Impact of age on the efficacy and safety of extended-duration thromboprophylaxis in medical patients

Subgroup analysis from the EXCLAIM randomised trial

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Summary

The EXCLAIM study enrolled hospitalized acutely ill medical patients with age ≥40 years and recently-reduced mobility into a trial of extended-duration anticoagulant thromboprophylaxis. This post-hoc analysis evaluated the impact of age on patient outcomes. After completion of open-label therapy with enoxaparin 40 mg once-daily (10 ± 4 days), eligible patients underwent randomisation to receive double-blind therapy of enoxaparin (n=2,975) or placebo (n=2,988) for 28 ± 4 days. During follow-up, the venous thromboembolism (VTE) risk increased with age in both treatment groups. In patients with age ≥75 years, those who received extended-duration enoxaparin had lower incidence of VTE (2.5% vs 6.7%; absolute difference [AD] [95% confidence interval]: −4.2% [−6.5, −2.0]), proximal deep-vein thrombosis (2.5% vs 6.6%; AD −4.1% [−6.2, −2.0]), and symptomatic VTE (0.3% vs 1.5%; AD −1.2% [−2.2, −0.3]), in comparison to those who received placebo. In patients with age ≤75 years, those who received enoxaparin had reduced VTE (2.4% vs 2.8%; AD −0.4% [−1.5, 0.7]) and symptomatic VTE (0.2% vs 0.7%; AD −0.6% [−1.0, −0.1]) in comparison to those who received placebo. In both age subgroups, patients who received enoxaparin had increased rates of major bleeding versus those who received placebo: age >75 years (0.6% vs 0.2%; AD +0.3% [−0.2, 0.9]), respectively; age ≤75 years (0.7% vs 0.2%; AD +0.5% [0.1, 0.9]). Patients in both age subgroups that received enoxaparin had similar low bleeding rates (0.6% and 0.7%, respectively). VTE risk increased with age, though the bleeding risk did not. Patients with age >75 years had a more favourable benefit-to-harm profile than younger patients.

Keywords

Venous thromboembolism, pulmonary embolism, deep-vein thrombosis, enoxaparin, thromboprophylaxis

Introduction

The incidence of venous thromboembolism (VTE) increases sharply as age advances (1–4). Population-based studies have suggested that the majority of VTE events occur in those aged ≥70 years (5–8). Similarly, the risk of bleeding associated with anticoagulant use increases with advanced age (9–12). Some clinicians’ concerns about bleeding outweigh their concerns regarding VTE, and this imbalance leads to underutilisation of pharmacologic thromboprophylaxis in patients at significant risk for VTE (13–15).

Multiple placebo-controlled randomised trials have demonstrated the safety and efficacy of standard-duration (6–14 days) pharmacological thromboprophylaxis in acutely ill medical patients (16–18). A post-hoc analysis of data from the MEDENOX (Medical Patients with Enoxaparin) study provided evidence of the potential clinical benefits associated with use of prophylactic doses of enoxaparin in elderly patients (1). The 2012 American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines described age of ≥70 years as a risk factor for VTE (19). However, the latest guidelines from the ACCP, the American College of Physicians, and the International Union of Angiology did not specifically address the concerns surrounding the clinical benefits and harms associated with providing anticoagulant thromboprophylaxis to elderly patients (19–21). Recent studies that evaluated the use of extended-duration regimens of anticoagulants for VTE prophylaxis in acutely ill medical patients...
Figure 1: EXCLAIM enrolment, randomisation, safety, and efficacy populations. Numbers are reported for the total population and age subgroups (age >75 years and ≤75 years). Prior to randomisation, during the open-label treatment phase, major bleeding occurred in 16 of 2,288 (0.7%) patients with age >75 years and in 20 of 5,127 (0.4%) of those with age ≤75 years. Includes 1 patient who did not receive enoxaparin during the open-label phase of the trial but received study treatment during the double-blind phase.

Safety population: all randomised patients who received at least one dose of study treatment during the double-blind treatment period. Efficacy population: all randomised patients who received at least one dose of study treatment and had at least one evaluable bilateral lower extremity venous compression ultrasound during the double-blind treatment period or up to 7 days later.
patients provided strong evidence that the period of increased risk for VTE in this population persists longer than the standard-duration of pharmacological prophylaxis regimens (22–24). The EXCLAIM (Extended CLinical prophylaxis in Acutely Ill Medical patients) study reported that extending the use of enoxaparin prophylaxis for 28 days beyond the standard 6–14 day regimen significantly reduced the risk of VTE more than it increased the risk for major bleeding in acutely ill medical patients with recently reduced mobility. These effects were observed most clearly in the subgroups of those aged >75 years and females, who the study identified through tests of interaction (22). This post-hoc subgroup analysis of the EXCLAIM trial evaluated the relationship between patient age and the potential clinical benefits and harms associated with extended-duration enoxaparin prophylaxis.

