

Incidence and predictors of bleeding events after fibrinolytic therapy with fibrin-specific agents

A comparison of TNK-tPA and rt-PA

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Background Fibrinolytic therapy increases the risk of bleeding events. TNK-tPA (tenecteplase) is a variant of rt-PA with greater fibrin specificity and reduced plasma clearance that can be given as a single bolus. We compared the incidence and predictors of bleeding events after treatment with TNK-tPA and rt-PA.

Methods and Results In the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT)-2 trial, 16 949 patients with acute myocardial infarction were randomly assigned a single weight-adjusted bolus of TNK-tPA or a 90-min infusion of rt-PA. A total of 4.66% of patients in the TNK-tPA group experienced major non-cerebral bleeding, in comparison with 5.94% in the rt-PA group ($P=0.0002$). This lower rate was associated with a significant reduction in the need for blood transfusion (4.25% vs 5.49%, $P=0.0003$) and was consistent across subgroups. Independent risk factors for major bleeding were older age, female gender, lower body weight, enrolment in the U.S.A. and a diastolic blood pressure <70 mmHg. Females at high risk (age >75 years and body weight <67 kg) were less likely to

have major bleeding when treated with TNK-tPA even after other risk factors were taken into account. A total of 0.93% of patients in the TNK-tPA and 0.94% of patients in the rt-PA group experienced an intracranial haemorrhage. Female patients >75 years of age who weighed <67 kg tended to have lower rates of intracranial haemorrhage when treated with TNK-tPA (3/264, 1.14% vs 8/265, 3.02%).

Conclusions The increased fibrin specificity and single bolus administration of TNK-tPA do not increase the risk of intracranial haemorrhage but are associated with less non-cerebral bleeding, especially amongst high-risk patients. (*Eur Heart J* 2001; 22: 2253–2261, doi:10.1053/euhj.2001.2686)

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Introduction

Fibrinolytic therapy reduces the risk of death in acute myocardial infarction, but it also increases the risk

of bleeding events^[1,2]. Of particular concern is the risk of intracranial haemorrhage estimated at 0.5 to 1.0% in large-scale studies. Demographic risk factors for intracranial haemorrhage include older age, lighter body weight, female sex, high blood pressure on admission, prior cerebrovascular disease and hypertension^[3,4]. Independent predictors of major bleeding complications are older age, lighter body weight, female sex and African ancestry in addition to use of coronary artery bypass surgery and invasive procedures^[5]. rt-PA (recombinant tissue plasminogen activator, alteplase), a relatively fibrin-specific agent, produced less

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non-cerebral bleeding than streptokinase both in the Gruppo Italiano per lo Studio della Sopra vivenza nell'Infarto Miocardico (GISSI)-2/International and Global Utilization of Streptokinase vs Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)-I trials^[6,7]. However, since rt-PA induced more intracranial haemorrhage in both trials, it is feasible that, because increased fibrin specificity is more effective in producing clot lysis, it also increases the risk of intracranial haemorrhage.

TNK-tPA (tenecteplase) is a bioengineered variant of rt-PA designed to be more fibrin-specific than other fibrinolytic agents, including the relatively fibrin-specific rt-PA^[8]. The Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT)-2 trial showed that TNK-tPA as compared with rt-PA is associated with fewer major bleeding events other than intracranial haemorrhage (4.66% for TNK-tPA vs 5.94% for rt-PA, $P=0.0002$)^[9]. A difference was also apparent in transfusion rates, with 4.25% of patients treated with TNK-tPA receiving a transfusion in comparison with 5.49% of patients treated with rt-PA ($P=0.0003$). The risk of intracranial haemorrhage, however, was virtually identical for the two treatments (0.93% for TNK-tPA vs 0.94% for rt-PA, $P=1.000$). This paper provides additional analyses on the nature of and risk factors for major bleeding events and intracranial haemorrhages among patients treated with these two fibrinolytic agents. The objective of the study was to identify subgroups of patients at higher risk of bleeding complications who might benefit from a more fibrin-specific agent like TNK-tPA.

Methods

ASSENT 2 was a double-blind, randomized trial designed to test the hypothesis that TNK-tPA and rt-PA are therapeutically equivalent in the reduction of mortality in acute myocardial infarction. Details of the ASSENT-2 study design, inclusion and exclusion criteria, trial medications, and procedures have been described elsewhere^[9].

