

The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL Study): an open-label randomised comparison

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Summary

Background Venous thromboembolism prophylaxis with low molecular weight heparin or unfractionated heparin is recommended in acute ischaemic stroke, but which regimen provides optimum treatment is uncertain. We aimed to compare the efficacy and safety of enoxaparin with that of unfractionated heparin for patients with stroke.

Methods 1762 patients with acute ischaemic stroke who were unable to walk unassisted were randomly assigned within 48 h of symptoms to receive either enoxaparin 40 mg subcutaneously once daily or unfractionated heparin 5000 U subcutaneously every 12 h for 10 days (range 6–14). Patients were stratified by National Institutes of Health Stroke Scale (NIHSS) score (severe stroke ≥ 14 , less severe stroke < 14). The primary efficacy endpoint was the composite of symptomatic or asymptomatic deep vein thrombosis, symptomatic pulmonary embolism, or fatal pulmonary embolism. Primary safety endpoints were symptomatic intracranial haemorrhage, major extracranial haemorrhage, and all-cause mortality. This study is registered with ClinicalTrials.gov, number NCT00077805.

Findings In the efficacy population (ie, one or more dose received, presence of deep vein thrombosis or pulmonary embolism, or assessment for venous thromboembolism), enoxaparin (n=666) and unfractionated heparin (669) were given for 10.5 days (SD 3.2). Enoxaparin reduced the risk of venous thromboembolism by 43% compared with unfractionated heparin (68 [10%] vs 121 [18%]; relative risk 0.57, 95% CI 0.44–0.76, $p=0.0001$; difference -7.9% , -11.6 to -4.2); this reduction was consistent for patients with an NIHSS score of 14 or more (26 [16%] vs 52 [30%]; $p=0.0036$) or less than 14 (42 [8%] vs 69 [14%]; $p=0.0044$). The occurrence of any bleeding was similar with enoxaparin (69 [8%]) or unfractionated heparin (71 [8%]; $p=0.83$). The frequency of the composite of symptomatic intracranial and major extracranial haemorrhage was small and closely similar between groups (enoxaparin 11 [1%] vs unfractionated heparin 6 [1%]; $p=0.23$). We noted no difference for symptomatic intracranial haemorrhage between groups (4 [1%] vs 6 [1%], respectively; $p=0.55$); the rate of major extracranial bleeding was higher with enoxaparin than with unfractionated heparin (7 [1%] vs 0; $p=0.015$).

Interpretation Our results suggest that for patients with acute ischaemic stroke, enoxaparin is preferable to unfractionated heparin for venous thromboembolism prophylaxis in view of its better clinical benefits to risk ratio and convenience of once daily administration.

Introduction

Stroke is a major health problem that is growing in importance.¹ WHO estimates that 15 million people have a stroke every year, and this number is rising.² Each year in the USA alone, 700 000 people have a first or recurrent stroke,³ 88% of which are ischaemic. Stroke is also the third most common cause of death and the leading cause of disability in adults.^{4,5}

Venous thromboembolism is a common but preventable complication of acute ischaemic stroke, and is associated with increased mortality and long-term morbidity and substantial health-care costs for its management.⁶ The risk of venous thromboembolism for patients who have had an acute ischaemic stroke is close to that for patients undergoing major surgical procedures.⁶ Without venous thromboembolism prophylaxis, up to 75% of patients with hemiplegia after stroke develop deep

vein thrombosis and 20% develop pulmonary embolism,^{7,8} which is fatal in 1–2% of patients with acute ischaemic stroke and causes up to 25% of early deaths after strokes.⁹

The benefits of prophylaxis have been seen in patients with acute ischaemic stroke, and low molecular weight heparin and unfractionated heparin are therefore recommended in guidelines from expert consensus groups.^{10–14} For physicians to select the most appropriate prophylactic regimen, they need to decide which will achieve maximum reduction of venous thromboembolism risk while keeping the risk of bleeding to a minimum. Up to now, small-scale studies have suggested that low molecular weight heparin is better than or equivalent to unfractionated heparin for prevention of venous thromboembolism after acute ischaemic stroke,^{15,16} but these studies were restricted in their ability to assess the benefit to risk ratio of the prophylactic treatments.

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Panel: Patient exclusion criteria

- Evidence of VTE at screening or evidence of active bleeding
- Evidence or history of intracranial haemorrhage, heparin-induced or enoxaparin-induced thrombocytopenia or thrombosis, or both
- Hypersensitivity to iodinated contrast media or iodine
- Spinal or epidural analgesia or lumbar puncture within the preceding 24 h
- Thrombolytic treatment within the preceding 24 h
- Comatose at screening (NIHSS score ≥ 2 for level of consciousness)
- Known or suspected cerebral aneurysm or arteriovenous malformation
- Confirmed malignant disease that might have posed an increased risk for bleeding or compromise follow-up or outcome assessment
- Impaired haemostasis, such as baseline platelet count $< 100\,000$ per μL , aPTT 1.5-times the laboratory upper limit of normal, or INR > 1.5
- Major surgery or major trauma within the preceding 3 months
- Expected need for full-dose treatment with therapeutic levels of an anticoagulant
- Treatment with LMWH or UFH at a prophylactic dose for more than 48 h before inclusion
- Allergy or known hypersensitivity to heparin or enoxaparin
- Bacterial endocarditis
- Prosthetic heart valve
- Known or suspected severe anaemia (haemoglobin < 100 g/L)
- Uncontrolled arterial hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 100 mm Hg) at randomisation or clinical hypertensive urgency
- Life expectancy less than 3 months due to comorbid disorders
- Participation in another clinical study within the preceding 30 days
- Any clinically relevant serious diseases, including severe liver disease or renal failure (creatinine clearance < 30 mL/min on at least two occasions)
- Female patients were not enrolled if they were breastfeeding, pregnant, or could become pregnant during the study.

aPTT=activated partial thromboplastin time. LMWH=low molecular weight heparin. INR=international normalised ratio. NIHSS=National Institutes of Health Stroke Scale. UFH=unfractionated heparin. VTE=venous thromboembolism.