Methods

Study design

The EXCLAIM study comprised an international, multicentre, parallel group, double-blind, randomised trial conducted at 370 hospitals across 20 countries. Previous publications provide the detailed methodology of the EXCLAIM study (22, 25). The institutional review board at each site approved the trial. This study was conducted in keeping with the principles of the declaration of Helsinki. Participation required written, informed patient consent. The authors had full access to the data and contributed to the drafting of the manuscript.

Study eligibility criteria, participants, and setting

In brief, the original eligibility criteria included age >40 years, an acute medical illness, a lack of contraindications to anticoagulant use, and life expectancy of ≥6 months (25). The eligibility criteria also required study participants to have recently reduced mobility, which the study classified into categories of (a) requiring total bed rest or being sedentary without bathroom privileges (level 1 immobility) or (b) having bathroom privileges (level 2 immobility), for up to 3 days prior to enrolment. The study also required participants to have anticipated reduced mobility for at least an additional 3 days. A subsequent protocol amendment (22, 25) modified the eligibility criteria to require participants with level 2 immobility to have at least one additional risk factor for VTE from the categories of age >75 years, previous VTE, and active or prior cancer.

Randomisation and interventions

Of the 7,500 patients enrolled between February 2002 and March 2006, 6,085 completed open-label thromboprophylaxis with once-daily 40 mg subcutaneous enoxaparin (Lovenox®/Clexane®, Sanofi, Paris, France) for the standard-duration of 10 ± 4 (mean ± standard deviation) days. Patients then underwent randomisation (1:1 ratio) to receive double-blind (participants and investigators blinded to treatment assignment) therapy of once-daily subcutaneous enoxaparin 40 mg or placebo for an additional 28 ± 4 days (22, 25).

Endpoints

EXCLAIM used VTE incidence as the primary efficacy endpoint and defined it as the composite of symptomatic or asymptomatic deep-vein thrombosis (DVT), symptomatic pulmonary embolism (PE), or fatal PE, that occurred during the double-blind treatment period (28 ± 4 days after randomisation) (22, 25). The study assessed VTE endpoints in the efficacy population, which comprised patients who received at least one dose of study treatment during the double-blind treatment period.
those who received at least one dose of study treatment and had at least one evaluable bilateral lower extremity venous compression ultrasound during the double-blind treatment period or up to 7 days later. The study also assessed all-cause mortality and safety endpoints in the safety population, which comprised all patients who received at least one dose of study treatment during the double-blind treatment period.

EXCLAIM used the incidence of major haemorrhagic complications as the primary safety endpoint. Major haemorrhage consisted of overt bleeding associated with a decrease in haemoglobin level of ≥3 g/dl (2 g/dl threshold used in this post-hoc analysis) or transfusion of ≥2 units of red blood cells/whole blood; surgical intervention; fatal bleeding; or retroperitoneal, intracranial, or intraocular bleeding. Secondary safety endpoints included incidence

