Br Heart J 1995;74:348–353

Rescue thrombolysis: alteplase as adjuvant treatment after streptokinase in acute myocardial infarction

J P Mounsey, J S Skinner, T Hawkins, A F N MacDermott, S S Furniss, P C Adams, P J L Kesteven, D S Reid

Abstract

***Background*—In acute myocardial infarction patients who do not reperfuse their infarct arteries shortly after thrombolytic treatment have a high morbidity and mortality. Management of this high risk group remains problematic, especially in centres without access to interventional cardiology. Additional thrombolytic treatment may result in reperfusion and improved left ventricular function.**

***Methods*—Failure of reperfusion was assessed non-invasively as less than 25% reduction of ST elevation in the electrocardiographic lead with maximum ST shift on a pretreatment electrocardiogram. 37 patients with acute myocardial infarction who showed electrocardiographic evidence of failed reperfusion 30 minutes after 1·5 MU streptokinase over 60 minutes were randomly allocated to receive either alteplase (tissue type plasminogen activator (rt-PA) 100 mg over three hours) (19 patients) or placebo (18 patients). 43 patients with electrocardiographic evidence of reperfusion after streptokinase acted as controls. Outcome was assessed from the Selvester Q wave score of a predischarge electrocardiogram and a nuclear gated scan for left ventricular ejection fraction 4–6 weeks after discharge.**

***Results*—Among patients in whom ST segment elevation was not reduced after streptokinase, alteplase treatment resulted in a significantly smaller electrocardiographic infarct size (14% (8%) *v* 20% (9%), P = 0·03) and improved left ventricular ejection fraction (44 (10%) *v* 34% (16%), P = 0·04) compared with placebo. This benefit was confined to patients who failed fibrinogenolysis after streptokinase (fibrinogen > 1 g/l). In patients in whom ST segment elevation was reduced after streptokinase, infarct size and left ventricular ejection fraction were not significantly different from those in patients treated with additional alteplase.**

***Conclusion*—Patients without electrocardiographic evidence of reperfusion after streptokinase may benefit from further thrombolysis with alteplase.**

Northern Regional Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne
J P Mounsey
T Hawkins
A F N MacDermott
S S Furniss
D S Reid

Department of Cardiology, Royal Victoria Infirmary, Newcastle upon Tyne
J S Skinner
P C Adams

Department of Haematology, Freeman Hospital, Newcastle upon Tyne
P J L Kesteven

Correspondence to: Dr J P Mounsey, Department of Cardiovascular Medicine, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH.

Accepted for publication 3 April 1995

(*Br Heart J* 1995;74:348-353)

Keywords: alteplase; rescue thrombolysis; streptokinase; acute myocardial infarction

Patients with acute myocardial infarction in whom coronary reperfusion does not occur soon after thrombolysis have a high incidence of impaired left ventricular function and high mortality.[1 2] Mechanical revascularisation may be attempted in these patients (rescue percutaneous transluminal coronary angioplasty),[3] but as most myocardial infarctions are treated in centres without immediate access to interventional facilities, other therapeutic approaches are needed. One possibility is to administer additional lytic treatment. This approach has been successful in patients with early reocclusion after initially successful reperfusion.[4] Initial treatment with more than one lytic agent has also been used in an attempt to improve reperfusion rate and to maintain patency.[5 6] However, sequential lytic treatment has not been tested in patients in whom reperfusion does not occur after a single agent. This approach is attractive because only patients at highest risk are exposed to the potential hazard of a second lytic agent.

Coronary reperfusion after thrombolysis can be assessed confidently only by acute coronary angiography. However, non-invasive markers of probable reperfusion have been developed which may allow therapeutic decisions to be made in centres without access to invasive facilities. Multiple algorithms have been developed to assess reperfusion non-invasively, but in this trial we focused on failure of rapid reduction of ST segment elevation.[7-9] This has been shown to be a reliable sign of persistent coronary occlusion after thrombolytic treatment,[7] which is readily available and interpretable without special equipment or skills.

