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ORIGINAL ARTICLES

Effect of early intravenous heparin on coronary patency, infarct size, and bleeding complications after alteplase thrombolysis: results of a randomised double blind European Cooperative Study Group trial

D P de Bono, M L Simoons, J Tijssen, A E R Arnold, A Betriu, C Burgersdijk, L Lopez Bescos, E Mueller, M Pfisterer, F Van de Werf, F Zijlstra, M Verstraete, for the European Cooperative Study Group

Glenfield General Hospital, Leicester
D P de Bono

Thoraxcentrum, Academisch Ziekenhuis Dijkzigt, Rotterdam, Netherlands
M L Simoons
T Tijssen

Medisch Centrum Alkmaar, Alkmaar, Netherlands
A E R Arnold
C Burgersdijk

Hospital Clinic I Provincial de Barcelona, Barcelona, Spain
A Betriu

Hospital Gregorio Maranon, Madrid, Spain
L Lopez Bescos

Spaarne Ziekenhuis, Haarlem, Netherlands
E Mueller

Department of Internal Medicine, University Clinics, Basel, Switzerland
M Pfisterer

Center for Medical Research, Katholieke Universiteit Leuven, Leuven, Belgium
F Van de Werf
M Verstraete

Ziekenhuis "De Weezenlanden", Zwolle, Netherlands
F Zijlstra

Correspondence to
Professor D P de Bono, Department of Cardiology, University of Leicester, Clinical Science Wing, Glenfield General Hospital, Leicester LE3 9QP.

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Abstract

***Objective*—To determine whether concomitant treatment with intravenous heparin affects coronary patency and outcome in patients treated with alteplase thrombolysis for acute myocardial infarction.**

***Design*—Double blind randomised trial.**

***Treatment regimens*—Alteplase 100 mg (not weight adjusted) plus aspirin (250 mg intravenously followed by 75–125 mg on alternate days) plus heparin (5000 units intravenously followed by 1000 units hourly without dose adjustment) was compared with alteplase plus aspirin plus placebo for heparin.**

***Setting*—19 cardiac centres in six European countries.**

***Subjects*—652 patients aged 21–70 years with clinical and electrocardiographic features of infarcting myocardium in whom thrombolytic therapy could be started within six hours of the onset of major symptoms.**

***Main outcome measure*—Angiographic coronary patency 48–120 hours after randomisation.**

***Results*—Coronary patency (TIMI grades 2 or 3) was 83·4% in the heparin group and 74·7% in the group given placebo for heparin. The relative risk of an occluded vessel in the heparin treated group was 0·66 (95% confidence interval 0·47 to 0·93). Mortality was the same in both groups. There were non-significant trends towards a smaller enzymatic infarct size and a higher incidence of bleeding complications in the group treated with heparin.**

***Conclusions*—Concomitant intravenous heparin improves coronary patency in patients with alteplase. Whether this can be translated into improved clinical benefit needs to be to be tested in a larger trial.**

The value of thrombolytic therapy in acute myocardial infarction is well established. Alteplase (single chain recombinant human tissue-type plasminogen activator, rt-PA) has been shown to be effective in securing or restoring coronary patency,[1,2] in limiting enzymatic infarct size and preserving left ventricular function,[3] and in improving survival[4] in patients with evolving myocardial infarction. There is limited evidence that alteplase may be more effective than other thrombolytic agents in securing early coronary patency.[5-7]

Most clinical trials so far conducted with alteplase in myocardial infarction have included the immediate co-administration of heparin followed by a maintenance heparin infusion.[1-4,8-10] The rationale for this has been the assumption that patients might be particularly susceptible to early reocclusion in the absence of continuing anticoagulation because alteplase has a short plasma half life and causes relatively little depletion of plasma fibrinogen. Topol and colleagues showed that administration of heparin immediately before the start of a four hour alteplase infusion did not improve patency as assessed by angiography 90 minutes after the start of the infusion.[11] Conversely, the HART (Heparin-Aspirin Reperfusion Trial) investigators,[12] and Bleich and colleagues[13] showed significantly worse patency rates at 18 hours and 48 hours respectively in patients given alteplase plus heparin placebo compared with those given alteplase plus a conventional heparin regimen.