Table 1a: Baseline characteristics of the safety population stratified by age group.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age ≤75 years</th>
<th>Age &gt;75 years</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>Extended-</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>duration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>enoxaparin</td>
<td>(n=2,085)</td>
</tr>
<tr>
<td></td>
<td>(n=2,097)</td>
<td></td>
</tr>
<tr>
<td>Age at baseline, mean ± SD, years</td>
<td>62.1 ± 9.4</td>
<td>61.5 ± 9.7</td>
</tr>
<tr>
<td>Men</td>
<td>1,082 (51.6)</td>
<td>1,123 (53.9)</td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
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<td>White</td>
<td>1,499 (71.5)</td>
<td>1,489 (71.4)</td>
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<tr>
<td>Black</td>
<td>171 (8.2)</td>
<td>168 (8.1)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>280 (13.4)</td>
<td>299 (14.3)</td>
</tr>
<tr>
<td>Other</td>
<td>147 (7.0)</td>
<td>129 (6.2)</td>
</tr>
<tr>
<td>BMI, mean ± SD, kg/m²</td>
<td>29.7 ± 8.9</td>
<td>29.7 ± 9.0</td>
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<tr>
<td>Primary enrolment diagnoses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute infection without septic shock</td>
<td>694 (33.1)</td>
<td>705 (33.8)</td>
</tr>
<tr>
<td>Acute respiratory insufficiency</td>
<td>698 (33.3)</td>
<td>684 (32.8)</td>
</tr>
<tr>
<td>Heart failure&lt;sup&gt;b&lt;/sup&gt;</td>
<td>327 (15.6)</td>
<td>330 (15.8)</td>
</tr>
<tr>
<td>Status post ischaemic stroke</td>
<td>139 (6.6)</td>
<td>130 (6.2)</td>
</tr>
<tr>
<td>Other</td>
<td>239 (11.4)</td>
<td>236 (11.3)</td>
</tr>
<tr>
<td>Level 1 immobility&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>916 (43.7)</td>
<td>880 (42.2)</td>
</tr>
<tr>
<td>Level 2 immobility&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>1,172 (55.9)</td>
<td>1,195 (57.3)</td>
</tr>
<tr>
<td>Cancer&lt;sup&gt;e&lt;/sup&gt;</td>
<td>143 (6.8)</td>
<td>170 (8.2)</td>
</tr>
<tr>
<td>History of VTE&lt;sup&gt;f&lt;/sup&gt;</td>
<td>85 (4.1)</td>
<td>88 (4.2)</td>
</tr>
<tr>
<td>Active or prior cancer</td>
<td>236 (11.3)</td>
<td>249 (11.9)</td>
</tr>
<tr>
<td>History of VTE</td>
<td>129 (6.2)</td>
<td>132 (6.3)</td>
</tr>
<tr>
<td>Obesity (BMI ≥30 kg/m²)</td>
<td>832 (39.7)</td>
<td>826 (39.6)</td>
</tr>
<tr>
<td>Venous insufficiency</td>
<td>261 (12.4)</td>
<td>250 (12.0)</td>
</tr>
<tr>
<td>Severe renal impairment&lt;sup&gt;g&lt;/sup&gt;</td>
<td>56 (2.7)</td>
<td>51 (2.4)</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>459 (21.9)</td>
<td>431 (20.7)</td>
</tr>
<tr>
<td>Chronic respiratory failure</td>
<td>828 (39.5)</td>
<td>836 (40.1)</td>
</tr>
</tbody>
</table>

All values n (%) unless stated otherwise. <sup>a</sup>Safety population: all randomised patients who received at least one dose of study treatment during the double-blind treatment period. <sup>b</sup>Modified New York Heart Association functional class III or IV. <sup>c</sup>22 patients in the total safety population (11 enoxaparin and 11 placebo) are not included due to missing immobility level data or not being classified with level 1 or 2 immobility. <sup>d</sup>Total bed rest or sedentary without bathroom privileges. <sup>e</sup>Total bed rest or sedentary with bathroom privileges. <sup>f</sup>Patients could have more than one risk factor for VTE. <sup>g</sup>Patients with severe renal impairment (creatinine clearance <30 ml/min) were identified using baseline creatinine levels and the Cockcroft-Gault method for estimating creatinine clearance, which adjusts for serum creatinine, age, weight, and sex. BMI, body mass index; SD, standard deviation; VTE, venous thromboembolism.
of minor haemorrhagic events, adverse events, and thrombocytopenia (22). The study assessed bleeding complications in the safety population during and up to 48 hours after the double-blind treatment phase.

A committee, blinded to study treatment assignment, adjudicated all suspected primary and secondary outcome events. The study used adjudicated outcomes for the analyses.

### Statistical analyses

In this post-hoc analysis, we used descriptive statistics to report the characteristics of the participants. We assessed the relationship between age at enrolment and primary efficacy and safety outcomes. Some analyses used age as a continuous variable. For post-hoc analyses that used age as a categorical variable, we chose age categories

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age ≤75 years</th>
<th>Age &gt;75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline, mean ± SD, years</td>
<td>62.0 ± 9.3</td>
<td>81.5 ± 4.4</td>
</tr>
<tr>
<td>Men</td>
<td>923 (52.4)</td>
<td>297 (40.0)</td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1,244 (70.7)</td>
<td>620 (83.4)</td>
</tr>
<tr>
<td>Black</td>
<td>144 (8.2)</td>
<td>29 (9.3)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>244 (13.9)</td>
<td>87 (11.7)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (0.7)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>BMI, mean ± SD, kg/m²</td>
<td>29.5 ± 8.6</td>
<td>26.2 ± 5.5</td>
</tr>
</tbody>
</table>

