Cerebrovascular events after myocardial infarction: analysis of the GISSI trial

Aldo P Maggioni, Maria G Franzosi, Maria L Farina, Eugenio Santoro, Maria G Celani, Stefano Ricci, Gianni Tognoni

Authors on behalf of the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI)

Abstract

***Objectives*—To describe the epidemiology of cerebrovascular events in patients given or not given fibrinolytic treatment and to assess the prognostic implications and risk factors.**

***Design*—Case series derived from the GISSI randomised trial.**

***Setting*—176 coronary care units in Italy giving various levels of care.**

***Patients*—5860 patients with acute myocardial infarction treated with 1·5 million units of intravenous streptokinase and 5852 patients not given fibrinolytic treatment.**

***Main outcome measures*—Cerebrovascular event, sex, age, blood pressure, history of previous infarct, site of infarction, and Killip class.**

***Results*—99 of 11712 patients (0·84%) had a cerebrovascular event. Older age, worse Killip class, and anterior location of infarction seemed to be risk factors for cerebrovascular events (40/3201 aged 65-75 *v* 42/7295 aged <65, odds ratio 2·18; 9/437 class 3 *v* 55/8277 class 1, 1·81; and 57/4878 anterior *v* 24/4013 posterior, 1·96). No significant difference was found in the rate of cerebrovascular events between patients treated with streptokinase and controls (45/5852 (0·92%) streptokinase *v* 54/5860 (0·77) control). More patients in the streptokinase group than in the control group had cerebrovascular events (especially haemorrhagic strokes) on day 0-1 after randomisation (27 streptokinase *v* 7, control), although this was balanced by late events in control patients (54 streptokinase *v* 45 control at one year). The mortality of patients who had a cerebrovascular event was higher than that of those who did not (47% (47/99) *v* 11·6% (1350/11 613)).**

***Conclusions*—Although the incidence of cerebrovascular events complicating myocardial infarction was low, they increased morbidity and mortality. Treatment with streptokinase did not significantly alter the incidence, but age and poor haemodynamic state were associated with an increased risk.**

Istituto di Ricerche Farmacologiche "Mario Negri," Via Eritrea 62, 20157 Milano, Italy
Aldo P Maggioni, MD, *cardiologist*
Maria G Franzosi, PHD, *study coordinator*
Maria L Farina, MD, *study coordinator*
Eugenio Santoro, MS, *data processing manager*
Gianni Tognoni, MD, *member of steering committee*

Clinica Neurologica, Università di Perugia, Perugia, Italy
Stefano Ricci, MD, *neurologist*
Maria G Celani, MD, *neurologist*

Correspondence to:
Dr Maggioni.

BMJ 1991;**302**:1428-31

Introduction

Cerebrovascular events are a well known complication after acute myocardial infarction, and, although they occur quite rarely, they may have severe or long term effects. Before fibrinolytic treatment was introduced the reported incidence after admission for acute myocardial infarction varied from 1% to 8·6% (median 3%),[1-7] and it was feared that its introduction would increase the incidence of acute haemorrhagic stroke.

The GISSI study (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto) was designed to assess the efficacy of 1·5 million units of intravenous streptokinase in a population of 5860 patients with acute myocardial infarction compared with a matched cohort of 5852 not given fibrinolytic treatment.[8] We have studied these patients to determine the incidence of cerebrovascular events in patients given or not given fibrinolytic treatment to assess the prognostic implications and the related risk factors. The clinical benefit of thrombolytic treatment after acute myocardial infarction had been clearly established, and it is now given routinely. The GISSI study may therefore provide the last opportunity for comparing patients given thrombolytic treatment and those not.

As the population randomised in this trial may be considered to provide a reliable spectrum of the different levels of care that patients with acute myocardial infarction may receive in general coronary care units, a reliable estimation can be obtained of the risk of cerebrovascular events with and without fibrinolytic treatment and of the risk factors in patients with acute myocardial infarction.