A total of 16 949 patients were randomized; of these, 16 504 received study medication. Patients were randomly assigned to one of two fibrinolytic agents: a bolus of TNK-tPA plus a bolus and infusion of rt-PA placebo, or a bolus and infusion of rt-PA plus a bolus of TNK-tPA placebo. TNK-tPA (or placebo) was administered as a single i.v. bolus in 5–10 s; 30 mg was administered to patients who weighed <60 kg, 35 mg was administered to patients who weighed 60–<70 kg, 40 mg was administered to patients who weighed 70–<80 kg, 45 mg was administered to patients who weighed 80–<90 kg, and 50 mg was administered to patients who weighed 90 kg or more.

rt-PA (or placebo) was given as a 15 mg bolus followed by a 0.75 mg . kg⁻¹ (up to 50 mg) infusion over 30 min and a 0.50 mg . kg⁻¹ (up to 35 mg) infusion over

60 min. Patients received 150–325 mg aspirin and i.v. heparin (a bolus of 4000 U and an infusion of 800 U . h⁻¹ for patients who weighed 67 kg or less; a bolus of 5000 U and an infusion of 1000 U . h⁻¹ for patients who weighed more than 67 kg, adjusted to maintain an activated partial thromboplastin time of 50–75 s for 48–72 h).

TNK-tPA or TNK-tPA–placebo was administered to 97.1% of the patients; the bolus of rt-PA or rt-PA–placebo was administered to 97.1% of the patients; the infusion of rt-PA or rt-PA–placebo was administered to 96.8% of patients. More than 96.0% of the patients received 95–105% of the planned dose of TNK-tPA or TNK-tPA–placebo (based on the estimated weight if actual weight was not available on admission); more than 97.0% of the patients received 95–105% of the planned dose of rt-PA or rt-PA–placebo.

Bleeding events were classified according to the GUSTO definitions^[7]. Major bleeding events included severe or life-threatening bleeding events and moderate bleeding events. Severe or life-threatening bleeding events were those that caused haemodynamic compromise requiring intervention (e.g. blood or fluid replacement, inotropic support, surgical repair) or that resulted in death. Moderate bleeding events were those that required blood transfusion but did not lead to haemodynamic compromise requiring intervention. Other bleeding events were classified as minor bleeding events. Intracranial haemorrhages were reported separately and are not included in the counts of bleeding events. All stroke data were reviewed by an independent stroke-assessment panel that classified the stroke as primary haemorrhagic (intracranial haemorrhage), ischaemic, ischaemic with conversion to haemorrhage, or of unknown cause (if no brain scans or necropsy results were available).

The results are presented according to the intention-to-treat analyses. Exploratory analyses were performed to assess treatment effects (TNK-tPA vs rt-PA) while controlling for baseline covariates. In the exploratory analyses, logistic regression models were fit for major bleeding events and intracranial haemorrhages. The following baseline factors were considered: age, sex, race, time to treatment from onset of symptoms, Killip class, infarct location, systolic blood pressure, diastolic blood pressure, heart rate, weight, geographical location (U.S.A. vs non-U.S.A.), medical history (diabetes, hypertension, previous myocardial infarction, previous bypass surgery, previous coronary intervention), current smoker and ex-smoker. Continuous variables were tested for linearity^[10] and broken into categories if linearity did not hold, or if clinically meaningful categories were preferred. Covariates that were correlated with treatment effect ($P<0.10$) and significant covariate-by-treatment interactions ($P<0.25$) were included in the model selection. A stepwise procedure was used to find variables that contributed independent information. All statistical analyses were performed using UNIX SAS, version 6, release 6.12.

Table 1 Major bleeding events and intracranial haemorrhages by baseline characteristics

Characteristics	Major bleeds (%)			ICH (%)	
	Total (n=16 949)	TNK-tPA (n=8461)	rt-PA (n=8488)	TNK-tPA (n=8461)	rt-PA (n=8488)
Sex					
Female	3921	7.37	10.16	1.44	1.77
Male	13 028	3.85	4.66	0.78	0.69
Age					
≤75 years	14 824	4.17	5.13	0.82	0.70
>75 years	2117	8.12	11.62	1.72	2.62
Weight					
<67 kg	3133	6.80	9.21	1.41	1.78
≥67 kg	13 757	4.17	5.20	0.83	0.76
Combined risk factors					
Females ≤75 years	2959	6.83	8.96	1.50	1.54
Females >75 years	961	9.03	13.87	1.26	2.47
Females >75 years and <67 kg	529	8.33	15.15	1.14	3.02
Race					
Caucasian	15 277	4.66	6.10	0.94	0.98
African descent	231	8.62	6.96	1.72	0.87
Asian	162	2.63	5.81	1.32	0
Other	836	3.37	3.56	0.72	0.24
Enrolment					
U.S.A.	3660	9.33	9.79	1.10	1.08
Non-U.S.A.	13 289	3.38	4.87	0.89	0.90
Smoking history					
Current smoker	7456	3.42	4.61	0.80	0.62
Ex-smoker	4465	5.59	6.28	1.12	1.03
Medical history					
Hypertension	6456	6.27	6.95	1.38	1.22
Diabetes	2713	6.21	5.49	0.87	0.68
Previous MI	2704	4.49	7.02	0.82	0.95
Killip class					
I	14 893	4.47	5.78	0.94	0.96
>1	2023	6.11	7.24	0.89	0.69

Denominators for the calculation of rates are slightly different for TNK-tPA and rt-PA.

