Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial

*Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators**

Summary

Background Bolus fibrinolytic therapy facilitates early efficient institution of reperfusion therapy. Tenecteplase is a genetically engineered variant of alteplase with slower plasma clearance, better fibrin specificity, and high resistance to plasminogen-activator inhibitor-1. We did a double-blind, randomised, controlled trial to assess the efficacy and safety of tenecteplase compared with alteplase.

Methods In 1021 hospitals, we randomly assigned 16 949 patients with acute myocardial infarction of less than 6 h duration rapid infusion of alteplase (⩽100 mg) or single-bolus injection of tenecteplase (30–50 mg according to bodyweight). All patients received aspirin and heparin (target activated partial thromboplastin time 50–75 s). The primary outcome was equivalence in all-cause mortality at 30 days.

Findings Covariate-adjusted 30-day mortality rates were almost identical for the two groups—6·18% for tenecteplase and 6·15% for alteplase. The 95% one-sided upper boundaries of the absolute and relative differences in 30-day mortality were 0·61% and 10·00%, respectively, which met the prespecified criteria of equivalence (1% absolute or 14% relative difference in 30-day mortality, whichever difference proved smaller). Rates of intracranial haemorrhage were similar (0·93% for tenecteplase and 0·94% for alteplase), but fewer non-cerebral bleeding complications (26·43 *vs* 28·95%, p=0·0003) and less need for blood transfusion (4·25 *vs* 5·49%, p=0·0002) were seen with tenecteplase. The rate of death or non-fatal stroke at 30 days was 7·11% with tenecteplase and 7·04% with alteplase (relative risk 1·01 [95% CI 0·91–1·13]).

Interpretation Tenecteplase and alteplase were equivalent for 30-day mortality. The ease of administration of tenecteplase may facilitate more rapid treatment in and out of hospital.

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Introduction

Rapid infusion of the tissue-plasminogen activator alteplase in association with aspirin and heparin, is the gold standard for pharmacological reperfusion in acute myocardial infarction. No other fibrinolytic regimen has been shown to be superior or equivalent to the administration of 100 mg alteplase given initially as a bolus followed by a step-down infusion over a period of 90 min (front-loaded approach) to lower 30-day mortality.[1]

Because of the ease of administration, bolus fibrinolysis facilitates rapid administration, including treatment before admission to hospital, and may ensure complete administration of the fibrinolytic agent, as well as a low rate of medication errors. Double-bolus administration of reteplase, a deletion mutant of alteplase with slower plasma clearance, was the first third-generation fibrinolytic. Apart from its ease of administration, the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO-III) trial[2] showed no efficacy or safety advantage for reteplase over front-loaded alteplase.[2]

Tenecteplase is a triple-combination mutant of alteplase developed to circumvent some of the limitations of current fibrinolytic therapies. Tenecteplase has a longer plasma half-life (20 *vs* 4 min), better fibrin specificity, and higher resistance to inhibition by plasminogen-activator inhibitor-1 than alteplase.[3] Efficacy for clot lysis of single-bolus administration of tenecteplase was studied in the Thrombolysis in Myocardial Infarction (TIMI) 10A and TIMI 10B trials,[4,5] and safety was assessed in the Assessment of the Safety of a New Thrombolytic (ASSENT-1) study.[6] The results of these studies suggested that a bodyweight-adjusted single bolus of 0·50–0·55 mg/kg tenecteplase would be equivalent to a 90 min regimen of alteplase for efficacy and safety. In this double-blind, randomised, controlled study, we formally tested this hypothesis.

Methods

Study population

We recruited patients from October, 1997, to November, 1998, in 1021 hospitals in 29 countries. To be eligible, patients had to: be aged 18 years or older; have onset of symptoms of acute myocardial infarction within 6 h before randomisation; have ST-segment elevations of 0·1 mV or more in two or more limb leads, or 0·2 mV or more in two or more contiguous precordial leads; or have left bundle-branch block. Exclusion criteria on admission were: hypertension, defined as 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 antagonists within the preceding 12 h; major surgery; biopsy of a parenchymal organ; or substantial trauma within 2 months before admission; any major head trauma and any other trauma occurring after onset of the current myocardial infarction; any known history of stroke, transient ischaemic attack, or dementia; any known structural damage to the central nervous system; current therapy with oral

