

# Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study

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## Summary

**Background** Patients with acute ischaemic stroke and atrial fibrillation have an increased risk of early stroke recurrence, and anticoagulant treatment with heparins has been widely advocated, despite missing data on the balance of risk and benefit.

**Methods** Heparin in Acute Embolic Stroke Trial (HAEST) was a multicentre, randomised, double-blind, and double-dummy trial on the effect of low-molecular-weight heparin (LMWH, dalteparin 100 IU/kg subcutaneously twice a day) or aspirin (160 mg every day) for the treatment of 449 patients with acute ischaemic stroke and atrial fibrillation. The primary aim was to test whether treatment with LMWH, started within 30 h of stroke onset, is superior to aspirin for the prevention of recurrent stroke during the first 14 days.

**Findings** The frequency of recurrent ischaemic stroke during the first 14 days was 19/244 (8.5%) in dalteparin-allocated patients versus 17/225 (7.5%) in aspirin-allocated patients (odds ratio=1.13, 95% CI 0.57–2.24). The secondary events during the first 14 days also revealed no benefit of dalteparin compared with aspirin: symptomatic cerebral haemorrhage 6/224 versus 4/225; symptomatic and asymptomatic cerebral haemorrhage 26/224 versus 32/225; progression of symptoms within the first 48 hours 24/224 versus 17/225; and death 21/224 versus 16/225. There were no significant differences in functional outcome or death at 14 days or 3 months.

**Interpretation** The present data do not provide any evidence that LMWH is superior to aspirin for the treatment of acute ischaemic stroke in patients with atrial fibrillation. However, the study could not exclude the possibility of smaller, but still worthwhile, effects of either of the trial drugs.

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## Introduction

Patients with atrial fibrillation have an increased risk of ischaemic stroke,<sup>1</sup> and strokes related to atrial fibrillation are often major, with a poor prognosis.<sup>2,3</sup> Atrial fibrillation is the most common potential source of cerebral embolism, and probably accounts for about 20% of all ischaemic strokes.<sup>4</sup>

Primary prevention trials in patients with atrial fibrillation have shown that oral anticoagulant therapy reduces the risk of stroke by 60–70%.<sup>5</sup> After a stroke, the prophylactic effect of oral anticoagulation is of equal magnitude,<sup>6</sup> but the best time to start anticoagulant therapy is not known.<sup>7</sup> In the European Atrial Fibrillation Trial patients were randomised late, and effective anticoagulation was not obtained within the first 2 weeks.<sup>6</sup>

Some early observational studies showed that the risk of recurrent ischaemic stroke was 10–20% during the first 2 weeks after stroke onset.<sup>8</sup> These and other studies also demonstrated a high frequency of haemorrhagic transformation of embolic infarcts,<sup>9</sup> and some reported symptomatic cerebral haemorrhages in association with early anticoagulation with heparin.<sup>10,11</sup> In an open randomised study, unfractionated heparin given intravenously was compared with no antithrombotic treatment.<sup>12</sup> The study was terminated prematurely after the inclusion of only 45 patients, because two recurrent strokes and two asymptomatic haemorrhagic transformations had occurred in the control group. However, in the International Stroke Trial, subgroup analysis of patients with atrial fibrillation given unfractionated heparin subcutaneously in fixed doses, showed that the reduction in recurrent ischaemic stroke was offset by an increase in cerebral haemorrhage.<sup>13</sup> Low-molecular-weight heparin (LMWH) has been tested before in acute stroke, but data on efficacy and safety are limited,<sup>14–18</sup> and LMWH has not been tested in patients with atrial fibrillation. Trials of LMWH for the treatment of venous thromboembolism<sup>19</sup> and acute coronary heart syndromes<sup>20,21</sup> strongly suggest that subcutaneous LMWH is superior to intravenous unfractionated heparin, with no excess risk of bleeding.<sup>19,20,22</sup> The pharmacokinetic profile of LMWH is favourable with high bioavailability and predictable plasma concentrations after subcutaneous administration. This allows the drug to be given once or twice daily without monitoring.<sup>22</sup> In our study, we have investigated whether subcutaneous LMWH is superior to aspirin for the prevention of early recurrent stroke in patients with atrial fibrillation.

