. Of 625 patients with no history of previous myocardial infarction the mortality was 54 out of 325 (16.6%) in the streptokinase group and 68 out of 300 (22.6%) in the heparin group. This difference

TABLE IV—Mortality with Respect to Treatment and Timing of Treatment

Interval between Onset of Symptoms and Infusion	Streptokinase Group		Heparin Group		Both Groups	
	Deaths/Patients at Risk	%	Deaths/Patients at Risk	%	Deaths/Patients at Risk	%
0-3 hours	12/108	11.1	10/82	12.2	22/190	11.6
4-6 "	20/99	20.2	26/95	27.4	46/194	23.7
7-12 "	18/85	21.2	16/80	20.0	34/165	20.6
13-18 "	7/38	18.4	10/39	25.6	17/77	22.1
19-24 "	8/31	25.8	10/29	34.5	18/60	30.0
≥25 "	3/10	30.0	3/11	27.2	10/21	28.6
Unknown, including preinfusion deaths	1/2	50.0	19/21	90.5	20/23	87.0
Total	69/373	18.5	94/357	26.3	163/730	22.3

TABLE V—Mortality with Respect to Treatment, Age, and Sex

Age in Years					Streptokinase Group		Heparin Group		χ^2	P
					Deaths/ Patients at Risk	%	Deaths/ Patients at Risk	%		
					Men					
<60	..	..	..	..	15/156	9.6	23/133	17.2	3.064	0.080
60-69	..	..	..	..	25/105	23.1	29/109	26.6	—	—
≥70	..	..	..	..	15/43	34.8	25/51	49.0	—	—
All ages					..	..	..	..	5.342	0.021
					Women					
<60	..	..	..	..	0/19	—	5/25	20.0	—	—
60-69	..	..	..	..	9/32	28.1	6/25	24.0	—	—
≥70	..	..	..	..	5/18	27.7	6/14	42.8	—	—
All ages					..	..	..	..	—	—
					Both Sexes					
<60	..	..	..	..	15/165	9.0	28/158	17.7	4.489	0.034
60-69	..	..	..	..	33/136	24.2	35/134	26.1	—	—
≥70	..	..	..	..	20/71	28.1	31/65	47.6	4.717	0.030

In grouping all men below 60 years of age the difference in mortality between the streptokinase-treated patients (9.6% of 156) and the heparin-treated patients (17.2% of 133) almost reaches 5% significance ($\chi^2=3.71$ (uncorrected), $P=0.054$ or $\chi^2=3.06$ corrected).

is not significant ($\chi^2=3.261$, $P=0.071$). The mortality in patients who had had a previous myocardial infarction was 8 out of 33 (24.2%) in the streptokinase group and 20 out of 42 (47.6%) in the heparin group ($\chi^2=3.375$, $P=0.066$).

Comparative Morbidity

The number of patients with complications during the infusion period (Table VI) was significantly higher in the streptokinase group (56.2%) compared with the heparin group (42.4%) ($\chi^2=12.88$, $P<0.001$), and this was mainly due to more patients in the streptokinase group showing a rise in temperature of more than 1°C and to a higher frequency of bleeding at puncture sites. Spontaneous haematoma, macroscopic haematuria, and melaena occurred equally but rarely in both treatment groups. Treatment was interrupted because of bleeding in six streptokinase-treated patients and two heparin-treated patients. To try to obtain an objective assessment of bleeding the blood haemoglobin concentration was measured during the first three days, and it did not vary significantly between the two groups.

After the end of the 24-hour infusion period "complications" were noted in 141 patients (41.2%) who received streptokinase and in 131 patients (41.1%) who received heparin (Table VII). Continuous monitoring, without continuous recording, was used to observe arrhythmia in this period in a limited number of patients only. Reinfarction seems to be significantly less frequent in patients treated with streptokinase.