We hypothesised that in patients who do not show reperfusion on electrocardiographic criteria after streptokinase treatment, additional lytic therapy with tissue type plasminogen activator (rt-PA, alteplase) may result in reperfusion and improved left ventricular function. One possible reason for failure of reperfusion may be failed fibrinogenolysis.[10] Accordingly, a secondary hypothesis was that adjuvant alteplase treatment would be most beneficial in patients who did not show fibrinogenolysis after streptokinase. We report the results of a prospective randomised trial of alteplase in patients who on electrocardiographic criteria failed to show reperfusion after streptokinase.

Patients and methods

Patients were eligible for inclusion in this study if they presented within six hours of the

onset of a first acute myocardial infarction. This was defined as chest pain of more than 30 minutes' duration unresponsive to glyceryl trinitrate; electrocardiographic ST segment elevation, either $\geqslant$ 2 mm in at least two contiguous leads V1-V6 or $\geqslant$ 1 mm in at least two contiguous limb leads; or ST depression of at least 2 mm with tall R waves in leads V1-V3 suggesting true posterior infarction.

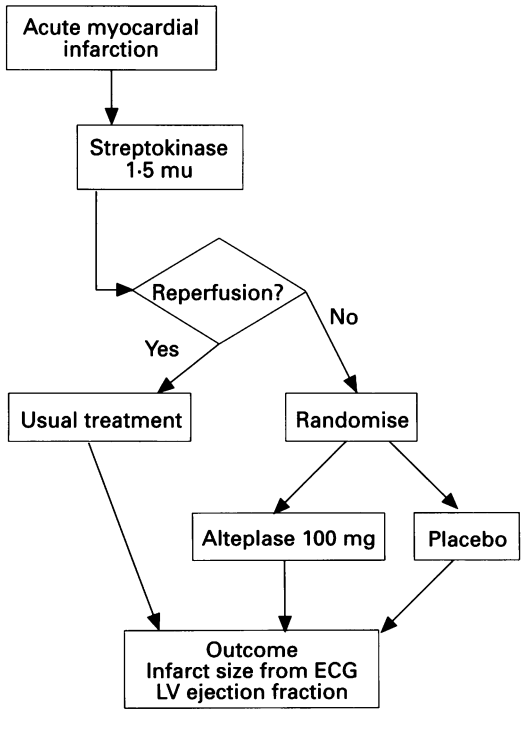
Specific exclusion criteria were previous Q wave myocardial infarction, previous coronary surgery, pre-existing right or left bundle branch block or fascicular block, and left ventricular hypertrophy. Patients were also excluded if they had any of the general contraindications to thrombolysis. These included active gastrointestinal bleeding during the preceding three months, cerebrovascular accident within the preceding six months, any history of cerebral haemorrhage or cerebral aneurysm, major surgery or trauma in the preceding 10 days (including prolonged cardiopulmonary resuscitation), sustained hypotension (systolic blood pressure less than 90 mm Hg) unresponsive to volume expansion, uncontrolled hypertension (systolic pressure persistently greater than 200 mm Hg on repeated measurement), proliferative diabetic retinopathy, or any history of bleeding diathesis. There was no upper age limit.

The study was approved by the Northern Health Authority Ethics Committee. All patients gave informed consent.

THROMBOLYTIC PROTOCOL

All patients received streptokinase (1·5 MU intravenously over 60 minutes) followed by heparin for at least 24 hours (fig 1). Aspirin was given unless contraindicated and other treatment was at the discretion of the responsible physician. Reperfusion was assessed non-invasively from an electrocardiogram recorded 90 minutes after the start of the streptokinase infusion. Probable reperfusion was defined as a reduction of ST segment elevation by 25% or more in the lead with the maximum ST shift on the admission electrocardiogram. Patients with electrocardiographic evidence of probable reperfusion received conventional treatment alone. Patients with persistent ST segment elevation (presumed failed reperfusion) received either alteplase (Boehringer) or an identical placebo in a double blind prospective trial. Assignment to treatment groups was made using a minimisation programme (Minim, supplied by Dr SJW Evans, department of Clinical Epidemiology, London Hospital Medical College) to ensure rough consistency between treatment groups for age, sex, and infarct site. Alteplase was administered in the standard dosing regimen of 100 mg over three hours (10 mg as a slow bolus injection followed by 50 mg over one hour and then an infusion of 20 mg/h over the next two hours).