A meta-analysis showed that low molecular weight heparin and heparinoids reduce the risk of deep vein thrombosis and symptomatic pulmonary embolism by around two-thirds compared with placebo or no treatment, with a two-fold increase in the risk of extracranial bleeding.¹⁷ Meta-analyses of low-dose and high-dose low molecular weight and unfractionated heparin regimens have suggested that low-dose low molecular weight heparin could provide the best benefit

to risk ratio in patients with acute ischaemic stroke by decreasing the risk of both deep vein thrombosis and pulmonary embolism without increasing the risk of intracranial or extracranial haemorrhage.^{18,19} However, in one meta-analysis the investigators warn against drawing conclusions on the basis of haemorrhagic complications because of the low numbers of events.¹⁸ Nevertheless, prophylactic regimens used for patients with stroke are quite varied because many physicians remain uncertain about the best treatment, and data from studies with high numbers of patients are needed to resolve this issue.

We have therefore done a large scale, multinational, randomised study to compare the efficacy and safety of the low molecular weight heparin enoxaparin with that of unfractionated heparin for venous thromboembolism prophylaxis in patients with acute ischaemic stroke.

Methods**Patients**

Patients were eligible for enrolment if they were 18 years or older with an acute ischaemic stroke confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) and unable to walk unassisted because of motor impairment, with a score of 2 or more as indicated by National Institutes of Health Stroke Scale (NIHSS)²⁰ for motor function of the leg. Onset of stroke symptoms had to have occurred within 48 h before randomisation. The panel shows exclusion criteria.

All patients provided written informed consent. The study was done according to the Declaration of Helsinki and local regulations. Approval to do the study was obtained from the institutional review board at all sites.

Study design

Eligible patients were stratified according to severity of the index stroke and then randomised on a 1 to 1 basis, with permuted blocks of four, within each of two strata: severe strokes (NIHSS score ≥ 14) and less severe strokes (NIHSS score < 14). The sponsor generated the randomisation schedule that was implemented centrally by an independent interactive voice-response system.

Within 48 h of the onset of stroke symptoms, patients received either enoxaparin 40 mg subcutaneously once daily or unfractionated heparin 5000 U subcutaneously every 12 h for 10 days (range 6–14). Study treatment was not blinded.

The primary efficacy endpoint was the cumulative occurrence of confirmed venous thromboembolism, defined as the composite of symptomatic or asymptomatic deep vein thrombosis, or symptomatic or fatal pulmonary embolism during the study treatment phase (up to day 14). All patients had deep vein thrombosis confirmed by bilateral contrast venography at the end of the treatment period, with the exception of patients for whom this method was not practical, and

ultrasonography was used to confirm deep vein thrombosis. Pulmonary embolism was confirmed by ventilation perfusion (VQ) or thoracic helical CT scan, or pulmonary angiography. Fatal pulmonary embolism was confirmed by autopsy. If deep vein thrombosis in an upper or lower limb or pulmonary embolism was suspected during treatment, a diagnostic algorithm was followed. For symptomatic deep vein thrombosis, compression ultrasonography (B-mode or duplex scan) of the veins of the affected limb was done within 48 h of symptom onset. A positive diagnosis of thrombosis was made on the basis of direct visualisation of the thrombus and incompressibility of the affected vein segment. Contrast venography was done with either the long-leg method²¹ or the Rabinov and Paulin method²² if an ultrasound scan was not diagnostic.

If symptomatic pulmonary embolism was suspected, a VQ lung scan was undertaken and interpreted on the basis of the standards published in the Prospective Investigation of Pulmonary Embolism Diagnosis.²³ If the results suggested an intermediate probability of pulmonary embolism or were uninterpretable, a further examination was done to confirm or reject the diagnosis, preferably with thoracic helical CT scan or pulmonary angiography, or both, or compression ultrasonography examination of the veins of the leg or a bilateral ascending venography of the legs, or both. In bilateral ascending venography, detection of a deep vein thrombosis in the legs associated with signs suggestive of pulmonary embolism led to confirmation of the diagnosis.

Secondary efficacy endpoints were occurrence of objectively verified symptomatic venous thromboembolism (deep vein thrombosis or pulmonary embolism, or both) at 30, 60, and 90 days from the time of randomisation; stroke recurrence within the study treatment period and at 30, 60, and 90 days after randomisation; stroke progression during the study treatment period identified by an increase in NIHSS score of 4 or more points from the highest previous score obtained at baseline or during study treatment that is due to additional new areas of focal brain ischaemia; NIHSS scores at days 4, 7, 10, and 14 during admission to hospital, at end of study treatment, and at the 30-day and 90-day follow-up; and modified Rankin scale scores at end of study treatment and at the 30-day and 90-day follow-up visits.