Results

Major bleeding events

A total of 394/8461 patients (4.66%) in the TNK-tPA group experienced a major bleeding event, in comparison with 504/8484 patients (5.94%) in the rt-PA group ($P=0.0002$). Table 1 shows the rates of major bleeding events by baseline characteristics. Overall, the risk of major bleeding was higher among patients who were older, female and of lower weight. The gradual increase in major bleeding events with increase in age and decrease in body weight in the two treatment arms combined is shown in Figs 1 and 2. Patients enrolled in the U.S.A. were more likely to have a major bleeding event than patients enrolled outside of the U.S.A. Rates of invasive procedures were also higher in the U.S.A. than outside the U.S.A.: 47.0% vs 17.6% for angioplasty; 14.9% vs 3.3% for bypass surgery and 6.9% vs 1.4% for intra-aortic balloon pumping. The lower rate of events among patients treated with TNK-tPA is consistent across these subgroups. For example, among female patients with the additional risk factors of age >75 years

and weight <67 kg, the major bleeding event rate was 8.33% in the TNK-tPA group and 15.15% in the rt-PA group. The only two subgroups in which the point estimate was for more bleeding with TNK-tPA were diabetes and African descent but these were entirely within the play of chance.

The site and the timing of major bleeding events are summarized in Table 2. Because bleeding events that occur within 24 h of treatment are more likely to be causally associated with the fibrinolytic agent than later events, the rates during the first 24 h were also compared. The results are shown in Table 2. The point estimates for both spontaneous and procedure-related bleeding events were lower for TNK-tPA than rt-PA. The lower rate of procedure-related bleeding events after TNK-tPA is not explained by differences in rates of invasive cardiac interventions in the first 24 h because 11.4% of subjects in the TNK-tPA group and 10.8% of subjects in the rt-PA group underwent an invasive cardiac procedure within the first 24 h of treatment (including coronary artery bypass surgery).

Table 3 shows the results of a multivariate analysis of major bleeding events. Compared with rt-PA, TNK-tPA