### Primary enrolment diagnoses

- **Acute infection without septic shock**
  - Extended-duration enoxaparin: 574 (32.6)
  - Placebo: 598 (33.8)
  - Extended-duration enoxaparin: 233 (32.1)
  - Placebo: 256 (34.5)
- **Acute respiratory insufficiency**
  - Extended-duration enoxaparin: 598 (34.0)
  - Placebo: 567 (32.1)
  - Extended-duration enoxaparin: 174 (24.0)
  - Placebo: 177 (23.8)
- **Heart failure**
  - Extended-duration enoxaparin: 273 (15.5)
  - Placebo: 290 (16.4)
  - Extended-duration enoxaparin: 184 (25.4)
  - Placebo: 185 (24.9)
- **Status post ischaemic stroke**
  - Extended-duration enoxaparin: 120 (6.8)
  - Placebo: 105 (5.9)
  - Extended-duration enoxaparin: 46 (6.3)
  - Placebo: 45 (6.1)
- **Other**
  - Extended-duration enoxaparin: 104 (5.9)
  - Placebo: 103 (5.8)
  - Extended-duration enoxaparin: 42 (5.8)
  - Placebo: 45 (6.1)
- **Level 1 immobility**
  - Extended-duration enoxaparin: 771 (43.8)
  - Placebo: 726 (41.1)
  - Extended-duration enoxaparin: 299 (41.2)
  - Placebo: 314 (42.3)
- **Level 2 immobility**
  - Extended-duration enoxaparin: 981 (55.7)
  - Placebo: 1,031 (58.5)
  - Extended-duration enoxaparin: 424 (58.5)
  - Placebo: 428 (57.6)
- **Cancer**
  - Extended-duration enoxaparin: 112 (6.4)
  - Placebo: 145 (8.2)
  - Extended-duration enoxaparin: 75 (10.3)
  - Placebo: 85 (11.4)
- **History of VTE**
  - Extended-duration enoxaparin: 65 (3.7)
  - Placebo: 78 (4.4)
  - Extended-duration enoxaparin: 35 (4.8)
  - Placebo: 42 (5.7)
- **Active or prior cancer**
  - Extended-duration enoxaparin: 186 (10.6)
  - Placebo: 216 (12.2)
  - Extended-duration enoxaparin: 120 (16.6)
  - Placebo: 147 (19.8)
- **History of VTE**
  - Extended-duration enoxaparin: 104 (5.9)
  - Placebo: 117 (6.6)
  - Extended-duration enoxaparin: 61 (8.4)
  - Placebo: 61 (8.2)
- **Obesity (BMI ≥30 kg/m²)**
  - Extended-duration enoxaparin: 688 (39.1)
  - Placebo: 698 (39.5)
  - Extended-duration enoxaparin: 152 (21.0)
  - Placebo: 152 (20.5)
- **Venous insufficiency**
  - Extended-duration enoxaparin: 224 (12.7)
  - Placebo: 219 (12.4)
  - Extended-duration enoxaparin: 124 (17.1)
  - Placebo: 132 (17.8)
- **Severe renal impairment**
  - Extended-duration enoxaparin: 50 (2.8)
  - Placebo: 47 (2.7)
  - Extended-duration enoxaparin: 43 (5.9)
  - Placebo: 45 (6.0)
- **Chronic heart failure**
  - Extended-duration enoxaparin: 386 (21.9)
  - Placebo: 374 (21.2)
  - Extended-duration enoxaparin: 245 (33.8)
  - Placebo: 273 (36.7)
- **Chronic respiratory failure**
  - Extended-duration enoxaparin: 699 (39.7)
  - Placebo: 691 (39.1)
  - Extended-duration enoxaparin: 295 (40.7)
  - Placebo: 297 (40.0)
to achieve similar size patient subgroups above and below the a priori 75 years age threshold that we specified for subgroup analyses in the original study. For simplicity, and because of reasonable subgroup sample sizes, we defined the age cut-offs at 5- and 10-year intervals. We calculated event rates and absolute risk differences and their confidence intervals (CIs) for efficacy and safety outcomes. We used 95.8% CIs (p<0.042) for VTE endpoints due to alpha-adjustment for the interim analysis (except for CI bars in Figure 4) (22, 25). We used 95% CIs values (p<0.05) for all other endpoints. We used Chi-square or Fisher’s exact tests to compare efficacy and safety outcomes between subgroups. To assess the risk for the primary efficacy endpoint up to day 28 post-randomisation, according to age in the two randomised treatment groups, we used logistic regression and plotted a fitted logistic regression line (with 95% CIs) and a smoothed regression line using locally weighted smoothing (LOESS curve). Survival analyses used Cox proportional hazards logistic regression modelling. Model assumptions were confirmed and regression diagnostics were performed. Number needed to treat (NNT) and number needed to harm (NNH) were calculated for the primary efficacy and safety endpoints and symptomatic VTE. Statistical analyses were conducted using SAS statistical software version 9.1 (SAS Institute, Cary, NC, USA).