The primary safety endpoints were symptomatic intracranial haemorrhage, major extracranial haemorrhage, and all-cause mortality up to 48 h after treatment. Intracranial haemorrhages were verified by head CT scan, brain MRI scan, or autopsy, and were classified, on the basis of scan results and the patient's clinical presentation, as asymptomatic haemorrhagic transformation, symptomatic haemorrhagic transformation, primary intracerebral haemorrhage, subarachnoid haemorrhage, or subdural or epidural haemorrhage. Major extracranial haemorrhage was defined as overt

bleeding resulting either in death, drop in haemoglobin concentration of 30 g/L or more, need for transfusion of two or more units of blood, surgical intervention or decompression of closed space to stop or control the event, or bleeding in a retroperitoneal or intraocular location. Clinically important bleeding was defined post hoc as the composite of symptomatic intracranial and major extracranial haemorrhages.

Secondary safety endpoints included minor extracranial haemorrhage, thrombocytopenia, and adverse events. Minor extracranial haemorrhage was defined as any clinically overt bleeding not meeting the criteria for major extracranial haemorrhage, and associated with at least one of the following: epistaxis lasting more than 5 min or needing intervention, ecchymosis or haematoma larger than 5 cm at its widest point,

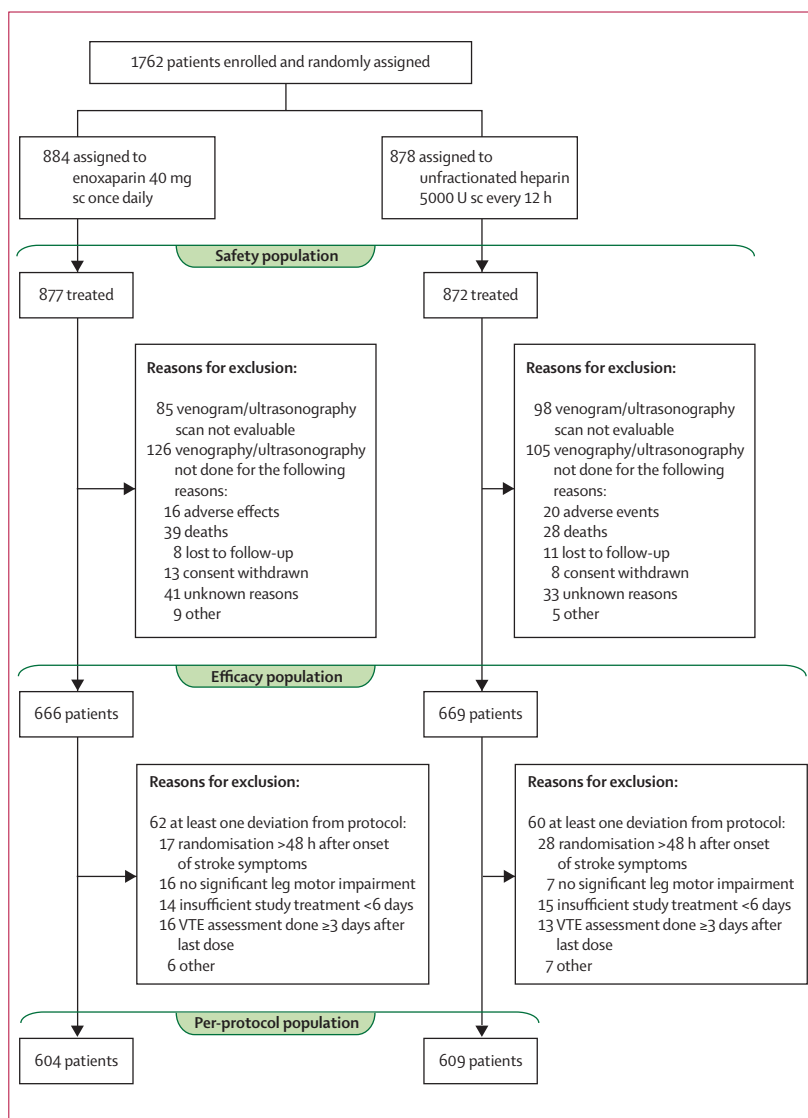


Figure 1: Trial profile

VTE=venous thromboembolism. sc=subcutaneously.

| | Enoxaparin (n=884) | Unfractionated heparin (n=878) |
|--------------------------------------|-----------------------|-----------------------------------|
| Age (years) | 65.9 (12.9) | 66.1 (12.9) |
| <65 | 371 (42%) | 372 (42%) |
| 65–75 | 312 (35%) | 265 (30%) |
| >75 | 201 (23%) | 241 (27%) |
| Male patient | 521 (59%) | 473 (54%) |
| Body-mass index (kg/m ²) | 27.0 (5.3) | 27.0 (5.3) |
| ≥30 | 179 (20%) | 183 (21%) |
| Race | | |
| White | 523 (59%) | 523 (60%) |
| Black | 68 (8%) | 55 (6%) |
| Asian | 182 (21%) | 193 (22%) |
| Hispanic | 73 (8%) | 68 (8%) |
| Others | 38 (4%) | 39 (4%) |
| NIHSS score | 11.3 (5.1) | 11.3 (5.1) |
| <14 | 648 (73%) | 626 (71%) |
| ≥14 | 236 (27%) | 252 (29%) |
| Motor leg function (NIHSS score) | | |
| 0 | 3 (<1%) | 0 |
| 1 | 16 (2%) | 10 (1%) |
| 2 | 356 (40%) | 381 (43%) |
| 3 | 316 (36%) | 293 (33%) |
| 4 | 193 (22%) | 387 (44%) |
| Risk factors for VTE | | |
| Venous stasis syndrome | 3 (<1%) | 11 (1%) |
| Varicosis | 19 (2%) | 16 (2%) |
| Previous VTE | 16 (2%) | 14 (2%) |
| Risk factors for stroke | | |
| Diabetes | 266 (30%) | 270 (31%) |
| Previous stroke | 246 (28%) | 249 (28%) |
| Hyperlipidaemia | 70 (8%) | 68 (8%) |
| Hypertension | 621 (70%) | 637 (73%) |
| Previous thrombolytic therapy | 50 (6%) | 58 (7%) |
| Concomitant antiplatelet therapy | 815 (92%) | 791 (90%) |
| Aspirin | 767 (87%) | 738 (84%) |
| Aspirin with dipyridamole | 36 (4%) | 45 (5%) |
| Clopidogrel | 189 (21%) | 174 (20%) |
| Dipyridamole | 40 (5%) | 47 (5%) |
| Ticlopidine | 28 (3%) | 28 (3%) |
| Other | 52 (6%) | 56 (6%) |

Data are number (%) or mean (SD). NIHSS=National Institutes of Health Stroke Scale. VTE=venous thromboembolism.