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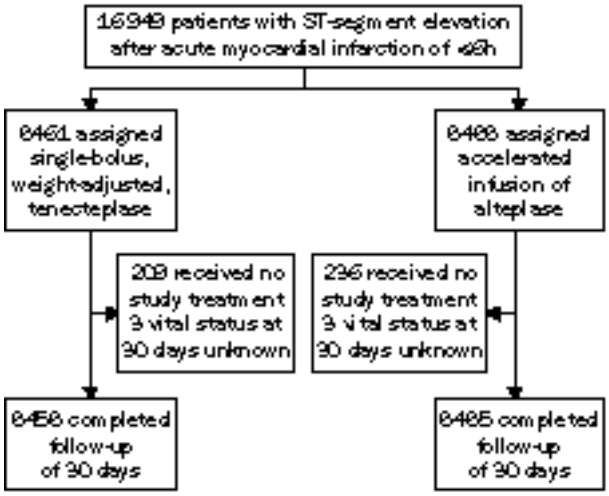

Figure 1: **Trial profile**

anticoagulation, with an international normalised ratio of more than 1·3; sustained cardiopulmonary resuscitation (more than 10 min) in the previous 2 weeks; pregnancy, lactation, or parturition in the previous 30 days (women of childbearing potential had to have a negative pregnancy test); any known active participation in another investigative drug study or device protocol in the previous 30 days; previous enrolment in this study; any other disorder that the investigator judged would place the patient at increased risk; and inability to follow the protocol and to comply with the follow-up requirements.

Randomisation and study treatments

After giving informed consent, patients were randomly assigned, through a central computerised telephone system, a bodyweight-adjusted bolus of tenecteplase plus bolus and infusion of placebo, or a bolus and infusion of alteplase plus bolus of placebo. We gave each patient a unique study number that corresponded with the number of a treatment kit.

Tenecteplase (or placebo) was administered over 5–10 s in a dose according to bodyweight: 30 mg to patients who weighed less than 60·0 kg, 35 mg to those who weighed 60·0–69·9 kg, 40mg to those who weighed 70·0–79·9 kg, 45 mg to patients who weighed 80·0–89·9 kg, and 50 mg to patients who weighed 90·0 kg or more.

Alteplase (or placebo) was given as a 15 mg bolus followed by a 0·75 mg/kg (up to 50 mg) infusion over 30 min and a 0·50 mg/kg (up to 35 mg) infusion over 60 min. All patients received 150–325 mg aspirin orally and intravenous heparin

Characteristic	Tenecteplase (n=8461)	Alteplase (n=8488)
Median age (years)*	61 (52–70)	61 (52–70)
Age >75 years	1047 (12·4%)	1070 (12·6%)
Female	1941 (22·9%)	1980 (23·3%)
Previous hypertension	3188 (37·7%)	3268 (38·5%)
Diabetes	1384 (16·4%)	1329 (15·7%)
Current smoker	3747 (44·3%)	3709 (43·7%)
Previous infarction	1335 (15·8%)	1369 (16·1%)
Previous bypass surgery	461 (5·5%)	523 (6·2%)
Median systolic blood pressure (mm Hg)*	133 (120–150)	133 (119–150)
Median diastolic blood pressure (mm Hg)*	80 (70–90)	80 (70–90)
Median heart rate (beats/min)*	72 (62–85)	73 (62–85)
Location of infarction		
Anterior	3335 (39·4%)	3409 (40·2%)
Inferior	4686 (55·4%)	4649 (54·8%)
Other	426 (5·0%)	411 (4·8%)
Killip class		
I	7428 (87·8%)	7465 (88·0%)
II	887 (10·5%)	874 (10·3%)
III	93 (1·1%)	98 (1·2%)
IV	35 (0·4%)	36 (0·4%)
Median time between onset of symptoms and treatment (h)*	2·7 (1·9–3·8)	2·8 (1·9–3·9)

Because of rounding, not all percentages total 100. *Median (IQR).