The trial protocol



COAGULATION STATE

Blood samples were taken in all patients before and after streptokinase to assess plasma fibrinogen concentration.[11] The results of this assay were not available at the time of randomisation. Fibrinogenolysis was defined as a fibrinogen concentration of $\leqslant$ 1·0 g/l at the end of the streptokinase infusion.

OUTCOME MEASUREMENTS

Electrocardiographic infarct size

Infarct size was estimated from electrocardiograms recorded on admission and at hospital discharge. Predicted infarct size was estimated from the admission electrocardiogram according to the method of Clemmensen *et al.*[12] In this method, empirical formulas are used to predict the proportion of the left ventricle at risk of myocardial infarction from a pretreatment electrocardiogram. For anterior myocardial infarctions, defined as those with maximum ST segment elevation in leads V1-V3, the formula is:

Predicted % anterior infarct size = 3 (1·5 (No of leads with ST elevation) − 0·4).

For inferior infarcts, defined as those with either maximum ST segment elevation in leads II, III, and a VF, or ST segment depression in leads V1-V3, the corresponding formula is:

Predicted % inferior infarct size = 3 (0·6(ΣST segments in leads II, III, and aVF) + 2) + 3 (1·5(No of non-inferior leads with ST elevation) − 0·4).

Resultant QRS estimated infarct size was estimated from the pre-discharge electrocardiogram by the Selvester QRS score.[13] This system contains 54 criteria and awards a maximum of 32 points. Each of these points represents about 3% of the left ventricle so, for comparison with the predicted infarct size, the Selvester score was multiplied by three to yield a measure of the proportion of infarcted left ventricle. The QRS score is of limited value in assessing infarct size.[14] We measured

it solely for comparison with potential infarct size (as assessed from the admission electrocardiogram), to assess non-invasively whether myocardial salvage had occurred. Interestingly, in our population Q wave score was significantly correlated with ejection fraction ($r = 0{\cdot}63$, $P < 0{\cdot}001$) in contrast to the data of Christian *et al.*[14]

All electrocardiographs were scored by two experienced cardiologists, each of whom were unaware of treatment assignment or outcome. ST elevation was measured to the nearest 0·5 mm in all leads except aVR.

Left ventricular ejection fraction

Left ventricular ejection fraction was assessed by nuclear gated blood pool imaging four to six weeks after hospital discharge. Global ejection fraction was estimated from the left anterior oblique projection with a standard computer software package. The left anterior oblique angulation was selected for each patient to achieve optimal separation of the right and left ventricles.

DATA ANALYSIS

Student's t test and the χ^2 test with Yates's correction when appropriate were used for statistical analysis. Significance was assumed to be $P < 0{\cdot}05$. Continuous variables are quoted as means (SD). Statistical analysis were performed using SPSS/PC. The sample size (> 32 randomly allocated patients) was calculated to detect an improvement in left ventricular ejection fraction of 10 percentage points, assuming σ to be 10%, α to be 0·05, and β to be 0·2.[15]

Table 1 Baseline patient characteristics. Values are means (SD) unless stated otherwise

	Streptokinase only (n = 43)	*Streptokinase + rtPA (n = 19)*	*Streptokinase + placebo (n = 18)*	*P value**
Age (years)	63 (9)	63 (10)	63 (10)	0·9
No (%) of men	30 (70)	11 (58)	13 (72)	0·4
No (%) with infarct site:				
Anterior	14 (32)	10 (53)	10 (56)	
Inferior	28 (65)	8 (42)	6 (33)	
Other	1 (2)	1 (5)	2 (11)	0·7
Time to streptokinase (h)	3·3 (1·9)	3·4 (1·9)	4·3 (2·1)	0·2
Time to rt-PA (h)	—	5·6 (1·9)	6·5 (2·2)	0·3

*For difference between rt-PA and placebo assessed by t or χ^2 test.