Table 1: Baseline characteristics

haematuria not associated with urinary catheter trauma, gastrointestinal haemorrhage not related to intubation or nasogastric tube placement, wound haematoma or haemorrhagic wound complications not associated with features of overt haemorrhage classified as major, or subconjunctival haemorrhage needing end of study treatment.

A steering committee was responsible for the design of the study, modifications to the study protocol, and

blinded adjudication of major haemorrhage events. A central adjudication committee did a blinded review of all images, including venograms, ultrasound, CT and VQ scans, and angiograms, and an independent data safety monitoring board ensured the proper conduct of the study and undertook four blinded safety data reviews before the database was locked. No modifications to the study protocol were recommended by the data safety monitoring board during the study.

Statistical analysis

The sample size was determined by assumption of a frequency of venous thromboembolism at day 14 of 20% in the unfractionated heparin group and 14% in the enoxaparin group, resulting in a 30% relative risk reduction in patients receiving enoxaparin compared with those receiving unfractionated heparin. To detect the treatment difference at the 5% (two-sided) level of significance with 80% power, and assuming an attrition rate of 30%, about 880 patients per treatment group (1760 in total) were needed.

The efficacy population was defined a priori as all randomly assigned patients who had taken one or more dose of study medication; had proven deep vein thrombosis or pulmonary embolism, or both; or had one or more contrast venography or ultrasonography assessment for venous thromboembolism during the study treatment period (10 days [range 6–14]). Venous thromboembolism assessment was allowed up to 72 h after the end of treatment; therefore, 17 days was the maximum time allotted for the final assessment. The primary outcome was also analysed in a per-protocol efficacy population consisting of all efficacy population patients who had no major protocol violations. The safety population included all patients who had taken one or more dose of study medication.

The primary efficacy analysis was done with the Cochran-Mantel-Haenszel statistic with baseline NIHSS risk group (low-risk group with NIHSS < 14 vs high-risk group with NIHSS ≥ 14) as the stratification factor. The blinded adjudicated data for venous thromboembolism were used in the analysis. χ^2 test or Fisher's exact test were used for unadjusted treatment comparisons. Time-to-event analysis for all-cause mortality was done with Cox proportional hazards model. Analyses were done with SAS statistical software (version 8.2).

This study is registered with ClinicalTrials.gov, number NCT00077805.

Role of the funding source

The protocol was written by the steering committee and revised on the basis of discussions with the sponsor (Sanofi-Aventis, Paris, France). Data were obtained by the sponsor, and data entry was undertaken by a contract research organisation (Parexel, Waltham, MA, USA). The data were maintained by the contract research organisation and analysed by the sponsor according to the statistical

| | Enoxaparin (n=666) | Unfractionated heparin (n=669) | Relative risk (95% CI)* | p† | Difference (95% CI) |
|----------------------|-----------------------|-----------------------------------|-------------------------|---------|-----------------------|
| VTE | 68 (10%) | 121 (18%) | 0.57 (0.44-0.76) | 0.0001 | -7.9% (-11.6 to -4.2) |
| PE‡ | 1 (<1%) | 6 (1%) | 0.17 (0.02-1.39) | 0.059 | -0.7% (-1.5 to 0) |
| Symptomatic VTE | 2 (<1%) | 7 (1%) | 0.29 (0.06-1.38) | 0.096 | -0.7% (-1.6 to 0.1) |
| Symptomatic DVT | 1 (<1%) | 4 (1%) | 0.25 (0.03-2.24) | 0.18 | -0.4% (-1.1 to 0.2) |
| Asymptomatic DVT§ | 66 (10%) | 114 (17%) | 0.57 (0.43-0.75) | <0.0001 | -7.1% (-10.8 to -3.5) |
| All DVT | 67 (10%) | 118 (18%) | 0.57 (0.43-0.75) | <0.0001 | -7.6% (-11.3 to -3.9) |
| Proximal | 30 (5%) | 64 (10%) | 0.47 (0.31-0.72) | 0.0003 | -5.1% (-7.8 to -2.3) |
| Distal | 44 (7%) | 85 (13%) | 0.52 (0.37-0.74) | 0.0002 | -6.1% (-9.2 to -2.9) |
| Proximal and distal¶ | 7 (1%) | 31 (5%) | 0.23 (0.10-0.51) | <0.0001 | -3.6% (-5.4 to -1.8) |

Data are number (%) unless otherwise indicated. DVT=deep vein thrombosis. PE=pulmonary embolism. VTE=venous thromboembolism. The individual numbers of events for each endpoint do not always add up to the total number because patients might have had more than one type of event. *Enoxaparin versus unfractionated heparin.