**Results**

In the EXCLAIM safety population, 1,781 patients (29.9%) had age >75 years (subgroup mean age 81.5 years) and 4,182 patients (70.1%) had age ≤75 years (subgroup mean age 61.8 years; Figure 1). The randomised treatment groups had similar age distributions (Figure 2). These age subgroups had generally similar baseline demographics, clinical characteristics, enrolment diagnoses, and risk factors (including the level of immobility), except for gender, weight, and rates of heart failure, renal failure, acute respiratory insufficiency, and some additional characteristics (Table 1). Within each age subgroup, the randomised treatment groups had quite similar baseline characteristics (Table 1).

**Efficacy**

For patients with age >75 years, extended-duration enoxaparin demonstrated absolute risk reductions of 4.2% (95% CI 2.0, 6.5) for all VTE, 4.1% (95% CI 2.0, 6.2) for proximal DVT, and 1.2% (95% CI 0.3, 2.2) for symptomatic VTE, in comparison with placebo, for outcomes assessed through 28 days after randomisation (Table 2). Patients with age ≤75 years who received extended-duration enoxaparin only showed a small risk reduction for all VTE and for proximal DVT, in comparison with those who received placebo, though they showed a slightly greater risk reduction for symptomatic VTE (0.6%; 95% CI 0.1, 1.0). For a comparison solely within patients randomised to placebo, those with age >75 years showed a higher incidence of all VTE and symptomatic VTE, compared with those with age ≤75 years (Table 2). In contrast, those randomised to extended-duration enoxaparin showed similar VTE rates within both age groups. Analysis of VTE rates over a continuum of age within each of the two randomised treatment groups showed an overall increase in risk of VTE with advancing age (Figure 3). The placebo group demonstrated a sharp and more pronounced increase in risk of VTE at higher ages compared with the extended-duration enoxaparin group.

To further analyse the association between age and VTE events, we stratified patient data according to five age categories (≤55; >55 to ≤65; >65 to ≤75; >75 to ≤80; and >80 years). The extended-duration enoxaparin group, in comparison to the placebo group, showed a lower incidence of VTE for all age subgroups except age >55 to ≤65 years (Figure 4). Compared with placebo, extended-
duration enoxaparin showed the largest reduction in the rate of VTE in the age >75 to ≤80 years and the age >80 years subgroups.

A multivariable logistic regression model showed an independent association between use of extended-duration enoxaparin and reduction in the rate of VTE, after adjusting for age (>75 or ≤75 years) and other pre-randomisation baseline characteristic variables (odds ratio for extended-duration enoxaparin compared with placebo, 0.61; 95% CI 0.44, 0.85; p=0.003). Multivariable logistic regression also showed that the incidence of VTE increased with age in the placebo group (p=0.0002) and in the enoxaparin group (p=0.181).

Regarding post-randomisation survival at day 30, the randomised treatment groups did not show a significant difference. Those in the >75 years cohort had all-cause mortality rates at day 30 of 3.1% (n=26) and 3.6% (n=31) for extended-duration enoxaparin and placebo groups, respectively (hazard ratio [HR], 0.86; 95% CI 0.51, 1.44; p=0.558). Those in the ≤75 years cohort had an all-cause mortality rate of 1.7% (n=34) in both treatment groups (HR, 1.00; 95% CI 0.62, 1.60; p=0.987).

Safety

Major bleeding rates were low in both age and randomised treatment groups (Table 3). In the >75 years of age cohort, the extended-duration enoxaparin group had small rate increases for total, major, or minor bleeding events (absolute differences [95%
CI]: $+1.1\% [-1.1, 3.2]$; $+0.3\% [-0.2, 0.9]$; and $+0.7\% [-1.4, 2.8]$, respectively; ▶ Table 3) in comparison to the placebo group. In the age ≤75 years cohort, the extended-duration enoxaparin group had more pronounced increases in the rates for all types of bleeding events (absolute differences [95% CI]: $+2.9\% [1.6, 4.2]$, $+0.5\% [0.1, 0.9]$, and $+2.6\% [1.4, 3.8]$ for total, major, and minor bleeding, respectively) in comparison to the placebo group.

