Articles

Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction

*The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators**

Summary

Background Current fibrinolytic therapies fail to achieve optimum reperfusion in many patients. Low-molecular-weight heparins and platelet glycoprotein IIb/IIIa inhibitors have shown the potential to improve pharmacological reperfusion therapy. We did a randomised, open-label trial to compare the efficacy and safety of tenecteplase plus enoxaparin or abciximab, with that of tenecteplase plus weight-adjusted unfractionated heparin in patients with acute myocardial infarction.

Methods 6095 patients with acute myocardial infarction of less than 6 h were randomly assigned one of three regimens: full-dose tenecteplase and enoxaparin for a maximum of 7 days (enoxaparin group; n=2040), half-dose tenecteplase with weight-adjusted low-dose unfractionated heparin and a 12-h infusion of abciximab (abciximab group; n=2017), or full-dose tenecteplase with weight-adjusted unfractionated heparin for 48 h (unfractionated heparin group; n=2038). The primary endpoints were the composites of 30-day mortality, in-hospital reinfarction, or in-hospital refractory ischaemia (efficacy endpoint), and the above endpoint plus in-hospital intracranial haemorrhage or in-hospital major bleeding complications (efficacy plus safety endpoint). Analysis was by intention to treat.

Findings There were significantly fewer efficacy endpoints in the enoxaparin and abciximab groups than in the unfractionated heparin group: 233/2037 (11·4%) versus 315/2038 (15·4%; relative risk 0·74 [95% CI 0·63–0·87], p=0·0002) for enoxaparin, and 223/2017 (11·1%) versus 315/2038 (15·4%; 0·72 [0·61–0·84], p<0·0001) for abciximab. The same was true for the efficacy plus safety endpoint: 280/2037 (13·7%) versus 347/2036 (17·0%; 0·81 [0·70–0·93], p=0·0037) for enoxaparin, and 287/2016 (14·2%) versus 347/2036 (17·0%; 0·84 [0·72–0·96], p=0·01416) for abciximab.

Interpretation The tenecteplase plus enoxaparin or abciximab regimens studied here reduce the frequency of ischaemic complications of an acute myocardial infarction. In light of its ease of administration, tenecteplase plus enoxaparin seems to be an attractive alternative reperfusion regimen that warrants further study.

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Introduction

Tenecteplase—a genetically engineered variant of alteplase—has provided a new standard of fibrinolytic therapy by virtue of its equivalent efficacy with regard to 30-day mortality, its reduced propensity for systemic bleeding complications, and its simple administration as a bolus.[1] Despite these advantages, however, there are still substantial challenges, including suboptimal macroperfusion and microperfusion, recurrent ischaemia, and reinfarction and intracranial haemorrhage, in the optimum care of patients with acute myocardial infarction.[2,3]

Antithrombotic agents are an important component of pharmacological reperfusion therapy for acute myocardial infarction. At present, unfractionated heparin and aspirin are routinely given to most patients. Low-molecular-weight heparins have only recently been studied with fibrinolytics. Unlike unfractionated heparin, low-molecular-weight heparins have more predictable kinetics, are less protein-bound, have less potential for platelet activation, and require no monitoring, providing a strong rationale for potentially better outcomes when given in combination with fibrinolytics.[4] Most studies have shown either less reocclusion, enhanced late patency of the infarct-related vessel, or a reduction in reinfarction rate when compared with unfractionated heparin.[5–8] Large-scale studies with low-molecular-weight heparins have not previously been done.

Pilot studies with platelet glycoprotein IIb/IIIa inhibitors and reduced-dose fibrinolytic agents have shown better patency of the epicardial infarct-related artery, and signs of improved tissue reperfusion.[9–11] The phase III Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-V trial showed a reduction in ischaemic complications of acute myocardial infarction with half-dose reteplase and abciximab compared with full-dose reteplase.[12] That trial, however, failed to show a significant reduction in 30-day mortality and there was a significant increase in non-cerebral bleeding complications.

The treatment of acute myocardial infarction requires combination of several therapies. We therefore did a large exploratory trial to develop evidence about whether specific combinations might provide clinical benefit. The aim of the study was to compare the efficacy and safety of three antithrombotic conjunctive therapies with tenecteplase: the first was the low-molecular-weight heparin enoxaparin given up to discharge or revascularisation for a maximum of 7 days; the second was the platelet glycoprotein IIb/IIIa inhibitor abciximab for 12 h; and the third was weight-adjusted unfractionated heparin for 48 h according to the guidelines of the American College of Cardiology and the American Heart Association (ACC/AHA).[13]

Patients and methods

Patients

We recruited patients in 575 hospitals in 26 countries. Inclusion criteria were identical to those of the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-2 trial:[1] age 18 years or older, onset of symptoms less than 6 h before randomisation, ST-segment elevation of at least 0·1 mV in two or more limb leads or at least 0·2 mV in two or more contiguous precordial leads, or left bundle-branch block. Exclusion criteria on admission were: systolic blood pressure of more than 180 mm Hg, diastolic blood pressure of more than 110 mm Hg, or both on repeated measurements; use of abciximab or other glycoprotein IIb/IIIa inhibitors within the preceding 7 days; major surgery, biopsy of a parenchymal organ or substantial trauma within 2 months; any head injury or other trauma occurring after onset of current myocardial infarction; any known history of stroke, transient ischaemic attack, or dementia; any known structural damage to the central nervous system; current treatment with oral anticoagulants; treatment with unfractionated heparin of more than 5000 U or a therapeutic subcutaneous dose of low-molecular-weight heparin within 6 h; known thrombocytopenia (<100 000 cells/μL); known renal insufficiency (serum creatinine concentration >221 μmol/L for men and >177 μmol/L for women); sustained cardiopulmonary resuscitation (more than 10 min) in previous 2 weeks; pregnancy, lactation, or parturition in the previous 30 days; active participation in another investigative drug or device study in the previous 30 days; previous enrolment in this study; any other disorder that would place the patient at increased risk; and inability to follow the protocol and to comply with the follow-up requirements.