It is important that the present uncertainty over the role of concomitant intravenous heparin with alteplase thrombolysis should be resolved. If heparin is not essential then treatment can be simplified and bleeding complications perhaps reduced. On the other hand if early intravenous heparin is important then the results of the GISSI 2[14] and International Study Group[15] trials comparing alteplase with other thrombolytic agents may be of limited relevance.

We present the results of a randomised, double blind trial designed to compare the effect of immediate intravenous heparin with heparin placebo on coronary patency in patients with clinical and electrocardiographic features of evolving acute myocardial infarc-

tion treated with intravenous alteplase plus intravenous or oral aspirin. The trial was also designed to evaluate the incidence of bleeding complications and the effects of heparin treatment on enzymatic infarct size and the prevalence of left ventricular thrombus.

Patients and methods

The trial was conducted in 19 centres in six European countries under the auspices of the European Cooperative Study Group. Centres are listed in the appendix.

ENTRY CRITERIA

Patients aged 21 to 70 years were recruited if they had chest pain typical of myocardial infarction lasting for 30 minutes or longer, if the necessary electrocardiographic criteria were met, and if an infusion of alteplase could be started within six hours of the onset of major symptoms. The electrocardiographic criteria were at least 0·3 mV ST segment elevation measured at 60 ms after the J point in two precordial leads (V1 to V4), and/or 0·2 mV ST elevation in two frontal plane leads or V5 and V6, and/or 0·1 mV ST elevation in two frontal plane leads or V5 and V6 combined with 0·2 mV ST depression in two precordial leads (V1–V4). All patients were required to have given informed consent in a form acceptable to the ethics of medical research committees of the institutions concerned.

EXCLUSION CRITERIA

Patients were excluded if they had had an earlier transmural myocardial infarct less than 14 days before or a previous infarct in a similar location. Patients at increased risk of haemorrhagic complications as defined in previous ECSG studies[3] were also excluded. Cardiogenic shock was not an exclusion criterion.

RANDOMISATION

Patients were registered and randomised by a telephone call to a randomisation centre. Randomisation was blocked by centre, and investigators were instructed to administer a "pack" of medication identified by a code number.

TREATMENT PROTOCOL

Analgesia was given as required. Aspirin was administered as a 250 mg intravenous bolus (continental centres) or as 300 mg orally (United Kingdom centres) followed by 75–125 mg orally on alternate days. Alteplase (Actilyse, Boehringer Ingelheim) was administered intravenously as a 10 mg bolus followed by 50 mg over the first hour and 20 mg over each of the subsequent two hours. The dose was not adjusted for weight. Heparin was administered intravenously as a bolus of 5000 units immediately before the start of the alteplase infusion followed by 1000 units per hour until angiography was performed. Heparin placebo (dilute albumin solution) was prepared in identical vials and given in the same way. Adjustment of the heparin dose according to haemostatic measurements was not permitted.

Guidelines for the correction of haemodynamic abnormalities were specified. Repeated administration of alteplase was permitted in the event of clinical reinfarction, with 50 mg of alteplase if reinfarction occurred within 24 hours or 100 mg if it occurred more than 24 hours after entry.

Heparin was continued after angiography at the discretion of the individual investigator; angioplasty or other necessary intervention was permitted after angiography at the discretion of the operator. Medication at hospital discharge and at follow up was recorded.

ANGIOGRAPHY

Coronary angiography was done 48–120 hours after the start of thrombolytic treatment. At least two projections of the right and three of the left coronary artery were required. Angiograms were recorded on 35 mm cine film and assessed centrally as in previous ECSG studies. Infarct related segments were identified from the angiographic appearances in conjunction with the electrocardiogram recorded before randomisation. Patency was reported in terms of TIMI grades[1] and ECSG stenosis grades.[2]

CARDIAC ENZYME ANALYSIS

Serial blood samples were taken at entry and at 12, 24, 36, 48, 72, and 96 hours. Plasma was separated by centrifugation and the supernatant stored at −20°C before transport on dry ice to a central laboratory. Hydroxybutyrate dehydrogenase (HBDH) activity was estimated in duplicate on each sample and used to calculate cumulative plasma release (Q(24), Q(72)) as a measure of infarct size.[16] The use of enzymatic measurements of infarct size as an outcome measure is subject to potential bias because samples may not be available from patients dying within 72 hours. We therefore imputed "worst case" measurements to these patients.

