Venous Thromboembolism Risk in Ischemic Stroke Patients Receiving Extended-Duration Enoxaparin Prophylaxis: Results From the EXCLAIM Study

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Background and Purpose—The optimal duration of venous thromboembolism prophylaxis in acute stroke patients is unknown. This subanalysis of the Extended Prophylaxis for Venous ThromboEmbolism in Acutely Ill Medical Patients With Prolonged Immobilization (EXCLAIM) study investigated extended-duration thromboprophylaxis with enoxaparin, compared with placebo following standard-duration enoxaparin, in ischemic stroke patients.

Methods—Acutely ill medical patients with recently reduced mobility received open-label enoxaparin 40 mg for 10±4 days, and they were then randomized to double-blind enoxaparin 40 mg daily or placebo for further 28±4 days. Venous thromboembolism incidence (symptomatic/asymptomatic deep-vein thrombosis, symptomatic/fatal pulmonary embolism) up to day 28 after randomization and major bleeding rates up to 48 h after the last dose of study treatment were reported.

Results—In total, 389 of 5963 (6.5%) randomized patients had ischemic stroke: 198 received extended-duration prophylaxis and 191 placebo. Extended-duration prophylaxis reduced venous thromboembolism incidence versus placebo (2.4% versus 8.0%; absolute risk difference, −5.6%; 95% CI, −10.5% to −0.7%), but it was associated with an increase in major bleeding (1.5% versus 0% in enoxaparin and placebo groups; absolute risk difference, +1.5%; 95% CI, −0.2% to 3.2%).

Conclusion—Extended-duration thromboprophylaxis with enoxaparin was associated with reduced venous thromboembolism risk and increased major bleeding in the subgroup of patients with ischemic stroke in the EXCLAIM study.


Key Words: anticoagulants ■ cerebrovascular disease/stroke ■ deep-vein thrombosis

A
cute ischemic stroke patients are at high risk of developing deep-vein thrombosis (DVT) and pulmonary embolism (PE), which are the major causes of mortality and morbidity in these patients.1,2 Some consensus guidelines recommend venous thromboembolism (VTE) prophylaxis with unfractionated heparin or low-molecular-weight heparins in acute stroke patients with restricted mobility, although there is no guidance on prophylaxis duration.2

The EXCLAIM (EXtended CLinical prophylaxis in Acutely Ill Medical patients) study reported that extended-duration enoxaparin (for a further 28 days after standard 10-day enoxaparin prophylaxis) reduced the risk of VTE but increased major bleeding complications. Women, older patients (>75 years), and sedentary patients experienced reduction in risk of VTE.1 This subanalysis assessed the risk of VTE and bleeding with extended-duration enoxaparin prophylaxis in patients with acute ischemic stroke.

Methods

The international, multicenter, prospective, double-blind randomized controlled EXCLAIM trial has been previously reported.3 Patients aged over 40 years, hospitalized for an acute medical illness with recent reduced mobility for a maximum of 3 days and an anticipated mobility reduction for a further 3 days, were eligible.3 Eligibility criteria were amended after a planned interim analysis (Supplementary Appendix).

Enrolled patients received open-label subcutaneous enoxaparin 40 mg daily for 10±4 days. Patients were then double-blind randomized to subcutaneous enoxaparin 40 mg daily or placebo for a further 28±4 days.

The primary efficacy end point was centrally adjudicated VTE, defined as the composite of symptomatic or asymptomatic proximal
DVT, symptomatic PE, or fatal PE, during the double-blind period of extended prophylaxis.

The primary safety end point was the incidence of major hemorrhagic complications during, and up to 48 h after, the double-blind treatment period.

**Statistical Analyses**

VTE and bleeding events were compared between groups using chi-square and Fisher exact tests. Univariate and multivariate logistic regression models were employed to look at the association between VTE and risk factors. Cox proportional hazard models were used to analyze the relationship between treatment and all-cause mortality.

**Results**

A total of 389 ischemic stroke patients were identified: in the safety population, 198 patients received extended-duration enoxaparin and 191 received placebo; in the efficacy population, 166 patients received extended-duration enoxaparin and 150 received placebo (Supplementary Appendix, Figure 1). The mean age was 68.1 years (66.9 years in the enoxaparin group; 69.4 years in the placebo group).