The protocol was approved by each hospital's institutional review board, and patients gave informd consent.

Methods

Patients were randomly assigned, via a central computerised telephone system, a bodyweight-adjusted single bolus of tenecteplase with enoxaparin, abciximab plus low-dose unfractionated heparin, or unfractionated heparin. Each patient was given a unique study number that corresponded with the number of a treatment kit. Study treatments were given on an open-label basis.

Tenecteplase was given over 5 s according to bodyweight: patients assigned enoxaparin or unfractionated heparin were given 30 mg if their bodyweight was less than 60 kg, 35 mg if it was 60–69 kg, 40 mg if it was 70–79 kg, 45 mg if it was 80–89 kg, and 50 mg if it was 90 kg or more. In patients assigned combination treatment with abciximab, half-dose tenecteplase was given with doses ranging from 15 mg to 25 mg according to the same weight categories as with the full dose.

Patients assigned weight-adjusted intravenous unfractionated heparin received a bolus of 60 U/kg (maximum of 4000 U) and initial infusion of 12 U/kg per h (maximum 1000 U/h) adjusted to maintain an activated partial thromboplastin time of 50–70 s for 48 h with subsequent heparin administration left to the discretion of the treating physician. The first blood sample for activated partial thromboplastin time measurement was drawn after 3 h. Patients assigned enoxaparin co-therapy received an intravenous bolus of 30 mg immediately followed by the first subcutaneous dose of 1 mg/kg. To achieve sustained anticoagulation, this subcutaneous dose was repeated every 12 h up to hospital discharge or revascularisation for a maximum of 7 days. The first two subcutaneous doses could not exceed 100 mg. Patients assigned abciximab co-therapy received a 0·25 mg/kg bolus and 0·125 μg/kg per min (maximum of 10 μg/min) for 12 h. Because abciximab has an anticoagulant effect, a lower dose of unfractionated heparin was given: 40 U/kg bolus (maximum of 3000 U) followed by 7 U/kg per h (maximum of 800 U/h) to achieve a partial thromboplastin time between 50 and 70 s. Also in this group, the first activated partial thromboplastin time was measured after 3 h. Aspirin (150–325 mg) was given to all patients. Intravenous boluses of unfractionated heparin, enoxaparin, and abciximab were to be given before bolus tenecteplase.

The primary endpoints were the composites of 30-day mortality, in-hospital reinfarction, or in-hospital refractory ischaemia (primary efficacy endpoint), and the above plus in-hospital intracranial haemorrhage or in-hospital major bleeding other than intracranial bleeding (primary efficacy plus safety endpoint).

Data were entered with the use of Oracle Clinical (version 3.1.1) and electronically transferred to the central database in Leuven, Belgium. Safety data were reported monthly to the data and safety monitoring committee. All stroke cases were reviewed by the same stroke committee that reviewed the stroke data in the ASSENT-2 trial. The members of this committee were unaware of treatment assignment. There was no central adjudication for the endpoints of reinfarction, refractory ischaemia, and bleeding complications. However, definitions were provided to the investigators who, in addition, had to reconfirm the occurrence of these endpoints on a special form.

Reinfarction in the first 18 h was defined as recurrent symptoms of ischaemia at rest accompanied by new or recurrent ST-segment elevations of 0·1 mV or more in at least two contiguous leads, lasting at least 30 min. After 18 h, the definition was: new Q waves in two or more leads, or further increases in concentrations of creatine kinase MB, troponins, or total creatine kinase above the upper limit of normal and increased over the previous value. Refractory ischaemia was defined as symptoms of ischaemia with ST-segment deviation or T-wave inversion persisting for at least 10 min despite medical management and not fulfilling the diagnosis of reinfarction. Non-cerebral bleeding complications were defined as major (requiring transfusion, intervention because of haemodynamic compromise, or both) or minor.

Statistical analysis

Statistical analysis was by intention to treat. No confirmatory statistical hypothesis was prespecified, but a detailed analysis plan was defined before the database was locked. This analysis plan was based on generating risk ratios and CIs for the pairwise comparisons of primary interest. These comparisons were presented with the two-sided 95% CI of the relative risk and with nominal p values. For the primary endpoints, Kaplan-Meier curves were constructed and log-rank tests were done. For each endpoint, a two-sided 95% CI was also calculated and an overall χ^2 test, comparing the three treatment groups, was done. Comparisons of interest were prespecified to first involve the unfractionated heparin and enoxaparin groups. If these were not different, they were to be pooled and compared with the abciximab group. Otherwise, each experimental group was to be compared with the unfractionated heparin reference group.

