Tinzaparin in acute ischaemic stroke (TAIST): a randomised aspirin-controlled trial

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Summary

Background Low-molecular-weight heparins and heparinoids are superior to unfractionated heparin in the prevention and treatment of venous thromboembolism, but their safety and efficacy in acute ischaemic stroke are inadequately defined.

Methods This randomised, double-blind, aspirin-controlled trial tested the safety and efficacy of treatment with high-dose tinzaparin (175 anti-Xa IU/kg daily; 487 patients), medium-dose tinzaparin (100 anti-Xa IU/kg daily; 508 patients), or aspirin (300 mg daily; 491 patients) started within 48 h of acute ischaemic stroke and given for up to 10 days. Primary intracerebral haemorrhage was excluded by computed tomography. Outcome was assessed, with treatment allocation concealed, by the modified Rankin scale at 6 months (independence [scores 0–2] *vs* dependence or death [scores 3–6]).

Findings Of 1486 randomised patients, two did not receive treatment and 46 were lost to follow-up. The proportions independent at 6 months were similar in the groups assigned high-dose tinzaparin (194/468 [41·5%]), medium-dose tinzaparin (206/486 [42·4%]), or aspirin (205/482 [42·5%]). There was no difference in effect in any predefined subgroup, including patients with presumed cardioembolic stroke. Other outcome measures were similar between the treatment groups (disability, case-fatality, and neurological deterioration rates). During the in-hospital treatment period no patient assigned high-dose tinzaparin developed a symptomatic deep-vein thrombosis compared with nine assigned aspirin. Conversely, seven patients assigned high-dose tinzaparin developed symptomatic intracerebral haemorrhage compared with one in the aspirin group.

Interpretation Treatment with tinzaparin, at high or medium dose, within 48 h of acute ischaemic stroke did not improve functional outcome compared with aspirin. Although high-dose tinzaparin was superior in preventing deep-vein thrombosis, it was associated with a higher rate of symptomatic intracranial haemorrhage.

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Introduction

Acute ischaemic stroke is characterised in most cases by large-vessel thromboembolic occlusion or small-vessel occlusion, and may be complicated by local thrombus extension, peripheral venous thromboembolism, and ischaemic cardiac events. Anticoagulation with heparin might reduce the likelihood of these events and improve functional outcome. Although unfractionated heparin is commonly recommended and used in the management of acute ischaemic stroke,[1–3] randomised controlled trials have not found it to be safe or effective in improving functional outcome.[4–6] However, studies in other vascular disorders, especially in the prevention and treatment of deep-vein thrombosis and pulmonary embolism, have found that low-molecular-weight (LMW) heparins are superior to unfractionated heparin in terms of both efficacy and safety.[7–9] Clinical differences between LMW and unfractionated heparins are likely to result from differences in their pharmacokinetic profile and activity:[10] LMW heparins have higher and more consistent bioavailability, a longer half-life, less protein binding, and dose-independent clearance, thereby producing a more predictable anticoagulant response. LMW heparins also have less antiplatelet activity than unfractionated heparin and do not increase vascular permeability, resulting in less bleeding. Finally, LMW heparins have greater anti-factor-Xa activity than unfractionated heparin, which preferentially inhibits anti-factor-IIa through activation of antithrombin.

Ten randomised controlled trials of LMW heparins or heparinoids in acute ischaemic stroke have been reported,[10] although only three of these[11–13] were designed to test the hypothesis that these drugs decrease the risk of death and disability after stroke. Only the small Fraxiparine in Ischaemic Stroke (FISS) study of nadroparin, with 312 patients, found positive results on its primary outcome[11] but this finding was not confirmed in the larger FISS bis trial (767 patients).[13] The Trial of Org 10172 in Acute Stroke Treatment (TOAST) reported, in a post-hoc analysis, that danaparoid increased the odds of a favourable outcome in patients with stroke secondary to presumed large-artery (atherosclerotic) disease.[12] A systematic review of these ten trials found that LMW heparins lowered the frequency of deep-vein thrombosis and pulmonary embolism but increased the risk of significant bleeding;[14] there was a non-significant decrease in the combined

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outcome of death and disability with LMW heparins, an effect that became significant in an exploratory analysis of the trials in which treatment could be started beyond 24 h after the onset of stroke.[14]

Tinzaparin sodium is a LMW heparin (peak molecular mass about 4500 Da) prepared by enzymatic degradation of porcine mucosal heparin. It is licensed for the prevention and treatment of deep-vein thrombosis and pulmonary embolism. One small pilot trial of tinzaparin in acute ischaemic stroke showed that the drug reduced the frequency of deep-vein thrombosis (Leo Pharmaceutical Products, unpublished). We report here the findings of a randomised aspirin-controlled trial assessing the safety and efficacy of tinzaparin in improving functional outcome after acute ischaemic stroke.

Methods

Participants

TAIST was a prospective randomised, multicentre, double-blind, aspirin-controlled trial that took place from July, 1997, in ten countries in Europe (Belgium, Denmark, Finland, France, Germany, Ireland, the Netherlands, Norway, Sweden, and the UK) and Canada. Recruitment was completed in June 1999, and follow-up in January 2000. The study was run according to the principles of the Declaration of Helsinki and the International Conference on Harmonisation of Good Clinical Practice. Study approval by national (UK) and local research ethics committees (all centres) was obtained. An independent and masked adjudication committee classified events for a separate and independent safety-monitoring committee. The trial was supervised by an advisory committee.

Patients admitted to hospital with a clinical syndrome of a stroke were eligible for the trial if they were aged between 18 and 90 years, could be treated within 48 h of stroke onset, and had given written informed consent. Consent from a relative was acceptable if the patient was semi-conscious, dysphasic, or confused in accordance with the practice of the local research ethics committee.