TABLE VI—Complications Occurring during Infusion of Streptokinase or Heparin

Nature of Complication	Streptokinase Group (373)		Heparin Group (357)		χ^2	P
	No.	%	No.	%		
Rigors	7	1.8	0	0	12.880	<0.001
Temp. rise $>1^\circ\text{C}$ ..	140	37.5	89	25.5	4.933	0.026
Rash	3	0.8	1	0.3		
Vomiting	17	4.5	18	5.1		
Shock	21	5.6	23	6.6	2.007	0.156
All bleeding sites ..	32	8.5	7	2.0	14.519	<0.001
New precordial pain	30	8.0	26	7.4	0.496	0.471
Reinfarction	2	0.5	3	0.8	0.002	—
Heart failure	11	2.9	13	3.7		
Arrhythmia	23	6.1	27	7.7		
Friction rub	2	0.5	7	2.0		
Systemic embolism	2	0.5	0	0		

TABLE VII—Complications Occurring after Infusion of Streptokinase or Heparin in Survivors

Nature of Complication	Streptokinase Group (340)		Heparin Group (320)		χ^2	P
	No.	%	No.	%		
Shock	12	3.5	18	5.6		
Heart failure	25	7.3	27	8.4		
Reinfarction	6	1.7	16	5.0	4.398	0.036
Peripheral embolism	4	1.1	2	0.6		
Arrhythmia	36	10.5	30	9.5		
Friction rub	2	0.5	5	1.5		
Heart rupture	5	1.4	5	1.5		
Pneumonia	33	9.7	19	5.9	2.945	0.084
Aneurysm	2	0.5	6	1.8		

There was no significant difference between the two treatment groups in the mean values of serum aspartate aminotransferase, serum alanine aminotransferase, and serum creatine phosphotransferase obtained during the first seven days of treatment nor was there a significant difference in the leucocyte counts before and on the first and second mornings after the start of the streptokinase or heparin infusion.

Sixty-nine patients in the streptokinase group and 94 in the heparin group died, and there were necropsy reports on 42 and 49 respectively. Heart rupture due to aneurysm was the cause of death in 10 streptokinase-treated and in 14 heparin-treated patients; cerebral bleeding was the cause of death in two patients in each group; heart failure with pulmonary oedema was considered to be the cause of death in nine streptokinase-treated and 12 heparin-treated patients. Generalized or local bleeding into the brain or heart was not a prevalent cause of death in streptokinase-treated patients.

Further Statistical Analysis

In the further analysis 34 patients have been excluded whose serial E.C.G. or enzyme evolution or both was not diagnostic for recent myocardial infarction. The total mortality therefore becomes 68 out of 357 (19.0%) patients in the streptokinase group and 93 out of 339 (27.4%) in the heparin group ($\chi^2=6.414$, $P=0.011$).

The eight patients who died before the start of treatment were in four different co-operating medical centres. By chance they all belonged to the heparin group. If these eight patients are also excluded there were 68 deaths among 357 patients (19.0%) in the streptokinase group and 85 deaths among 331 patients (25.6%) in the heparin group. This difference is also significant ($\chi^2=3.994$, $P=0.046$). It is tempting to exclude these eight patients from the analysis, since none had streptokinase or heparin. However, if they were excluded so also should at least some of the patients who died during the infusion. Exclusion of the 34 patients whose E.C.G. was undiagnostic is far more defensible.

There seems to be no significant difference in mortality between the two treatment groups when the patients are classified according to the location of the infarction.

No prognostic stratification was made before the start of the trial. A retrospective stratification was attempted by combining all data, irrespective of mode of treatment, and then determining which features or combination of features seemed to be prognostically significant. The following factors were considered: age, sex, obesity, history of angina, previous infarction, or atherosclerosis and the presence of diabetes, heart failure, arrhythmia, conduction disturbances, or shock on admission to hospital. There appeared to be a significantly higher mortality when the patients were aged over 60 (men $P<0.05$, women $0.025<P<0.05$), when the patient had had a previous infarction ($0.05<P<0.1$), and when heart failure ($P<0.005$) or shock ($P<0.005$) was present on admission to hospital. The presence of a left ($P<0.005$) or right ($0.025<P<0.05$) bundle-branch block also had an unfavourable prognosis. None of the other features mentioned had any prognostic significance, nor was either treatment significantly more effective in patients with one of the unfavourable prognostic criteria. However, in the presence of more than one unfavourable prognostic criterion streptokinase was more effective than heparin. Details substantiating this statement will be presented in a forthcoming publication. Streptokinase was also found to be significantly better than heparin in patients with either obesity or diabetes.