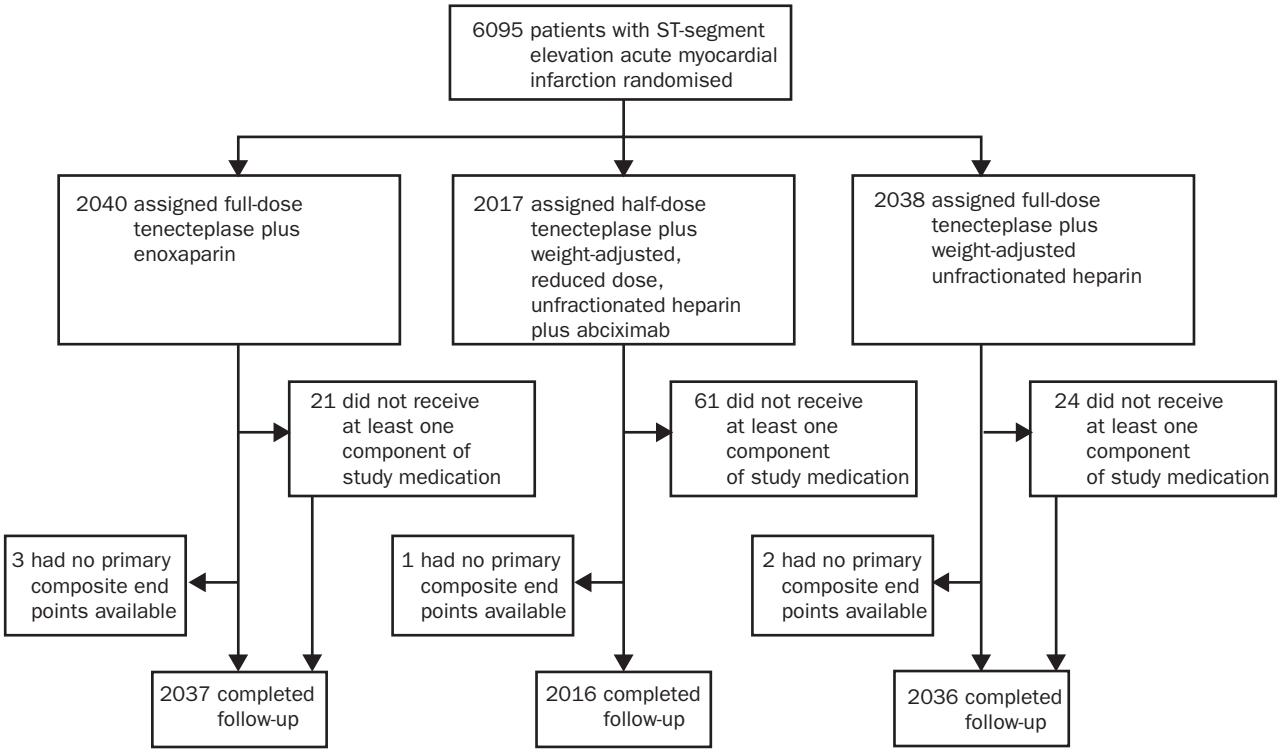

Figure 1: **Trial profile**

On the basis of ASSENT-2, the estimated frequency of the primary efficacy endpoint in the group allocated full-dose tenecteplase and unfractionated heparin was 13·8%. The frequency of the primary efficacy plus safety endpoint in this group was 17·7%.[1] On the basis of phase-II studies, we assumed that the two experimental groups would result in a better, or at least similar, outcome when compared with standard treatment. The sample size and power calculations were therefore based on non-inferiority of the two experimental groups versus the reference group. The study had 80% power to exclude, with 95% confidence (one-sided), a 1% higher rate of the primary endpoints compared with the reference group, provided the point estimate in the experimental treatment group was 1·7% lower for the efficacy endpoint and 2·0% lower for the efficacy plus safety endpoint.

Results

6095 patients were enrolled between May, 2000, and April, 2001, of whom 5989 received study medication (figure 1). The baseline characteristics were similar in the three groups (table 1). Overall, the study populations were similar to those of previous trials on thrombolytics. As expected, the time from randomisation to bolus tenecteplase was significantly longer in the abciximab group because of the complexity of the treatments and the

	Enoxaparin (n=2040)	Abciximab (n=2017)	Unfractionated heparin (n=2038)
Mean (SD) age (years)	61 (12)	61 (12)	61 (13)
Age >75 years	263/2040 (13%)	233/2016 (12%)	271/2038 (13%)
Women	463/2040 (23%)	494/2017 (24%)	478/2038 (23%)
Mean (SD) weight (kg)	79 (15)	79 (16)	79 (15)
Mean (SD) height (cm)	170 (9)	170 (9)	170 (10)
Mean (SD) time from onset of symptoms to randomisation (h)	2·7 (1·7)	2·7 (1·4)	2·8 (1·6)
Mean (SD) time from randomisation to tenecteplase (h)	0·26 (0·16)	0·40 (0·24)	0·27 (0·17)
Killip class			
I	1823/2039 (89%)	1738/2017 (88%)	1786/2033 (88%)
II/III	209/2039 (10%)	227/2017 (11%)	238/2033 (12%)
IV	7/2039 (0·3%)	7/2017 (0·4%)	9/2033 (0·4%)
Mean (SD) systolic blood pressure (mm Hg)	134 (22)	133 (22)	133 (23)
Infarct location			
Anterior	802/2040 (39%)	782/2014 (39%)	772/2037 (38%)
Inferior	1144/2040 (56%)	1135/2014 (56%)	1164/2037 (57%)
Other	94/2040 (4·6%)	97/2014 (4·8%)	101/2037 (5·0%)
Mean (SD) heart rate (bpm)	75 (17)	75 (17)	74 (17)
Hypertension	826/2037 (41%)	819/2015 (41%)	824/2031 (41%)
Diabetes	381/2039 (19%)	355/2014 (18%)	363/2031 (18%)
Previous myocardial infarction	290/2040 (14%)	267/2016 (13%)	293/2035 (14%)
Prior CABG	73/2038 (3·6%)	66/2013 (3·3%)	53/2029 (2·6%)
Prior PCI	126/2019 (6·2%)	119/1999 (6·0%)	182/2012 (6·4%)
Current smoker	884/1992 (44%)	935/1981 (47%)	930/1988 (47%)

CABG=coronary-artery bypass graft; PCI=percutaneous coronary intervention.