Table 2 Main outcome measures

	Streptokinase only (n = 43)	*Streptokinase + rtPA (n = 19)*	*Streptokinase + placebo (n = 18)*	*P value**
Mean (SD) infarct size (%):				
Predicted	21 (8)	26 (13)	25 (8)	0·9
Resultant	10 (9)	14 (8)	20 (9)	0·03
Ejection fraction (%)	49 (13)	44 (10)	34 (16)	0·04

*For difference between alteplase and placebo assessed by t or χ^2 test.

Table 3 Lytic state

	Streptokinase only (n = 43)	*Randomised group (n = 37)*	*P value*
Mean (SD) fibrinogen (g/l):			
Initially	3·6 (1·4)	3·8 (1·3)	0·5
60 minutes after streptokinase	1·0 (1·1)	1·3 (1·0)	0·2
No (%) of patients without fibrinogenolysis 60 minutes after streptokinase	17 (40)	24 (65)	0·01

Results

A total of 129 patients fulfilled the entry requirements and were screened for inclusion in the trial. Forty three patients (33·3%) did not show a reduction in ST segment elevation (presumed failed reperfusion); of these, 37 were randomly allocated to receive alteplase (19 patients) or placebo (18 patients); the six remaining patients did not give their consent. Eighty six patients (66·6%) showed a reduction in ST segment elevation of $\geqslant 25\%$, 90 minutes after the initiation of streptokinase (presumed reperfusion); 43 of them were recruited into the control (streptokinase only) group. Table 1 shows the baseline characteristics of the patient cohort. Overall mean age was 63·1 (9) years and 54 (68%) patients were men. Randomised patients were well matched for baseline infarct site, but there was a significant excess of inferior infarcts among patients with presumed reperfusion (65% (28) compared with 38% (20) in the randomised group, $P = 0{\cdot}043$). Mean time from the onset of symptoms to initiation of thrombolysis was 3·6 (1·9) hours (range 0·6–10·25) overall; in randomised patients the time from the onset of symptoms to initiation of rt-PA or placebo was 6·0 (2·1) hours (range 2·1–10·8). There were no systematic differences in time to treatment between the treatment groups.

EFFECTS ON INFARCT SIZE AND EJECTION FRACTION

Table 2 shows the effects of the three thrombolytic regimens on infarct size and ejection fraction. Predicted infarct size, as estimated from the admission electrocardiogram was similar in all three groups. However, resultant infarct size, estimated from the predischarge electrocardiogram, was significantly smaller in patients randomly allocated to alteplase compared with those allocated placebo. Similarly, patients randomly allocated to alteplase had significantly higher ejection fractions at four to six weeks than patients who received placebo. Patients with presumed reperfusion after streptokinase alone were not significantly different from patients without presumed reperfusion who received alteplase. One patient from each of the three treatment arms died in hospital and therefore did not have a gated blood pool scanning (see below). Two further patients refused to have gated scanning. Both received active alteplase and neither had cardiac failure on routine follow up. Their predicted pretreatment infarct sizes were 38% and 26%; their predischarge QRS infarct sizes were respectively 12% and 9%—thus both showed electrocardiographic evidence of myocardial salvage.

INFLUENCE OF FIBRINOGENOLYSIS

Table 3 shows fibrinogen concentrations in control (streptokinase only) and randomised patients. There were no significant differences in mean concentrations initially or 60 minutes after streptokinase. Overall 41 out of 80 (51%) patients did not show fibrinogenolysis at 60 minutes. These included 24 out of 37 (65%) patients who were later randomised and 17

Table 4 Influence of fibrinogenolysis. Values are means (SD) unless stated otherwise

	Streptokinase only	*Streptokinase + alteplase*	*Streptokinase + placebo*	*P value**
	Fibrinogen ≤ 1 g/l 60 minutes after streptokinase			
No of patients	26	7	6	
Infarct size (%):				
Predicted	21 (7)	29 (19)	25 (8)	0·6
Resultant	11 (8)	15 (7)	17 (6)	0·6
Ejection fraction (%)	49 (13)	46 (12)	41 (13)	0·6
	Fibrinogen >1 g/l 60 minutes after streptokinase			
No of patients	17	12	12	
Infarct size (%):				
Predicted	22 (10)	23 (9)	25 (9)	0·6
Resultant	9 (11)	13 (8)	21 (10)	0·04
Ejection fraction (%)	47 (16)	44 (10)	30 (17)	0·04