Subjects and methods

Patients were recruited to the GISSI trial from 176 coronary care units throughout Italy, representing four fifths of all the coronary care units in teaching, general, and community hospitals. No age restriction was imposed, and the only exclusion criterion was the presence of contraindications to thrombolytic treatment[8]; cerebrovascular events in the six months preceding the acute myocardial infarction were considered to be an absolute contraindication to thrombolytic treatment. Eligible patients were randomised by telephoning the coordinating centre, which operated 24 hours a day. Treatment was assigned from a list generated by computer that allowed blocking and stratification by hospital. After allocation the patient was irrevocably in the trial. Whether or not the treatment assigned was actually given, patients remained in their original allocated treatment group on an intention to treat basis.

The clinical variables and concomitant treatment, including treatment after fibrinolysis, were similar in both groups of patients (those receiving streptokinase and those receiving no thrombolytic treatment). If a patient had a cerebrovascular event a copy of his or her complete clinical record, including computed tomograms when available, was dispatched to the study's scientific secretariat. Clinical records of all patients with cerebrovascular events were then reviewed by an ad hoc committee (comprising one senior cardiologist, (APM) and two neurologists (SR, MGC)) blind to the treatment that the patients had received, to qualify the events with respect to aetiology and their possible attribution to fibrinolysis.

We defined stroke as a sudden focal neurological deficit lasting more than 24 hours. Ischaemic and haemorrhagic stroke were differentiated on the basis of the results of computed tomography or necropsy. Transient ischaemic attack was defined as a sudden focal neurological deficit in which symptoms cleared completely in less than 24 hours. Analysis referred to the period spent in hospital and one year follow up.

We used the Killip scale to stratify the severity of

myocardial infarction at admission: class 1=absence of rales over lung fields and absence of third heart sound; class 2=rales over 50% or less of the lung fields or the presence of a third heart sound; class 3=pulmonary oedema; class 4=cardiogenic shock.

Significance was analysed by χ^2 tests. Results are presented as Mantel-Haentzel odds ratios with 95% confidence intervals. Proportional hazard models by Cox were used to assess the simultaneous effects of patient characteristics on the occurrence of cerebrovascular events. The factors considered in the models were age (<65, 65-75, >75 years), sex, previous acute myocardial infarction, systolic blood pressure at randomisation (<100, 100-150, >150 mm Hg), diastolic blood pressure at randomisation (<100, 100-110 mm Hg), infarct site (posterior-inferior, anterior-lateral), and Killip scale at admission (1-4). The results of the adjusted analysis are presented as relative risks with 95% confidence intervals.

Results

Of the 11712 patients with acute myocardial infarction randomised in the GISSI study, 99 (0·84%) had a cerebrovascular event while in hospital (table I). The incidence of cerebrovascular events did not differ significantly between patients treated with streptokinase and those in the control group (54/5860 (0·92) treated patients *v* 45/5852 (0·77) control patients; odds ratio 1·20, 95% confidence interval 0·76 to 1·87). These results were confirmed by the Cox proportional hazard model adjusting for age, sex, previous acute myocardial infarction, Killip scale at admission, infarct site, and systolic and diastolic blood pressures (relative risk 1·24, 0·83 to 1·85) (table I).

We considered the relation between cerebrovascular events and fibrinolysis and also the general clinical epidemiology of cerebrovascular events in patients with acute myocardial infarction. Both groups were similar with respect to sex, previous myocardial infarction, and systolic and diastolic blood pressures, though patients who developed cerebrovascular events after acute myocardial infarction were likely to be older than patients who did not (table II). Cerebrovascular events occurred somewhat more often in patients with more extensive cardiac damage and with anterior-lateral infarcts. Adjusting the analysis for clinical variables did not modify the direction or the strength of the association (table II).