Table 1: **Baseline characteristics**

	Enoxaparin (n=2040)	Abciximab (n=2017)	Unfractionated heparin (n=2038)	p
Calcium-channel blockers	216/2026 (11%)	202/1996 (10%)	215/2022 (11%)	0·82
Intravenous nitrates	1490/2037 (73%)	1423/1999 (71%)	1489/2031 (73%)	0·25
β-blockers	1707/2037 (84%)	1687/2001 (84%)	1696/2034 (83%)	0·73
ACE inhibitors	1270/2034 (62%)	1204/2001 (60%)	1271/2025 (63%)	0·18
Angiotensin II inhibitors	63/2016 (3·1%)	57/1990 (2·9%)	63/2018 (3·1%)	0·87
Statins	1062/2027 (52%)	995/1999 (50%)	1024/2023 (51%)	0·24
Aspirin				
<12 h or upon randomisation	1969/2040 (97%)	1959/2017 (97%)	1974/2036 (97%)	0·53
In hospital	1948/2039 (96%)	1900/2008 (95%)	1933/2035 (95%)	0·40
Ticlopidine/clopidogrel	605/2034 (30%)	556/1998 (28%)	649/2025 (32%)	0·014
Oral anticoagulants	87/2028 (4·3%)	95/1994 (4·8%)	105/2027 (5·2%)	0·41
Abciximab	133/2038 (6·5%)	84/2007 (4·2%)	180/2033 (8·9%)	<0·0001
Other glycoprotein IIb/IIIa inhibitors	139/2038 (6·8%)	75/2008 (3·7%)	144/2034 (7·1%)	<0·0001
Low-molecular-weight heparins	325/2038 (16%)	526/2008 (26%)	584/2034 (29%)	<0·0001
Thrombolytics	40/2039 (2·0%)	38/2009 (1·9%)	58/2036 (2·9%)	0·08

ACE=angiotensin-converting enzyme.

Table 2: **Number of patients who received concomitant medications during stay in hospital**

	Enoxaparin (n=2040)	Abciximab (n=2017)	Unfractionated heparin (n=2038)	p
30-day mortality, in-hospital reinfarction, or in-hospital refractory ischaemia	233/2037 (11·4%)	223/2017 (11·1%)	314/2038 (15·4%)	0·0001
30-day mortality, in-hospital reinfarction, in-hospital refractory ischaemia, in-hospital ICH, or in-hospital major bleeds (other than ICH)	280/2037 (13·8%)	287/2016 (14·2%)	347/2036 (17·0%)	0·0081
Death at 30 days	109/2037 (5·4%)	133/2017 (6·6%)	122/2038 (6·0%)	0·25
In-hospital reinfarction	54/2040 (2·7%)	44/2017 (2·2%)	86/2038 (4·2%)	0·0009
In-hospital refractory ischaemia	93/2040 (4·6%)	64/2017 (3·2%)	132/2038 (6·5%)	<0·0001
In-hospital ICH	18/2040 (0·9%)	19/2017 (0·9%)	19/2038 (0·9%)	0·98
Major bleeding (other than ICH)	62/2040 (3·0%)	87/2016 (4·3%)	44/2035 (2·2%)	0·0005

ICH=intracranial haemorrhage.

Table 3: **Frequency of composite and single endpoints at hospital discharge and at 30 days**

need to give the boluses of heparin and abciximab before the tenecteplase bolus. Concomitant medications given in hospital are listed in table 2. High proportions of patients received β-blockers, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, statins, and thienopyridines. Abciximab and glycoprotein IIb/IIIa inhibitors other than study medication were given most frequently in the groups assigned full-dose tenecteplase and unfractionated heparin or enoxaparin. Likewise, low-molecular-weight heparins other than study medication were most frequently given to patients assigned unfractionated heparin or abciximab.

The primary efficacy and efficacy plus safety endpoints and their individual components in the three treatment groups are shown in table 3. The combined efficacy and safety outcome in the full-dose tenecteplase plus unfractionated heparin group of 17·0% was similar to that estimated (17·7%) before the trial commenced. The Kaplan-Meier curves for these primary endpoints are shown in figures 2 and 3. Log-rank tests were highly significant. Early after treatment, the curves for the enoxaparin and abciximab groups started to separate from that of unfractionated heparin. At 48 h, the end of the unfractionated heparin infusion, differences in the primary endpoints among the three groups were already present. For the primary efficacy endpoint, event rates were 6·1% for full-dose tenecteplase plus enoxaparin, 5·2% for half-dose tenecteplase plus abciximab, and 8·8% for full-dose tenecteplase plus unfractionated heparin (p<0·0001). For the primary efficacy plus safety endpoint, the rates were 8·1, 8·2, and 10·3%, respectively (p=0·022).