*For difference between alteplase and placebo assessed by *t* test.

out of 43 (40%) control (streptokinase only) patients. The proportion of patients who did not show fibrinogenolysis was significantly higher among those later randomised—that is, those who presumably failed to reperfuse—than among controls—that is those who presumably reperfused (65% compared with 40%, P = 0·01). Among randomised patients, seven of the 19 (37%) who received alteplase and six of the 18 (33%) who received placebo showed fibrinogenolysis after streptokinase (P = 0·9).

Table 4 summarises the effect of fibrinogenolysis after streptokinase on infarct size and ejection fraction. In patients who showed neither reperfusion nor fibrinogenolysis after streptokinase, infarct size was significantly smaller and ejection fraction better preserved among those who received active alteplase than among those who received placebo; patients who received alteplase were not significantly different from those with presumed reperfusion after streptokinase alone. By contrast, in the group who did not show reperfusion but showed fibrinogenolysis after streptokinase there was no significant difference in either resultant infarct size or ejection fraction between alteplase and placebo groups. Likewise, among these patients, neither group was significantly different from patients with presumed reperfusion and fibrinogenolysis after streptokinase alone. In patients with presumed reperfusion after streptokinase alone outcome was similar regardless of fibrinogen concentration; fibrinogenolysis was not predictive of outcome.

MORTALITY AND COMPLICATIONS

Mortality at six weeks was 3·75%. Three patients died, one from each of the three treatment arms. There were five episodes of bleeding, only one of which, a gastrointestinal haemorrhage, required transfusion. This occurred in a patient randomly allocated placebo. Minor bleeds included two haemoptyses, one epistaxis, and one rectal bleed. There were no cerebral haemorrhages.

Discussion

In this prospective study we found that patients with acute myocardial infarction whose ST segment elevation did not reduce by 25% or more 90 minutes after initiation of streptokinase and who received additional lytic treatment with alteplase had improved left ventricular function and smaller Q wave scores than patients who received placebo. A prespecified subgroup analysis suggested that the improvement in outcome was confined to patients who also did not show fibrinogenolysis—that is, fibrinogen concentration was > 1·0 g/l after streptokinase. In the small group of patients without reduction in ST segment elevation 90 minutes after streptokinase and fibrinogen concentrations ≤ 1·0 g/l, adjuvant alteplase conferred no extra benefit.

We chose a reduction in ST segment elevation of 25% or more as the non-invasive indicator of probable reperfusion. We previously found that this sign is highly sensitive (> 95%) but non-specific (43%) for coronary reperfusion when assessed angiographically 90 minutes after treatment with anisoylated streptokinase plasminogen activator complex.[7] Hogg *et al* reported a high sensitivity (93%) for a fall in ST segment elevation of 50%, but their post thrombolytic electrograms were recorded much later than in our study (at 302 (141) minutes).[16] When the criterion of Hogg *et al* was applied to a population with angiographically proved reperfusion at 90 minutes, sensitivity for reperfusion fell to only 68%.[7]

Frequent (every 5–10 minutes) measurement of ST segment height is a more sensitive indicator of reperfusion than sampling at two fixed points. Shah *et al* showed that comparison of a single pretreatment electrocardiogram with one taken at 90 minutes failed to detect impending reperfusion in more than 10% of patients.[17] If we had sampled ST segments more frequently, fewer patients may have received adjuvant thrombolysis. However, we wanted to identify failed reperfusion and to maximise the potential impact of alteplase in the patients who needed it—and this argued for treatment to be given as early as possible. Inevitably an arbitrary time limit must be applied in this situation and we chose 90 minutes after the initiation of streptokinase. A secondary consideration in the use of electrocardiographic assessment at fixed time points was a desire to test the efficacy of a management strategy which could be widely applied. Continuous ST segment monitoring requires more nursing time than is usually available in a busy coronary care unit. Relief of chest pain was not used in the current study because, although it is a sensitive sign of timing of reperfusion when followed sequentially,[17] its assessment at a fixed time point is difficult, especially if it is not concordant with the electrocardiographic results.