## Methods

### Design

HAEST was a multicentre, randomised, double-blind, and double-dummy trial of LMWH versus aspirin for the early treatment of

\*Details of members of the study group are given at the end of the paper

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patients with atrial fibrillation and acute ischaemic stroke. The protocol was approved by the Regional Committee for Medical Research Ethics, the Norwegian Medicines Control Authority, and the Norwegian Social Science Data Services. Written informed consent was obtained from participating patients, and the ethical principles of the Declaration of Helsinki were adopted.

#### Eligibility criteria

Patients aged 18 years or older with acute ischaemic stroke and atrial fibrillation were eligible for inclusion in the trial. Randomisation had to take place within 30 h of stroke onset, and a cerebral scan by computed tomography was mandatory to exclude cerebral haemorrhage. Atrial fibrillation had to be documented with an electrocardiogram on admission or within the 24 months before the stroke. In the initial phase of the trial, patients with recent myocardial infarction ( $\leq 4$  weeks), and patients with specific echocardiographic findings suggestive of cardiogenic embolism were also eligible. However, these two entry criteria were dismissed per protocol after the inclusion of the first 50 patients, because only three patients had been randomised on the basis of myocardial infarction. Patients who, as determined by the clinician, had a clear indication for anticoagulant therapy or a clear contraindication for antithrombotic therapy were excluded from the trial. Other exclusion criteria were Scandinavian Stroke Scale (SSS) score below 8,<sup>23</sup> serious persistent hypertension on repeated measurements (systolic pressure  $>200$  mm Hg or diastolic pressure  $>110$  mm Hg), previous severe mental or physical disability that might interfere with the assessment of the patient, other serious disease or disease with life expectancy less than 6 months, and pregnancy or breast feeding.

#### Treatment

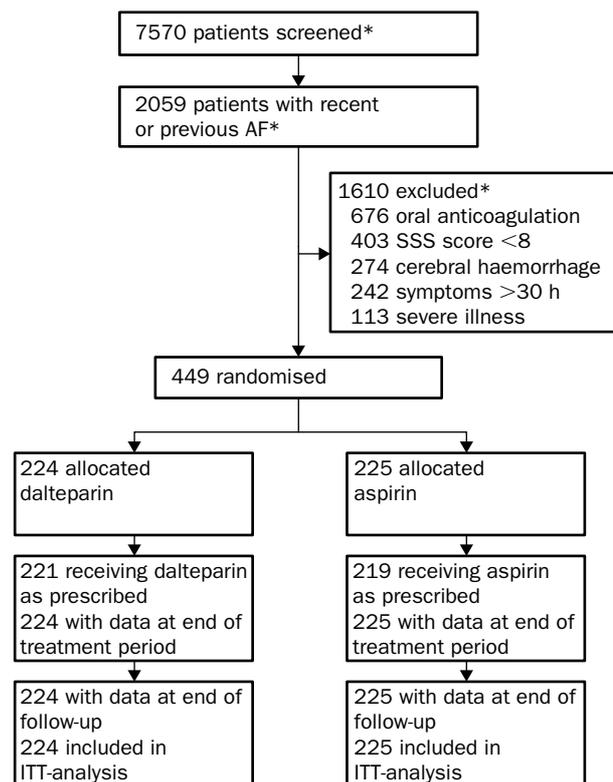
The patients were allocated to double-dummy treatment with dalteparin 100 IU/kg subcutaneously twice a day (Fragmin, Pharmacia and Upjohn, Stockholm, Sweden) and placebo tablets every day, or aspirin tablets 160 mg every day (Albyl-E, Nycomed Pharma, Oslo, Norway) and placebo ampoules subcutaneously twice a day. If the patients could not swallow, 160 mg suppositories (aspirin or placebo), made on request by Ullevål Hospital Pharmacy, were administered. In patients using aspirin before the stroke, aspirin was discontinued at randomisation. The aim was to have treatment start as soon as possible and to continue for 14 days (at least 11, at most 17 days), or until earlier discharge. At the end of the trial period the clinicians were encouraged to start oral anticoagulant treatment, but this and any other aspect of treatment were left to the discretion of the clinician in charge.

#### Randomisation procedure

After informed consent had been obtained, the patients were block-randomised by assignment to sequential numbered packages containing either active drug and corresponding placebo (double-dummy masking).<sup>24</sup> Within each centre, random allocation to dalteparin or aspirin was balanced for every four consecutive patients. The randomisation schedule was computer-generated (SAS, version 6.10), and was known only to the Clinical Trials Support Unit at Ullevål Hospital Pharmacy until closure of the database. Once a medication package had been opened, the corresponding patient was irrevocably included in the study. Clinicians could depart from the allocated trial medication if a clear reason to do so emerged, but they could not withdraw a patient from follow-up.