The relative risks in the total population and in the prespecified subgroups are presented in figures 4 and 5. The rates of the composite endpoints were lower among patients treated with enoxaparin or abciximab than among those treated with unfractionated heparin. Conventional statistical testing for full-dose tenecteplase plus enoxaparin versus full-dose tenecteplase plus unfractionated heparin resulted in p values of 0·0002 and 0·0037, respectively, for the primary efficacy and efficacy plus safety composite endpoints. The half-dose tenecteplase plus abciximab

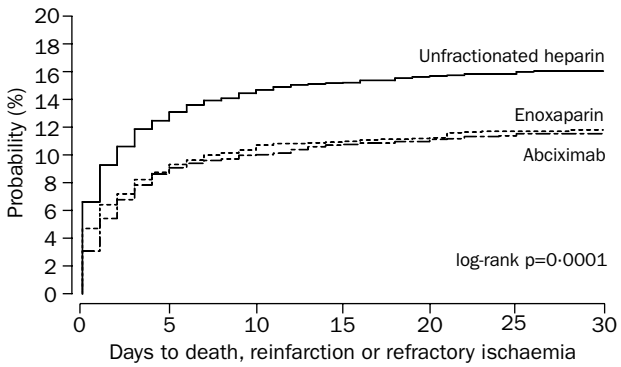

Figure 2: **Kaplan-Meier curves for primary efficacy endpoint**

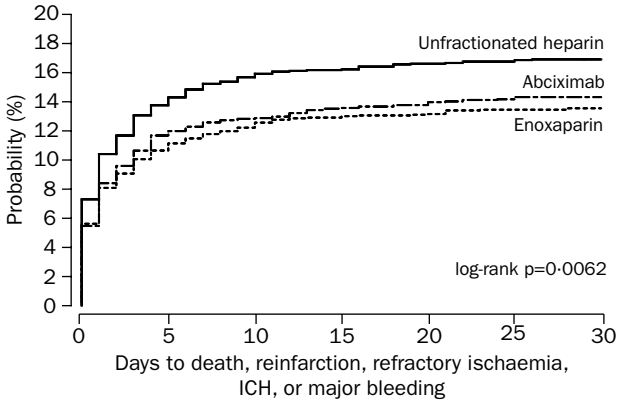

Figure 3: **Kaplan-Meier curves for primary efficacy plus safety endpoint**

ICH=intracranial haemorrhage.

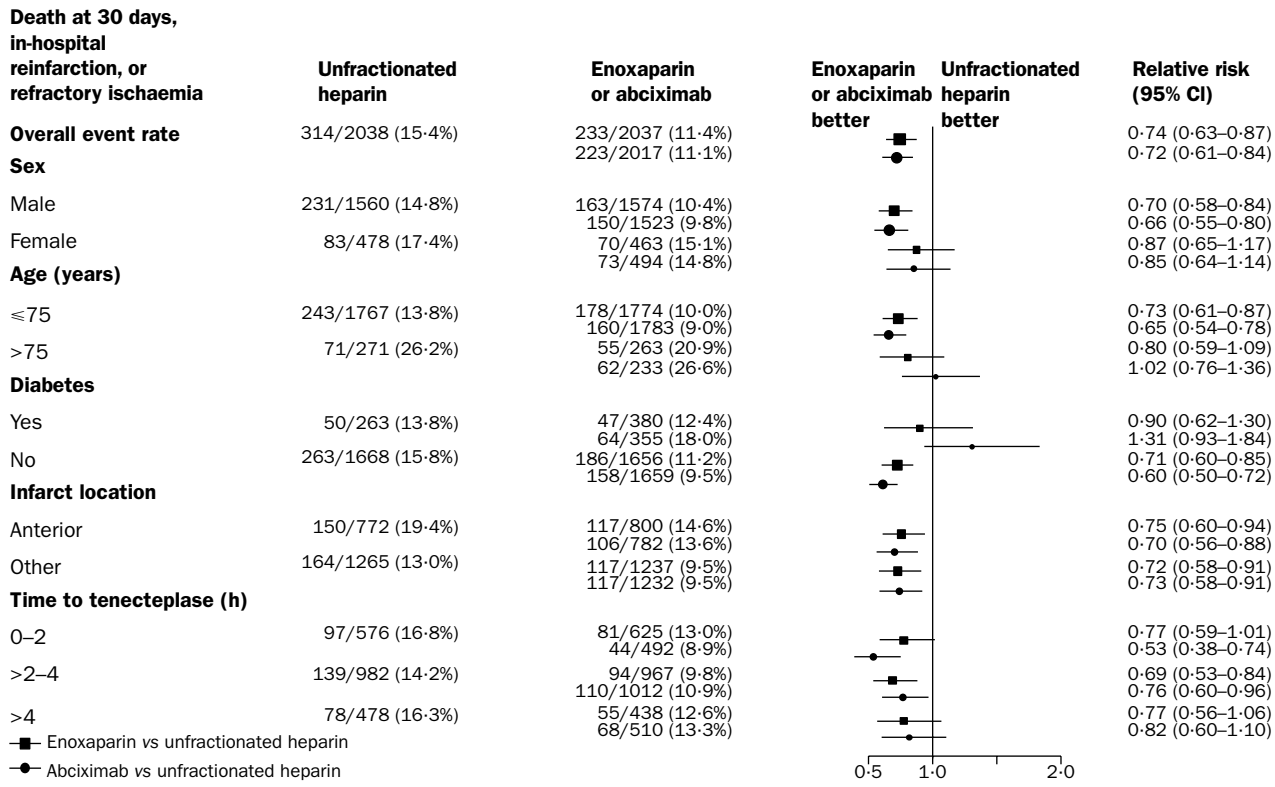

Figure 4: **Relative risks and 95% CIs for primary efficacy composite endpoint in total study population and in prespecified subgroups**