Patients were excluded if they met one or more of the following criteria: computed tomographic evidence of intracranial haemorrhage, midline shift of more than 5 mm, or a non-stroke diagnosis; coma (including consciousness score on the Scandinavian neurological stroke scale of 2 or less); pure sensory stroke; mild stroke (score on Scandinavian neurological stroke scale above 53); stroke complicating trauma or a medical or surgical procedure; stroke or myocardial infarction within the previous 3 months; preceding moderate or severe disability (modified Rankin scale, 3–5); confounding neurological or psychiatric disease; a condition mimicking stroke (eg, hypoglycaemia, Todd's paresis); a congenital bleeding disorder; clinically significant blood loss within the previous 3 months or a current active peptic ulcer; significant hypertension within 6 h of enrolment (systolic blood pressure above 220 mm Hg or diastolic above 120 mm Hg); significant anaemia (haemoglobin less than 80 g/L, 4·96 mmol/L), thrombocytopenia (platelet count less than 100×10^9/L), liver dysfunction (international normalised ratio >1·5, aminotransferases more than three times higher than normal) or renal dysfunction (creatinine more than three times higher than normal); clinical endocarditis; allergic asthma; recent history of long-term systemic steroid therapy; recent anticoagulant therapy or need for anticoagulation or thrombolysis; severe concomitant medical conditions (eg, AIDS, metastatic cancer); pregnancy (positive pregnancy test) or breastfeeding; previous participation in TAIST; or participation in another trial within the previous 2 weeks.

Design and procedures

Patients were assessed at baseline and, with concealment of treatment allocation, at days 1, 4, 7, and 10 of treatment, and at 3 and 6 months of follow-up. The primary outcome was independence, assessed as the proportion with a score on the modified Rankin scale[15] of 0, 1, or 2 at 6-month follow-up. Prespecified secondary and tertiary 6-month outcomes included median score on the modified Rankin scale, proportion of patients achieving a modified Rankin score of 0 or 1, proportion of patients achieving a Barthel index of more than 90,[15] death, and SF-36 health survey scales. Prespecified secondary 3-month outcomes included median score on the modified Rankin scale, and proportion of patients achieving a modified Rankin score of 0–2 and Barthel index of more than 90. Outcomes assessed at the end of treatment included proportion of patients with neurological deterioration (a decrease in score on the Scandinavian neurological stroke scale of at least 5 points or decrease in the consciousness part of Scandinavian neurological stroke scale of more than 2 points), having a recurrent stroke (classified as ischaemic, haemorrhagic, or unknown type), symptomatic deep-vein thrombosis (confirmed by venography or ultrasonography), or pulmonary embolism (confirmed by high-probability ventilation-perfusion scan, pulmonary angiography, or necropsy), and death. Hospital-related events included discharge disposition and length of stay. The primary outcome was analysed by prespecified subgroups: sex, age (<80 years, 80–90 years), stroke severity (Scandinavian neurological stroke scale score <30, 30–40, >40), time to treatment (<24 h, >24 h), presumed cause of stroke by the TOAST criteria (cardioembolism, large-vessel, small-vessel[16]), and clinical syndrome by the Bamford classification.[17] The investigators were guided on how to use the main outcome scales (modified Rankin scale, Barthel index, Scandinavian neurological stroke scale) before the start of the trial.

Safety analyses assessed events experienced by treated patients categorised by time of onset—ie, during the treatment or follow-up periods. Critical events, validated and categorised by an independent critical event committee unaware of treatment allocation, included: death, recurrent stroke, symptomatic intracranial haemorrhage (clinical deterioration associated with intracranial bleeding on computed tomography or necropsy), major bleeding (clinically overt bleeding associated with one or more of transfusion of at least two units of red cells, a fall in haemoglobin of 20 g/L [1·24 mmol/L] or more, bleeding leading to permanent cessation of treatment), pulmonary embolism, deep-vein thrombosis, thrombocytopenia (platelet count less than 100×10^9/L or fall by more than 40% from baseline), and cardiac failure. A second computed tomography scan was done at the end of treatment (10 days plus or minus 2 days, or earlier if clinically warranted) to allow the frequency of intracranial bleeding to be assessed. Both baseline and second computed tomography scans were evaluated by a review board, with treatment allocation concealed.

The protocol was amended to limit recruitment to patients with moderate or severe stroke (Scandinavian neurological stroke scale score <40) in February 1998 (after enrolment of about 800 patients) to overcome

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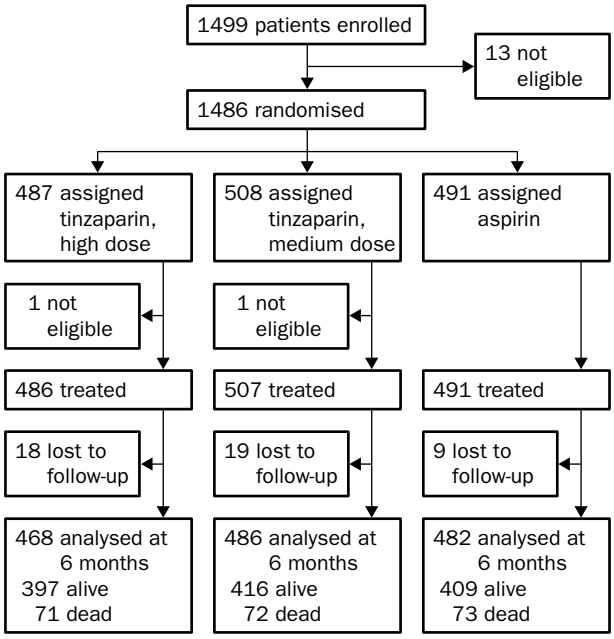

Figure 1: **Trial profile**
Screening logs were not kept at all centres (see text).

earlier disproportionate enrolment of those with mild stroke.