Adjuvant thrombolysis was administered when the patency of the infarcted artery would be expected to be 50–60% (thrombolysis in myocardial infarction (TIMI) grade II or III).[1] Patencies after streptokinase treatment improve to about 75% at three hours,[1] so if probable reperfusion status had been assessed at this stage the proportion of patients requiring additional lytic treatment would have been reduced. In the event, although the anticipated persistent occlusion rate was 40–50% at the

time of assessment, only 33% of our patients met the electrocardiographic criteria for persistent occlusion.

A fall in ST segment elevation of 25% or more is of limited value in predicting coronary patency—that is, the specificity is low—but, after single agent thrombolysis, patients who have such a fall but no angiographic evidence of reperfusion have well preserved left ventricular function.[7] The converse electrocardiographic sign—persistent ST segment elevation after thrombolysis—is highly predictive of persistent coronary occlusion and impaired left ventricular function.[7] In our previous study ejection fraction was as low as 28% in this group, compared with 47% in patients with reduced ST segment elevation of 25% or more.

The thrombolytic action of streptokinase is associated with a systemic lytic state; failure to achieve fibrinogenolysis 90 minutes after initiation of lytic treatment is associated with persistent coronary occlusion.[10] We found that when fibrinogen concentrations were measured at 60 minutes patients with presumed reperfusion—that is, those with reduced ST segment elevation—had an overall good outcome regardless of whether they showed fibrinogenolysis. Among the 40% of these who did not show fibrinogenolysis the favourable outcome may possibly be attributed to late fibrinogenolysis with subsequent clot lysis or to the presence of a preformed collateral circulation. In patients with presumed failed reperfusion—that is, persistent ST segment elevation—alteplase improved outcome only in the 65% with failed fibrinogenolysis—that is, fibrinogen concentration > 1 g/l. In those with fibrinogenolysis, outcome was good and not improved by rt-PA. A possible explanation of this is that, although streptokinase did not cause reperfusion it reduced plasma viscosity and so improved peri-infarct microcirculation sufficiently to limit infarct size.[18,19] The streptokinase induced reduction in plasma viscosity closely parallels fibrinogen concentrations and so will not occur in patients who do not show defibrination. Alternatively, these patients may have been destined to show reperfusion late with streptokinase alone, alteplase thus being of no further benefit.

Combination thrombolysis using streptokinase and rt-PA results in a superior patency rate (TIMI grade II or III) at 90 minutes when compared with either rt-PA or streptokinase given as monotherapy in conventional regimens.[5,6] In the GUSTO (global utilisation of streptokinase and alteplase for occluded coronary arteries) trial this improvement in patency did not translate to an improvement in either left ventricular function or mortality[6]—only accelerated alteplase was superior to the other regimens in this respect.[1] Also in the GUSTO trial—and presumably also in the general population of patients with infarction—flow of TIMI grade III at 90 minutes achieved by whatever regimen was the best predictor of outcome. Left ventricular function was identical in the groups with flow of TIMI grades 0, I, and II at 90 minutes. Our data are not strictly comparable with either those of the GUSTO[6] or KAMIT (Kentucky acute myocardial infarction)[5] trials. We studied patients treated initially with streptokinase, presumably with flow of TIMI grade 0 or I flow at 90 minutes and found an improved outcome after additional, delayed rt-PA treatment. A high risk population was selected for intervention and, by the surrogate end point of left ventricular function, an improvement was observed. This improvement was similar in magnitude to that observed in the ISAM (intravenous streptokinase in acute myocardial infarction) trial of streptokinase and placebo,[20] but it was much larger than that observed early after infarction in the TAMI (thrombolysis and angioplasty in myocardial infarction) and TIMI (thrombolysis in acute myocardial infarction) trials.[21,22] The value of left ventricular function as a surrogate end point in trials of lytic treatment has been questioned.[23,24] In the general population of patients with infarction ejection fraction is about 50% in both thrombolytic and placebo groups.[24] We observed a greater ejection fraction in the treatment group probably because the study population was confined to high risk patients with persistently occluded arteries. These patients had most left ventricle to gain, or lose. A larger trial would be needed to determine whether the improvement in left ventricular function we observed would translate into a mortality benefit.