Discussion

A postmortem finding of coronary occlusion is thought to occur in about 75% of patients succumbing to myocardial infarction (Kagan *et al.*, 1968). Some authors have reported figures of 91% (Chapman, 1968) and 30% (Meadows, 1965). Negative pathological evidence supports the belief that myocardial ischaemia commonly causes fatal failure of the circulation by precipitating ventricular arrhythmia (Edwards, 1969). In most patients with myocardial infarction intravascular

thrombosis is the last stage of progressive atherosclerotic narrowing, so that even when an occlusion is cleared by thrombolytic agents the coronary vessels remain narrowed. Also fibrin does not contribute greatly to the bulk of an arterial thrombus, so that not all patients with myocardial infarction would benefit from thrombolytic treatment. Moreover, the myocardium can survive only if ischaemia lasts for a shorter time than the period required to initiate and obtain complete thrombolysis. However, in theory, restoration of blood flow in an area where ischaemia is only partial would result in improved myocardial function and decreased irritability.

Therefore only limited benefit can be expected from new treatments in myocardial infarction. Since startling improvements in survival are unlikely, we need increasingly precise measures of therapeutic effect to obtain a small reduction in fatality rates, which in as common a disease as myocardial infarction may save a large number of lives. This implies a need for trials among large numbers of patients and controls (Fletcher, 1969). A multicentre trial has much to offer, since large numbers of patients can more easily be collected and because when many physicians co-operate the risk of unconscious bias is decreased.

When our trial was planned the prevailing view was that the control group should receive heparin treatment. The value of heparinization in patients with recent myocardial infarction has been challenged (Brown and MacMillan, 1965). It has been suggested that heparin may increase ventricular irritability because it causes a rise in plasma free fatty acid (Gupta *et al.*, 1966). However, a recent investigation performed in a controlled setting failed to show a correlation between significantly raised plasma levels of free fatty acids and ventricular arrhythmias (Rosso *et al.*, 1970).

Our trial showed that the mortality rate in a group of patients treated with a standard dose of streptokinase within 24 hours after the onset of clinical symptoms was significantly lower than in a group treated with heparin. In the first analysis all cases were included and assigned to the treatment group to which the patient had been allocated originally, even if the patient had died before or during the first hours of treatment. It was realized that any change from the original random allocation would alter the initial equality of the two groups. It is essential to make no change in the fundamental equality in mortality risk before treatment if there is to be an unbiased assessment of the effect of treatment.

Death was taken as the main yardstick for assessing the effect of treatment, and that meant that only those patients who died contributed directly to the final analysis. No attempt was made to use figures for deaths from specific causes, since a small change in fatality from cardiovascular causes without an overall difference in deaths from all causes may indicate either a diagnostic shift or at most a trivial benefit. It is worth noting, however, that reinfarction while in hospital was less frequent in the streptokinase-treated (6 out of 340) than in the heparin-treated patients (16 out of 320), this difference being significant ($P=0.036$).

The three major causes of death in acute myocardial infarction are arrhythmia or asystole, failure of the heart as a pump, and cardiac rupture. The availability of cardiac monitoring facilities varied from centre to centre, but the technique of recording arrhythmia was identical for both treatment groups in each centre and at all phases of the study. Death due to heart failure was less frequently observed in the streptokinase group (23.5% of all deaths in the group) than in the heparin group (40.4% of all deaths in the group). This difference is significant ($P=0.001$). According to the postmortem findings death was due to rupture of the ventricular wall in 10 out of 42 patients treated with streptokinase and in 14 out of 49 treated with heparin, but this difference is not significant.