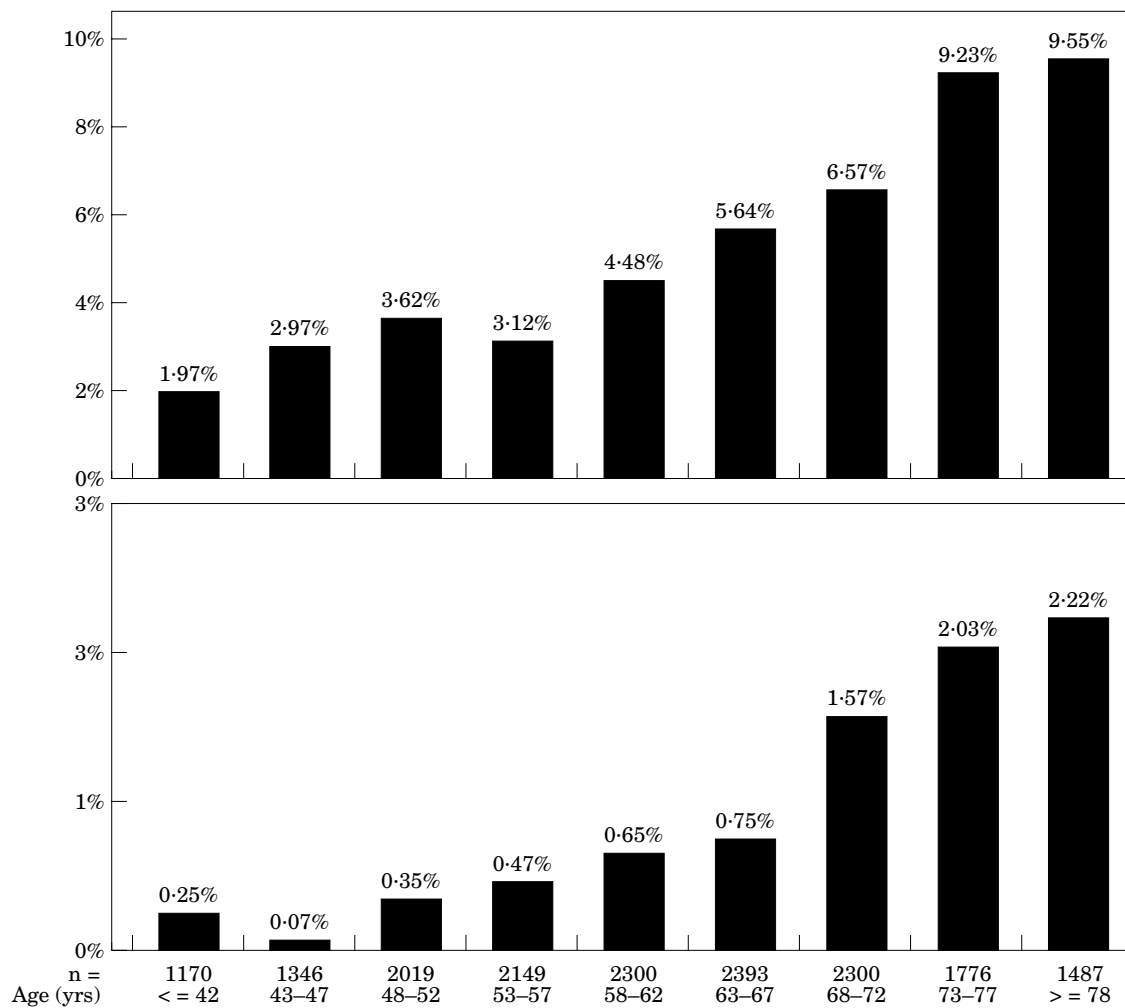


Figure 1 Rates of intracranial haemorrhage (lower panel) and major non-cerebral bleeding events (upper panel) in different age categories (increments of 5 years). Data from the TNK-tPA and rt-PA groups were combined.

was associated with fewer major bleeding events even when other risk factors were taken into account. Independent risk factors were older age, female gender, lower body weight, diastolic blood pressure <70 mmHg and enrolment in the U.S.A. Two interaction terms reached statistical significance, indicating that the treatment effects of TNK-tPA and rt-PA were different from those in the total population. Females above the age of 75 years and who weighed <67 kg benefited more from TNK-tPA than others. In contrast, patients with a history of hypertension benefited less from TNK-tPA than those without a history of hypertension. Nevertheless, under the same baseline conditions, patients with a history of hypertension still tended to have a lower risk when treated with TNK-tPA rather than rt-PA (OR=0.960, not significant).

Multivariate analysis for major bleeding events was also performed on patients who did not undergo invasive procedures (n=9033, 53.4%). Treatment assignment, age, gender, body weight and location (U.S.A. vs non-U.S.A.) remained independent predictors of major

bleeding events. Diastolic blood pressure was no longer a significant independent predictor (Table 4).

The rates of major bleeding events according to post-randomization aPTT levels are summarized in Table 5. The rates of major bleeding events were highest among subjects in whom no aPTT measurements were performed, and in whom the aPTT measurement exceeded the target range. Patients treated with TNK-tPA generally had lower major bleeding rates than patients treated with rt-PA regardless of aPTT levels, with the exception of patients for whom no aPTT measurement was available at 6 h.

Intracranial haemorrhage

A total of 0.93% patients in the TNK-tPA group and 0.94% patients in the rt-PA group experienced an intracranial haemorrhage, confirmed by the stroke-assessment panel. In univariate analyses, risk of intracranial haemorrhage was associated with advancing