†Adjusted for National Institutes of Health Stroke Scale score stratification for VTE, but unadjusted for other criteria. ‡Three PE events were fatal (one with enoxaparin and two with unfractionated heparin). §Confirmed by ultrasound: five of 66 (8%) enoxaparin, nine of 114 (8%) unfractionated heparin; confirmed by venography: 61/66 (92%) enoxaparin, 104/114 (91%) unfractionated heparin. ¶Events also counted in proximal DVT and distal DVT.

Table 2: Incidence of venous thromboembolic events up to day 14 in the efficacy group

analysis plan, which was reviewed by the steering committee. The steering committee had full access to the data and vouches for its integrity and completeness. The statistician (MC) did all data analyses and vouches for the accuracy of the analyses. The steering committee was responsible for interpretation of the data and in the decision to submit for publication.

Results

In total, 1762 acute ischaemic stroke patients were randomly assigned between August, 2003, and April, 2006, at 200 centres in 15 countries (Australia, Austria, Brazil, Canada, Colombia, Czech Republic, India, Israel, Italy, South Korea, Mexico, Poland, South Africa, Turkey, and USA). Figure 1 shows the trial profile. Of the randomised patients, 13 (seven in enoxaparin group and six in unfractionated heparin group) did not receive study treatment and were not included in the safety or efficacy populations. A further 414 patients (211 in enoxaparin group and 203 in unfractionated heparin group) were not included in the efficacy population. The primary outcome was assessed in 1096 (82%) patients by venography alone (41% in both treatment groups), 182 (14%) by ultrasonography alone (7% in both groups), and 49 (4%) with both venography and ultrasonography (2% in both groups). The mean time until venography was 10.5 days (SD 3.2) in each group.

Table 1 shows baseline characteristics. In the efficacy population, the mean duration of prophylaxis was 10.5 days (3.2) for both treatment groups. The mean duration from index stroke to initiation of prophylaxis was 1.2 days (0.8) for enoxaparin and 1.2 days (0.7) for unfractionated heparin. In both groups, a similar number of patients received either aspirin or platelet inhibitors, or both, for more than 6 days after randomisation (726 [82%] with enoxaparin and 698 [80%] with unfractionated heparin).

Enoxaparin significantly reduced the frequency of venous thromboembolism in the efficacy population at

| | NIHSS score <14 | | NIHSS score ≥14 | |
|------------|---------------------|-------|---------------------|-------|
| | Occurrence (95% CI) | p | Occurrence (95% CI) | p |
| VTE | | | | |
| Enoxaparin | 8.3% (5.90-10.70) | 0.004 | 16.3% (10.53-21.97) | 0.004 |
| UFH | 14.0% (10.91-17.02) | | 29.7% (22.94-36.49) | |
| DVT | | | | |
| Enoxaparin | 8.1% (5.73-10.48) | 0.005 | 16.3% (10.53-21.97) | 0.005 |
| UFH | 13.6% (10.54-16.58) | | 29.1% (22.41-35.88) | |

UFH=unfractionated heparin.

Table 3: Occurrence of venous thromboembolism (VTE) and deep vein thrombosis (DVT) according to National Institutes of Health Stroke Scale (NIHSS)

| | NIHSS score <14 | | NIHSS score ≥14 | |
|--|----------------------|------|-----------------------|------|
| | Occurrence (95% CI) | p | Occurrence (95% CI) | p |
| Total | | | | |
| Enoxaparin | 6.2% (4.34 to 8.06) | 0.96 | 12.5% (8.24 to 16.76) | 0.97 |
| UFH | 6.3% (4.36 to 8.18) | | 12.4% (8.31 to 16.49) | |
| Clinically significant intracranial | | | | |
| Enoxaparin | 0.3% (-0.12 to 0.74) | 0.97 | 0.9% (-0.33 to 2.05) | 0.47 |
| UFH | 0.3% (-0.12 to 0.77) | | 1.6% (0.04 to 3.16) | |
| Major extracranial | | | | |
| Enoxaparin | 0.5% (-0.06 to 0.99) | 0.09 | 1.7% (0.05 to 3.40) | 0.04 |
| UFH | 0 | | 0 | |
| Clinically important | | | | |
| Enoxaparin | 0.8% (0.10 to 1.45) | 0.28 | 2.6% (0.54 to 4.63) | 0.45 |
| UFH | 0.3% (-0.12 to 0.77) | | 1.6% (0.04 to 3.16) | |

Clinically important bleeding is defined as the composite of major extracranial and symptomatic intracranial haemorrhages. UFH=unfractionated heparin.

Table 4: Occurrence of haemorrhage according to National Institutes of Health Stroke Scale (NIHSS)

day 14 compared with unfractionated heparin (relative risk [RR] reduction 43%; difference -7.9%, 95% CI -11.6 to -4.2; table 2). Similar results were seen in the per-protocol population (62 [10%] vs 112 [18%], respectively;

RR 0.56, 0.42–0.75, $p=0.0001$; difference -8.1% , -12.0 to -4.2). The relative reduction of risk of venous thromboembolism seen with enoxaparin, compared with un-

fractionated heparin, was maintained at day 30 (70 [11%] vs 121 [18%], $p<0.0001$), day 60 (70 [11%] vs 122 [18%], $p<0.0001$), and at day 90 (70 [11%] vs 122 [18%], $p<0.0001$).

The reduction in the risk of venous thromboembolism with enoxaparin compared with unfractionated heparin at day 14 was consistent for both total deep vein thrombosis (RR reduction 43%) and proximal deep vein thrombosis (53%; table 2). There was a non-significant 83% reduction in the risk of pulmonary embolism (table 2).

The incidence of symptomatic venous thromboembolism did not significantly differ between the enoxaparin and unfractionated heparin groups at days 14 (table 2), 30 (one [0.2%] vs three [0.4%], $p=0.62$), 60 (one [0.2%] vs one [0.2%], $p=1.0$), and 90 (one [0.2%] vs 0, $p=0.50$).