Patients were randomly assigned in equal proportions to treatment with high-dose tinzaparin, medium-dose tinzaparin, or aspirin in permuted blocks with stratification by centre and stroke severity (Scandinavian neurological stroke score 0–29 or >29).

Treatment masking was achieved by a double-dummy technique; each patient received either tinzaparin plus aspirin placebo or tinzaparin placebo plus aspirin. Investigators remained unaware of treatment allocation during follow-up. Each patient had to receive one injection and two tablets daily during the treatment period.

Treatment was given daily for 10 days, or until discharge if earlier, and consisted of a subcutaneous injection of tinzaparin sodium or matching placebo, and oral aspirin or matching placebo, in addition to standard care. Tinzaparin (in sodium metabisulphite in water for injection) was given at a dose of 175 anti-Xa IU/kg daily (high-dose; made up as 20 000 anti-Xa IU/mL) or 100 anti-Xa IU/kg daily (medium-dose; made up as 11 430 anti-Xa IU/mL) in graduated prefilled syringes of 0·9 mL. Tinzaparin placebo consisted of water for injection given in 0·9 mL graduated prefilled syringes. Aspirin was given as two tablets of 150 mg or matching placebo; it was administered to patients who were dysphagic by enteral tube once access was achieved.

The dose of tinzaparin was not adjusted during treatment, a practice which is routine in the prophylaxis and treatment of venous thromboembolism. Study agents could be stopped if the patient withdrew consent, for safety reasons (unacceptable adverse events including symptomatic intracranial haemorrhage, major extracranial bleeding, pulmonary embolism, deep-vein thrombosis, thrombocytopenia). Non-trial antiplatelet agents, anticoagulants, thrombolytics, dextran, and non-steroidal anti-inflammatory agents could not be given during the treatment period. Leg compression stockings were recommended in all patients who were not fully mobile. Systematic use of oral antithrombotic agents

Characteristic	High-dose tinzaparin (n=487)	Medium-dose tinzaparin (n=508)	Aspirin (n=491)
Demography			
Age (years, median)	74	73	74
Male	260 (53·4%)	283 (55·7%)	265 (54·0%)
Clinical			
Previous TIA	79 (16·3%)	84 (16·6%)	79 (16·1%)
Previous stroke	67 (13·8%)	67 (13·2%)	60 (12·2%)
Previous myocardial infarction	86 (17·7%)	82 (16·1%)	64 (13·0%)
Intermittent claudication	31 (6·4%)	34 (6·7%)	29 (5·9%)
Previous hypertension	238 (48·9%)	242 (47·6%)	248 (50·5%)
Diabetes mellitus	83 (17·0%)	86 (16·9%)	81 (16·5%)
Hyperlipidaemia	73 (15·0%)	78 (15·4%)	75 (15·3%)
Smoking, current	120 (24·6%)	138 (27·2%)	124 (25·3%)
Atrial fibrillation	65 (13·3%)	61 (12·0%)	55 (11·2%)
Recent antiplatelet therapy*	188 (38·7%)	192 (37·8%)	183 (37·3%)
Stroke			
Time to CT scan (h, median)	12·5	11·0	12·9
Time to treatment (h, median)	24·8	24·5	25·3
Side of lesion, right	216 (45·7%)	237 (47·6%)	244 (47·0%)
SNSS score (median)	33	34	34
Bamford classification of infarct			
Total anterior circulation	173 (35·5%)	177 (34·9%)	173 (35·2%)
Partial anterior circulation	149 (30·6%)	173 (34·1%)	151 (30·8%)
Lacunar	147 (30·2%)	132 (34·1%)	143 (29·1%)
Posterior circulation	17 (3·5%)	25 (4·9%)	24 (4·9%)
TOAST classification†			
Cardioembolic	135 (28·0%)	121 (24·2%)	112 (23·1%)
Large vessel (atherosclerosis)	139 (28·9%)	180 (36·2%)	166 (34·2%)
Small vessel (lacunar)	190 (39·3%)	166 (33·2%)	178 (36·5%)
Other	54 (11·2%)	60 (12·0%)	64 (13·1%)
Blood pressure (mm Hg, mean [SD])			
Systolic	156·5 (23·8)	155·8 (22·2)	155·6 (23·3)
Diastolic	83·9 (12·4)	84·6 (12·1)	83·9 (12·7)
Weight (kg, median)	71	73	72
ECG normal	213 (43·8%)	228 (45·0%)	236 (48·3%)
Infarct on baseline CT	311 (64·0%)	294 (57·9%)	293 (59·7%)

Data are number of patients unless otherwise stated. TIA=transient ischaemic attack; CT=computed tomography; SNSS=Scandinavian neurological stroke scale. *Aspirin, clopidogrel, dipyridamole, or ticlopidine within 48 h before stroke. †Patients can be in more than one category.

Table 1: **Baseline characteristics of participating patients**

(antiplatelet or anticoagulant) was recommended for secondary prevention once the 10-day treatment period was over.