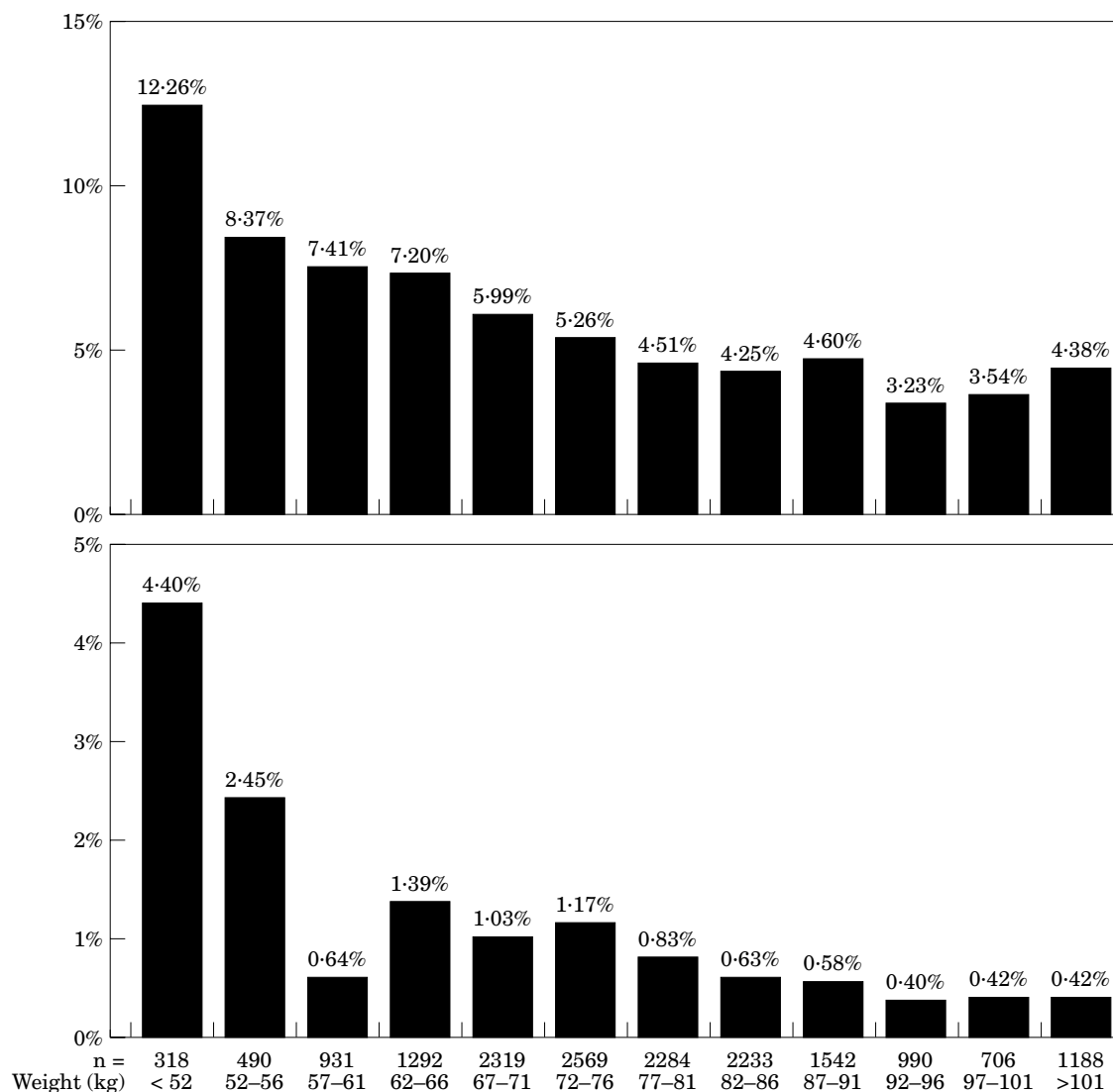


Figure 2 Rates of intracranial haemorrhage (lower panel) and major non-cerebral bleeding events (upper panel) in differing (estimated) weight categories (increments of 5 kg). Data from TNK-tPA and rt-PA groups were combined.

age, lower weight, female sex and history of hypertension (Table 1). A gradual increase in the rates of intracranial haemorrhage was observed with older age and lower body weight (Figs 1 and 2). Although the intracranial haemorrhage rates overall were similar for TNK-tPA and rt-PA, the small number of subjects with multiple known risk factors for intracranial haemorrhage—female, age >75 years, and weight <67 kg—tended to have lower rates of intracranial haemorrhage when treated with TNK-tPA (3/264, 1.14% for TNK-tPA vs 8/265, 3.02% for rt-PA).

Table 5 shows the rates of intracranial haemorrhage by post-treatment aPTT levels. Intracranial haemorrhage rates were highest among patients for whom an aPTT measurement was not available. There were no apparent differences in the risk of intracranial haemorrhage between the TNK-tPA or rt-PA groups according to aPTT levels.

Table 6 shows the results of a multivariate analysis of intracranial haemorrhages. Increasing age, lower body weight, history of hypertension and systolic blood pressure >140 mmHg on admission were independent risk factors for intracranial haemorrhage, while use of TNK-tPA vs rt-PA did not add to the model.

Discussion

The purpose of this analysis was to evaluate the observed differences in major bleeding events between patients treated with TNK-tPA and rt-PA, and to further examine the risk factors for intracranial haemorrhage among patients treated with these two fibrin-specific thrombolytic agents.