HAEMATOLOGY

Serial measurements were made of haemoglobin concentration and haematocrit. Blood samples were taken for measurements at a central laboratory of fibrinogen, activated partial thromboplastin time (APTT), and D dimer before treatment was started; at 45 minutes; and at 12, 24, and 26 hours. These measurements were made at a central laboratory and the results will be reported separately.

ECHOCARDIOGRAPHY

Cross sectional echocardiography was performed 48–120 hours after the start of thrombolytic therapy with the aim of identifying left ventricular thrombus. Images were stored on videotape and analysed at a central laboratory by observers who were blind to the treatment allocation.

HAEMORRHAGIC COMPLICATIONS

Haemorrhagic complications were recorded in case record forms according to preset criteria. Major haemorrhagic complications were investigated further by supplementary question-

Table 1 Baseline characteristics for all analysable patients

Characteristic	Placebo (n = 320)	Heparin (n = 324)
Age (yr) (range)	56 (26–72)	57 (25–70)
Male (%)	281 (88)	279 (86)
Mean (SD) weight (Kg)	75·28 (12·18)	73·64 (11·14)
Anterior infarct (%)	141 (44)	131 (40)
Previous infarct (%)	17 (5)	20 (6)
History of angina (%)	166 (52)	179 (55)
History of hypertension (%)	84 (26)	76 (24)
Current smoker (%)	201 (63)	200 (62)
Systolic blood pressure (mm Hg) (range)	131 (60–220)	134 (60–220)
Diastolic blood pressure (mm Hg) (range)	84 (50–130)	87 (30–150)
Heart rate per minute (beats/min) (range)	73 (35–120)	74 (34–150)
Haemodynamic state (%):		
Normal	263 (82)	260 (81)
Right heart failure	5 (2)	6 (2)
Mild left heart failure	42 (13)	40 (12)
Overt left heart failure	4 (1)	3 (1)
Shock	6 (2)	14 (4)
Onset symptoms until start infusion (min) (range)	169 (45–392)	170 (32–380)
Randomisation until angiography (h)	83	80

naires and reviewed by a central clinical events committee.

STUDY END POINTS

The main end point of the study was the centrally assessed angiographic patency of the infarct related coronary artery at 48–120 hours. Other outcome measures investigated were (*a*) enzymatic infarct size as estimated by the cumulative release of HBDH into plasma at 72 hours (HBDH-Q72); (*b*) clinical events and bleeding complications up to 48–120 hours angiography and during the whole hospital stay; (*c*) the prevalence of echocardiographically assessed left ventricular thrombus.

TRIAL SIZE AND POWER CALCULATION

Power calculations before the trial started indicated that if a patency rate of 80% at 48–120 hours was assumed for the group receiving alteplase, aspirin, and heparin then a trial size of 440 patients would be required to demonstrate a 14% difference in patency with 80% power at the p = 0·05 level. Assuming at 27% incidence of bleeding complications in the group receiving heparin, a trial of this size would detect a 12% difference in bleeding complications with the same power. The design allowed for two interim analyses at 100 and 200 patients by an independent ethics monitoring group, with "stopping rules" set at patency rates of 80% and ⩽50% for the heparin and placebo group respectively for the first analysis and 80% and ⩽60% for the second analysis (p = 0·02). During the course of the trial it became apparent that the pooled patency rate at 48–120 hours for the first 200 patients was of the order of 78%—that is, either the patency rates for heparin and no heparin were very similar, or the initial patency rate estimate had been pessimistic. The steering committee, without itself having access to the unblinded data but having asked the chairman of the independent ethics monitoring group to review the safety data on approximately 300 patients and confirm that there were no *ethical* objections to continuing the study, then decided to extend the trial to include 650 patients. It is accepted that *any* alteration in trial size after the start of a trial might increase the risk of a type 1 error, but we though this was more than compensated by the increase in precision resulting from an increase in trial size.