In ischemic stroke patients, extended-duration prophylaxis with enoxaparin was associated with a reduction in the incidence of VTE at 1 month compared with placebo (2.4% versus 8.0%, respectively, Table 1). No cases of symptomatic VTE were observed in patients who received extended-duration enoxaparin during the double-blind phase versus 2 events (both symptomatic DVT) in those who received placebo (Table 1). There was one fatal PE in the placebo group.

Major bleeding occurred in 1.5% (3/198) of patients who received extended-duration prophylaxis versus none in the placebo (Table 1). There was one fatal intracranial bleeding event and a trend toward increased rates of total bleeding in patients receiving extended-duration enoxaparin (Table 1).

Prior VTE and obesity were associated with an increased rate of VTE (Supplementary Appendix, Table 1). In the multivariate analysis, only prior VTE was an independent predictor of VTE (P=0.0088). The multivariate model indicated that the adjusted odds ratio for treatment effect was 0.32, versus 0.28 unadjusted, suggesting that any imbalance in well-recognized VTE risk factors between the treatment groups has a very limited impact on treatment effect.

**Discussion**

This subanalysis showed that extended-duration prophylaxis with enoxaparin reduced the VTE incidence and increased major bleeding in the subgroup of patients with ischemic stroke in the EXCLAIM study. Without VTE prophylaxis, ischemic stroke patients remain at high risk of VTE for at least 1 month after the index stroke.

Our findings support earlier data that the risk of VTE is reduced when stroke patients receive extended-duration VTE prophylaxis.4–6 Stroke patients often experience long periods of immobility, a known risk factor for VTE.4,6 Autopsy evidence suggests that while fatal PEs are rare in the first week after a stroke, they are most frequent, and become the main cause of mortality, in the second-to-fourth weeks after the stroke.7,8 A previous study reported that prolonged thromboprophylaxis during stroke rehabilitation may reduce the incidence of VTE in stroke patients.5

Prior VTE was predictive of post–stroke VTE in a multivariate analysis. This subanalysis suggests that extended thromboprophylaxis is associated with a reduced risk of VTE and an increase in major bleeding in ischemic stroke patients. The

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**Table 1. Efficacy and Safety End Points During the Double-Blind Treatment Phase in Ischemic Stroke Patients**

<table>
<thead>
<tr>
<th>Parameter, n (%)</th>
<th>Extended-Duration Enoxaparin*</th>
<th>Placebo*</th>
<th>Absolute Difference (%) (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE at day 28 (Efficacy Population)</td>
<td>n=166</td>
<td>n=150</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE all</td>
<td>4 (2.4)</td>
<td>12 (8.0)</td>
<td>−5.6 (−10.5 to −0.7)</td>
<td>0.0236</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td>−0.7 (−2.0 to 0.6)</td>
<td>0.4747</td>
</tr>
<tr>
<td>DVT</td>
<td>4 (2.4)</td>
<td>11 (7.3)</td>
<td>−4.9 (−9.7 to −0.1)</td>
<td>0.0398</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>0 (0.0)</td>
<td>2 (1.3)</td>
<td>−1.3 (−3.2 to 0.5)</td>
<td>0.1356</td>
</tr>
<tr>
<td>Asymptomatic DVT</td>
<td>4 (2.4)</td>
<td>9 (6.0)</td>
<td>−3.6 (−8.0 to 0.9)</td>
<td>0.1086</td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>0 (0.0)</td>
<td>2 (1.3)</td>
<td>−1.3 (−3.2 to 0.5)</td>
<td>0.1356</td>
</tr>
<tr>
<td>All-cause mortality (Safety Population)</td>
<td>n=198</td>
<td>n=191</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-day</td>
<td>5 (2.6)</td>
<td>8 (4.2)</td>
<td>−1.7 (−5.2 to 1.9)</td>
<td>0.369</td>
</tr>
<tr>
<td>90-day</td>
<td>8 (4.0)</td>
<td>11 (5.8)</td>
<td>−1.7 (−6.0 to 2.6)</td>
<td>0.440</td>
</tr>
<tr>
<td>180-day</td>
<td>10 (5.0)</td>
<td>12 (6.3)</td>
<td>−1.2 (−5.8 to 3.4)</td>
<td>0.606</td>
</tr>
<tr>
<td>Bleeding (Safety Population)</td>
<td>n=198</td>
<td>n=191</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12 (6.1)†</td>
<td>5 (2.6)</td>
<td>3.4 (−0.6 to 7.5)</td>
<td>0.0972</td>
</tr>
<tr>
<td>Major (hemoglobin decrease ≥2 g/dL)§</td>
<td>3 (1.5)</td>
<td>0 (0.0)</td>
<td>1.5 (−0.2 to 3.2)</td>
<td>0.0881</td>
</tr>
<tr>
<td>Minor</td>
<td>9 (4.5)</td>
<td>5 (2.6)</td>
<td>1.9 (−1.7 to 5.6)</td>
<td>0.3082</td>
</tr>
</tbody>
</table>