The reduced risk of major bleeding associated with TNK-tPA is robust and consistent across major

Table 2 Major non-cerebral bleeding events within 24 h and 30 days by site

Bleeding location	TNK-tPA (n=8461) (%)		rt-PA (n=8488) (%)	
	Within 24 h	Within 30 days	Within 24 h	Within 30 days
Any major bleeding*	2.00%	4.66%	2.38%	5.94%
CABG subgroup†	0.09%	1.02%	0.13%	1.32%
Haematoma				
All	1.10%	1.99%	1.59%	2.69%
Arterial puncture site	0.22%	0.63%	0.29%	0.75%
Venous puncture site	0.26%	0.52%	0.52%	0.85%
Gastrointestinal	0.53%	0.97%	0.46%	1.01%
Oropharyngeal	0.18%	0.19%	0.12%	0.21%
Epistaxis	0.11%	0.15%	0.09%	0.18%
Genitourinary	0.26%	0.38%	0.33%	0.41%
Retroperitoneal	0.07%	0.14%	0.06%	0.09%

*Moderate or severe bleeding excluding intracranial haemorrhages.

†Subjects who had coronary artery bypass grafting (CABG). Bleeding events could be preceded or followed by CABG.

Table 3 Multivariate model of major non-cerebral bleeding events

Variable	Odds ratio	95% Confidence ratio
TNK-tPA vs rt-PA	0.681	(0.561, 0.825)
Age: 10-year increments	1.405	(1.317, 1.499)
Sex: female vs male	1.477	(1.257, 1.735)
Diastolic blood pressure: <70 mmHg vs ≥70 mmHg	1.326	(1.139, 1.544)
Weight: <67 kg vs ≥67 kg	1.377	(1.151, 1.648)
Location: non-U.S.A. vs U.S.A.	0.414	(0.358, 0.479)
Treatment by hypertension interaction	1.410	(1.144, 1.739)
Treatment by high-risk females* interaction	0.518	(0.318, 0.843)

*High-risk females: females >75 years and <67 kg.

Table 4 Multivariate model of major non-cerebral bleeding events, excluding patients with invasive procedures

Variable	Odds ratio	95% Confidence ratio
TNK-tPA vs rt-PA	0.715	(0.568, 0.903)
Age: 10-year increments	1.533	(1.378, 1.706)
Sex: female vs male	1.441	(1.110, 1.871)
Weight: <67 kg vs ≥67 kg	1.372	(1.051, 1.792)
Location: non-U.S.A. vs U.S.A.	0.636	(0.446, 0.906)

subgroups. Patients with the composite risk profile of female gender, age >75 years and weighing <67 kg, experienced an even greater reduction in risk of bleeding when treated with TNK-tPA. This observation is not

explained by differences in rates of invasive cardiac procedures, or by differences in aPTT levels. There are at least two possible explanations for this difference. The first is that the TNK-tPA's fibrin specificity reduces risk, in accordance with prior observations from the GUSTO-I and GISSI-2/International trials that more fibrin-specific fibrinolytic agents are associated with fewer non-cerebral bleeding events^[6,7]. The second is that the weight-adjusted dosing regimen used for TNK-tPA provides additional protection. It is likely that both explanations contribute to the reduction in risk of major bleeding events.

The risk factors for major bleeding events observed in ASSENT-2 are similar to those reported in earlier clinical trials, notably the GUSTO-I trial^[5]. These include older age, lower body weight and female sex. Patients enrolled in the U.S.A. were at higher risk than patients enrolled outside the U.S.A., an observation also made in GUSTO-I that can be partly attributed to the higher rates of invasive procedures in the U.S.A. However, after excluding patients with invasive procedures, U.S.A. patients remained at increased risk of major bleeding complications. A lower threshold for blood transfusion (and therefore for reporting moderate bleeding events) in the U.S.A. and/or a greater general severity of illness of U.S.A. patients may explain the remaining differences in bleeding rates. In the analysis of the GUSTO-I data Berkowitz *et al.* reported that patients of African descent also had a higher likelihood of bleeding, especially when treated with rt-PA rather than streptokinase^[5], and Sane *et al.*^[11] have shown that, in African Americans, rt-PA treatment results in a higher degree of circulating fibrinogen depletion. In ASSENT-2, patients of African descent had slightly higher rates of major bleeding when treated with TNK-tPA (8.62% vs 6.96%), $P=ns$). The data from GUSTO-I and the present study would suggest that increased fibrin specificity in this population increases rather than decreases the risk of bleeding. However, the small number of patients of African descent included in the studies precludes drawing any firm conclusions about potential differences. The impact of ethnicity on the efficacy and safety of novel treatments needs to be studied more carefully in the future. As in GUSTO-I, a lower diastolic blood pressure (<70 mmHg in this study; 80 mmHg vs 90 mmHg in GUSTO-I) was associated with a higher risk of major bleeding events in multivariate analysis. A possible explanation for this observation is that low diastolic blood pressures may indicate increased stiffness of the arterial wall e.g. due to atherosclerosis and, therefore, a higher risk of bleeding especially when invasive procedures are performed. If patients who underwent invasive procedures were excluded, a lower diastolic blood pressure would not be a risk factor, in this trial or in GUSTO-I.