Table 2 Perfusion and infarct related stenosis grades at 48–120 hour angiography

	Placebo	Heparin
No angiography performed	21	14
Infarct related vessel not identifiable	15	9
Angiography not between 48 and 120 hours	31	36
Perfusion grades (TIMI) (%):		
Non-perfusion (0)	58 (22·9)	32 (12·1)
Minimal perfusion (1)	6 (2·4)	12 (4·5)
Partial perfusion (2)	21 (8·3)	21 (7·9)
Complete perfusion (3)	168 (66·4)	200 (75·5)
Stenosis grades (%):		
Total occlusion	58 (22·9)	32 (12·1)
91–99% stenosis no complete filling	14 (5·5)	21 (7·9)
91–99% stenosis complete filling	47 (18·6)	41 (15·5)
50–90% stenosis	118 (46·6)	152 (57·4)
<50% stenosis	16 (6·3)	19 (7·2)

Risk ratio for non or minimal perfusion (TIMI 0 or 1) = 0·66 (95% confidence interval 0·47 to 0·93)
Risk ratio for functional occlusion (stenosis grade 5 or 6) 0·7 (95% confidence interval 0·52–0·96)
TIMI perfusion grades: 0 = no perfusion; 1 = penetration with minimal perfusion; 2 = Partial perfusion; 3 = Complete perfusion. ECSG stenosis grades: 0 = normal vessel; 1 = <50% diameter stenosis; 2 = diameter stenosis between 50 and 90% with complete filling of distal vessel within three cardiac cycles; 3 = diameter stenosis between 50 and 90% without complete filling of distal vessel within three cardiac cycles; 4 = diameter stenosis >90% with complete filling of distal vessel within three cardiac cycles; 5 = diameter stenosis >90% without complete filling of distal vessel within three cardiac cycles; 6 = total occlusion.

STATISTICAL EVALUATION

Relative risks and 95% confidence intervals were calculated according to Gardner and Altman.[17] The Mann–Whitney U test was used to compare HBDH activities.

TRIAL ORGANISATION

The organisation, coordination, and ethical superivision structure of the trial is described in the appendix.

Results

PATIENT NUMBERS AND BASELINE CHARACTERISTICS

Six hundred and fifty two patients were registered and allocated to receive either heparin (n = 328) or heparin placebo (n = 324). Eight patients were excluded from analysis—six because of errors in labelling the trial medication in one participating hospital and two because case record forms were not returned. Two patients aged over 70 were included inadvertently and have been retained in the analysis. Table 1 lists the baseline characteristics of all analysable patients (n = 644). These characteristics were evenly distributed between the groups. Electrocardiographic entry criteria were verified by the clinical events committee: 11 placebo and 13 heparin group patients were judged not to have fulfilled the stipulated entry criteria but they were retained in the analysis. Six hundred and two patients continued their trial medication up to the time of angiography (or to 120 hours). Twenty one patients in each group stopped trial medication before angiography: four in the heparin and three in the placebo group died and 14 in the heparin and 12 in the placebo group stopped because of bleeding, recurrent chest pain, or other complications.

ANGIOGRAPHY

Central angiographic evaluation was perfor-

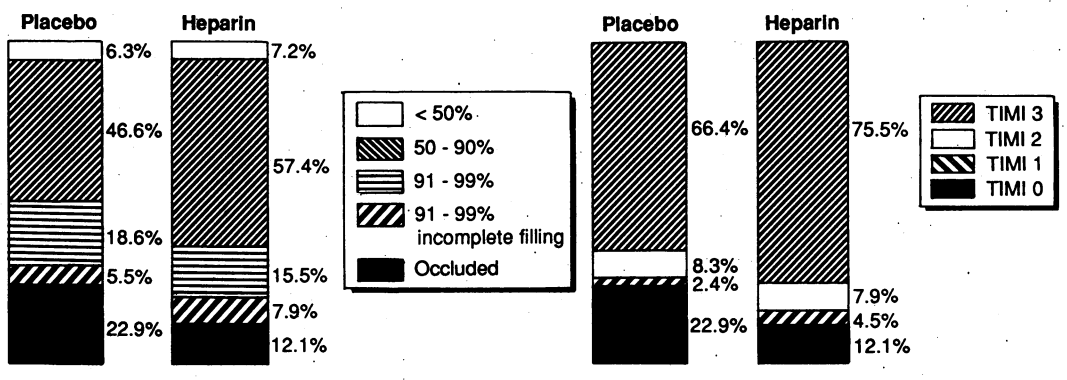

Figure 1 Histograms showing distribution of TIMI perfusion grades in infarct related vessels and ECSG stenosis grades in infarct related segments in patients who had angiography between 48 and 120 hours. (Grades are defined in the legend to table 2).

med on cine films from 609 patients (95%). No angiography was performed in 14 heparin group patients (death seven, complication two, refusal one, other reasons four) and 21 placebo group patients (death six, complication two, refusal six, other reasons seven).