Statistical analyses

The study was designed to detect an absolute difference in death or dependency (modified Rankin scale score 3–6) of 10% assuming a frequency of 60% in the aspirin-treated group,[5,11] with 80% power, an overall significance of 5%, and a dropout rate of 5%. As a result, 500 patients were needed in each group to give 470 evaluable patients per group. Efficacy analyses included all patients who received at least one dose of medication and who provided any efficacy data, analysed by intention to treat. Safety analyses included all patients who received at least one dose of study medication and who were not lost to follow-up. The direct effect of treatment on safety and efficacy events (eg, deep-vein thrombosis and symptomatic intracranial haemorrhage) was assessed at the end of treatment plus 5 days to allow the pharmacodynamic effects of aspirin and tinzaparin to dissipate. The primary analyses compared each tinzaparin group with the aspirin group. Deaths were analysed by Kaplan-Meier methods and Cox's regression models. $p<0·05$ was taken as statistically significant (two-sided). No formal adjustment of p values was made to account for the two comparisons between tinzaparin groups and aspirin or for the multiple outcomes in the study. The robustness of the results to multiplicity

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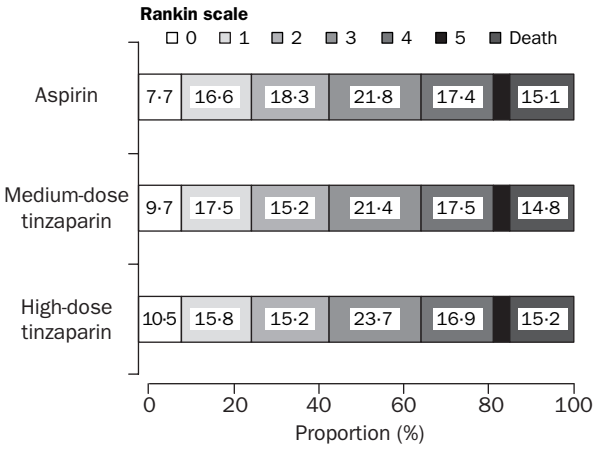

Figure 2: **Effect of treatment on independence, dependence, and death (Rankin scale) at 6 months**

adjustment was assessed by the conservative Bonferroni method. Analyses were done with SAS (version 8); StatExact (version 2.01) was used to calculate exact confidence intervals for tables that included small numbers.

Results

Written informed consent was obtained from 1499 patients presenting to 100 centres. Emerging exclusion criteria prevented randomisation of 13 patients and treatment of two randomised patients. The intention-to-treat analyses are based on 1484 treated participants, all of whom received at least one dose of tinzaparin or aspirin (figure 1). 1150 (77·5%) patients met all the protocol criteria for enrolment and received at least 7 days of treatment ("protocol population"). Screening logs were maintained at 33 centres; of 7946 patients presenting to these sites, 574 (median 8·8%) were enrolled. Centres recruited between one and 91 participants. Most patients were white (96·3%) and lived at home (95·4%) before the stroke. The final diagnosis was confirmed as ischaemic stroke in 99·5% of participants. The interval between stroke onset and treatment was less than 6 h in 3·1% of patients, less than 12 h in 18·0%, less than 24 h in 47·2%, and less than 30 h in 62·6%. In 11 (0·7%) patients the treatment was unmasked by the investigator: owing to surgical or medical need to stop antithrombotic therapy in six cases; need for open-label heparin in three; myocardial infarction in one; and at the family's request in one case.

No differences were noted between the treatment groups at baseline (table 1). Management of patients in hospital was similar for the three groups: overall, 38·6% were admitted to an acute stroke unit and 30·8% to a stroke rehabilitation unit. Post-treatment secondary prevention with an oral antiplatelet or anticoagulant agent (as appropriate) was recommended in the trial, and was prescribed in 88·2% of patients. Losses to follow-up at 6 months totalled 48 (3·2%) which was less than that assumed in the sample-size calculation.

The proportion of patients who returned to independence (score on modified Rankin scale 0–2) at 6 months was 42·1% for the trial as a whole and similar in the three treatment groups (figure 2, table 2). No differential effects of treatment with tinzaparin and aspirin on independence were seen in any of the prespecified subgroups, including age, severity, clinical type, presumed aetiological type, and time to treatment (table 3, figure 3). The findings in the per-protocol analysis were similar (table 2). In a post-hoc analysis, there was no interaction between previous antiplatelet therapy (taken within 48 h of study entry) and therapy with tinzaparin (modified Rankin scale score 0–2: high-dose tinzaparin 42·1%, medium-dose tinzaparin 38·6%, aspirin 40·0%).