Table III shows frequency and aetiology of cerebrovascular events. An excess of cerebrovascular events was evident with streptokinase on day 0-1 after randomisation. In addition all the patients that had a haemorrhagic stroke were in the streptokinase group. After day 1 the pattern reversed, with more patients in the control group having cerebrovascular events such that the overall difference between the groups was not significant. Results of computed tomography or necropsy, or both, were not available for most patients with cerebrovascular events so the cause could not be defined.

Table IV shows the clinical characteristics of patients treated with streptokinase who had a haemorrhagic stroke. Though the small number does not allow a true comparison with the whole cohort, there is no evidence of any concentration of the event in any subgroup (for example, older patients).

As expected, the outcome in patients who had a cerebrovascular event was worse that that in those who did not (Table V). Of 99 patients with cerebrovascular events, 47 (47%) died during the hospital stay compared with 1350 of 11613 (11·6%) patients who did not have such events. At one year's follow up 62 (63%) patients who had had cerebrovascular events were dead, compared with 2223 (19%) who had not had one. Among patients with cerebrovascular events the overall mortality was similar in the streptokinase and control groups (odds ratio 0·65; 95% confidence interval 0·30 to 1·44), though six of the eight patients with confirmed haemorrhagic strokes died in hospital. Mortality at one year was also similar (0·97; 0·43 to 2·21) (table V). The median hospital stay for patients discharged from hospital was 24 days for patients who had had cerebrovascular events and 14 days for those who had not.

TABLE I—*Relation between cerebrovascular events and treatment with streptokinase*

Treatment group	No of patients	No (%) of patients with cerebrovascular event	Odds ratio* (95% confidence interval)	Relative risk† (95% confidence interval)
Control	5852	45 (0·77)	1	1
Streptokinase	5860	54 (0·92)	1·20 (0·76 to 1·87)	1·24 (0·83 to 1·85)
Total	11712	99 (0·84)		

*Mantel-Haentzel unadjusted odds ratios.
†From Cox model adjusted for age, sex, systolic and diastolic blood pressures, previous acute myocardial infarction, infarct site, and Killip scale at entry.

TABLE II—*Distribution of cerebrovascular events by treatment group and prognostic factors**

	Streptokinase group		Control group		All patients			
	No of patients	No (%) with cerebrovascular event	No of patients	No (%) with cerebrovascular event	No of patients	No (%) with cerebrovascular event	Odds ratio† (95% confidence interval)	Relative risk‡ (95% confidence interval)
Age (years):								
<65	3681	19 (0·5)	3614	23 (0·6)	7295	42 (0·6)	1	1
65-75	1588	25 (1·6)	1613	15 (0·9)	3201	40 (1·2)	2·18 (1·41 to 3·39)	2·10 (1·33 to 3·29)
>75	591	10 (1·7)	623	7 (1·1)	1214	17 (1·4)	2·45 (1·37 to 4·39)	2·42 (1·33 to 4·39)
Sex:								
Male	4703	44 (0·9)	4696	34 (0·7)	9399	78 (0·8)	1	1
Female	1157	10 (0·9)	1156	11 (1·0)	2313	21 (0·9)	1·09 (0·52 to 2·29)	0·86 (0·52 to 1·42)
Systolic blood pressure (mm Hg):								
100-150	4131	31 (0·8)	4231	37 (0·9)	8362	68 (0·8)	1	1
<100	337	4 (1·2)	287	2 (0·7)	624	6 (1·0)	1·20 (0·49 to 2·95)	1·42 (0·60 to 3·36)
>150	1392	19 (1·4)	1334	6 (0·4)	2726	25 (0·9)	1·15 (0·71 to 1·85)	1·29 (0·78 to 2·16)
Diastolic blood pressure (mm Hg):								
<100	4457	45 (1·0)	4521	40 (0·9)	8978	85 (0·9)	1	1
100-110	1258	9 (0·7)	1198	5 (0·4)	2456	14 (0·6)	0·60 (0·32 to 1·09)	0·55 (0·29 to 1·02)
Previous infarct:								
No	4905	40 (0·8)	4926	40 (0·8)	9831	80 (0·8)	1	1
Yes	927	14 (1·5)	889	5 (0·6)	1816	19 (1·0)	1·29 (0·72 to 2·30)	1·17 (0·70 to 1·94)
Infarct site:								
Posterior-inferior	2009	18 (0·9)	2004	6 (0·3)	4013	24 (0·6)	1	1
Anterior-lateral	2434	25 (1·0)	2444	32 (1·3)	4878	57 (1·2)	1·96 (1·20 to 3·20)	1·95 (1·20 to 3·16)
Killip class:								
1	4171	31 (0·7)	4106	24 (0·6)	8277	55 (0·7)	1	1
2	1332	19 (1·4)	1340	32 (1·0)	2672	32 (1·2)	1·81 (1·15 to 2·84)	1·67 (1·03 to 2·52)
3	191	3 (1·6)	246	6 (2·4)	437	9 (2·1)	3·14 (1·50 to 6·57)	2·97 (1·44 to 6·09)
4	146	1 (0·7)	134	2 (1·5)	280	3 (1·1)	1·61 (0·19 to 13·45)	2·81 (0·84 to 9·39)