The distribution of infarct related segments was evenly balanced between groups. Table 2 and figure 1 show the perfusion and stenosis grades of patients having angiography within the specified 48–120 hour interval. Figure 2 shows the relation between patency and the time that angiography was performed. There was no significant difference between the groups in the proportion of patients having angiography at different times. Patency, whether assessed by TIMI perfusion grades or by ECSG stenosis grades, was significantly better in patients allocated to heparin treatment. The relative risk of an occluded vessel (TIMI grade 0 or 1) at 48–120 hour angiography in the heparin group as compared with the placebo group was 0·66, with 95% confidence intervals of 0·47 to 0·93. The difference remains when *all* angiograms are considered (patency 83·7% for heparin group *v* 75·1% for placebo, relative risk of an occluded vessel 0·65, 95% C.I. 0·47 to 0·93). Imputing a closed vessel to all patients whose angiograms were not recorded does not alter the conclusion.

CLINICAL EVENTS AND REINFARCTION

Two hundred and sixty nine patients in the heparin group and 303 patients in the placebo group showed enzymatic evidence of myocardial infarction in the form of a rise in plasma creatine kinase to more than twice the normal activity. Two hundred and forty four patients in the heparin and 251 in the placebo groups developed new Q waves consistent with infarction. The trends towards reduced frequency of enzymatic evidence of infarction and of new Q waves in the heparin group were not statistically significant.

Table 3 shows the incidence of recurrent chest pain, clinical reinfarction, and mortality in the two treatment groups: events have been divided into those occurring between allocation and angiography and between angiography and discharge. There was no overall difference between heparin and placebo groups, but there was a non-significant trend towards fewer clinical ischaemic events in the period before angiography in the patients receiving heparin. A second dose of alteplase was given to 26 patients—11 allocated to heparin and 15 to placebo. Twenty one patients received 50 mg (eight heparin, 13 placebo) and five received 100 mg (three heparin and two placebo).

ENZYMATIC INFARCT SIZE

Enzymatic infarct size expressed as Q_{72} HBDH could be calculated from serial measurements in 258 placebo group and 246 heparin group patients. Mean Q_{72} HBDH was 672 units for the placebo group and 646 units for the heparin group (p = NS). We were able to use extrapolated values for missing measurements to calculate the infarct size for 309 placebo group and 304 heparin group patients: mean values for Q_{72} HBDH were 659 units and 646 units respectively (p = NS). Imputing "worst case" values to patients who had died gave estimates for 313 placebo group and 309 heparin group patients: 673 units *v* 646 units (p = NS). There was a trend towards reduced infarct size of about 4% in patients receiving heparin—this did not reach conventional significance levels. The Q_{24}/Q_{72} HBDH ratio (a measure of the rapidity of enzyme release) had mean values of 0·68 for 258 placebo group patients and 0·69 for 246 heparin group patients (p = NS).

BLEEDING COMPLICATIONS AND HAEMOSTATIC VALUES

Mean haemoglobin concentrations and haematocrit at admission and discharge did not

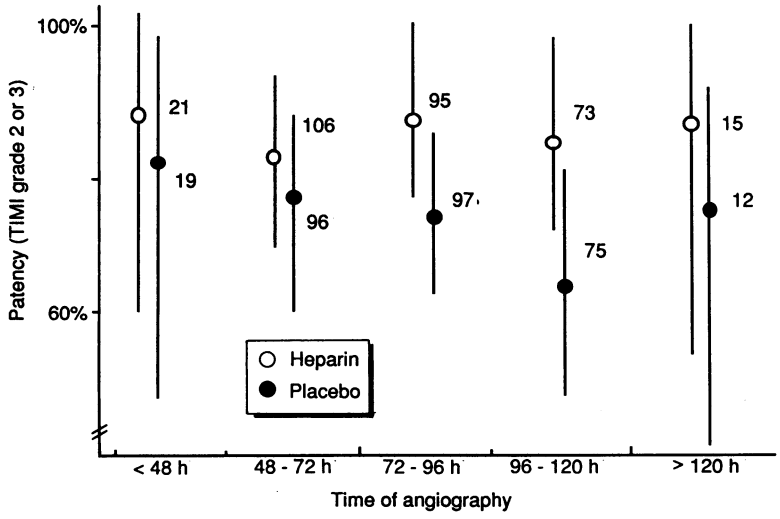

Figure 2 Means and 95% confidence intervals for TIMI grade 2 or 3 perfusion in angiograms performed at different times in heparin and placebo groups.