Risk factors for intracranial haemorrhage in this trial were similar to those reported in other trials. Increased age, lighter body weight, history of hypertension and systolic hypertension on admission were associated with a higher risk of intracranial haemorrhage. As in other

Table 5 APTT levels post-treatment

	Major bleeds (%)		ICH (%)	
	TNK-tPA (n=8461)	rt-PA (n=8488)	TNK-tPA (n=8461)	rt-PA (n=8488)
6 h				
Not done	7.88	6.88	1.68	1.74
Less than target range	3.57	4.25	0.76	0.68
In target range	3.21	5.06	0.83	0.52
More than target range	5.65	6.83	0.87	0.94
12 h				
Not done	6.74	7.23	2.11	1.94
Less than target range	2.83	4.82	0.62	0.76
In target range	4.04	5.30	0.57	0.38
More than target range	6.53	7.01	0.66	0.88

Denominators for the calculation of rates are slightly different for TNK-tPA and rt-PA.

Table 6 Multivariate model of intracranial haemorrhages

Variable	Odds ratio	95% Confidence ratio
TNK-tPA vs rt-PA	1.002 ^{ns}	(0.732, 1.372)
Age: 10-year increments (older vs younger)	1.633	(1.404, 1.898)
Weight: 10-kg increments (heavier vs lighter)	0.787	(0.696, 0.890)
Systolic blood pressure: <140 mmHg vs ≥140 mmHg	1.570	(0.414, 0.785)
Hypertension: no vs yes	0.669	(0.487, 0.920)

ns=not significant.

trials, there was no threshold for the effect of age, body weight and systolic pressure on the risk of intracranial haemorrhage.

In a recent meta-analysis, bolus and infusion administration of fibrinolytic agents with widely different pharmacological properties, have been compared^[12]. A higher rate of intracranial haemorrhage was observed after bolus treatment. Since the pharmacokinetic profile of single bolus TNK-tPA is similar to that of a front-loaded 90-min infusion of rt-PA^[13], similar rates of intracranial haemorrhage would be expected and were observed: 0.93% for TNK-tPA and 0.94% for rt-PA. This is reassuring, because fibrin specificity has been previously associated with increased risk of intracranial haemorrhage in large studies such as GUSTO-I^[4] and GISSI-2/International^[6]. It is possible that the weight-adjusted dosing regimen used for TNK-tPA offsets any potential increased risk associated with increased fibrin specificity. Of all patients given TNK-tPA only 258 (3.2%) received doses greater than those recommended. Rates of intracranial haemorrhage and death in this subgroup (1.2% and 6.6%, respectively) were not significantly different from those of the total population^[14].

It is interesting that those patients previously thought to be at high risk for intracranial haemorrhage (i.e. females above 75 years of age and weighing <67 kg) did not have especially high rates of intracranial haemorrhage when treated with TNK-tPA (1.1% vs 1.5% for all other females). This was not the case for the 'high risk' females treated with rt-PA, where the rates were increased (3.0% vs 1.6%). Although dividing the population into subgroups can lead to chance finding, these data do support the safety of bolus TNK-tPA vs rt-PA in the higher risk groups. These observations are important in view of recent concerns about the benefit and safety of fibrinolytic therapy in patients over the age of 75 years. In a large registry study an excess mortality was observed in this age category especially in females^[15]. High rates of major bleeding complications, including intracranial haemorrhage, may have outweighed the benefit of fibrinolytic therapy in this age category. However, a recent re-analysis of the clinical outcomes by the Fibrinolytic Therapy Trialists (FTT) secretariat in 3300 patients over the age of 75 presenting within 12 h of symptom onset and with ST-segment elevation or bundle branch block, revealed a significant 15% relative mortality reduction by fibrinolytic therapy^[16]. Taken together, the current data indicate that elderly patients fulfilling the eligibility criteria should be given fibrinolytic therapy if mechanical reperfusion is not immediately available. The tendency towards lower mortality and lower bleeding rates observed with TNK-tPA in ASSENT-2 in the elderly, especially the high-risk females, suggest that TNK-tPA may be the fibrinolytic agent of choice if pharmacological reperfusion is indicated in these patients.