In patients randomised to placebo, those >75 years had increased rates of minor and total bleeding events in comparison to the younger patients; both age subgroups had an overall major bleeding rate of 0.2% (▶ Table 3). In patients randomised to enoxaparin, the two age subgroups had similar rates of all types of bleeding.

When stratified by additional age categories, in comparison to those randomised to placebo, those randomised to extended-duration enoxaparin showed a higher incidence of major bleeding across all age subgroups except those with age >80 years. However, all groups had low (<1%) major bleeding rates, and the rates did not appear to increase with advanced age in either randomised treatment groups (▶ Figure 5). The low event rate made analysis of major bleeding over a continuum of age unfeasible.

**Benefit-to-harm assessment**

For the evaluation of extended-duration enoxaparin in patients with age >75 years, the NNT for all VTE (NNT=24) and the NNT for symptomatic VTE (NNT=83) outweighed the NNH for major bleeding (NNH=287). In other words, in comparison to placebo, giving 24 patients extended-duration enoxaparin would prevent 1 patient from developing any VTE, giving 83 patients extended-duration enoxaparin would prevent 1 patient from developing a symptomatic VTE, and giving 287 patients extended-duration enoxaparin would cause 1 patient to develop major bleeding. For patients with age ≤75 years, the NNT for all VTE (NNT=259) did not outweigh the NNH for major bleeding (NNH=210). In contrast, the NNT for symptomatic VTE (NNT=177) did outweigh the NNH for major bleeding in this younger age group.

**Discussion**

This post-hoc subgroup analysis of the EXCLAIM study of acutely ill medical patients with recently reduced mobility demonstrated that those with age >75 years showed risk reductions in the composite endpoint of all VTE events and its components of proximal DVT and symptomatic VTE, through 28 days post-randomisation, associated with extended-duration thromboprophylaxis in
comparison to placebo. In comparison to those of younger age, the group with age >75 years demonstrated greater efficacy associated with extended-duration thromboprophylaxis. Both age groups experienced low rates of major bleeding (<1%). The older age group only had a small increase in major bleeding associated with extended-duration thromboprophylaxis, in comparison to placebo, whereas the younger group had a slightly larger increase. Both age groups showed no significant effect of extended-duration throm-

Table 3: Incidence of bleeding and AEs in the total safety population\textsuperscript{a} stratified by age group.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Age \leq 75 years</th>
<th>Age &gt;75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enoxaparin \textsuperscript{b} (n=2,097)</td>
<td>Placebo \textsuperscript{b} (n=2,085)</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>132 (6.3)</td>
<td>70 (3.4)</td>
</tr>
<tr>
<td>Major</td>
<td>15 (0.7)</td>
<td>5 (0.2)</td>
</tr>
<tr>
<td>Minor</td>
<td>120 (5.7)</td>
<td>65 (3.1)</td>
</tr>
<tr>
<td>AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEAE</td>
<td>503 (24.0)</td>
<td>502 (24.1)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>140 (6.7)</td>
<td>129 (6.2)</td>
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<tr>
<td>TEAE leading to</td>
<td>68 (3.2)</td>
<td>88 (4.2)</td>
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<tr>
<td>discontinuation</td>
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<td>of study drug</td>
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</tr>
<tr>
<td>Serious AE leading</td>
<td>17 (0.8)</td>
<td>23 (1.1)</td>
</tr>
<tr>
<td>to death</td>
<td></td>
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All values n (%) unless stated otherwise. \textsuperscript{a}Safety population: all randomised patients who received at least one dose of study treatment during the double-blind treatment period. \textsuperscript{b}95% CI values (p<.005). AD, absolute difference; AE, adverse event; CI, confidence interval; TEAE, treatment emergent AE.

Figure 5: Incidence of primary safety endpoint (major bleeding), stratified by age subgroups, during and up to 48 hours after the double-blind treatment period\textsuperscript{a}. Vertical bars represent 95% confidence intervals. \textsuperscript{a}Assessed in the safety population: all randomised patients who received at least one dose of study treatment during the double-blind treatment period.
boprophylaxis on survival. Using prevention of VTE to represent benefit and occurrence of major bleeding to represent harm, the elderly had a favourable benefit-to-harm ratio whereas the younger age group did not.