Table 3 Incidence of death, recurrent chest pain, and clinical reinfarction in heparin and placebo group patients between allocation and angiography and between angiography and hospital discharge

	Placebo (n=320) (%)	*Heparin (n=324) (%)*
Events between randomisation and angiography or 120 hours		
Death	2 (0·6)	4 (1·2)
Recurrent chest pain*	37 (11·6)	30 (9·3)
with ST elevation + enzyme rise	3 (0·9)	2 (0·6)
with ST elevation only	23 (7·2)	21 (6·5)
other	11 (3·4)	7 (2·2)
Intracranial bleeding	0	2 (0·6)
Other intracranial events	0	0
Other thromboembolic events	0	0
Events presenting after angiography or 120 hours		
Death	9 (2·9)	5 (1·6)
Recurrent chest pain*	30 (9·4)	31 (9·6)
with ST elevation + enzyme rise	7 (2·2)	8 (2·5)
with ST elevation only	20 (6·3)	22 (6·8)
other	3 (0·9)	2 (0·6)
Intracranial bleeding	0	0
Other intracranial events	1 (0·3)	2 (0·6)
Other thromboembolic events	1 (0·3)	3 (0·9)

*Recurrent chest pain occurring before angiography (<120 h) was assessed by the clinical events committee; after angiography (or >120 h) assessment is that of the investigator

differ significantly between groups. Mean haemoglobin at admission was 9·5 mmol/l in the heparin group (haematocrit 44·2%) and 9·6 mmol/l (haematocrit 44·1%) in the placebo group. The mean lowest haemoglobin concentration recorded during hospital admission was 8·3 mmol/l (haematocrit 37·9%) in the heparin group and 8·2 mmol/l (haematocrit 38·0%) in the placebo group.

Table 4 lists the incidence of bleeding complications occurring between allocation and angiography and between angiography and discharge. There was a non-significant trend towards more frequent bleeding complications in the heparin group. Both episodes of intracerebral bleeding were verified by computerised tomographic scanning and occurred in patients allocated to heparin. One patient developed a left hemiparesis nine hours after allocation and survived to leave hospital: the other developed symptoms 14 hours after randomisation and died after 19 days. One patient allocated to heparin developed neurological symptoms three hours before angiography and died five hours after angiography from cardiac rupture. He was found to have cerebral oedema and moderate subarachnoid bleeding at necropsy. Both the remaining events occurred after angiography and in patients allocated to placebo treatment. One had symptoms suggestive of a transient ischaemic attack five hours after angiography, was found to have a meningioma on computed tomography, and was discharged alive. The other had a transient ischaemic attack 60 hours after angiography and recovered completely.

Table 4 Incidence of bleeding complications between randomisation and angiography and between angiography and discharge

	Placebo (n=320) (%)	*Heparin (n=324) (%)*
Between randomisation and angiography:		
Total patients with bleeding complications (%):	48 (15·1)	57 (17·6)
Total number of bleeding complications	51	67
Haematoma at puncture site	25 (7·8)	32 (9·9)
Haematoma at other site	7 (2·2)	7 (2·2)
Prolonged bleeding after puncture	5 (1·6)	5 (1·6)
Prolonged bleeding at other site	1 (0·3)	1 (0·3)
Retroperitoneal bleed	1 (0·3)	0
Haemoptysis	0	2 (0·6)
Haematemesis	4 (1·3)	0
Haematuria	2 (0·6)	8 (2·5)
Gingival	5 (1·6)	5 (1·6)
Melena	0	0
Intracranial bleed	0	2 (0·6)
Other	1 (0·3)	5 (1·6)
Between angiography and discharge:		
Total patients with bleeding complications (%):	9 (2·8)	16 (4·9)
Total number of bleeding complications	14	16
Haematoma at puncture site	9 (2·8)	9 (2·8)
Haematoma at other site	1 (0·3)	1 (0·3)
Prolonged bleeding after puncture	0	2 (0·6)
Prolonged bleeding at other site	0	0
Retroperitoneal bleed	0	0
Haemoptysis	0	0
Haematemesis	2 (0·6)	0
Haematuria	0	2 (0·6)
Gingival	0	0
Melena	1 (0·3)	0
Intracranial bleed	0	0
Other	1 (0·3)	2 (0·6)