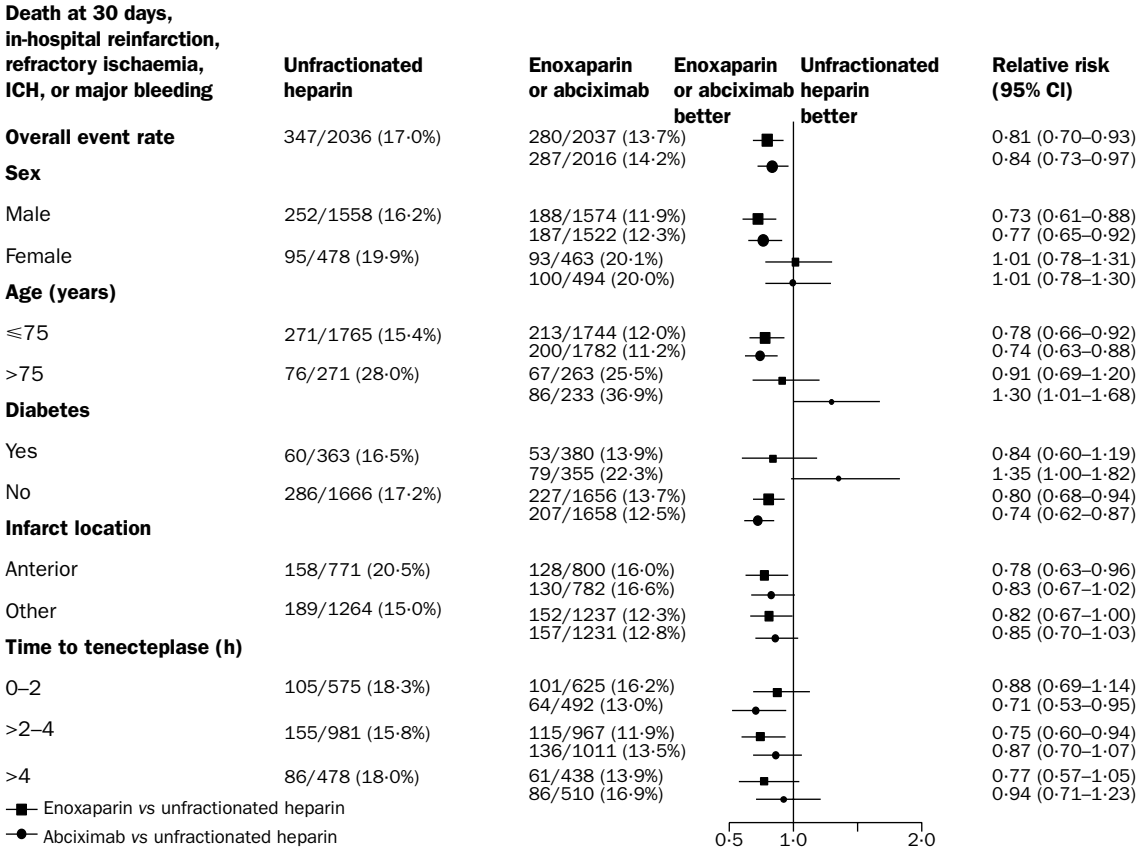

Figure 5: **Relative risks and 95% CIs for primary efficacy plus safety composite endpoint in total study population and in prespecified subgroups**
ICH=intracranial haemorrhage.

	Enoxaparin (n=2040)	Abciximab (n=2017)	Unfractionated heparin (n=2038)	p
Sustained hypotension	42/2040 (2·1%)	56/2017 (2·8%)	55/2038 (2·8%)	0·27
Pulmonary oedema, cardiogenic shock, or both	106/2040 (5·2%)	105/2017 (5·2%)	115/2038 (5·6%)	0·78
Major arrhythmias	173/2040 (8·5%)	186/2017 (9·3%)	212/2038 (10·5%)	0·11
Invasive cardiac procedures				
Any	661/2037 (32·5%)	645/2008 (32·1%)	719/2035 (35·3%)	0·06
IABP	53/2038 (2·6%)	31/2009 (1·5%)	56/2034 (2·8%)	0·01
Urgent CABG	34/2037 (1·7%)	31/2008 (1·5%)	34/2034 (1·7%)	0·94
Non-urgent CABG	48/2038 (2·4%)	58/2009 (2·9%)	71/2035 (3·5%)	0·10
Urgent PCI	242/2036 (11·9%)	182/2009 (9·1%)	292/2035 (14·4%)	<0·0001
Non-urgent PCI	355/2037 (17·4%)	390/2009 (19·4%)	335/2035 (16·5%)	0·04
Pericarditis	14/2040 (0·7%)	21/2017 (1·0%)	12/2038 (0·6%)	0·23
Acute mitral regurgitation	2/2040 (0·1%)	6/2017 (0·3%)	5/2038 (0·3%)	0·35
Pulmonary embolism	2/2040 (0·1%)	5/2017 (0·3%)	1/2038 (0·1%)	0·19
Tamponade	8/2040 (0·4%)	6/2017 (0·3%)	6/2038 (0·3%)	0·89
Acute ventricle septum defect	11/2040 (0·5%)	8/2017 (0·4%)	10/2038 (0·5%)	0·85
Electromechanical dissociation	27/2040 (1·3%)	31/2017 (1·5%)	28/2038 (1·4%)	0·84
Killip class >1	89/1972 (4·5%)	95/1935 (4·9%)	94/1942 (4·8%)	0·82
Anaphylaxis	0	0	1/2038 (0·1%)	0·67

IABP=intra-aortic balloon pump; CABG=coronary-artery bypass graft; PCI=percutaneous coronary intervention.