Multiple studies have recognised the association between increased age and VTE risk in acutely ill medical patients (2, 3, 5, 26). Elderly patients have a high prevalence of impaired mobility, hospitalisations for acute medical illness, and comorbid conditions that contribute to the development of VTE (27–30). Although the combination of a higher frequency of some conventional and some age-specific risk factors may explain much of the increased risk of VTE in these patients, studies have identified advanced age as an independent risk factor for VTE (7, 19, 30).

Moving beyond the use of the basic age threshold used in the pre-planned sub-analyses for EXCLAIM, which carries with it the inherent danger of grouping together patients who have different risk levels of adverse outcomes (31), we designed this post-hoc analysis to evaluate the potential impact of age on the risk for VTE and the treatment effects of extended-duration enoxaparin prophylaxis. Analyses of VTE incidence along the continuum of age in the placebo group of EXCLAIM indicated that the baseline risk for VTE increased with age. The much weaker correlation observed in the corresponding analysis of the enoxaparin group suggested that potential differences in the treatment effect may have varied by age.

Although VTE risk and treatment effect increased with advancing age, the study did not identify a similar trend for major bleeding. Other studies, that included different types of patients in different settings, have suggested that bleeding complications with anticoagulant drugs occur more frequently in older patients than in younger individuals. These studies identified age (e.g. age >75 years) as one of the most important variables in determining an individual’s risk for major bleeding with anticoagulants (32–35). However, this study of extended-duration enoxaparin prophylaxis had a low major bleeding rate (<1%), and we did not observe a significant difference in the rate of major bleeding between patients with age >75 years and those with age ≤75 years within each randomised treatment group. Notably, the small fraction of patients who experienced significant bleeding during the open-label phase (i.e. those at highest risk for anticoagulant-related bleeding during randomised therapy) did not undergo randomisation (0.7% [16/2,288] of patients with age >75 years and 0.4% [20/5,127] of those with age ≤75 years). The EXCLAIM study showed rates of bleeding during the open-label treatment phase similar to those seen in previous studies of standard-duration low-molecular-weight heparin (LMWH) thromboprophylaxis, which had rates of 0.49–1.7% in patients randomised to active treatment group and 0.16–1.1% in patients randomised to placebo (16, 17).

Similar to the shorter-term results of age-based sub-analyses from trials that evaluated the use of standard-duration thromboprophylaxis in acutely ill medical patients (36, 37), the results of this EXCLAIM study post-hoc analysis suggest that prophylactic doses of extended-duration enoxaparin may have a favourable risk-to-benefit ratio for patients with age >75 years. In the setting of no difference in mortality between randomised treatment groups, the NNT for all VTE and the NNT for symptomatic VTE each outweighed the NNH for major bleeding for patients with age >75 years. However, for patients with age ≤75 years, while the NNT for symptomatic VTE did outweigh the NNH for major bleeding, the NNT for all VTE did not. Other studies conducted both prior to EXCLAIM and during the conduct of this trial have also suggested that patients >75 years have a favourable risk-to-benefit ratio for standard-duration thromboprophylaxis with a LMWH (1, 8, 36–40).

Current ACCP guidelines do not recommend the use of extended-duration thromboprophylaxis in acutely ill medical patients (19). However, at the time of the most recent guideline update, the level of evidence supporting the extended regimen was very low. Recently published studies of extended-duration thromboprophylaxis in acutely ill medical patients that assessed newer oral anticoagulants that directly inhibit factor Xa did not mirror the findings of EXCLAIM and this post-hoc analysis of EXCLAIM (24, 41). The ADOPT (Apixaban for the Prevention of Thrombosis-related Events in Patients With Acute Medical Illness) trial did not show a significant efficacy (all VTE) benefit for extended-duration apixaban over standard-duration enoxaparin thromboprophylaxis at day 30 after randomisation (2.7% vs 3.1%; p=0.44), and both drugs had similar short-term day 10 efficacy (1.7% vs 1.6%) (24, 41). However, apixaban did show an association with increased major bleeding during extended-duration anticoagulation in comparison with placebo (0.47% vs 0.19%; p=0.04), although it showed no significant increase in major bleeding during the standard-duration (0.25% vs 0.12%; p=0.12) (24). The MAGELLAN (Venous Thromboembolic Event Prophylaxis in Medically Ill Patients) study showed a slight efficacy (all VTE) benefit of extended-duration rivaroxaban over standard-duration enoxaparin thromboprophylaxis at day 35 after randomisation (4.4% vs 5.7%; p=0.021), although both drugs had similar short-term day 10 efficacy (2.7%). Similar to the ADOPT study, the MAGELLAN study showed increased major bleeding during extended-duration rivaroxaban in comparison with placebo (1.1% vs 0.4%; p<0.001). In addition, the MAGELLAN study showed increased major bleeding with rivaroxaban in comparison with enoxaparin during standard-duration thromboprophylaxis (0.6% vs 0.3%; p=0.032) (41). To date, the ADOPT and MAGELLAN investigators have not published a sub-study that describes outcomes based on age.