Outcome	High-dose tinzaparin (n=486)	Medium-dose tinzaparin (n=507)	Aspirin (n=491)	Odds ratio (95% CI)	
				High-dose tinzaparin *vs* aspirin	Medium-dose tinzaparin *vs* aspirin
End of treatment plus 5 days					
Deep-vein thrombosis*	0	3 (0·6%)	9 (1·8%)	0 (0–9·29)†	0·32 (0·07–1·14)†
Pulmonary embolism*	2 (0·4%)	4 (0·8%)	4 (0·8%)	0·50 (0·06–2·85)†	0·97 (0·22–4·31)†
Venous thromboembolism‡	2 (0·4%)	6 (1·2%)	13 (2·6%)	0·15 (0·03–0·68)†	0·44 (0·17–1·17)†
Recurrent stroke (ischaemic or unknown)*	16 (3·3%)	24 (4·7%)	15 (3·1%)	1·08 (0·53–2·21)	1·58 (0·82–3·04)
Symptomatic ICH*	7 (1·4%)	3 (0·6%)	1 (0·2%)	7·15 (1·10–163)†	2·91 (0·31–77·0)†
Extracranial bleeding*					
Major	4 (0·8%)	2 (0·4%)	2 (0·4%)	2·03 (0·36–15·9)†	0·97 (0·10–9·33)†
Non-major	38 (7·8%)	22 (4·3%)	24 (4·9%)	1·65 (0·97–2·80)	0·88 (0·49–1·60)†
Thrombocytopenia*	0	2 (0·4%)	2 (0·4%)	0 (0–2·18)	0·97 (0·10–9·33)†
Cardiac failure*	11 (2·3%)	11 (2·2%)	11 (2·2%)	1·01 (0·43–2·35)	0·97 (0·42–2·25)
Neurological deterioration§	58 (12·1%)	58 (11·9%)	58 (11·9%)	1·02 (0·69–1·51)	1·00 (0·68–1·47)
SNSS score at day 10 (median)	42 (??–??)	44 (??–??)	42 (??–??)	..	..
Death by day 10	18 (3·7%)	28 (5·5%)	17 (3·5%)	1·07 (0·55–2·11)	1·63 (0·88–3·02)
Day 90					
Rankin scale 0–2	181 (38·4%)	188 (38·3%)	206 (42·5%)	0·85 (0·65–1·09)	0·84 (0·65–1·09)
Barthel index 60–100	308 (65·4%)	313 (63·7%)	320 (66·0%)	0·97 (0·75–1·27)	0·91 (·,70–1·18)
Death	60 (12·3%)	60 (11·8%)	58 (11·8%)	1·05 (0·72–1·55)	1·00 (0·68–1·47)
Day 180					
Rankin scale 0–2‖	194 (41·5%)	206 (42·4%)	205 (42·5%)	0·96 (0·74–1·24)	0·99 (0·77–1·28)
Rankin scale 0–2¶	139 (39·5%)	172 (45·1%)	162 (41·6%)	0·91 (0·68–1·23)	1·15 (0·87–1·53)
Barthel index 60–100	316 (67·5%)	326 (67·11%)	324 (67·2%)	1·01 (0·77–1·33)	0·99 (0·76–1·30)
Death	71 (14·6%)	72 (14·2%)	73 (14·9%)	0·98 (0·69–1·40)	0·95 (0·67–1·35)
Hospital events					
Hospital stay (days, median)	17 (??–??)	17 (??–??)	15 (??–??)	..	..
Discharged home	319 (80·4%)	316 (76·1%)	320 (77·9%)	1·16 (0·83–1·63)	0·91 (0·66–1·26)

Data are number of individuals unless otherwise stated. ICH: Intracranial haemorrhage; SNSS: Scandinavian neurological stroke scale. *Adjudicated by critical events committee. †Exact CI with mid-p adjustment. ‡Post-hoc analysis. §Neurological deterioration: a decrease in consciousness on SNSS >2 points and/or a decrease in SNSS >5 points. ‖Primary endpoint. ¶Per-protocol population: n=1150, respectively).

Table 2: **Efficacy and safety measures at 10, 90, and 180 days.**

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Independence at 6 months was associated, in univariate analyses, with several baseline factors: younger age, male sex, atrial fibrillation, stroke severity, systolic blood pressure, and a history of diabetes mellitus, but not temperature or treatment group. These factors were added in a multivariate analysis; age, stroke severity, systolic blood pressure, atrial fibrillation, and a history of diabetes mellitus remained as prognostic factors; treatment group, sex, and temperature were not related to outcome. No significant interactions between treatment group and any prognostic factor were observed.

There were no differential treatment effects between tinzaparin and aspirin on any of the secondary measures of functional outcome, including the Rankin scale and Barthel index at 3 months, and the Barthel index at 6 months (table 2).

Tinzaparin was associated with a lower frequency of deep-vein thrombosis than was aspirin, an effect that was significant in the high-dose group (table 2). There was also a lower frequency of patients with pulmonary embolism in the high-dose tinzaparin group, though it was not significant. As a result, treatment with high-dose tinzaparin was associated with a lower rate of total venous thromboembolic events (deep-vein thrombosis or pulmonary embolism). No differences in the frequency of recurrent stroke (ischaemic or unknown type) or neurological deterioration were seen between the three groups (table 2).

474 patients (31·8%) had treatment withdrawn before day 10, including 245 (16·5%) who were discharged early and 52 (3·5%) who experienced unacceptable adverse events (table 4).

All-cause death rates at 10 days and 3 and 6 months were 4·2%, 12·0%, and 14·6% across the trial (table 2). Adjudicated causes of death did not differ between treatment groups, although there were more deaths after symptomatic intracranial haemorrhage among patients assigned high-dose tinzaparin (not significant, table 5). Only eight of the 62 cases of fatal pneumonia (table 5) were temporally related to treatment and the proportions did not differ between the groups (high-dose tinzaparin two, medium-dose tinzaparin one,

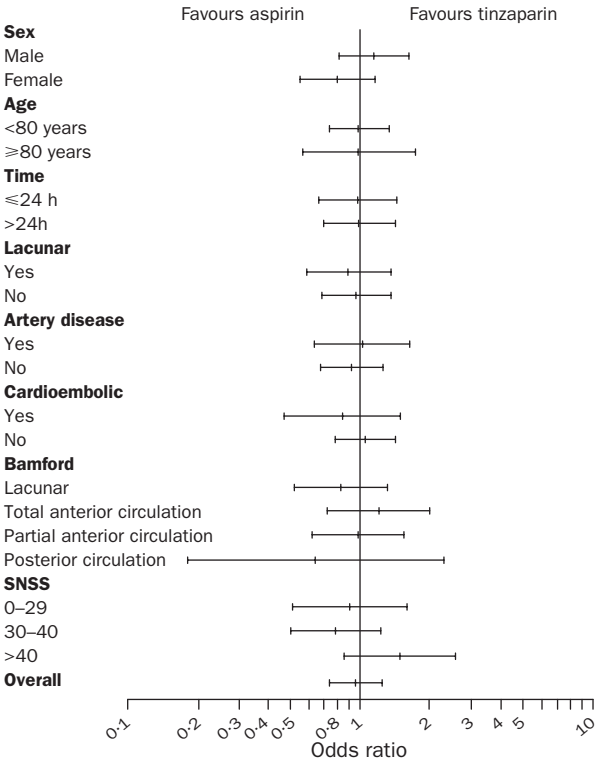

Figure 3: **Effect of treatment on the primary outcome (Rankin scale 0–2) at 6 months in predefined subgroups for medium-dose and high-dose tinzaparin versus aspirin**