#### Monitoring of quality

Monitoring of data registration was done centrally on the sequential return of case-record forms. These were checked and sent back if erroneous or incomplete. To ensure standardisation of assessment of patient outcome, participating centres were visited and given formal instructions on procedures. Written instructions were distributed to every centre, and collaborators' meetings were held twice a year throughout the trial period to instruct and encourage participants.



#### Trial profile

\*Total numbers of patients screened and patients excluded are estimated from recruitment logs recorded at four centres responsible for the inclusion of 28% of the patients in the study. ITT=intention to treat. AF=atrial fibrillation.

#### Follow-up, events, and outcomes

During the treatment period, trained personnel assessed neurological status by the SSS,<sup>23</sup> on a daily basis during the first week and every second day during the second week. In addition, SSS was always done on clinical deterioration. Cerebral computed tomography was done before randomisation, repeated after 7 days, and on clinical deterioration. Echocardiography was done during the treatment period in 307/449 of cases, and blood samples for routine and specialised analyses were collected at defined intervals.

In case of a clinical deterioration, a general clinical examination, SSS, and cerebral computed tomography were done. If a patient died during the treatment period, the responsible clinician classified the cause of death. Necropsy or post-mortem cerebral computed tomography was desirable, but not mandatory, particularly in case the cause of death was uncertain.

At 14 days, or earlier discharge, outcome was assessed by the Bartel Index,<sup>25</sup> modified Rankin Scale,<sup>26</sup> and according to the outcome scale used in the International Stroke Trial.<sup>27,28</sup>

At 3 months, the patients were assessed by the International Stroke Trial scale. The patients were contacted by the trial coordinating centre by mail, 15 who did not respond were telephoned.

The primary event was recurrent ischaemic stroke during the first 14 days. Recurrent ischaemic stroke was defined as a clinical sudden and persistent ( $>48$  h) deterioration occurring after the first 48 h following stroke onset, which equals a loss of three or more points in the SSS, excluding cerebral haemorrhage, intercurrent illness, and effect of medication (eg, insomnia medication). Clinical deterioration within the first 48 h was classified as recurrent ischaemic stroke only if it originated in a vascular area other than that of the index stroke (eg, the opposite hemisphere).

Secondary events and outcomes were as follows—cerebral haemorrhage within 14 days (classified according to the ECASS protocol<sup>29</sup>), both asymptomatic (including haemorrhagic infarcts

grade 1 or 2, or parenchymal haemorrhages grade 1 or 2) and symptomatic (associated with haemorrhagic infarct grade 2 or parenchymal haemorrhage grade 1 or 2); progression of symptoms (defined as a clinical deterioration, as defined for the primary event, occurring within the first 48 h after stroke onset); death from any cause within 14 days; combined frequency of recurrent ischaemic stroke, progression of symptoms, and death within 14 days; neurological outcome at 14 days, as measured by SSS; outcome at 14 days, as measured by the Barthel Index, modified Rankin Scale, and International Stroke Trial scale; and outcome at 3 months, as measured by the International Stroke Trial scale.

All clinical events were evaluated and classified by an independent endpoint adjudication committee unaware of treatment allocation. Cerebral scans by computed tomography were assessed by a central, independent reading panel without access to information about clinical history or treatment allocation.

### Statistical methods

Our assumption was that the frequency of recurrent ischaemic stroke during the first 14 days would be 4% or less on LMWH and 12% or more on aspirin. With a significance level ( $\alpha$ ) of 5% and a power (1- $\beta$ ) of 80%, the minimal sample size was estimated to be 408 patients. To allow for loss to follow-up, 449 patients were included. No interim analyses were done.

All analyses were according to the intention-to-treat principle. The comparisons of frequencies of events involved simple analyses of total numbers of patients, using 2x2 tables. The effect of treatment was given as odds-ratios (OR) with 95% CI. Comparisons of outcome also involved non-parametric testing (Mann-Whitney and Kruskal-Wallis) of median outcome or total numbers of patients in the two treatment groups, with two-sided p values to show significance.<sup>24</sup> Control for the confounding effect of sex was achieved by logistic regression,<sup>30</sup> but no other adjustments for the effect of differences in risk factors were made. Descriptive statistics are reported as median values with 25–75 percentiles unless otherwise stated. We used SPSS, version 8.0, for statistical analysis.