LEFT VENTRICULAR THROMBUS

Echocardiographic assessment of left ventricular thrombus was attempted in 613 patients. The central assessment committee decided that 532 echocardiograms were technically adequate for assessment. Left ventricular thrombus was present in 10 patients (3·7%) allocated to heparin and in 18 patients (6·8%) allocated to heparin placebo (relative risk 0·55, 95% CI 0·26 to 1·16).

Discussion

The present study shows that patients treated with intravenous alteplase, oral or intravenous aspirin, and concomitant intravenous heparin had a higher coronary patency rate at 48–120 hours than patients randomised to receive alteplase, aspirin, and heparin placebo. These results are consistent with two previous smaller studies that also reported enhanced patency in patients receiving heparin after alteplase thrombolysis,[12 13] although the absolute difference in patency was less pronounced in the present study. Coronary patency after thrombolysis depends on two competing time-dependent processes—one tending to increase perfusion as a consequence of ongoing thrombolytic activity and the other to reduce it as a result of continuing fibrin deposition. There is no single time point at which angiography will give a complete picture of the dynamic balance between patency and occlusion. Despite considerable differences in early patency it has previously been shown that late (10–22 day) angiography shows little difference in coronary patency between patients treated with a thrombolytic agent and patients receiving either a placebo or non-thrombolytic treatment such as heparin + aspirin or heparin + nitrates;[18] it is likely that angiography in the 48–120 hour time window will underestimate rather than overestimate real differences in perfusion over the first 24 hours after thrombolysis. Another difference between the present study and other trials is that we gave a relatively large initial dose of aspirin.

The difference in perfusion rates between heparin and placebo groups was similar in angiograms performed at different times within the 48–120 hour period. The number of angiograms performed before 48 hours was small, and in these patients early angiography

was usually performed for clinical indications such as recurrent chest pain. The National Heart Institute of Australia study showed that patients randomised 24 hours after the start of thrombolytic therapy to continue receiving intravenous heparin or to receive aspirin plus dipyridamole had similar coronary patency rates at one week,[19] and it is possible that any beneficial effects of the additional anticoagulation provided by heparin are shown only within the first 24 hours.

There was a trend towards a smaller enzymatic infarct size in the heparin group but this did not reach conventional significance levels. The difference in enzymatic infarct size measured by similar techniques in a previous study comparing alteplase plus heparin and aspirin with placebo plus heparin and aspirin, in which the differences in early patency would be expected to be much greater, was 20%.[3] No mortality difference between the treatment groups was seen and overall mortality was low. It is possible that patients recruited to the present study might not be fully representative of the whole myocardial infarct population. This does not invalidate the conclusions about patency rates, but it might account for the low mortality and morbidity observed. A tendency to bias recruitment towards less seriously ill patients might also dilute any expected difference in infarct size. There was no overall difference in the incidence of reinfarction between the heparin and placebo groups, although there was a non-significant trend towards a more frequent recurrence of ischaemia in the placebo group between allocation and angiography. Similarly, there was no significant difference in the incidence of major haemorrhagic or thromboembolic events. However, the precision with which a trial of this size can predict the true incidence of rare events such as cerebral haemorrhage is limited. The prevalence of echocardiographically detected left ventricular thrombus was low in both groups, with more thrombi in the placebo group but with 95% confidence intervals for relative risk including zero.

Do the results of the present study affect the interpretation of the recently completed GISSI 2[15] and International Study Group[16] trials comparing streptokinase and alteplase? These protocols randomised patients receiving alteplase and aspirin either to no heparin or to subcutaneous heparin starting at 12 hours and showed no effect of heparin either on a "combined outcome" measure or on survival. We cannot say whether the GISSI 2 and International Study Group results would have been different had alteplase been combined with intravenous heparin, but in the light of this and other smaller trials it seems that the alteplase-alone regimen used was not optimal in terms of restoring coronary patency. The relation between coronary patency and outcome has been disputed, but not disproved, and it seems likely from our present data that the patency rates achieved with alteplase alone would be very similar to those expected, on the basis of previous trials,[5,6] with streptokinase.