Events by time to treatment	High-dose tinzaparin (n=487)	Medium-dose tinzaparin (n=508)	Aspirin (n=491)
Modified Rankin Scale score 0–2			
<12 h	34/82 (41·5%)	41/88 (46·6%)	38/84 (45·2%)
12–24 h	51/135 (37·8%)	59/143 (41·3%)	50/135 (37·0%)
24–36 h	54/123 (43·9%)	62/131 (47·3%)	64/126 (50·8%)
>36 h	52/122 (42·6%)	43/120 (35·8%)	49/130 (37·7%)
Symptomatic intracranial haemorrhage			
<12 h	4/84 (4·8%)	1/94 (1·1%)	0/86
12–24 h	2/142 (1·4%)	2/148 (1·4%)	0/137
24–36 h	0/127	0/134	1/129 (0·8%)
>36 h	1/126 (0·8%)	0/125	0/132

Data are number of individuals.

Table 3: **Functional outcome and symptomatic intracranial haemorrhage by timing of treatment**

	High-dose tinzaparin (n=487)	Medium-dose tinzaparin (n=508)	Aspirin (n=491)
Reason for withdrawal			
Discharged before day 10	84 (17·2%)	84 (16·5%)	77 (15·7%)
Medical deterioration	24 (4·9%)	19 (3·7%)	16 (3·3%)
Exclusion criteria emerging	20 (4·1%)	16 (3·1%)	8 (1·6%)
Unacceptable adverse events	20 (4·1%)	16 (3·1%)	16 (3·3%)
Voluntary	4 (0·8%)	4 (0·8%)	1 (0·2%)
Other	24 (4·9%)	18 (3·5%)	21 (4·3%)
Died	22 (4·5%)	27 (5·3%)	16 (3·3%)
Total withdrawn from treatment	198 (40·7%)	165 (32·5%)	140 (39·9%)

Data are number of individuals. Patients may be withdrawn for ⩾ 1 reason.

Table 4: **Reasons for withdrawal from randomised treatment**

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Cause	Median time from stroke onset to death (days)	High-dose tinzaparin (n=486)	Medium-dose tinzaparin (n=507)	Aspirin (n=491)
Initial stroke	5	10 (14%)	20 (28%)	11 (15%)
Symptomatic intracranial haemorrhage	9	8 (11%)	3 (4%)	1 (1%)
Extracranial bleeding	9	0	0	1 (1%)
Cardiac death	17	9 (13%)	11 (15%)	7 (10%)
Other cardiovascular cause	18	3 (4%)	1 (1%)	0
Pulmonary embolism	20	5 (7%)	3 (4%)	3 (4%)
Pneumonia	30	21 (30%)	10 (14%)	31 (43%)
Other sudden death	43	5 (7%)	7 (10%)	6 (8%)
Other cause	59	7 (10%)	8 (11%)	8 (11%)
Other infection	65	1 (1%)	3 (4%)	3 (4%)
Recurrent stroke	75	2 (3%)	6 (8%)	2 (3%)
Total deaths		71	72	73

Table 5: **Adjudicated causes of death up to day 180**

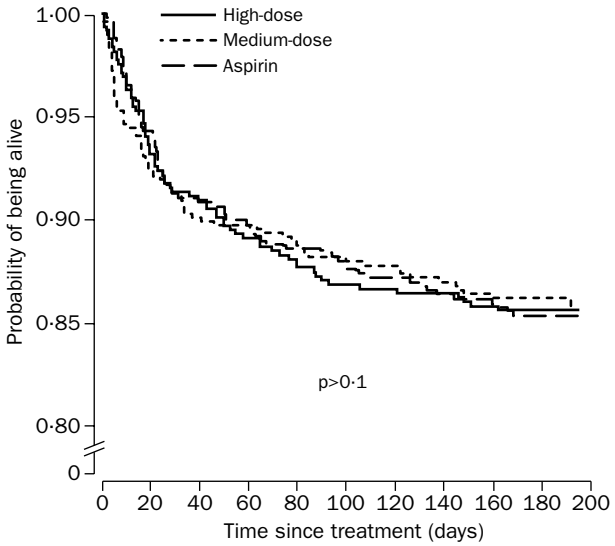

Figure 4: **Kaplan-Meier survival plot for the three treatment groups**

aspirin five). Analysis of a Kaplan-Meier survival plot did not reveal any difference between the three treatment groups (log-rank test p>0·1, figure 4). In a Cox's regression multivariate model, age, male sex, stroke severity, and a history of diabetes mellitus were associated with end-of-trial case-fatality; treatment assignment, systolic blood pressure, temperature, and atrial fibrillation were not related.

The safety-monitoring committee regularly reviewed data and considered the study in the context of other trials of LMW heparins in stroke. The rate of symptomatic intracranial haemorrhage was significantly higher among patients assigned high-dose tinzaparin than in those assigned aspirin, and was more common in patients treated within 24 h of stroke onset than in those treated later (tables 2, 3). No differences in major or minor extracranial bleeding, thrombocytopenia, or cardiac failure were seen among the three groups. In post-hoc analyses, there was no interaction between previous antiplatelet therapy (taken within 48 h of study entry) and therapy with tinzaparin in terms of symptomatic intracranial haemorrhage (high-dose tinzaparin two cases [1·1%], medium-dose tinzaparin two cases [1·0%], aspirin one case [0·5%]) or major extracranial haemorrhage (one case in each tinzaparin group, none in the aspirin group).