CI, confidence interval; DVT, deep-vein thrombosis; VTE, venous thromboembolism.

*Two patients in the extended-duration enoxaparin group and 3 patients in the placebo group had a recurrent ischemic stroke during the double-blind period.

†Two patients had intracranial bleeding (one was a fatal event); 1 patient had gastrointestinal bleeding.

§Results were the same with the ≥3 g/dL hemoglobin decrease thresholds for major bleeding.
question on the optimal duration of VTE prevention in this patient group remains open, calling for additional studies in this setting.

Conclusions
Ischemic stroke patients with reduced mobility remain at high risk for VTE for at least 1 month following the index stroke. In the subgroup of patients with ischemic stroke, extended-duration prophylaxis with enoxaparin was associated with a reduction in the incidence of VTE and an increase in major bleeding.

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The EXCLAIM study was sponsored by Sanofi. The authors received editorial/writing support in the preparation of this article, which was funded by Sanofi.

Disclosures
Dr Turpie has worked as a consultant for Sanofi, Bayer, J&J, Astellas, Merck, Takeda, and Portola and has received speaker’s bureau fees from Bayer, BMS/Pfizer, Boehringer-Ingehelm, J&J, GSK, and Sanofi; Dr Hull has worked as a consultant for Sanofi; has received honoraria from Sanofi, Leo Pharma, GSK, Bayer, and Pfizer; Dr Schellong has worked as a consultant and received honoraria for lectures from Sanofi, Boehringer-Ingehelm, Bayer, Daiichi Sankyo, BMS, and Pfizer; Dr Tapson has worked as a consultant and received grant support from Sanofi and Bayer; has worked as a consultant for Covidien, Bacchus, and Biolex and has received honoraria from Sanofi, Eisai, and Genentech; Dr Monreal has received consultant fees from Bayer and Boehringer-Ingehelm and honoraria from Sanofi; Dr Samama has worked as a consultant for Sanofi, Eli Lilly, Pfizer, Boehringer-Ingehelm, and BMS and has received honoraria from GSK, Sanofi, BMS, and Bayer; Dr Chen is an employee of Sanofi US; Dr Yusen has worked as a consultant for Sanofi, has received honoraria from Sanofi and SCIOS, and has received research funding/grant support from Bayer, Pfizer, Amgen, ParinGenix, and Sanofi.

References
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SUPPLEMENTAL MATERIAL

Interim analysis

After a planned interim analysis, eligibility criteria were amended for patients with level 2 immobility (total bed rest or sedentary with bathroom privileges) to include only those with additional VTE risk factors: age >75 years, a history of VTE, or active or prior cancer.

For further reference please see:


Assessment of outcomes

The primary efficacy endpoint was assessed in the total efficacy population that included all randomized patients who received at least one dose of study medication during the double-blind treatment period, had a confirmed VTE within 7 days after cessation of study treatment, or had at least one interpretable ultrasound evaluation during the double-blind treatment period (day 28±4). Bleeding parameters were assessed in the total safety population, which included the sub-
populations of all randomized ischemic stroke patients and all acutely medically ill non-stroke patients who received at least one dose of study medication during the double-blind period.

**Results – bleeding during open-label treatment**

During the open-label phase of the study, 29/454 (6.4%) patients experienced bleeding, of which 6 (1.3%) was adjudicated as major bleeding and 23 (5.1%) were classified as minor bleeds.