## Results

### Recruitment and follow-up

From February, 1996, to November, 1998, 449 patients were recruited at 45 Norwegian centres. During the trial, recruitment logs of consecutive patients admitted with a stroke were recorded at four centres, responsible for the inclusion of 28% of all patients. 2124 patients with acute stroke were screened, and 126 (5.9%) of these were included in the study. The main reasons for not including patients with acute stroke and atrial fibrillation were: oral anticoagulation before the stroke (42%), SSS score below eight (25%), cerebral haemorrhage (17%), duration of symptoms over 30 h (15%), and severe mental or somatic illness before the stroke (7%). Outcome data were 100% complete for both 14 days outcome and 3 months outcome (figure).

### Protocol violations

All randomised patients were included in the intention-to-treat-analysis, including one patient who was included four days after onset of symptoms, two patients without documented atrial fibrillation, three patients who did not have a stroke, and six patients with cerebral infarction combined with haemorrhagic transformation (n=2) or parenchymatous haemorrhage (n=4) on computed tomography before inclusion. Nine patients were randomised, but not treated in accordance with the protocol (three in the dalteparin group and six in the aspirin group).

### Patient characteristics

At randomisation, the main prognostic factors were well balanced between the two treatment groups, except for

	Dalteparin (n=224)	Aspirin (n=225)
<b>Age (years), median (range)</b>	80 (55–96)	80 (44–98)
<b>Female</b>	111 (50%)	137 (61%)
<b>Premorbid status</b>		
Estimated Rankin Scale, score 0–1	195 (87%)	186 (83%)
Smoking	46 (21%)	36 (16%)
Aspirin medication	96 (43%)	105 (47%)
Hypertension	90 (40%)	89 (40%)
Coronary heart disease	80 (36%)	77 (34%)
Heart failure	49 (22%)	56 (25%)
Diabetes mellitus	28 (13%)	38 (17%)
Stroke or TIA	51 (23%)	57 (25%)
Venous thromboembolism	13 (6%)	7 (3%)
<b>Baseline data</b>		
Delay (h), median (25–75 percentiles)	21 (12–27)	20 (11–25)
SSS (score), median (25–75 percentiles)	39 (22–49)	39 (22–48)
Atrial fibrillation*		
On admission	199 (89%)	201 (89%)
Prior to admission	23 (10%)	21 (9%)
Stroke syndrome†		
Lacunar	45 (20%)	26 (12%)
Partial anterior	116 (52%)	122 (54%)
Total anterior	47 (21%)	55 (24%)
Posterior	15 (7%)	21 (9%)
Cerebral CT scan		
Infarct visible	184 (82%)	177 (79%)
"New" infarct visible	178 (79%)	168 (75%)
Blood pressure (mm Hg), median (25–75 percentiles)		
Systolic	170 (150–188)	160 (145–180)
Diastolic	95 (84–107)	93 (80–105)
Laboratory tests, median (25–75 percentiles)		
Haemoglobin (g/dL)	14.2 (13.2–14.9)	13.7 (12.7–14.6)
Platelets ( $\times 10^9/L$ )	204 (172–240)	216 (175–260)
Cholesterol (mmol/L)	5.5 (4.6–6.4)	5.7 (4.8–6.6)
CRP ( $\mu g/L$ )	8.0 (5.0–13.3)	7.0 (5.0–12.0)

TIA=transient ischaemic attack. CT=computed tomography.

Data represent number of patients (%), unless otherwise specified.

\*Three patients without atrial fibrillation were included per protocol on basis of recent myocardial infarction, and two patients were included without documented atrial fibrillation.

†Two patients could not be classified according to the Oxfordshire Community Stroke Project classification algorithm.<sup>31</sup>

**Table 1: Characteristics at randomisation for both treatment groups**

more females in the aspirin group<sup>31</sup> (table 1). Atrial fibrillation was documented on admission in 89% of the patients, and had been documented in 10% within the 24 months before the stroke. Three patients with sinus rhythm and recent myocardial infarction were included in the early phase in accordance with the original protocol.