The occurrence of venous thromboembolism was higher for patients with an NIHSS score of 14 or more than for those with a score of less than 14 (table 3). Compared with unfractionated heparin, enoxaparin reduced the frequency of venous thromboembolism for patients with an NIHSS score less than 14 (RR 0.59, 95% CI 0.41–0.85, $p=0.0043$; difference -5.7% , -9.6 to -1.8%), and for those with an NIHSS score of 14 or more (0.55, 0.36–0.83, $p=0.0036$; difference -13.5% , -22.3 to -4.6 ; figure 2). A post-hoc analysis of the major subgroups showed consistent reductions of the risk of venous thromboembolism by enoxaparin compared with unfractionated heparin (figure 2).

The occurrence of any bleeding at the end of treatment plus up to 48 h afterwards was similar between groups (table 5). The frequency of symptomatic intracranial haemorrhage was also similar between groups, and the incidence of major extracranial haemorrhage was higher

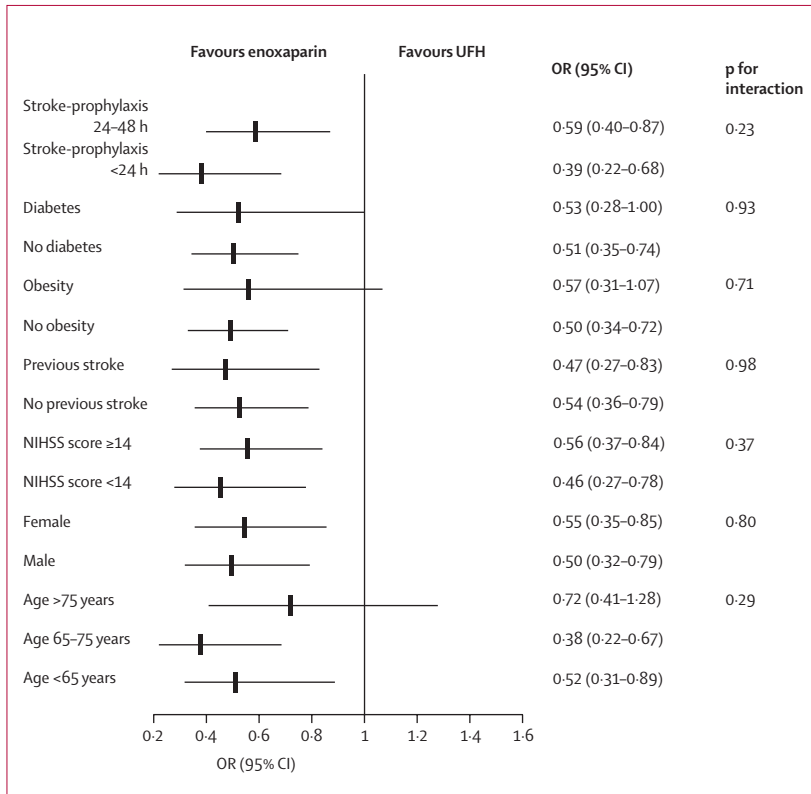


Figure 2: Forest plot for risk for venous thromboembolism in patients with acute ischaemic stroke by patient characteristics for enoxaparin and unfractionated heparin
NIHSS=National Institutes of Health Stroke Scale. OR=odds ratio. UFH=unfractionated heparin.

| | Enoxaparin (n=877) | Unfractionated heparin (n=872) | Relative risk (95% CI) | p* | Difference (95% CI) |
|--|--------------------|--------------------------------|------------------------|--------|----------------------|
| Bleeding at end of treatment + 48 h | | | | | |
| Total† | 69 (8%) | 70 (8%) | 0.98 (0.71-1.35) | 0.90 | -0.2% (-2.7% to 2.4) |
| Symptomatic intracranial haemorrhage | 4 (1%) | 6 (1%) | 0.66 (0.19-2.34) | 0.55 | -0.2% (-0.9% to 0.5) |
| Death of patient with symptomatic intracranial haemorrhage | 3 (<1%) | 4 (1%) | .. | .. | -0.1% (-0.7% to 0.5) |
| Major extracranial haemorrhage‡ | 7 (1%) | 0 | .. | 0.015 | 0.8% (0.2% to 1.4) |
| Resulting in death | 2 (<1%) | 0 | .. | .. | 0.2% (-0.1% to 0.5) |
| Drop of haemoglobin ≥30 g/L | 7 (1%) | 0 | .. | .. | 0.8% (0.2% to 1.4) |
| Transfusion of ≥2 units of blood | 5 (1%) | 0 | .. | .. | 0.6% (0.1% to 1.1) |
| Clinically important haemorrhage | 11 (1%) | 6 (1%) | 1.82 (0.68-4.91) | 0.23 | 0.6% (-0.4% to 1.5) |
| Death of patient with clinically important haemorrhage§ | 5 (1%) | 4 (1%) | 1.24 (0.33-4.65) | 1.0 | 0.1% (-0.6% to 0.8) |
| Minor extracranial haemorrhage¶ | 42 (5%) | 48 (6%) | 0.87 (0.58-1.30) | 0.50 | -0.7% (-2.8% to 1.4) |
| All-cause mortality up to day 14 | 48 (6%) | 45 (5%) | 1.12 (0.75-1.69) | 0.58** | .. |
| All-cause mortality up to day 90 | 100 (12%) | 103 (12%) | 1.01 (0.77-1.33) | 0.96** | .. |

Data are number (%) unless otherwise indicated. *Fisher's exact test if $n<6$ in one group. χ^2 test if $n\geq 6$ in one group. †Some patients had more than one bleeding event. ‡Three were gastrointestinal bleeding, one surgical stoma of tracheostomy, one duodenal ulcer haemorrhage, one haematuria, and one haemoglobin decrease. §Defined as the composite of major extracranial and symptomatic intracranial haemorrhages. ¶All intracranial haemorrhages were regarded as major. ||Hazard ratio. **Log-rank test.