*Data unavailable on all patients for some factors. †Mantel-Haentzel unadjusted odds ratio. ‡Cox model adjusted for all prognostic factors in table.

TABLE III—*Timing and aetiology of cerebrovascular events*

	Total No of events		No of events day 0-1		No of events after day 1	
	Streptokinase group	Control group	Streptokinase group	Control group	Streptokinase group	Control group
Transient ischaemic attack	5	5	2		3	5
Stroke:	49	40	25	7	24	33
Ischaemic	9	7	3	1	6	6
Haemorrhagic	8		7		1	
Undefined	32	33	15	6	17	27
Total	54	45	27	7	27	38

TABLE IV—*Clinical characteristics of patients with haemorrhagic stroke (all patients received streptokinase)*

Case No	Age (years)	Sex	Blood pressure (mm Hg)	Treatment with heparin	Killip scale	Site of infarct	Discharge or death
1	71	M	140/90	No	1	Anterior	Death
2	63	M	115/80	No	1	Anterior	Death
3	61	M	130/80	No	1	Posterior-inferior	Death
4	75	M	145/90	Yes	1	Posterior-inferior	Discharge
5	73	M	160/100	No	1	ST depression	Death
6	59	F	130/70	No	2	Anterior	Death
7	66	M	160/90	No	2	Anterior	Discharge
8	65	M	120/90	No	1	Posterior-inferior	Death

TABLE V—*Mortality in hospital and during one year follow up among patients with and without cerebrovascular event*

	Total No of patients	No (%) who died in hospital	No (%) who had died at 1 year
Without cerebrovascular event:	11 613	1 350 (11·6)	2 223 (19·1)
With cerebrovascular event:	99	47 (47)	62 (63)*
Control group	45	24 (53)	28 (64)*
Streptokinase group	54	23 (43)	34 (63)

*One patient lost to follow up.

Discussion

EPIDEMIOLOGICAL FACTORS

The study shows the overall low incidence of cerebrovascular events complicating acute myocardial infarction (0·84%). Historical data show wide differences in rates of these events.[1-7] These studies are hard to compare because of differences in the numbers of patients studied, use of computed tomography, and types of treatment of acute myocardial infarction, but our rate of cerebrovascular events was lower than those in other studies. We excluded patients who had had cerebrovascular events in the six months preceding the index acute myocardial infarction as patients with recent transient ischaemic attacks or mild stroke can have a higher risk of stroke, though the risk is probably higher for all patients who have had a cerebrovascular event in the previous year. We do not know whether such patients were equally distributed between the streptokinase and control groups, but the large number of patients admitted to the study protects against a broad bias and enables us to regard our figures as more representative of acute myocardial infarction than those described in some small series. Our data have been confirmed by the second international study of infarct survival (ISIS-2) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) trial, thus probviding a reliable estimate based on about 42 000 patients.[9,10]

The association between clinical or epidemiological characteristics and stroke was expected, and the strength of this analysis seems to be borne out by the representativeness of our population with respect to the general population with acute myocardial infarction and by the close comparability of the incidence and outcome in patients receiving and not receiving streptokinase.