### Compliance

Median duration of treatment was 13 days (25–75 percentiles 11–14). Altogether 90 (20%) patients ended treatment before the schedule 14 $\pm$ 3 days. The reasons were

	Dalteparin (n=224)	Aspirin (n=225)	OR (95% CI)	p
Recurrent ischaemic stroke	19 (8.5%)	17 (7.5%)	1.13 (0.57–2.24)	0.73
Symptomatic cerebral haemorrhage	6 (2.7%)	4 (1.8%)	1.52 (0.42–5.46)	0.54
Asymptomatic and symptomatic cerebral haemorrhages	26 (11.6%)	32 (14.2%)	0.79 (0.44–1.43)	0.41
Progression of symptoms	24 (10.7%)	17 (7.6%)	1.47 (0.77–2.82)	0.26
Death, any cause	21 (9.4%)	16 (7.1%)	1.35 (0.69–2.66)	0.40
Recurrence, progression or death	51 (22.8%)	36 (16.0%)	1.55 (0.96–2.49)	0.074
Recurrence, progression, death or symptomatic cerebral haemorrhage	55 (24.6%)	38 (16.9%)	1.60 (1.01–2.54)	0.048
Extracerebral haemorrhage	13 (5.8%)	4 (1.8%)	3.40 (1.09–10.61)	0.028
Venous thromboembolism	1 (0.4%)	5 (2.2%)	0.20 (0.02–1.70)	0.22
Acute myocardial infarction	1 (0.4%)	3 (1.3%)	0.33 (0.3–3.22)	0.62
Pneumonia	15 (6.7%)	16 (7.1%)	0.94 (0.45–1.95)	1.0
Urinary tract infection	8 (3.6%)	5 (2.2%)	1.63 (0.53–5.06)	0.42

All analyses by  $\chi^2$  test of association between categorical variables and by Fisher's exact test.

**Table 2: Events after 14 days**

	Dalteparin (n=224)	Aspirin (n=225)	Odds dalteparin/ aspirin	OR
<b>Cerebral haemorrhage</b>				
Haemorrhagic infarction grade 1	14	20	0.7	1.00
Haemorrhagic infarction grade 2	4	6	0.7	1.00
Parenchymal haemorrhage grade 1	4	4	1.0	1.43
Parenchymal haemorrhage grade 2	4	2	2.0	2.86
<b>Total</b>	<b>26</b>	<b>32</b>	<b>..</b>	<b>..</b>

Table 3: Frequency of symptomatic and asymptomatic cerebral haemorrhage after 14 days

death (n=36), cerebral haemorrhage (7), recurrent stroke or progression of symptoms (5), extracerebral bleeding complications (5), venous thromboembolism (5), hip fracture (1), early discharge from hospital (22), and unspecified (9). Overall compliance with the study treatment was 98.8% of all prescribed doses in the dalteparin group and 98.3% in the aspirin group.

The use of concomitant treatment was well balanced between the treatment groups. Non-trial heparin was used by four patients, all in the aspirin group, as low-dose prophylaxis against deep-vein thrombosis. Non-trial aspirin was used by four patients in the dalteparin group and five patients in the aspirin group. At the end of the treatment period, oral anticoagulant treatment had been started in 107 patients in the dalteparin group and 110 patients in the aspirin group.

#### Primary event

The frequency of recurrent ischaemic stroke during the first 14 days was 19/224 (8.5%) in dalteparin-allocated patients versus 17/225 (7.5%) in aspirin-allocated patients (table 2). The OR was 1.13 (95% CI 0.57–2.24), which indicates no significant benefit of dalteparin. The OR remained unchanged after adjusting for sex in logistic-regression analysis (1.19 [0.60–2.36]).

#### Secondary events and outcomes

The frequency of symptomatic cerebral haemorrhage during the first 14 days was 6/224 (2.7%) on dalteparin versus 4/225 (1.8%) on aspirin (1.52 [0.42–5.46], table 2). The frequency of symptomatic and asymptomatic cerebral haemorrhages detected on control computed tomography was 26/224 (11.6%) on dalteparin versus 32/225 (14.2%) on aspirin (0.79 [0.44–1.43]). However, the haemorrhages occurring in the dalteparin-group were more severe (table 3).