Rescue angioplasty has been advocated for patients with persistent coronary occlusion or early recurrent ischaemia after thrombolysis.[25] Repeat thrombolysis is beneficial in patients with early recurrent ischaemia after myocardial infarction.[4] Our data suggest that additional lytic treatment may also be beneficial in patients with evidence of persistent coronary occlusion after thrombolysis. Most cardiac centres do not have access to immediate angioplasty; our data suggest that additional thrombolysis may be substituted with benefit to the patient.

Combination thrombolysis results in a significant excess of haemorrhagic strokes over single agent thrombolysis in all regimens so far tested. In GUSTO the haemorrhagic stroke rate for combination treatment was 0·94%,[6] which is almost double the rate for streptokinase alone, 0·49–0·54%. We did not set up our study to test formally the safety profile of combination thrombolytic treatment in persistent coronary occlusion, but the absence of treatment related complications suggests that serious haemorrhage rates greatly in excess of those seen in GUSTO are unlikely.

In conclusion, among patients with acute myocardial infarction in whom streptokinase does not reduce ST segment elevation by 25% or more after 90 minutes, further thrombolysis with rt-PA resulted in significantly better left ventricular function and a smaller resultant electrocardiographic infarct size when compared with placebo. This improvement in infarct size and left ventricular function was confined to patients who did not show fibrinogenolysis (fibrinogen concentration

> 1 g/l) after streptokinase. These findings need to be confirmed in a larger, preferably multicentre, trial. Our data suggest, however, that in acute myocardial infarction treatment with an additional thrombolytic agent should be considered if ST segment elevation fails to resolve and if plasma fibrinogen concentration remains above 1·0 g/l.

We acknowledge the expert help of Dr D Appleton, department of medical statistics, University of Newcastle upon Tyne, in both the planning and the analysis of this trial. We acknowledge the gift of alteplase and identical placebo from Boehringer Ingelheim.