No direct evidence has been presented that the delayed subcutaneous heparin regimens used in the GISSI 2 and International Study Group trials are comparable with the intravenous heparin regimen used in the present study and in several previous trials. High dose subcutaneous heparin is capable of inducing systemic anticoagulation, but there is a delay between its initiation and an optimal anticoagulant effect, and the lack of benefit from heparin in the GISSI 2 and International Study Group trials may have been a result of the specific regimen used.[20] Possible mechanisms for a beneficial effect of early intravenous heparin have been reviewed by White,[21] and it seems likely that aspirin even in relatively high dosage is not a complete substitute.

It is clear that we still have an incomplete understanding of the best way to control the thrombotic process after successful thrombolysis. The present study suggests that early treatment with intravenous heparin does indeed contribute to the efficacy of alteplase thrombolysis.

Appendix 1

PARTICIPATING CENTRES AND PHYSICIANS

Medisch Centrum Alkmaar, Netherlands, (C Burgersdijk, A E R Arnold); University Clinics, Basel, Switzerland, (M Pfisterer); Hospital Mutua de Terrassa, Barcelona, Spain, (L Saenz Cusi); Hospital de la Santa Creu, Barcelona, Spain, (J Garcia Picart, M Garcia Moll); Hospital Clinico y Provincial, Barcelona, Spain, (A Betriu); Thoraxcentrum, Academisch Ziekenhuis Dijkzigt, Rotterdam, Netherlands, (M L Simoons); Leyenburg Ziekenhuis, Den Haag, Netherlands, (G A van der Kley); Hôpital St Luc, Brussels, Belgium, (J Col); Royal Infirmary, Edinburgh, (D de Bono, P Bloomfield); Hospital de Santa Cruz, Lisbon, Portugal, (R Seabra Gomes); Hospital Gregorio Maranon, Madrid, Spain, (L Lopez Bescos); Imelda Ziekenhuis, Bonheiden, Belgium, (G Verstreken); Hart Ziekenhuis, Tienen, Belgium, (L de Wolf); Algemeen Ziekenhuis St Jozef, Mechelen, Belgium, (H van Brabandt); Spaarne Ziekenhuis, Heemstede, Netherlands, (H H Kruyswijk); Spaarne Ziekenhuis, Haarlem, Netherlands, (E Mueller); Hospital Universario, Alcala de Herares, Madrid, Spain, (M Sanchez Garcia); Hospital La Paz, Madrid, Spain, (L Lopez Sendon, L Martin Jadraque); Ziekenhuis "De Weezenlanden", Zwolle, Netherlands, (F Zijlstra).

Appendix 2

TRIAL ORGANISATION

Steering Committee

Chairman—M Verstraete (Leuven); *Members*—P Raynaud (Tours), F Van de Werf (Leuven), W Schmidt (Ingelheim am Rhein), R Uebis (Aachen), W Rutsch (Berlin), D de Bono (Leicester), M L Simoons (Rotterdam), P Serruys (Rotterdam).

Ethical and Data Monitoring Committee

Chairman—D Wood (Southampton); *Members*—J Hampton (Nottingham), L Wilhelmsen (Goteborg), W Scharper (Bad Nauheim), D Julian (London).

Angiographic Assessment
D de Bono (Leicester), A Betriu (Barcelona), C Burgersdijk (Alkmaar), M J B van den Brand (Rotterdam), E Benit (Leuven).
Clinical Events and ECG Assessment Committee
J L Willems (Leuven), M L Simoons (Rotterdam), M Pfisterer (Basel).
Echo Assessment
G Sutherland (Rotterdam), B Denef (Leuven), J A Henneman (Alkmaar).
Core laboratory for enzyme analysis
G Willems, W T H Hermans, B Kop (Research Institute for Cardiovascular Diseases, Maastricht, Netherlands).
Core laboratory for haemostasis measurements
M Verstraete, J Arnout (Centrum voor Thrombose en Vasculair Onderzoek, Katholieke Universiteit Gasthuisberg, Leuven, Belgium).
Data centre
K M Hoolboom-Nijssen, I van Oosterom-de Waard, L Jamine, Y Koppelaars, J C Kelder, L Muller, J Tijssen, L Rodenburg (Westzeedijk 120, Rotterdam, Netherlands).

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