Some risk factors for cerebrovascular events after thrombolysis have already been identified. Recent stroke, recent head trauma, intracranial tumour, and arteriovenous malformation(s) are all absolute contraindications to thrombolytic treatment. We withheld streptokinase only from patients who had had a stroke more than six months before the acute myocardial infarction, whereas other authors recommend avoiding thrombolytic treatment in all patients who have ever had a stroke. Among patients without absolute contraindications to streptokinase treatment, older age, a worse Killip class, or anterior location of acute myocardial infarction seemed to be risk factors for cerebrovascular events. Sex and history of acute myocardial infarction had no association, and this has been confirmed in other studies.[1-7,9-11] We excluded patients with blood pressure above 200/100 mm Hg, but when this was taken into account higher systolic or diastolic pressure did not seem to be risk factors.

Komrad *et al* found no association between age and stroke.[1] In our study, patients aged 65-75 and patients aged over 75 were respectively 2·10 and 2·42 times more likely to have a stroke after acute myocardial infarction than those under 65. Other groups have also found that older age predisposes to cerebrovascular events.[3,11,12] Though the risk of cerebrovascular events is definitely increased in older people, there is no evidence of a further excess of events in the older patients receiving thrombolytic treatment. As is the case with many other procedures older people can gain from thrombolytic treatment despite some increased risk.

Poor haemodynamic state as manifested by a higher Killip class was confirmed to be associated with an increased risk of cerebrovascular events.[1,3] A possible explanation is that severe myocardial infarction complicated by reduced cardiac output favours the development of stroke as a result of poor cerebral perfusion, especially in elderly people, who often have subcritical cerebrovascular stenosis.[13,14]

A series of recent studies using echocardiography investigated the pathophysiology and epidemiology of stroke after acute myocardial infarction.[15-18] The characteristics of patients that were associated with thrombus formation after acute myocardial infarction mirrored those characteristics associated with stroke. Most patients with significant mural thrombus had had an anterior myocardial infarction. Patients with good left ventricular function or inferior acute myocardial infarction rarely had a thrombus detectable by echocardiography. The echocardiographic diagnosis of thrombus was associated with an increased risk of peripheral embolisation and stroke, while the risk of embolic stroke was minimal when thrombus was detectable by echocardiography. Our results confirm the association between anterior site of acute myocardial infarction and stroke, though no echocardiographic data were available on the incidence of left ventricular mural thrombi.

PHARMACOLOGICAL FACTORS

We found that streptokinase did not generate a significant excess of overall incidence of cerebrovascular events (table I) or of related death after admission and during one year's follow up.

The time of occurrence of cerebrovascular events of different aetiology only partially reflected the expected patterns: an expected (drug associated) excess of haemorrhagic strokes on day 0-1 does not completely explain the increased number of other strokes in the streptokinase group compared with the control group. Similarly, no clear explanation exists for the partial catch up in the number of events in the control group after day 1. This pattern is, however, reproduced in other large studies.[9,19] The clear excess of cerebrovascular events on day 0-1 and of definite haemorrhagic

TABLE VI—*Incidence of cerebrovascular complications in patients given thrombolytic drugs and control patients in different trials*