Discussion

The use of anticoagulation in acute ischaemic stroke remains controversial. Although the results of previous trials have been inconsistent and inconclusive, many physicians continue to administer LMW heparins to patients with acute ischaemic stroke. In this trial, the largest to date of a LMW heparin in acute stroke, we found that neither high-dose nor medium-dose tinzaparin improved the proportion of patients achieving independence, assessed as a Rankin score of 0–2, compared with aspirin. This finding applied to patients with a wide range of characteristics. The motivation for undertaking this trial arose from the positive results of the small FISS trial (312 patients)[11] of a LMW heparin, and the neutral observation for unfractionated heparin in the International Stroke Trial.[5] We hypothesised that the superior efficacy and lower hazard seen for LMW heparins than for unfractionated heparin in other vascular disorders (notably in the prevention and treatment of venous thromboembolism[7,8]) would translate into an overall benefit in acute ischaemic stroke. TAIST differed from earlier trials in that tinzaparin was compared with aspirin, not an inactive control. We used aspirin because it was shown conclusively in the International and Chinese Stroke Trials to improve functional outcome after ischaemic stroke;[5,18] a similar approach of comparing a LMW heparin with aspirin was also used in the Heparin in Acute Embolic Stroke Trial (HAEST) study.[19]

Heparins are widely used routinely in the management of patients with presumed cardioembolic stroke on the grounds that anticoagulants are effective in such patients in secondary prevention, and in patients with venous embolic disease. Nevertheless, no trial of unfractionated or LMW heparin, including TAIST, has found efficacy in this subgroup of patients.[5,11–14,19] TOAST reported, in a retrospective analysis, that patients with presumed large-artery stroke might benefit from intravenous danaparoid,[12] a finding not confirmed in TAIST. Indeed, tinzaparin was not, at either dose, superior to aspirin in any subgroup of patients, whether analysed by age, sex, stroke severity, TOAST subtype, clinical subtype, or time to treatment. Heparins are used in many patients with progressing strokes and, although TAIST was not designed to address this question specifically, rates of neurological deterioration did not differ between the tinzaparin and aspirin groups.

Several possible explanations for the neutral findings of TAIST can be put forward. First, and most likely, LMW heparins may simply be ineffective in improving functional outcome after acute ischaemic stroke, as suggested by the results of individual phase III trials[12,13,19] and a recently published meta-analysis.[14] Only the FISS study had positive results, and the small size of that trial and inconsistency of its results (nadroparin decreased rates of death and dependency at 6 months but not 3 months)[11] suggest a false-positive result. Although the total randomised evidence for LMW heparins in acute ischaemic stroke is not large (fewer than 5000 patients), the consistent results across the studies suggest that TAIST is unlikely to have been falsely neutral.

Second, TAIST had broad inclusion criteria and recruited patients irrespective of clinical syndrome or severity. Perhaps, therefore, the trial included a population of patients with stroke that was either too mild or too severe to allow treatment to be effective. During the trial, the protocol was amended to decrease this risk by limiting recruitment to patients with more severe strokes (Scandinavian neurological stroke scale

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score 40 or less). As a result, the overall rate of independence at 6 months was 42·5% in the aspirin group, very close to the value (40%) used in the sample-size calculation, and similar to that seen in the control group in FISS bis (Barthel index >85 43·2%).[13] The end-of-trial case-fatality rate for the control group (14·9%) suggests that the strokes in the TAIST patients were, on average, neither too severe nor too mild in comparison with TOAST, HAEST, FISS, and FISS bis (6·1%, 16·4%, 19·0%, 27·2%, respectively).[11–13,19]

Third, we may have used an inappropriate dose of tinzaparin or aspirin. We studied a high dose (175 anti-Xa IU/kg daily), which is effective for the treatment of deep-vein thrombosis and pulmonary embolism, and a medium dose (100 anti-Xa IU/kg daily), which is not used in routine clinical practice, that might provide a suitable balance between efficacy and safety. A low dose (eg, 50 anti-Xa IU/kg daily), which was shown to be effective for the prevention of venous thromboembolism, might have caused fewer symptomatic intracranial haemorrhages than higher doses. However, because the rate of this complication was low in the trial, even in the group assigned high-dose tinzaparin, a decrease in this rate through use of low-dose tinzaparin is unlikely to have affected the overall efficacy greatly. The absolute dose of tinzaparin was adjusted for weight, as done previously in trials showing positive results in the treatment of pulmonary embolism,[20,21] so patients were anticoagulated to a similar degree whatever their size. The dose of aspirin (300 mg daily) was as used in the International Stroke Trial, and was found in that trial to be mildly effective in reducing the risks of early recurrent stroke and late death and dependency.[5] The effects of tinzaparin and aspirin on laboratory measures of thrombosis were not assessed in individual patients for logistical reasons, and this approach mirrors clinical practice. Whether we should have tested the combination of LMW heparins and aspirin against aspirin alone is a debatable point, but the International Stroke Trial did not report any significant positive interaction between unfractionated heparin and aspirin on functional outcome.