Table 5: Safety outcomes

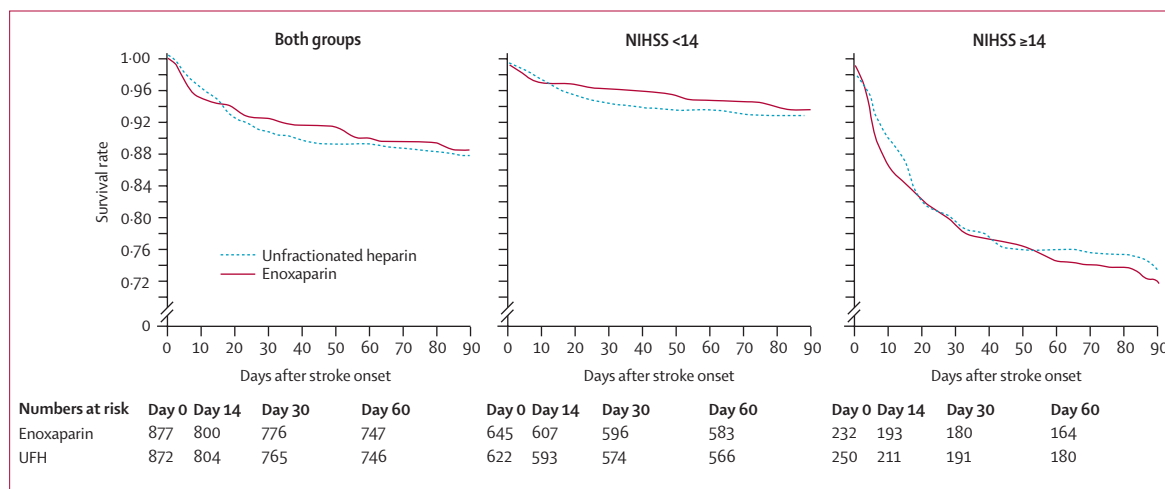


Figure 3: Kaplan-Meier survival analysis in the enoxaparin and unfractionated heparin groups
UFH=unfractionated heparin.

with enoxaparin than with unfractionated heparin (table 5). The incidence of clinically important haemorrhage was small and did not differ between groups. There were no differences in deaths of patients with clinically important haemorrhage between groups.

The occurrence of any bleeding was about two-fold higher for patients with a score of 14 or more than for those with a score less than 14 (table 4). No significant differences in the occurrence of any bleeding or symptomatic intracranial haemorrhage were noted between the enoxaparin and unfractionated heparin groups (table 4). There was a higher incidence of major extracranial haemorrhages in the enoxaparin group than in the unfractionated heparin group. This difference was significant for patients with an NIHSS score of 14 or more but not significant for those with an NIHSS score less than 14 (table 4). The incidence of clinically important haemorrhage was similar between the enoxaparin and unfractionated heparin groups (table 5).

All-cause mortality rate up to day 14 and 90 did not differ in the enoxaparin and unfractionated heparin groups (table 5). Kaplan-Meier analysis (figure 3) showed no differences in the survival of patients who received enoxaparin or unfractionated heparin, or for those with an NIHSS score less than 14 or 14 or more.

The rate of mortality for reasons other than venous thromboembolism, stroke, or haemorrhage was similar in the enoxaparin group (67 [8%]) and unfractionated heparin group (73 [8%]).

Discussion

We have shown that enoxaparin 40 mg subcutaneously once daily is significantly more effective than unfractionated heparin 5000 U subcutaneously every 12 h for the prevention of venous thromboembolism in patients with acute ischaemic stroke, and noted a consistent reduction in the risk of proximal deep vein thrombosis.

The risk of pulmonary embolism was lower in patients receiving enoxaparin than in those receiving unfractionated heparin, although this difference was not significant. The magnitude of the risk reduction for venous thromboembolism was maintained at least up to 90 days.

The occurrence of symptomatic intracranial haemorrhage, a complication of major importance to physicians treating patients with acute ischaemic stroke, was similar between groups. Although the incidence of major extracranial haemorrhage was significantly higher in the enoxaparin group than in the unfractionated heparin group, these bleeding events, which were mainly gastrointestinal, did not lead to increased mortality. We also assessed clinically important bleeding, a combined endpoint defined post hoc to be used as a meaningful way for clinicians to adequately balance benefits and risks of treatment of patients with acute ischaemic stroke. Similar criteria have been used in several studies of venous thromboembolism prophylaxis.²⁴ There was a low frequency of clinically important bleeding with no significant difference between groups.

Although the occurrence of venous thromboembolism was about two-fold higher in patients with an NIHSS score of 14 or more than in those with a score less than 14 (in line with previous studies²⁵), a similar reduction in venous thromboembolism risk with enoxaparin versus unfractionated heparin was noted in both groups of patients. This consistent reduction of risk was also seen in patients with acute ischaemic stroke and diabetes, obesity, a previous stroke, age younger than 65 years, 65–75 years, or older than 75 years, and was not dependent on sex. Importantly, a delay in initiation of prophylaxis for up to 48 h after the onset of stroke did not affect the reduction in venous thromboembolism risk with enoxaparin compared with unfractionated heparin.