Dalteparin was associated non-significantly with a higher frequency of progression of symptoms within the first 48 h (24/224 [10.7%] vs 17/225 [7.6%], OR=1.47 [95% CI 0.77–2.82] and more deaths after 14 days (21/224 [9.4%] vs 16/225 [7.1%], 1.35 [0.69–2.66], table 2). The causes of death were equally distributed in the two treatment groups (table 4).

	Dalteparin (n=224)	Aspirin (n=225)
<b>Cause of death</b>		
Initial stroke	6 (2.7%)	5 (2.2%)
Recurrent ischaemic stroke	4 (1.8%)	4 (1.8%)
Cerebral haemorrhage	2 (0.9%)	1 (0.4%)
Pneumonia	4 (1.8%)	2 (0.8%)
Coronary heart disease	3 (1.3%)	2 (0.8%)
Other vascular disease	2 (0.9%)	0
Other non-vascular disease	0	2 (0.8%)
<b>Total</b>	<b>21 (9.4%)</b>	<b>16 (7.1%)</b>

The causes of death were verified by necropsy or post-mortem computed tomography in 8/37 (22%) of cases.

Table 4: Causes of death (14 days)

Outcome	Dalteparin (n=224)	Aspirin (n=225)	OR (95% CI)	p
<b>SSS, median (25–75 percentile)*</b>				
Score day 14	49 (27–55)	49 (26–55)	..	0.97
Change from day 1 to day 14	5 (0–10)	6 (1–12)	..	0.32
<b>Barthel Index†</b>				
Favourable outcome (score 19–20)	78 (34.8%)	76 (33.8%)	0.92 (0.61–1.37)	0.69
<b>Modified Rankin Scale†</b>				
Favourable outcome (score 0–2)	97 (43.3%)	103 (45.8%)	0.91 (0.62–1.31)	0.64
<b>IST Scale†</b>				
Fully recovered, independent	40 (17.9%)	39 (17.3%)	}	0.81
Not recovered, but independent	43 (19.2%)	42 (18.7%)		
Dependent	120 (53.6%)	128 (56.9%)		
Dead	21 (9.4%)	16 (7.1%)		

\*Data represent points on scale; analysis by the Mann-Whitney test.

†Data represent number of patients (%); analyses by  $\chi^2$  test of association between categorical variables and by Fisher's exact test.

Table 5: Outcome at 14 days

Outcome	Dalteparin (n=224)	Aspirin (n=225)	p
Fully recovered, independent	51 (22.8%)	48 (21.3%)	}
Not recovered, but independent	25 (11.2%)	31 (13.8%)	
Dependent	108 (48.2%)	109 (48.4%)	
Dead, any cause	40 (17.9%)	37 (16.4%)	

Analyses by  $\chi^2$  test of association between categorical variables and by Fisher's exact test.

Table 6: Outcome at 3 months

The frequency of the prespecified combined factors of the non-haemorrhagic end-point recurrent ischaemic stroke, progression of symptoms, and death was 51/244 (22.8%) in the dalteparin group versus 36/225 (16.4%) in the aspirin group (1.55 [0.96–2.49], table 2). Adding symptomatic cerebral haemorrhage, which was not specified per protocol, the frequency was 55/224 (24.6%) in the dalteparin group versus 38/225 (16.9%) in the aspirin group (1.60 [1.01–2.54], p=0.048).

Dalteparin was associated with a significantly higher frequency of extracerebral haemorrhages (13/224 [5.8%] on dalteparin vs 4/225 [1.8%] on aspirin, 3.40 [1.09–10.61]). Symptomatic venous thromboembolism was detected in one of the patients allocated dalteparin and in five of the aspirin patients (not significant).

There was no significant difference in outcome at 14 days (table 5), as measured by the SSS, Barthel Index, modified Rankin Scale, and International Stroke Trial scale. The percentage of patients dependent or dead was 63.0% in the dalteparin group and 64.0% in the aspirin group (not significant). At 3 months, there was still no difference in outcome (table 6). The percentage dead or dependent was 66.1% in patients allocated to dalteparin and 64.8% in patients allocated to aspirin (not significant).