Table 1: **Baseline characteristics of patients**

	Tenecteplase (n=8461)	Alteplase (n=8488)
Aspirin (≤12 h)	97·3	97·5
Heparin		
Bolus	94·5	94·4
Infusion	99·3	99·2
Intravenous nitrates	72·8	72·2
β-blockers	80·7	80·8
Angiotensin-converting-enzyme inhibitors	53·2	53·9
Angiotensin II inhibitors	1·9	1·9
Other thrombolytics	2·7	2·3
Low-molecular-weight heparin	21·1	21·7
Glycoprotein IIb/IIIa antagonists	7·6	7·6
Ticlopidine/clopidogrel	22·6	22·4
Statins	31·4	31·8

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

(bolus of 4000 U and infusion of 800 U/h for patients who weighed 67 kg or less; 5000 U bolus and infusion of 1000 U/h for patients who weighed more than 67 kg), adjusted to maintain an activated partial thromboplastin time of 50–75 s for 48–72 h. When a bedside monitor was used, the target activated partial thromboplastin time was 60–85 s, which corresponds to the 50–75 s target obtained with standard laboratory reagents.

The primary endpoint was all-cause mortality at 30 days. Secondary endpoints included net clinical benefit, defined as absence of death or non-fatal stroke at 30 days, major non-fatal cardiac events in hospital, and stroke. All stroke data were reviewed by an independent stroke-assessment panel that classified the stroke as primary haemorrhagic, ischaemic, ischaemic with conversion to haemorrhage, or of unknown cause (if no brain scans or necropsy results were available). Non-cerebral bleeding episodes were classified as major (requiring blood transfusion, intervention because of haemodynamic compromise, or both) or minor.

Statistical analysis

We aimed to show therapeutic equivalence of single-bolus tenecteplase compared with front-loaded alteplase. To show equivalence or non-inferiority in all-cause mortality is judged to be an appropriate study approach to establish that a variant of a standard treatment achieves a clinical benefit similar to that of the standard treatment, provided that appropriate criteria of equivalence are prespecified.[7–9] We adopted a stringent definition of equivalence and developed the null hypothesis that 30-day mortality after tenecteplase would exceed 30-day mortality after alteplase by more than 1% or that the relative risk in 30-day mortality with tenecteplase compared with alteplase would

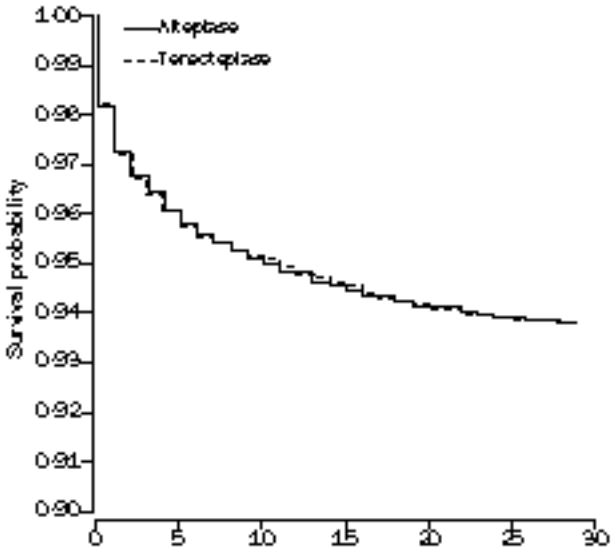

Figure 2: **Kaplan-Meier survival curves in the two treatment groups**

	Tenecteplase (%)	Alteplase (%)	Absolute difference		Relative risk	
			(90% CI)	p*	(90% CI)	p*
Primary analysis	6·179	6·151	0·028 (−0·554 to 0·609)	0·0059	1·004 (0·914 to 1·104)	0·0278
Unadjusted analysis	6·160	6·176	−0·016 (−0·624 to 0·592)	0·0060	0·997 (0·904 to 1·101)	0·0264
Logistic regression	6·089	6·140	−0·051 (−0·623 to 0·522)	0·0025	0·992 (0·903 to 1·089)	0·0147

*Based on test for equivalence.

Table 3: **30-day mortality**

exceed 14%, whichever difference proved smallest. With the assumption of a 30-day mortality rate with alteplase of 7·2% and equal mortality with tenecteplase, a sample size of about 16 500 patients would provide 80% power to reject the null hypothesis with a one-sided significance level of 5%.

Our primary analysis was a non-parametric, covariate-adjusted analysis of all randomised patients according to intention to treat.[10] Missing 30-day mortality data were imputed according to the null hypothesis: 7·2% for alteplase and 8·2% for tenecteplase. The baseline covariates were: age, Killip class, heart rate and systolic blood pressure on admission, and infarct location. These covariates contain 90% of the prognostic information of the baseline clinical data.[11] Adjustment for small differences in baseline covariates between the two treatment groups increased the power of the study.