In assessing therapeutic effect the quality of life after survival as well as its duration are important. A possible but rather poor measure of the effect of treatment in those who survived is provided by the length of stay in hospital and the condition

of the patient at discharge. No doubt clinical trials will be devised in which the comparisons will not be based on relative patient mortality. Fletcher (1969) believed that the use of more sensitive biochemical and haemodynamic measurements will provide objective measures that will permit assessment of the effects of new drugs in small groups of surviving patients. One practical application of this would be to show a quantitative difference in myocardial irritability, as manifest by cardiac arrhythmia, between the control and treatment groups, as proposed in an automated system by Simborg *et al.* (1966).

The controversy which surrounds anticoagulant therapy in patients who survive the acute phase of myocardial infarction invites a sober interpretation of this and similar clinical trials of thrombolytic therapy in acute myocardial infarction. Our findings showed a limited reduction in mortality in acute myocardial infarction when treated with streptokinase, and this beneficial effect was not outweighed by the risk of bleeding or other side effects. Our results are in agreement with the findings of another well-designed collaborative trial in which patients with myocardial infarction of less than 12 hours' duration were allocated at random to streptokinase or laevulose treatment for 18 to 24 hours. In this as yet unpublished study the mortality was 14.5% in the streptokinase-treated group (131 patients) and 26% in the laevulose-treated group (138 patients) ($\chi^2=4.854$, $P=0.028$, our calculations) (Schmutzler *et al.*, 1970). Further extensive trials of streptokinase in acute myocardial infarction are highly desirable.

We wish to thank Miss Gun Setterberg for her invaluable help in the analysis of the data. The streptokinase (Kabikinase) was kindly supplied by Drs. H. Dahlström and B. Strindberg, AB Kabi, Stockholm, to whom we are indebted for help in the organization of the trial. The skilled advice of Professor E. Meulepas, biostatistician, Faculty of Medicine, University of Louvain, is gratefully acknowledged. Our thanks are also due to the International Cardiology Foundation for a grant towards the cost of this study.

Appendix

Criteria for Electrocardiographic Diagnosis

Professor H. Kesteloot, University of Louvaine, made the final retrospective electrocardiographic diagnosis for all patients admitted to the trial, and he prepared and used the diagnostic criteria set out below.

CRITERIA FOR RECENT MYOCARDIAL INFARCTION

Transmural or Subepicardial Infarction.—The presence of a Pardee curve either of at least 1 mm in any of the standard leads or V5-V6 or of 3 mm in V1-V4. This had to be followed by a progressive return to the normal baseline and a subsidence of the T wave in the leads where a raised ST segment was present originally. A Pardee curve (raised ST segment) of at least 2 mm in any of the standard leads or V5-V6 and of at least 3 mm in V1-V4 was required for the diagnosis of a recent myocardial infarction in cases where no further electrocardiographic changes were found. These stricter criteria were also used in cases with either a complete right or left bundle-branch block. The raised ST segment had to be present in the leads where the R wave was highest. Mirror ST depressions had to be present in leads opposite to the leads where the raised ST was present.

Subendocardial Infarction.—Such an infarction was called recent when a straight downward ST segment depression of at least 1 mm at its origin was present in any of the standard unipolar augmented leads. The ST depression had to be more than 2 mm in any of the precordial leads. A rapid and progressive subsidence of the T wave in the ensuing days also was necessary.

CRITERIA FOR NON-TRANSMURAL MYOCARDIAL INFARCTION

Subepicardial Infarction.—This diagnosis was made whenever the Pardee curve disappeared and pathological Q waves failed to develop.

Subendocardial Infarction.—The criteria mentioned above were used. In both subepicardial and subendocardial infarction a progressive reduction of the height of the R wave also occurred frequently.