1 GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both, on coronary artery patency, ventricular function and survival after acute myocardial infarction. *N Engl J Med* 1993; **329**:1615–22.
2 Vogt A, von Essen R, Tebbe U, Feuerer W, Appel KF, Neuhaus KL. Impact of early perfusion status of the infarct related artery on short term mortality after thrombolysis for acute myocardial infarction: retrospective analysis of four German multi-center studies. *J Am Coll Cardiol* 1993;**21**:1391–5.
3 Fung AY, Lai P, Topol EJ, Bates ER, Buordillon PDV, Walton JA, *et al.* Value of percutaneous transluminal angioplasty after unsuccessful intravenous streptokinase therapy in acute myocardial infarction. *Am J Cardiol* 1986;**58**:686–91.
4 Barbash GI, Hod H, Roth A, Faibel HE, Mandel Y, Miller HI, *et al.* Repeat infusions of tissue type plasminogen activator in patients with acute myocardial infarction and early recurrent ischaemia. *J Am Coll Cardiol* 1990;**16**: 779–83.
5 Grines CL, Nissen SE, Booth DC, Gurley JC, Chelliah N, Wolf R, *et al.* A prospective, randomized trial comparing combination half dose tissue type plasminogen activator and streptokinase with full dose tissue type plasminogen activator. *Circulation* 1991;**84**:540–9.
6 GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;**329**:673–82.
7 Saran RK, Been M, Furniss SS, Hawkins T, Reid DS. Reduction in ST segment elevation after thrombolysis predicts either coronary reperfusion or preservation of left ventricular function. *Br Heart J* 1990;**64**:113–7.
8 Barbash GI, Roth A, Hod H, Miller HI, Rath S, Har-Zahav Y, *et al.* Rapid resolution of ST segment elevation and prediction of clinical outcome in patients undergoing thrombolysis with alteplase (recombinant tissue plasminogen activator): results of the Israeli study of early intervention in myocardial infarction. *Br Heart J* 1990; **64**:241–7.
9 Krucoff MW, Croll MA, Pope JA, Granger CB, O'Conner CM, Sigmon KN, *et al.* Continuous 12-lead ST segment recovery analysis in the TAMI 7 study. *Circulation* 1993;**88**:437–47.
10 Brugeman J, van der Meer J, Takens BH, Hillege H, Lie KI. A systemic non-lytic state and local thrombolytic failure of anistreplase in acute myocardial infarction. *Br Heart J* 1990;**64**:355–8.
11 Clauss A. Rapid physiological coagulation method in determination of fibrinogen. *Acta Haematol* 1957;**17**:237–40.
12 Clemmensen P, Grande P, Saunamaki K, Pederson F, Svendsen JH, Wagner NB, *et al.* Effect of intravenous streptokinase on the relation between initial ST predicted size and final QRS estimated size of acute myocardial infarcts. *J Am Coll Cardiol* 1990;**16**:1252–7.
13 Wagner GS, Freye CJ, Palmeri ST, Roark SF, Stack NC, Ideker RE, *et al.* Evaluation of a QRS scoring system for estimating myocardial infarct size. I. Specificity and observer agreement. *Circulation* 1982;**65**:342–7.
14 Christian TF, Clements IP, Behrenbeck T, Huber KC, Chesebro JH, Gersh BJ, *et al.* Limitations of the electrocardiogram in estimating infarct size after acute reperfusion therapy for myocardial infarction. *Ann Intern Med* 1991;**114**:264–70.
15 Gore SM, Altman DG. *Statistics in practice.* London: British Medical Association, 1982:6–8.
16 Hogg KJ, Hornung RS, Howie CA, Hockings N, Dunn FG, Hillis WS. Electrocardiographic prediction of coronary artery patency after thrombolytic treatment in acute myocardial infarction: use of the ST segment as a non-invasive marker. *Br Heart J* 1988;**60**:275–80.
17 Shah PK, Cercek B, Lew AS, Ganz W. Angiographic validation of bedside markers of reperfusion. *J Am Coll Cardiol* 1993;**21**:55–61.
18 Moriaty AJ, Hughes R, Nelson SD, Balnave K. Streptokinase and reduced plasma viscosity: a second benefit. *Eur J Haematol* 1988;**41**:25–36.
19 Arntz HR, Perchalla G, Roll D, Heitz J, Schafer JH, Schroder R. Blood rheology in acute myocardial infarction: effects of high dose i/v streptokinase compared to placebo. *Eur Heart J* 1992;**13**:275–80.
20 Voth E, Tebbe U, Schicha HS, Neuhaus KL, Schroder R for the ISAM study group. Intravenous streptokinase in acute myocardial infarction (ISAM) trial: serial evaluation of left ventricular function up to 3 years after infarction estimated by radionuclide ventriculography. *J Am Coll Cardiol* 1991;**18**:1610–6.
21 Harrison JK, Califf RM, Woodlief LH, Kereiakes D, George BS, Stack RS, *et al.* Systolic left ventricular function after reperfusion therapy for acute myocardial infarction. *Circulation* 1993;**87**:1531–41.
22 Cheesbro JH, Knatteraud G, Roberts R, Borer J, Cohen LS, Dalen J. Thrombolysis in myocardial infarction (TIMI) trial phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. *Circulation* 1987;**76**:142–54.
23 Califf RM, Harrelson-Woodlief L, Topol EJ. Left ventricular ejection fraction may not be useful as an endpoint of thrombolytic therapy comparative trials. *Circulation* 1990;**82**:1847.
24 Van de Werf F. Discrepancies between the effects of coronary reperfusion on survival and left ventricular function. *Lancet* 1989;**i**:1367–89.
25 Califf RM, Topol EJ, Stack RS, Ellis SG, George BS, Kereiakes DJ, *et al.* Evaluation of combination thrombolytic therapy and timing of cardiac catheterization in acute myocardial infarction. Results of thrombolysis and angioplasty in myocardial infarction—phase 5 randomized trial. *Circulation* 1991;**83**:1543–56.