## Discussion

It has long been a controversy whether patients with acute ischaemic stroke and atrial fibrillation should receive anticoagulant treatment with heparins.<sup>7,32–35</sup> Our results provide no evidence that high-dose LMWH is superior to aspirin, either for the prevention of recurrent ischaemic stroke of any other event during the first 14 days, or for the improvement of outcome at 14 days or 3 months. Our results are consistent with the effect of unfractionated heparin,<sup>13</sup> LMWHs,<sup>14,18</sup> or heparinoid<sup>36</sup> in patients with any type of acute ischaemic stroke. They are also consistent with the International Stroke Trial subgroup analysis of patients with atrial fibrillation, which showed no net benefit of fixed medium-dose unfractionated heparin given subcutaneously, compared with no heparin.<sup>13</sup> Taken together, the evidence provides no indication of net benefit of early anticoagulation

with any type of anticoagulant agent or in any subgroup of patients with acute ischaemic stroke.<sup>37</sup>

Our estimates of the effect of LMWH in patients with atrial fibrillation were based on the results from the primary and secondary stroke-prevention studies.<sup>5,6</sup> In these studies, oral anticoagulant treatment reduced the risk of recurrent stroke by two-thirds relative to no antithrombotic treatment, compared with only one-fifth on aspirin. In the acute phase of stroke the risk of recurrence has been assumed to be about 10–20%,<sup>8</sup> and our assumption was that the risk of recurrent stroke would be reduced to 4% or less on LMWH, compared with 12% or more on aspirin.

The observed incidence of early recurrent stroke in our trial was 8%, in accordance with what we anticipated. This was lower than in observational studies,<sup>8</sup> but somewhat higher than in recent acute-stroke trials.<sup>13,36</sup> The reasons for the different estimates may be different definitions of recurrence, and different monitoring of patients. In the present study, patients were carefully monitored with the SSS, which allowed reliable detection of any clinically significant recurrence. Despite a plausible hypothesis and a relatively high incidence of early recurrence, our study could not show a superior effect of LMWH in the prevention of early stroke recurrence. One reason may be that the risk of recurrent stroke observed on aspirin was lower than stipulated. As a consequence, the study did not have sufficient power to detect reliably an effect of the expected, or smaller, magnitude. Although the results are highly internally consistent, we cannot exclude the possibility of an effect either way in one of the outcome measures or in the overall result.

Another explanation for the absence of treatment effect of LMWH relative to aspirin could be misclassification of the primary event. Early recurrence may be caused by a diversity of pathophysiological processes, not only by thromboembolism. Non-thrombotic processes may even explain most of the early recurrences, such as neurotoxic substances or vascular oedema.<sup>38</sup> We may thus have overestimated the incidence of thromboembolic events and thereby diluted the effect of LMWH. Alternatively, recurrences are true thromboembolic manifestations, caused by emboli originating from an organised heparin-unresponsive thrombus within the heart, or the dose of LMWH used was inadequate.

The rationale for the selection of type and dose of LMWH was based on circumstantial evidence of the efficacy of dalteparin for the prophylaxis and treatment of venous thromboembolism<sup>19</sup> and for the treatment of unstable coronary syndromes.<sup>20,21</sup> Moreover, a safety study of dalteparin, given in doses used in the present study, indicated a low risk of cerebral bleeding complications.<sup>15</sup> The dose selected is identical to the dose used for the treatment of venous thromboembolism, but is slightly lower than the dose used for the treatment of acute coronary syndromes (100 U/kg *vs* 120 U/kg twice daily). Although unlikely, we cannot completely rule out the possibility that a higher dose would have given a different result. To increase the dose in these patients, however, could have increased substantially the rate of severe bleeding complications.

Our study did not show any significant increase in symptomatic cerebral haemorrhage on dalteparin compared with aspirin. However, the trial was not sized to provide reliable estimates on the comparative effects of LMWH and aspirin on symptomatic cerebral haemorrhage, and our data cannot exclude the possibility of an excess risk

either way. The incidence of any type of cerebral haemorrhage was almost the same in the two groups, but there was a trend towards more severe bleedings on dalteparin. Still, we find the low rate of haemorrhages on dalteparin surprising, given that our patients were old, with major disabling strokes, and mostly with large middle-cerebral-artery infarcts.

Despite lack of evidence, heparins are often recommended for the prevention and treatment of progressive stroke.<sup>39</sup> In our study, progressions occurring from randomisation until 48 h after stroke onset were seen more frequently on LMWH, and our results therefore do not support routine use of LMWH in this setting.

It is now clear that heparins given in both prophylactic and therapeutic doses protect against venous thromboembolism in patients with acute stroke.<sup>37</sup> Our study did not systematically screen for venous thromboembolism, but we also detected more cases with venous thromboembolism in the aspirin group.