CRITERIA FOR LOCATION OF TRANSMURAL INFARCTION

(1) **Diaphragmatic Infarction.**—A Q wave of >0.04 sec in aVF and $>25\%$ of the amplitude of R in aVF; a Q wave of >0.03 sec and ST-T evolution in aVF, typical of myocardial infarction. An increase in the Q duration in aVF with at least 0.02 sec with typical ST-T segment changes, in the presence of a Q wave in L2 of >0.02 sec. The appearance of Q wave in L3 >5 mm deep and >0.04 sec duration in the presence of an R wave in L3 >1 mm (without a pathological Q wave in aVF). A Q wave of >0.05 sec and $>33\%$ of the R wave in aVF in the presence of a complete left bundle-branch block.

(2) **Posterolateral Infarction.**—A Q wave >0.03 sec. Q wave >0.02 sec plus typical sequential ST-T segment changes and an R loss of $>1/3$ in V6 (only V6 was used in the evaluation, since more lateral leads were not available in the electrocardiograms from some centres).

(3) **Anteroseptal Infarction.**—A QS wave in V1-V2 or V1-V4. Decreasing R V1 to V3 in the presence of sequential ST-T segment changes.

(4) **Anterior Infarction.**—A QS wave in either V2-V3, V2-V4, or V2-V5. A Q wave >0.03 sec in at least two consecutive leads between V2 and V5.

(5) **High Lateral Infarction.**—A Q wave >0.03 sec with a R wave >3 mm in aVL, with sequential ST-T wave changes. A Q wave >0.03 sec in aVL in the presence of a Q wave in V5, V6, and complete left bundle-branch block.

(6) **Posterior Infarction.**—A Q wave >0.03 sec in V6 with an R wave >5 mm and an S wave <1 mm in V1, in the absence of a pathological Q wave in D3, aVF.

(7) **Transmural Infarction in Presence of Wolff-Parkinson-White Syndrome.**—An R loss of $>50\%$ in leads V2-V4 in the presence of typical evolution of a Pardee curve. The development of Q waves was prevented by the existence of a pre-excitation wave.

The infarctions described under 1 and 6 have been classified as diaphragmatic (inferior) infarctions, and those described under 3, 4, and 5 as anterior infarctions.

CONDUCTION DISTURBANCES

The conduction disturbances noted were: A-V block first degree, A-V block second degree, A-V block third degree, complete A-V block, complete right bundle-branch block, and complete left bundle-branch block; left parietal block (R/S <0.5 in L2 in the absence of an S wave in a VL and a QRS duration <0.12 sec); and right parietal block (terminal R wave V1 of at least 1 mm, with QRS duration <0.12 sec).

RHYTHM DISTURBANCES

Rhythm disturbances noted were nodal rhythm, auricular fibrillation, auricular flutter, paroxysmal auricular tachycardia, and ventricular tachycardia.

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Relationship between Plasma Level and Therapeutic Effect of Nortriptyline

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British Medical Journal, 1971, 3, 331-334

Summary

The relationship between plasma concentration of nortriptyline and therapeutic effect after two weeks' treatment with the drug was investigated in 29 psychiatric inpatients. Endogenous depression was diagnosed in all patients. Amelioration of depressive symptoms was estimated as reduction in score on a

rating scale, based on a psychiatric interview. Amelioration was not correlated to the patient's sex or age. There was a curved relationship between plasma level of nortriptyline and therapeutic effect. Amelioration was most pronounced in the intermediate plasma level range (50-139 ng nortriptyline/ml plasma) and was slight both at lower and at higher plasma levels. This type of relationship may be due to the dual action of tricyclic antidepressants which has been found in animal experiments. On larger dosages a phenothiazine-like blockade of the monoaminergic receptor is added to the blockade of monoamine reuptake thought to be related to the antidepressant action of the drugs.

This study thus suggests two possible reasons for a therapeutic failure with nortriptyline: a too low or a too high plasma level. The large individual variation in the pharmacokinetics of the tricyclic antidepressants makes prediction of plasma level from dosage in a given individual virtually impossible without knowledge of rate of elimination and apparent

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