Previous studies suggested that low molecular weight heparin was either at least as effective as, or more effective

than, unfractionated heparin for reduction of the risk of venous thromboembolism in patients with acute ischaemic stroke.^{15,16} Our data confirm the preliminary observations reported by Hillbom and colleagues.¹⁶ These investigators compared venous thromboembolism prophylaxis with a 40 mg once daily dose of enoxaparin versus unfractionated heparin 5000 IU three times daily in 212 acute ischaemic stroke patients. In the efficacy analysis (n=148), patients given enoxaparin had fewer venous thromboembolism events than did those receiving unfractionated heparin (20% vs 35%, absolute difference 15%, 95% CI 0·8–29·2, p=0·044). However, that study was not designed to show that enoxaparin is better than unfractionated heparin for reduction in venous thromboembolism risk. Furthermore, both studies used venography to screen for deep vein thrombosis and had a similar duration of prophylaxis (6–14 days). The overall mortality rate in Hillbom and co-workers' study¹⁶ was higher than that reported in our study, which might partly be explained by improvement of patient care in recent years.

Diener and colleagues¹⁵ showed that the frequency of a composite endpoint of proximal deep vein thrombosis, pulmonary embolism, or death related to venous thromboembolism did not differ significantly for patients with acute ischaemic stroke receiving certoparin 3000 U once daily compared with those receiving unfractionated heparin 5000 U thrice daily (7% vs 10%, p=0·0011 for non-inferiority). However, there were some notable differences in design between our study and that of Diener and co-workers.¹⁵ The Diener study was not designed to show whether low molecular weight heparin was better than unfractionated heparin for prevention of venous thromboembolism, and used duplex or compression ultrasonography rather than venography for screening proximal deep vein thrombosis.¹⁵ Additionally, the index stroke was less severe (mean baseline NIHSS score 8·2–8·8) than it was for patients in our study (mean baseline NIHSS score 11·3), and the duration of prophylaxis was longer (12–16 days).

A potentially important difference between the PREVAIL study and many of the previous trials was the choice of the unfractionated heparin dosing regimen. In previous studies,^{15,16} a three times daily unfractionated heparin regimen was used, whereas we chose a twice daily regimen. After careful review of existing published work and the absence of a direct comparison of twice daily and three times daily unfractionated heparin regimens or precise guidance in international consensus guidelines, we selected a twice daily regimen. This decision was based on a meta-analysis showing that both regimens of the drug are effective in reducing the risk of venous thromboembolism compared with placebo or no prophylaxis (60% reduction in risk with unfractionated heparin twice daily and 72% three times daily),²⁶ and studies suggesting that unfractionated heparin three times daily might have a less favourable safety profile than has low molecular weight heparin.^{27,28}

Hillbom's findings¹⁶ also showed a trend towards more haemorrhagic transformation of acute ischaemic stroke in patients receiving unfractionated heparin thrice daily than in those receiving enoxaparin. As a result, physicians use varied prophylactic regimens for patients with stroke, including a twice daily unfractionated heparin regimen. Since this study did not compare low molecular weight heparin with unfractionated heparin thrice daily, the risk reduction for efficacy and safety for these prophylactic regimens is difficult to conclude, although there was a similar 43% relative risk reduction for venous thromboembolism in both our study and that of Hillbom.¹⁶ On the basis of our data, the number needed to treat to avoid one venous thromboembolism is 13 whereas the number needed to harm as a result of clinically important bleeding is 173, showing a clear net clinical benefit in favour of enoxaparin for prophylaxis of venous thromboembolism in patients with acute ischaemic stroke. Furthermore, the significant reduction in the incidence of venous thromboembolism also indicated a significant reduction in proximal deep vein thrombosis with enoxaparin compared with unfractionated heparin. This result has important clinical implications as there is a strong predictive correlation between proximal deep vein thrombosis and the risk of symptomatic venous thromboembolism.²⁹

A limitation of our study was its open-label design. An open-label study is subject to bias in the declaration of potential endpoints. In PREVAIL, the primary efficacy endpoint of venous thromboembolism was composed largely of asymptomatic events that were assessed systematically. Neurological worsening, which included an increase in the NIHSS score of 4 or more points, triggered assessment of possible symptomatic intracranial haemorrhages. All endpoints were adjudicated by a central, blinded adjudication committee. Furthermore, as in many other similar studies, symptomatic deep vein thrombosis and pulmonary embolism events might have been under-reported, especially in this high-risk population of patients who probably have confounding diagnoses.

Enoxaparin is preferable to unfractionated heparin for venous thromboembolism prophylaxis in this high-risk medically ill patient population in view of its better clinical benefits to risk ratio and convenience of once daily administration.

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Contributors

All authors participated in the study design, collection of data, interpretation of results, and writing and critically reviewing or revising the report. All authors have seen and approved the final version of the report, and were fully responsible for content and editorial decisions.

Conflict of interest statement

All authors were members of the PREVAIL study steering committee. DS has received honoraria from Sanofi-Aventis for speaker bureau and consultancy. CK has received honoraria for membership of speaker bureaus for Boehringer-Ingelheim and Sanofi-Aventis, and from Organon for consultancy. WO'R was a principal investigator at a study site for both PREVAIL and EXCLAIM studies (sponsored by Sanofi-Aventis). GP has received honoraria from Sanofi-Aventis, Pfizer, BMS, and Leo for consultancy. GA has been a member of scientific advisory boards and a principal investigator in clinical trials funded by AstraZeneca, Sanofi-Aventis, Novartis, and Boehringer Ingelheim.

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