Table 4: **Frequency of in-hospital cardiac events and procedures**

versus full-dose tenecteplase plus unfractionated heparin comparisons for the same primary endpoints yielded nominal p values of <0·0001 and 0·0142. After correcting for multiple testing (Bonferroni), conventional significance was reached for the primary efficacy endpoint in the abciximab group (p=0·0002) but not for the efficacy plus safety endpoint (p=0·057). For both the efficacy and efficacy plus safety endpoints, statistical significance was reached in the enoxaparin group (p=0·0009 and p=0·0146, respectively).

The lower point estimate of the relative risk of the composite endpoints was consistent across subgroups for the combination of full-dose tenecteplase and enoxaparin. For the combination of half-dose tenecteplase and abciximab, lower point estimates were seen in most subgroups, except in patients older than 75 years and those with diabetes (figures 3 and 4). For the efficacy composite endpoint, the test for an interaction between treatment and diabetes was significant (p=0·0004). For the efficacy plus safety composite endpoint, the treatment interaction tests were significant for age (p=0·0010) and diabetes (p=0·0007). In women, lower point estimates of the relative risks of the efficacy composite endpoint were found in both experimental groups, whereas for the efficacy plus safety composite endpoint, the point estimates were on the line of unity.

No significant differences in 30-day mortality were present (table 3). In-hospital reinfarction and refractory ischaemia occurred less frequently in patients treated with enoxaparin or abciximab than in those treated with unfractionated heparin. The rates of in-hospital death or reinfarction were also lower in the enoxaparin and abciximab groups than in the unfractionated heparin group: 138/2040 (6·8%) and 148/2017 (7·3%) and 185/2038 (9·1%), respectively (p=0·0198). No significant reductions in other major cardiac complications were seen, with the exception of a significantly lower need for urgent percutaneous coronary interventions (ischaemia-driven percutaneous coronary intervention before hospital discharge) in patients on enoxaparin or abciximab than in patients on unfractionated heparin (table 4). The data on in-hospital strokes are summarised in table 5. Total stroke and intracranial haemorrhage rates were similar in the three groups. A few haemorrhagic conversions were seen in each of the three treatment groups. Strokes could not be classified in only in a few patients.

Non-cerebral bleeding complications, need for transfusion, and rates of thrombocytopenia are given in table 6. Significantly more major bleeding complications (p=0·0002), more transfusions (p=0·001), and a higher rate of thrombocytopenia (p=0·0001) were seen in the abciximab group compared with the unfractionated heparin group. In patients older than 75 years and in diabetics, the rate of major bleeding complications was three times higher with abciximab than with unfractionated heparin: 11/271 (4·1%) versus 31/233 (13·3%), and 8/363 (2·2%) versus 25/355 (7·0%), respectively. More major bleeding complications and blood transfusions were also seen in the enoxaparin group compared with unfractionated heparin, although these differences were not significant. There was no excess of thrombocytopenia in this treatment group. The total number of readmissions to hospital was similar in the three treatment groups: 254/1986 (12·8%) for enoxaparin, 221/1946 (11·4%) for abciximab, and 239/1984 (12·1%) for unfractionated heparin (p=0·39). A few additional strokes occurred after hospital discharge in the three groups. Total stroke rates and the rates of death or disabling stroke at 30 days remained similar: 39/2040 (1·9%) and 122/2037 (6·0%) for full-dose tenecteplase and enoxaparin, 37/2017 (1·8%) and 141/2016 (7·0%) for half-dose tenecteplase and abciximab, and 34/2038 (1·7%) and 132/2038 (6·5%) for full-dose tenecteplase and unfractionated heparin, respectively (p=0·83 for total stroke and p=0·43 for death or disabling stroke).

Discussion

The results of the group treated with full-dose tenecteplase and weight-adjusted unfractionated heparin in this trial were very similar to those of ASSENT-2. In

	Enoxaparin (n=2040)	Abciximab (n=2017)	Unfractionated heparin (n=2038)	p
Total strokes	33/2040 (1·62%)	30/2017 (1·49%)	31/2038 (1·52%)	0·94
Intracranial haemorrhage	18/2040 (0·88%)	19/2017 (0·94%)	19/2038 (0·93%)	0·98
Ischaemic stroke*	13/2040 (0·64%)	8/2017 (0·40%)	11/2038 (0·54%)	0·57
Haemorrhagic conversion	1/2040 (0·07%)	1/2017 (0·07%)	0/2038	0·77
Unclassified	3/2040 (0·15%)	3/2017 (0·15%)	1/2038 (0·05%)	0·59

*Including haemorrhagic conversion.