Trial	Total No of events				Haemorrhagic stroke				Ischaemic stroke			
	Treated group		Control group		Treated group		Control group		Treated group		Control group	
	Total No of patients	No (%) of cases	Total No of patients	No (%) of cases	Total No of patients	No (%) of cases	Total No of patients	No (%) of cases	Total No of patients	No (%) of cases	Total No of patients	No (%) of cases
Streptokinase:												
Yusuf *et al*[21]	1905	17 (0·9)	1854	12 (0·6)								
ISAM[22]					859	4 (0·5)	882	0				
GISSI[8]	5860	54 (0·9)	5852	45 (0·8)								
ISIS-2[9]	8490	61 (0·7)	8491	67 (0·8)								
GISSI-2[10]	6199	54 (0·9)			6199	15 (0·2)			6199	24 (0·4)		
Alteplase:												
TIMI-II[23]:												
150 mg	520	14 (2·7)			520	11 (2·1)						
100 mg	2742	31 (1·1)			2742	15 (0·5)						
ASSET[20]	2512	28 (1·1)	2493	25 (1·0)	2512	7 (0·3)	2493	2 (0·1)	2512	11 (0·4)	2493	17 (0·7)
TAMI[24]	708	13 (0·8)			708	4 (0·6)			708	9 (1·3)		
GISSI-2[10]	6182	70 (1·1)			6182	19 (0·3)			6182	28 (0·5)		
Anistreplase:												
AIMS[19]	624	8 (1·3)	634	4 (0·6)	624	2 (0·3)	634	1 (0·2)				

stroke in the streptokinase group confirms that fibrinolytic treatment does increase the risk of treatment related events, although this seems to be balanced by the late, and possibly ischaemic, strokes in untreated patients. The differences were not significant and, more importantly, they did not seem to be clinically relevant. The clinical characteristics of patients with defined haemorrhagic stroke did not suggest any specific feature as a detectable risk factor for the event (table V). Though streptokinase can never be regarded as completely safe, in controlled but otherwise normal conditions of care it does not produce a significant excess of overall cerebrovascular events in the absence of classic contraindications.

The prognosis of patients with cerebrovascular events and acute myocardial infarction is poor.[7 9 19 20] We found that cerebrovascular events strongly increased the risk of dying (table V) and that those patients who survived spent a longer median time in hospital than did those without cerebrovascular events (24 days *v* 14 days). This suggests that the general clinical condition of patients with cerebrovascular events may be worse.

No information was available on overall residual disability. For clinical purposes it can be claimed that the expected incidence of a cerebrovascular event after streptokinase infusion in the course of acute myocardial infarction is generally low and closely overlaps across studies (table VI). Aspirin and subcutaneous heparin plus aspirin did not produce an excess of haemorrhagic strokes when used in association with streptokinase.[9 10]

An incidence of intracranial bleeding similar to that shown with streptokinase was reported for anistreplase[19] and a 100 mg dose of alteplase,[10] whereas a higher dose of alteplase (150 mg) was associated with a four to five times higher incidence of intracranial bleeding.[23]

In conclusion, thrombolysis in patients with acute myocardial infarction is definitely associated with a small risk of stroke, similar to the risk in patients not receiving thrombolytic treatment. This acceptable risk must be taken as the reference level of cerebrovascular events during thrombolytic treatment and should be taken into account when new thrombolytic strategies are proposed.

1 Komrad MS, Coffey CE, Coffey KS, McKinnis R, Massey EW, Califf RM. Myocardial infarction and stroke. *Neurology* 1984;**34**:1403-9.

2 McAllen PM, Marshall J. Cerebrovascular incidents after myocardial infarction. *J Neurol Neurosurg Psychiatry* 1977;**40**:951-5.

3 Thompson PL, Robinson JS. Stroke after acute myocardial infarction: relation to infarct size. *BMJ* 1978;ii:457-9.

4 Fulton RM, Duckett K. Plasma fibrinogen and thromboembolism after myocardial infarction. *Lancet* 1976;ii:1161-4.

5 Veterans Administration Cooperative Clinical Trial. Anticoagulants in acute myocardial infarction. *JAMA* 1973;**225**:724-9.