In addition to the primary analysis, we did an unadjusted analysis (without covariates) and logistic regression of the primary endpoint in the same study population. The same analyses were repeated in the as-treated population.

For the primary endpoint, we report two-sided 90% boundaries and p values testing for equivalence. For all other exploratory analyses two-sided 95% CI and p values are given.

Safety data, especially bleeding complications and stroke rates in the two groups, were reported monthly to the data and safety monitoring committee. Because of consistent and potentially relevant differences in non-cerebral bleeding complications, which emerged when the safety data of 13 620 patients became available, the committee requested that treatment status be revealed to them. After analysis of these data, the committee recommended that the trial be continued as planned. The committee also recommended that the total sample size be increased to compensate for randomised but non-treated patients. No mortality data were reported to the committee during the course of the trial. It was agreed that mortality data would be provided only if the 95% boundaries of 30-day mortality in the total population became more than 9% or less than 5%, or if the lower boundary of the difference between the two treatment groups exceeded 2%. We checked these criteria with an automatic computer program when 4000, 8000, and 12 000 patients had been randomised, but they were never met during the course of the trial.

Data were entered with the use of Oracle Clinical (version 3.0.3.5) and electronically transferred to the central database in Leuven, Belgium. Quality of the data was ensured by double data entering and by verification of collected data against medical records in at least 10% of patients and in at least one patient per site. Furthermore, we monitored all patients with a stroke or a serious unexpected drug-related adverse event.

	Proportion of patients in category (%)*	Tenecteplase (n=8461)	Alteplase (n=8488)	Relative risk (95% CI)	p
Age (years)					
⩽75	87·4	4·6	4·3	1·063 (0·915–1·235)	0·425
>75	12·5	17·4	19·3	0·903 (0·754–1·081)	0·286
Sex					
Male	76·8	5·0	4·8	1·039 (0·894–1·209)	0·627
Female	23·1	10·0	10·6	0·943 (0·784–1·134)	0·563
Age and sex					
⩽75, male	70·0	3·9	3·7	1·058 (0·883–1·268)	0·566
⩽75, female	17·5	7·1	6·6	1·084 (0·831–1·415)	0·561
>75, male	6·8	16·1	16·1	1·003 (0·771–1·305)	1·000
>75, female	5·7	18·9	23·1	0·819 (0·640–1·048)	0·114
Time to treatment (h)					
0–2	30·0	5·0	4·9	1·017 (0·799–1·296)	0·897
>2–4	46·8	6·3	5·5	1·157 (0·970–1·379)	0·106
>4	22·4	7·0	9·2	0·766 (0·617–0·952)	0·018
Infarct location					
Anterior	39·8	8·0	8·2	0·975 (0·830–1·146)	0·789
Other	60·0	5·0	4·8	1·026 (0·865–1·218)	0·783
Previous myocardial infarction					
Yes	15·9	9·8	8·6	1·137 (0·897–1·441)	0·318
No	83·9	5·5	5·7	0·965 (0·843–1·105)	0·609
Killip class					
I	87·8	4·7	4·8	0·983 (0·851–1·134)	0·818
II	10·4	13·5	13·4	1·011 (0·797–1·281)	0·944
III	1·1	29·0	24·5	1·185 (0·740–1·899)	0·516
IV	0·4	51·4	61·1	0·842 (0·556–1·273)	0·477
Hypertension					
Yes	38·1	8·0	7·6	1·050 (0·888–1·241)	0·578
No	61·7	5·0	5·2	0·962 (0·816–1·135)	0·657
Diabetes					
Yes	16·0	8·8	8·7	1·002 (0·786–1·278)	1·000
No	83·8	5·6	5·7	0·993 (0·868–1·136)	0·942
Previous CABG					
Yes	3·9	9·8	7·7	1·280 (0·776–2·111)	0·406
No	95·9	6·0	6·1	0·987 (0·875–1·115)	0·844

CABG=coronary-artery bypass graft.
*Percentages do not total 100% for all categories because of missing data.