Table 5: **In-hospital stroke rates**

	Enoxaparin (n=2040)	Abciximab (n=2017)	Unfractionated heparin (n=2038)	p
Any thrombocytopenia	24/2040 (1·2%)	64/2017 (3·2%)	27/2038 (1·3%)	<0·0001
Thrombocytopenia				<0·0001
<20 000 cells/μL	2/2040 (0·1%)	10/2017 (0·5%)	3/2038 (0·2%)	
20 000–50 000 cells/μL	4/2040 (0·2%)	13/2017 (0·6%)	4/2038 (0·2%)	
50 000–100 000 cells/μL	18/2040 (0·9%)	41/2017 (2·0%)	20/2038 (1·0%)	
Bleeding episodes				
Total	522/2040 (25·6%)	801/2017 (39·7%)	429/2038 (21·1%)	<0·0001
Major	62/2040 (3·0%)	87/2016 (4·4%)	44/2035 (2·2%)	0·0005
Minor	460/2040 (22·6%)	713/2016 (35·3%)	381/2035 (18·7%)	<0·0001
Blood transfusion	70/2040 (3·4%)	84/2017 (4·2%)	47/2038 (2·3%)	0·0032

Table 6: **Rate of in-hospital thrombocytopenia and non-cerebral bleeding complications**

ASSENT-2, a higher and not fully weight-adjusted dose of unfractionated heparin was given and the first partial thromboplastin time was measured 6 h after start of treatment. Nonetheless, total mortality, reinfarction, total stroke, and intracranial haemorrhage rates were almost identical in both trials. However, there were fewer major bleeding complications (2·2% *vs* 4·7%) and less need for blood transfusion (2·3% *vs* 4·3%) in the present trial than in ASSENT-2. These results indirectly support the use of a more fully weight-adjusted dose of unfractionated heparin, as recommended in the ACC/AHA guidelines, together with earlier monitoring of the partial thromboplastin time. This unfractionated heparin dosing, however, was not associated with a reduction in the rate of intracranial haemorrhage, by contrast with the findings of a recent post-hoc analysis of the Intravenous nPA for the Treatment of Infarcting Myocardium Early (InTIME)-II data.[14]

Compared with unfractionated heparin, adjunctive therapy with abciximab or enoxaparin reduces ischaemic complications of acute myocardial infarction treated with tenecteplase. These reductions were found to be present early after the start of treatment. The results obtained with half-dose tenecteplase plus abciximab are very similar to those with half-dose reteplase and abciximab seen in GUSTO-V, and support the hypothesis that a more potent antiplatelet agent increases flow in the infarct-related coronary artery. In both trials, these benefits are obtained at the cost of a higher rate of thrombocytopenia, major bleeding complications, and blood transfusions. No benefit, and perhaps even harm, was seen in patients older than 75 years and in diabetics. By contrast with the present study, a 0·6% reduction in 30-day mortality was found in diabetic patients enrolled in GUSTO-V. Whether the findings in diabetics from the smaller ASSENT-3 study is due to chance or some other reason is unknown. Conversely, the data from both trials for this combination in elderly patients are consistent. Taken together, they suggest that caution should be exercised regarding the use of conjunctive therapy with abciximab in elderly patients with an acute myocardial infarction treated with a fibrinolytic agent. Further studies in the important and growing population of elderly patients with an acute myocardial infarction are warranted and might involve lower doses of these agents and mechanical approaches to reperfusion. The GUSTO-V and current results with half-dose fibrinolytic and abciximab suggest that there might be a role for this combination treatment in younger patients who are likely to undergo early coronary interventions. This speculation needs to be formally tested in future trials.

The reductions in ischaemic complications in the full-dose tenecteplase plus enoxaparin group were similar to those seen in the abciximab group, but were more consistent. Importantly, no increase in intracranial haemorrhage rate, no excess in thrombocytopenia, and only a modest and non-significant increase in major bleeding complications was seen despite the length of treatment. In view of the present data and the ease of administration, enoxaparin might be regarded as an attractive alternative anticoagulant treatment when given in combination with tenecteplase. Whether enoxaparin is a desirable anticoagulant in conjunction with less fibrin-specific agents, whether enoxaparin can replace unfractionated heparin in combination with a platelet glycoprotein IIb/IIIa inhibitor and a reduced dose fibrinolytic, and what role various pharmacological combinations will ultimately have in conjunction with early coronary intervention need to be determined.

The overall 30-day mortality rates in our study were low and probably result from selection of patients and an improvement in associated medical treatment and intervention. However, time to treatment remained similar to that of other large trials of fibrinolytic therapy, emphasising the opportunity provided by prehospital therapy with simple regimens. This opportunity is currently being explored in the ASSENT-3 plus study which will compare the two full-dose tenecteplase cohorts administered out-of-hospital versus a matched population from the current study.

Our study has some limitations. Ascertainment of selected components of the composite endpoints in this open trial was investigator-determined and subject to bias. Our goal was to examine whether addition of a low-molecular-weight heparin or a platelet glycoprotein IIb/IIIa inhibitor to a fibrinolytic agent had promise as a therapeutic approach, and thus we did not define statistical hypotheses a priori. Nonetheless, the strength and consistency of the results suggest that they are probably not due to bias or chance. The observed treatment effects with both experimental groups exceeded what was expected in this intermediate-sized trial and raises the question as to whether our exploratory experimental approach will be useful in future assessments of promising combinations and various dosing regimens before large, definitive trials are done. The different duration of heparin therapy in the enoxaparin versus the unfractionated heparin group also deserves comment. We chose a 7-day course of enoxaparin to conform with previous studies[5-8] in the hope of reducing recurrent ischaemic complications and preventing reocclusion; the 48-h infusion of unfractionated heparin is a standard antithrombotic strategy used in previous trials such as ASSENT-2.[1] The longer exposure to enoxaparin possibly contributed to its increased efficacy and to the increased trend for bleeding.

Taking into account efficacy and safety, the combination of full-dose tenecteplase and long-term administration of enoxaparin emerged as the best treatment in this trial. Because of additional advantages such as the ease of administration and the lack of need for monitoring of anticoagulation, this combination should be regarded as an attractive alternative pharmacological reperfusion strategy deserving further study.

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