6 Medical Research Council Working Party on Anticoagulant Therapy in Coronary Thrombosis. Assessment of short-term anticoagulant administration after myocardial infarctions. *BMJ* 1969;i:335-42.

7 Califf RM, Massey EW. Myocardial infarction and stroke in the thrombolytic era. In: Califf RM, Mark DB, Wagner GS, eds. *Acute coronary care in the thrombolytic era*. Chicago: Year Book Medical Publishers, 1988:539-47.

8 Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;i:297-401.

9 Second International Study of Infarct Survival (ISIS-2) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;ii:349-60.

10 Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-2: a factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12 490 patients with acute myocardial infarction. *Lancet* 1990;**336**:65-71.

11 Puletti M, Morocutti C, Tronca M, *et al*. Cerebrovascular accidents in acute myocardial infarction. *Ital J Neurol Sci* 1987;**8**:245-8.

12 Grines CL, DeMaria AN. Optimal utilization of thrombolytic therapy for acute myocardial infarction: concepts and controversies. *J Am Coll Cardiol* 1990;**16**:223-31.

13 Chin PL, Kaminiski J, Rout M. Myocardial infarction coincident with cerebrovascular accidents in the elderly. *Age Ageing* 1977;**6**:29-37.

14 Dimant J, Grob B. Electrocardiographic changes and myocardial damage in patients with acute cerebrovascular accidents. *Stroke* 1977;**8**:448-54.

15 Asinger RW, Mikell FL, Elsperger J, Hodges M. Incidence of left-ventricular thrombosis after acute transmural myocardial infarction: serial evaluation by two-dimensional echocardiography. *N Engl J Med* 1981;**305**:297-302.

16 Weinreich DJ, Burke JF, Pauletto JF. Left ventricular mural thrombi complicating acute myocardial infarction: long-term follow-up with serial echocardiography. *Ann Intern Med* 1984;**100**:789-94.

17 Turpie AGG, Robinson JG, Doyle DJ, *et al*. Comparison of high-dose with low-dose subcutaneous heparin to prevent left ventricular mural thrombosis in patients with acute transmural anterior myocardial infarction. *N Engl J Med* 1989;**320**:352-7.

18 Johannessen KA, Nordrehaug JE, von der Lippe G, Vollset SE. Risk factors for embolisation in patients with left ventricular thrombi and acute myocardial infarction. *Br Heart J* 1988;**60**:104-10.

19 AIMS (ASPAC (anisolylated plasminogen streptokinase activator complex) intervention mortality study) Trial Study Group. Long-term effects of intravenous anistreplase in acute myocardial infarction: final report of the AIMS study. *Lancet* 1990;**335**:427-31.

20 Anglo Scandinavian Study of Early Thrombolysis (ASSET). Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction. *Lancet* 1988;ii:525-30.

21 Yusuf S, Collins R, Peto R, *et al*. Intravenous and intracoronary fibrinolytic therapy in acute myocardial infarction: overview of results on mortality, reinfarction and side-effects from 33 randomized controlled trials. *Eur Heart J* 1985;**6**:556-72.

22 The Intravenous Streptokinase in Acute Myocardial Infarction (ISAM) Study Group. A prospective trial of intravenous streptokinase in acute myocardial infarction (ISAM). Mortality, morbidity, and infarct size at 21 days. *N Engl J Med* 1986;**314**:1465-71.

23 The Thrombolysis in Myocardial Infarction (TIMI) Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction. *N Engl J Med* 1989;**320**:618-27.

24 O'Connor CM, Califf RM, Massey EW, et al. Stroke and acute myocardial infarction in the thrombolytic era: clinical correlates and long-term prognosis. *J Am Coll Cardiol* 1990;**16**:533-40.

(Accepted 17 April 1991)