Table 4: **30-day mortality in subgroups**

Complication	Frequency (%)		Relative risk (95% CI)	p
	Tenecteplase (n=8461)	Alteplase (n=8488)		
Reinfarction	4·1	3·8	1·078 (0·929–1·250)	0·325
Recurrent angina	19·4	19·5	0·995 (0·935–1·058)	0·877
Sustained hypotension	15·9	16·1	0·988 (0·921–1·058)	0·737
Cardiogenic shock	3·9	4·0	0·965 (0·832–1·119)	0·664
Major arrhythmias	20·5	21·2	0·968 (0·913–1·027)	0·281
Pericarditis	3·0	2·6	1·124 (0·941–1·343)	0·209
Invasive cardiac procedures				
PTCA	24·0	23·9	1·006 (0·953–1·061)	0·843
Stent placement	19·0	19·7	0·968 (0·910–1·029)	0·302
CABG	5·5	6·2	0·884 (0·783–0·999)	0·049
IABP	2·6	2·7	0·968 (0·805–1·163)	0·736
Killip class >I	6·1	7·0	0·991 (0·982–0·999)	0·026
Tamponade or cardiac rupture	0·6	0·7	0·816 (0·558–1·193)	0·332
Acute mitral regurgitation	0·6	0·7	0·886 (0·613–1·281)	0·571
Ventricular septum defect	0·3	0·3	0·817 (0·466–1·434)	0·568
Anaphylaxis	0·1	0·2	0·376 (0·147–0·961)	0·052
Pulmonary embolism	0·09	0·04	2·675 (0·710–10·080)	0·145

PTCA=Percutaneous transluminal coronary angioplasty; CABG=coronary-artery bypass graft; IABP=Intra-aortic balloon pump.

Table 5: **Frequency of in-hospital cardiac events and procedures**

Results

16 949 patients were randomised between October, 1997, and November, 1998, of whom 16 504 received study medication (figure 1). In 445 patients (209 assigned tenecteplase, 236 assigned alteplase), no study medication was administered because of: detection of exclusion criteria after randomisation (135 patients), technical reasons, such as broken vials (49), death or adverse event immediately after randomisation (23), or other reasons (238), of which primary angioplasty (46), administration of open-label thrombolytics (80), or both (17), were the most frequent.

All results presented are based on the intention-to-treat analyses. The analysis of the as-treated population, which should also be considered in an equivalence study,[7] provided nearly identical results with similar significance.

	Frequency (%)		Relative risk (95% CI)	p
	Tenecteplase (n=8461)	Alteplase (n=8488)		
Total strokes	1·78	1·66	1·074 (0·856–1·349)	0·555
Intracranial haemorrhage	0·93	0·94	0·991 (0·727–1·350)	1·000
Ischaemic stroke*	0·72	0·64	1·133 (0·787–1·632)	0·514
Haemorrhagic conversion	0·07	0·09	0·752 (0·261–2·168)	0·790
Unclassified	0·13	0·08	1·576 (0·611–4·065)	0·358

Five patients had more than one type of stroke.
*Including haemorrhagic conversion.

Table 6: **Frequency of strokes**

	Tenecteplase (n=8461)	Alteplase (n=8488)	p
Bleeding episodes			
Total	26·43	28·95	0·0003
Major	4·66	5·94	0·0002
Minor	21·76	22·99	0·0553
Units transfused blood			
Any	4·25	5·49	0·0002
1–2	2·59	3·24	
>2	1·66	2·24	

Table 7: **Non-cerebral bleeding complications**

The baseline characteristics were similar in the two groups (table 1). Overall, the study populations were similar to those of previous trials on thrombolytic therapy. In particular, the median time from symptom onset to treatment was 2·8 h.

The first bolus (tenecteplase or placebo) was given to 97·1%, the second bolus (alteplase or placebo) to 97·1%, and the infusion (alteplase or placebo) to 96·8% of randomised patients. More than 96·0% of patients in the two groups received 95–105% of the planned weight-adjusted dose of tenecteplase (or placebo); more than 97·0% of patients received 95–105% of the planned dose of alteplase (or placebo). Compliance with antithrombotic cotherapy was more than 94% in all patients for heparin bolus and more than 99% for heparin infusion. Aspirin was given to more than 97·0% of patients. Other concomitant medications are listed in table 2. High proportions of patients received β-blockers, angiotensin-converting-enzyme inhibitors, low-molecular-weight heparins, and statins.

Vital status at 30 days was unknown in six patients (tenecteplase three, alteplase three). Total mortality at 30 days was almost identical in the two groups (table 3) and the Kaplan-Meier survival curves were superimposable (figure 2). The one-sided 95% CI of the absolute and relative differences in 30-day mortality fulfilled the prespecified criteria of equivalence (table 3).

Mortality rates in the prespecified subgroups are given in table 4. The two treatments did not differ significantly except for a lower mortality with tenecteplase in patients asigned treatment after 4 h.