Fourth, we may have chosen the wrong primary outcome. Efficacy was assessed with two measures of dependency, the Barthel index and the Rankin scale. Both measures are standard in acute stroke trials,[15] and both are sensitive to therapy-related change, as seen in trials with positive results for alteplase, prourokinase, or ancrod.[22–24] The timing of outcome measurements may also influence the assessment of efficacy, but we found no benefit at 6 months, as used in many heparin trials,[5,11–13,19] or at 3 months, as used in neuroprotection and other vascular studies in acute stroke.[22–25]

Fifth, we may have studied patients too late (up to 48 h) after stroke, although almost half of the participants were treated within 24 h. Although there is much debate about time windows for the treatment of acute stroke, early treatment is clearly important for thrombolysis, in which the aim is to open an occluded artery and restore cerebral perfusion, and neuroprotection, which is designed to protect the "penumbra" (tissue at risk) in the face of ischaemia. By contrast, many of the events that LMW heparins might help to prevent, including stroke extension, recurrence, and venous thromboembolism, occur hours or days after the ictus and so a longer time window for treatment is reasonable. Thus, in the absence of a solid theoretical rationale and clinical data favouring early treatment with anticoagulants for acute ischaemic stroke, a pragmatic time window was chosen reflecting worldwide clinical practice—ie, that although many patients present to hospital within 12 h, many are admitted later. This approach was also used in the International and Chinese Stroke Trials.[5,18] After the start of TAIST, a meta-analysis of previous trials on LMW heparins suggested that treatment might be more effective when given after 24 h, partly because earlier administration was associated with a greater risk of symptomatic intracranial haemorrhage.[14] Although TAIST did not confirm differential efficacy by treatment time, it did find that symptomatic intracranial haemorrhage tended to occur in the patients treated within 24 h of stroke onset. These findings emphasise that assumptions about treatment time windows are suspect, because unexpected confounding factors may appear, and that trial protocols should be inclusive rather than exclusive.

Lastly, treatment might have been given for too short a period, especially in patients discharged within 10 days. However, three-quarters of patients received at least 7 days of therapy (per-protocol population), and there was no evidence of efficacy in this group.

Although tinzaparin did not alter functional outcome, it did have predictable effects on venous thromboembolism and bleeding. Tinzaparin showed dose-dependent reductions in deep-vein thrombosis compared with aspirin, although only the difference for the higher dose of tinzaparin showed statistical significance. However, the overall frequency of symptomatic deep-vein thrombosis in the trial was low, presumably reflecting that other routine measures for preventing venous thromboembolism (such as adequate hydration, compression stockings, and early mobilisation) were effectively controlling this problem. A non-significant decrease in pulmonary embolism was seen for high-dose tinzaparin. Conversely, treatment with tinzaparin was associated with a dose-dependent increase in symptomatic intracranial haemorrhage, although only the difference for the higher dose of tinzaparin was significant. A non-significant increase in major extracranial bleeding was seen for high-dose tinzaparin. The frequency of thrombocytopenia, a recognised complication of heparin treatment, was very low and did not differ between tinzaparin and aspirin.

In addition to an effect on venous thromboembolism, another way by which LMW heparins might work is the prevention of early stroke recurrence or extension, although we did not try to distinguish between these two (as attempted in HAEST).[19] Prevention of stroke recurrence is probably the mechanism by which aspirin works,[5,18] but neither TAIST nor a meta-analysis of previous trials[14] suggest this is the case for LMW heparins. Surprisingly, this finding contrasts with the results of the International Stroke Trial, in which unfractionated heparin did decrease the risk of recurrent stroke, although the effect was exactly balanced by an increase in symptomatic intracranial haemorrhage.

What then is the future role for LMW heparins when used without concomitant antiplatelet therapy in acute ischaemic stroke? First, high-dose LMW heparins (tinzaparin 175 anti-Xa IU/kg daily or equivalent) cannot be recommended for the routine treatment of ischaemic stroke because the drug does not improve functional outcome and has a definite hazard, a view already propounded.[26,27] Second, although the risks of deep-vein thrombosis and pulmonary embolism are reduced, the real and greater threat of symptomatic intracranial haemorrhage (many cases of which are fatal) and falling incidence of venous thromboembolism mean

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that high-dose LMW heparins should not be used for routine prophylaxis. Nevertheless, LMW heparins (or unfractionated heparin) should be used in proven deep-vein thrombosis or pulmonary embolism, and may still be appropriate in patients with arterial dissection, basilar-artery thrombosis (although the evidence is empirical), or venous stroke,[28] or those at particularly high risk of venous thromboembolism (eg, those with a paretic leg who are morbidly obese or who have a history of deep-vein thrombosis or thrombophilic tendency). Finally, the consistent results of all the trials of LMW heparins suggest there is little purpose in further trials of these drugs, when used alone, in acute ischaemic stroke. The results of the International Stroke Trial,[5] which are qualitatively similar to those seen with LMW heparins, and the very low likelihood that unfractionated heparin will be superior to LMW heparins, also suggest that future testing of unfractionated heparin in acute ischaemic stroke[29] is unlikely to show benefit.

However, the role of low-dose LMW heparins in combination with an antiplatelet agent remains to be assessed. This combination could yet be shown to be effective, because the International Stroke Trial suggested that the combination of low-dose unfractionated heparin and aspirin might be superior to aspirin alone in improving functional outcome.[5] Furthermore, staggering of treatment might be appropriate, with aspirin given at the time of diagnosis and low-dose LMW heparin for the prophylaxis of venous thromboembolism after 1 or 2 days when the risk of inducing intracranial haemorrhage has declined.

Contributors

Philip Bath prepared the protocol, supervised and reviewed the progress of the trial, recruited patients, and wrote the paper. Ewa Lindenstrom prepared the protocol, supervised and reviewed the progress of the trial, and was involved in revising the paper. Gudrun Boysen, Peter De Deyn, Pal Friis, Didier Leys, Reijo Marttila, Jan-Edwin Olsson, Desmond O'Neill, Bernd Ringelstein, Jan-Jacob van der Sande, and Alexander Turpie supervised and reviewed the progress of the trial, recruited patients, and were involved in revising the paper. Jean-Marc Orgogozo chaired the Safety Monitoring Committee and was involved in revising the paper.

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