**Study limitations**

There are limitations to this subanalysis. The small sample size and low event rates may reduce the statistical power of comparisons between treatment groups. Intracranial bleeding was not assessed by systematic computerized tomography scans. Stroke severity was measured by the level of resulting immobility instead of using specific scale scores such as the National Institute of Health Stroke Scale or the modified Rankin scale scores. This may limit the generalizability of our findings and restricts our ability to comment on the comparative benefits of extended-duration enoxaparin thromboprophylaxis in patients with severe, compared with less severe, ischemic stroke.

**Enrolling Investigators:**


Israel – A. Shlomo Berliner, G. Lugassy, M. Ellis, B. Brenner.


**United Kingdom** – A. Cohen, M. Gormley, A.J. Moriarty.


_Underlined names_ indicate national coordinators.
Table 1. Univariate analysis of the incidence of VTE at day 30 in ischemic stroke patients with associated risk factors.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>n (N)</th>
<th>Rate (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (158)</td>
<td>5.1</td>
<td>1.0000</td>
</tr>
<tr>
<td>Female</td>
<td>8 (158)</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td><strong>Age &gt;75 y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 (91)</td>
<td>5.5</td>
<td>0.8241</td>
</tr>
<tr>
<td>No</td>
<td>11 (225)</td>
<td>4.9</td>
<td></td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0 (15)</td>
<td>0.0</td>
<td>0.9794</td>
</tr>
<tr>
<td>No</td>
<td>16 (301)</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic heart failure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0 (18)</td>
<td>0.0</td>
<td>0.9774</td>
</tr>
<tr>
<td>No</td>
<td>16 (298)</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td><strong>History of VTE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (12)</td>
<td>25.0</td>
<td>0.0055</td>
</tr>
<tr>
<td>No</td>
<td>13 (304)</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (71)</td>
<td>9.9</td>
<td>0.0440</td>
</tr>
<tr>
<td>No</td>
<td>9 (245)</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td><strong>Venous insufficiency</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>4 (40)</td>
<td>10.0</td>
<td>0.1388</td>
</tr>
<tr>
<td>No</td>
<td>12 (276)</td>
<td>4.3</td>
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**Chronic respiratory failure**

<table>
<thead>
<tr>
<th>Yes</th>
<th>2 (14)</th>
<th>14.3</th>
<th>0.1288</th>
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<tr>
<td>No</td>
<td>14 (302)</td>
<td>4.6</td>
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**Immobilization level**

<table>
<thead>
<tr>
<th>Level 1 immobility*</th>
<th>11 (232)</th>
<th>4.7</th>
<th>0.6650</th>
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<tr>
<td>Level 2 immobility†</td>
<td>5 (84)</td>
<td>6.0</td>
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</table>

**Number of risk factors experienced**

<table>
<thead>
<tr>
<th>No risk factor</th>
<th>3 (137)</th>
<th>2.2</th>
<th>0.0885</th>
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<tbody>
<tr>
<td>One risk factor</td>
<td>8 (115)</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>Two risk factors</td>
<td>2 (45)</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>Three or more risk factors</td>
<td>3 (19)</td>
<td>15.8</td>
<td></td>
</tr>
</tbody>
</table>

VTE, venous thromboembolism

* Total bed rest or sedentary patients without bathroom privileges

† Level 1 with bathroom privileges
Figure 1. EXCLAIM ischemic stroke population

* Randomized patients receiving at least one dose of enoxaparin or placebo

† Randomized patients receiving at least one dose of enoxaparin or placebo and evaluable for the primary efficacy endpoint

7500 patients enrolled

7415 received open-label prophylaxis

6085 patients randomized

5963 patients randomized and receiving at least one dose of enoxaparin or placebo

389 ischemic stroke patients

5574 non-ischemic stroke patients

198 received extended-duration enoxaparin

191 received placebo

2777 received extended-duration enoxaparin

2797 received placebo

166 received extended-duration enoxaparin

150 received placebo

2319 received extended-duration enoxaparin

2360 received placebo

n = 85 excluded
Adverse events: 2
Lost to follow-up: 5
Died: 4
Withdrew consent: 38
Other: 26
Progressive disease: 1
Missing data: 9

n = 1331 excluded
Adverse events: 312
Lost to follow-up: 35
Died: 70
Withdrew consent: 332
Other: 512
Progressive disease: 70

n = 122 excluded
Adverse events: 5
Lost to follow-up: 19
Died: 11
Withdrew consent: 32
Other: 20
Progressive disease: 1
Missing data: 34