Non-fatal in-hospital cardiac events and the use of procedures are shown in table 5. Although the differences were small, significantly fewer patients in the tenecteplase group than in the alteplase group were in a Killip class higher than I or underwent bypass surgery. No other significant differences were seen.

In 18 patients who had stroke, no brain imaging or necropsy could be done. The rate of haemorrhagic stroke was similar in the two treatment goups (0·93% for tenecteplase, 0·94% for alteplase) with a slightly, but not significantly, higher rate of ischaemic and total stroke after treatment with tenecteplase (table 6). The overall rate of death or non-fatal stroke was 7·11% with tenecteplase and 7·04% with alteplase (relative risk 1·01 [95% CI 0·91–1·13]).

Non-cerebral bleeding complications are shown in table 7. Significantly fewer bleeding complications were found in the tenecteplase group (26·1 *vs* 28·4%, p<0·0003), resulting in a significantly lower need for blood transfusion in this group (4·3 *vs* 5·5%, p=0·0002).

Discussion

Single-bolus tenecteplase was equivalent to front-loaded alteplase in the effect on 30-day mortality. The upper boundaries (0·61% and 10·00%) were well below the

prespecified upper confidence limits of equivalence of 1% or 14%.

There was no particular subgroup of patients in whom tenecteplase or alteplase was significantly better, with the exception of patients treated after 4 h; this group had a better outcome with tenecteplase, with a significant absolute 2% difference in 30-day mortality. As with alteplase, which was compared with streptokinase in the TIMI-1 study,[12] the higher fibrin specificity of tenecteplase probably leads to better dissolution of the older fibrin clot and, therefore, to a better clinical outcome. A similar observation was made in the GUSTO-III trial.[2] In that study, the more fibrin-specific agent alteplase was associated with a better outcome in late-treated patients than the less fibrin-specific agent reteplase.

The 30-day mortality rates seen in our trial were the lowest reported in a large trial of thrombolytic therapy. Comparisons between trials are difficult to make but the demographic and baseline haemodynamic features of the patients in this trial seem similar to those of other large trials such as GUSTO-I and GUSTO-III.[2,13] The low mortality we saw may be explained by the use of effective fibrinolytics and probably by the use of effective concomitant medications such as β-blockers and angiotensin-converting-enzyme inhibitors in a large proportion of patients. Futhermore, the use of low-molecular-weight heparins, glycoprotein IIb/IIIa inhibitors, ticlopidine, or clopidogrel and statins in substantial numbers of patients may have contributed to the favourable clinical outcomes.

Fewer non-cerebral bleeding complications were seen and fewer blood transfusions were required in the tenecteplase group than in the alteplase group. The higher fibrin specificity is probably also responsible for this clinical advantage. In previous large comparative trials, such as the GISSI-2/International[14] and the GUSTO-I trial,[13] fewer non-cerebral bleeding complications were seen with the more fibrin-specific agent alteplase than with streptokinase.

Total stroke rates were a little higher in the tenecteplase group because of a slightly higher rate of ischaemic stroke after tenecteplase.The stroke rates seen in this trial were similar to those seen in the previous large thrombolysis trial GUSTO-III.[2] Despite a lower dose of concomitant heparin, rates of intracranial haemorrhage with front-loaded alteplase in this trial and in GUSTO-III were higher than in GUSTO-I. This finding can be explained by the inclusion of more patients at risk of haemorrhagic stroke (eg, elderly, women) and by the more frequent brain imaging. The nearly identical rates of intracranial haemorrhage with tenecteplase and alteplase in this trial suggest that, by contrast with non-cerebral bleeding complications, greater fibrin specificity does not lower the risk of cerebral bleeding.

Single-bolus, weight-adjusted tenecteplase is the first fibrinolytic regimen shown to be equivalent to front-loaded alteplase in terms of 30-day mortality. The similar rates of intracranial haemorrhage and the lower risk of non-cerebral bleedings show that tenecteplase is also safer than front-loaded alteplase. These features, together with the ease of administration, make it an attractive fibrinolytic regimen that may further facilitate the institution of early reperfusion therapy in patients with an acute myocardial infarction. Whichever agent is used, shorter time to treatment increases the benefit of reperfusion. Given the persistent delay in starting reperfusion therapy after symptom onset, prehospital thrombolysis with single-bolus tenecteplase seems to be an approach worth testing.

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