The rates of intracranial haemorrhage in this study were higher than in previous trials. Over the years an increase in intracranial haemorrhage rates has been observed in large-scale trials of fibrinolytic therapy (Table 7). The inclusion of more elderly patients, the more frequent brain imaging but also the more liberal use of heparin because of revascularization procedures

Table 7 30-Day mortality and stroke after front-loaded rt-PA in large trials

	GUSTO-I n=10 396	GUSTO-III n=4921	COBALT n=3584	ASSENT-2 n=8487	InTIME-II n=5022
Baseline risk factors					
Age (years)	62	63	62	61	61
>75 year (%)	10.5	13.5	13.1	12.6	13.5
Females (%)	25	27	24	23	25
SBP (mmHg)	130	134	140	133	138
HR (beats.min ⁻¹)	73	73	75	73	76
Killip class >1 (%)	15	15	16	12	12
Anterior (%)	39	48	43	40	41
Time to Rx (h)	2.8	2.7	2.9	2.8	2.9
Mortality at 30 days (%)	6.31	7.24	7.53	6.18	6.75
Total stroke (%)	1.55	1.79	1.53	1.66	1.53
ICH (%)	0.72	0.87	0.81	0.94	0.64
>75 years	2.1	1.7	3.6	2.6	1.5
Heparin use					
Bolus	5000 U	5000 U	5000 U	4000 U to 5000 U	70 U . kg ⁻¹ (max 4000 U)
Infusion	1000 U . h ⁻¹ if ≤80 kg 1200 U . h ⁻¹ if >80 kg	800 U . h ⁻¹ if <80 kg 1000 U . h ⁻¹ if ≥80 kg	1000 U . h ⁻¹	800 U . h ⁻¹ if ≤67 kg 1000 U . h ⁻¹ if >67 kg	15 U . kg ⁻¹ (max 1000 U . h ⁻¹)
aPTT (s)	60–85	50–75	60–85	50–75	50–70
First ↓ dose	≥24 h	≥12 h	≥6 h	≥6 h	≥3 h*

Data are mean values or proportions (%); * after protocol amendment.

SBP=systolic blood pressure; HR=heart rate; Rx=treatment; ICH=intracranial haemorrhage.

may have played a role. The low rate of intracranial haemorrhage observed with rt-PA in the Intravenous NPA for the Treatment of Infarcting Myocardium Early (InTIME)-II trial^[17] and a retrospective analysis of recent large-scale trials of fibrinolytic therapy^[18] suggest that a reduced and fully weight-adjusted dose of heparin, together with earlier monitoring of the aPTT, may further reduce the risk of intracranial haemorrhage. On the basis of these observations and in line with the new AHA/ACC guidelines^[19], lower, fully weight-adjusted doses of heparin are currently given in conjunction with TNK-tPA. It is possible that this reduced dosing of heparin may further decrease the intracranial haemorrhage rates after TNK-tPA. The reason that TNK-tPA was associated with fewer non-cerebral bleedings but with similar intracranial haemorrhage rates when compared with rt-PA is still unknown. Intrinsic differences in susceptibility for bleeding between the cerebral and non-cerebral microvasculature (e.g. due to amyloid deposits) may be a cause. Another explanation could be that a potentially protective effect against intracranial haemorrhage is critically dependent on the dose of co-administered heparin and that such a protective effect can only become apparent with lower doses of heparin. The ASSENT-3 trial will provide important data in this regard. In that trial a low, fully weight-adjusted dose of unfractionated heparin (60 U . kg⁻¹ bolus with a maximum of 4000 U and 12 U . kg⁻¹ . h⁻¹ infusion with a maximum of 1000 U . h⁻¹) with early aPTT measurements is being studied in conjunction with TNK-tPA. Other anticoagulants such as low-molecular-weight heparins (e.g. enoxaparin, also tested with TNK-

tPA in ASSENT-3) and direct antithrombins (e.g. hirulog tested in association with streptokinase in HERO-2) may prove to be safer than unfractionated heparin. The results of large-scale trials with these agents are eagerly awaited.

Conclusions

Patients treated with TNK-tPA for acute myocardial infarction were less likely to experience a major bleeding event than if they were treated with rt-PA. This difference persisted across subgroups with differing levels of risk, and it is particularly marked for the high-risk subgroup of female patients above 75 years of age and weight <67 kg.

Overall TNK-tPA and rt-PA were associated with nearly identical risks of intracranial haemorrhage. The point estimate of lower rates of intracranial haemorrhage in older, lower-weight female patients treated with TNK-tPA suggests that high-risk patients can be treated at least as safely with TNK-tPA as with rt-PA. Our study indicates that an appropriately weight-adjusted dose of the more fibrin-specific agent TNK-tPA offers a safety benefit over accelerated infusion of rt-PA in the treatment of acute myocardial infarction.

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