Internal validity was ensured by strict randomisation (to ensure a good balance between the two treatment groups for the recorded, and, presumably, unrecorded prognostic factors), good compliance, double-blinded and complete follow-up, and blinded and independent evaluation of events and outcomes. We also believe our trial population to be close to the population usually admitted for acute stroke and atrial fibrillation. Our patients were old, with high comorbidity and severe strokes, compared with stroke registries<sup>2</sup> and other acute stroke trials.<sup>13,36,40</sup>

We conclude that our data do not provide any evidence that high-dose LMWH is superior to aspirin for the treatment of patients with acute ischaemic stroke and atrial fibrillation. However, the study cannot exclude the possibility of smaller, but still worthwhile, effects of either of the trial drugs. We suggest that these patients should receive aspirin in the acute phase of stroke and that short-term prophylactic use of low-dose LMWH for the prevention of venous thromboembolism should be considered. Most of these patients should be given long-term oral anticoagulant treatment,<sup>9</sup> but the best time to initiate oral anticoagulation cannot be answered from this study.

#### HAEST study organisation

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*Safety monitoring committee*—T R Pedersen (chairman), H Arnesen.

*End-point adjudication committee*—T Dahl (chairman), H Nordal.

*CT reading panel*—P H Nakstad (chairman), U Johnsen.

*ECG and echocardiography review committee*—G Smith (chairman), F T Gjestvang, K Bjørnstad.

#### HAEST study group

The following centres and main investigators participated in HAEST. Numbers randomised are in parentheses.

*Aker sykehus*: L Holø (17); *Aust-Agder sentralsykehus*: R Solhoff (9);

*Buskerud sentralsykehus*: E B Jørgensen (15); *Bærum sykehus*: I L Løfsnes

(10); *Diakonhjemmets sykehus*: T J Svendsen (10); *Diakonissehjemmets*

*sykehus Haraldsplass*: H Næss (4); *Fylkessjukehuset i Haugesund*: R Ofstad

(8); *Fylkessjukehuset i Kristiansund*: V Kvambe (15); *Fylkessjukehuset i*

*Lærdal*: S Urnes (6); *Fylkessjukehuset i Molde*:

H Heggdal (13); *Fylkessjukehuset i Volda*: S Hareide (1); *Fylkessjukehuset*

*på Nordfjordeid*: Ø Dahl-Eriksen (14); *Fylkessjukehuset på Stord*:

D Saggurthi (15); *Fylkessjukehuset på Voss*: F Berge (9); *Gjøvik*

*fylkessykehus*: F Moen (18); *Hammerfest sykehus*: L Eriksen (11); *Harstad*

*sykehus*: O Kildahl-Andersen (4); *Haukeland sykehus*:

L Thomassen (7); *Hedmark sentralsykehus*: A Græsdal (4); *Innherred*

*sykehus*: E Ellekjær (5); *Kirkenes sykehus*: A Vejle (1); *Kongsberg sykehus*:

K Berget (9); *Kongsvinger sykehus*: T Asak (26); *Lillehammer fylkessykehus*:

E Brandt (5); Lister sykehus: T Ormland (8); Lovisenberg diakonale sykehus: B Holm (8); Nordland sentralsykehus: J Olavsen (11); Orkdal Sanitetsforenings sykehus: U Rian (10); Rana sykehus: P Nesje (2); Regionsykehuset i Tromsø: S H Johnsen (2); Regionsykehuset i Trondheim: B Indredavik (8); Ringerike sykehus: A A Pettersen, L Thoresen (8); Sandefjord sykehus: S B Krogseth (3); Sandnessjøen sykehus: A G Karlsson (10); Sentralsykehuset i Møre og Romsdal: O R Skogen (13); Sentralsykehuset i Sogn og Fjordane, Florø: A Bondevik (1); Sentralsykehuset i Sogn og Fjordane, Førde: F Bergqvist (12); Stokmarknes sykehus: F Larssen-Aas (8); Sykehuset Østfold Fredrikstad: A B Spenning (1); Sykehuset Østfold Moss: Y Rønning (3); Telemark sentralsykehus: A Andersen (5); Ullevål sykehus: E Berge, J Rygh (73); Vefsn sykehus: K Sjøbrend (9); Vest-Agder sentralsykehus: P Friis (13); Vestfold sentralsykehus: P Skogen (6).

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