Some methodological limitations affect the findings and/or the interpretation of the results of this study. The post-hoc subgroup analysis has more potential for spurious findings in comparison with the primary study analysis (31). The primary study was not powered to: (a) fully detect differences between patient subgroups; (b) adequately discern the competing risks and benefits of thromboprophylaxis in terms of its effects on recurrent VTE and associated death and death associated with major bleeding; or (c) detect differences in all-cause mortality between the treatment groups. The sample sizes of the >75 years and ≤75 years cohorts limited the power to detect differences and the precision of our estimates. Another important limitation relates to the eligibility amendment, because the enrolment of patients in the level 2 mobility category markedly decreased after its implementation. Regarding outcomes, the study did not collect data that allowed for assessment of clinically relevant non-major bleeding. Also, the exclusion criteria may have impacted more heavily on the screening.
rate for the elderly due to comorbidities, and this would affect the generalisability of the findings from this subgroup analysis.

Recent guidelines recommend providing thromboprophylaxis to acutely ill medical patients considered at increased risk for VTE for 6–21 days (until full mobility is restored or hospital discharge, whichever comes first), and they highlight the use of assessment tools for identifying patients at high risk for both VTE and bleeding (19, 20). The risk scoring described in the ACCP guidelines incorporates age of ≥70 years as a VTE risk factor of equivalent impact (in point score) as the risk factors of acute myocardial infarction, ischaemic stroke, heart failure, and obesity, and the guidelines incorporate age of ≥85 years as a bleeding risk factor (19).

The results of this study suggest that although VTE risk may increase with age in acutely ill medical patients, the risk for major bleeding related to extended-duration prophylactic doses of anticoagulants does not necessarily follow the same trend. Given the increased risk for VTE, the positive treatment effect, and the associated limited increase in major bleeding observed in acutely ill medical patients that have age >75 years, the study findings suggest that this population has a favourable risk-to-benefit ratio for receiving thromboprophylaxis beyond the standard duration of 6–14 days. Based on the limitations of this subgroup analysis, further formal evaluation of the findings in a prospective, confirmatory trial (42–44) would significantly improve the strength of the evidence regarding the potential benefits and harms of providing thromboprophylaxis to the elderly.

What is known about this topic?
- The risk of venous thromboembolism extends beyond the standard-duration thromboprophylaxis period in acutely ill medical patients.
- Previous studies have not assessed the impact of age on the benefits and harms of extended-duration thromboprophylaxis in acutely ill medical patients.

What does this paper add?
- This post-hoc subgroup analysis of the EXCLAIM study of acutely ill medical patients with recently reduced mobility demonstrated that those with age >75 years who received extended-duration enoxaparin thromboprophylaxis, in comparison to those that received placebo, showed risk reductions in the composite endpoint of all venous thromboembolism (VTE) events, and its components of proximal deep-vein thrombosis and symptomatic VTE, at 28 days post-randomisation.
- Patients with age >75 years showed greater efficacy associated with extended-duration thromboprophylaxis in comparison to those of younger age.
- Both age groups experienced low rates of major bleeding; in comparison to younger patients, those with age >75 years had a smaller increase in major bleeding associated with extended-duration thromboprophylaxis.
- Using prevention of VTE to represent benefit and occurrence of major bleeding to represent harm, the older age group had a very favourable benefit-to-harm ratio, whereas the younger age group did not.

References

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Conflicts of interest
Dr. Yusen has received research grants from Pfizer, Bristol-Myers Squibb, Bayer, Agen Biomedical, and ParinGenix; honoraria from Bayer, GlaxoSmithKline, and Sanofi; has acted as an expert witness for Ortho Pharmaceuticals, Organon, and Merck; and has acted as a consultant for Bayer, GlaxoSmithKline, Sanofi, and Scios, Inc. (Johnson & Johnson). Prof. Hull has received research support/grant funding from Sanofi and Leo Pharma; honoraria from Sanofi, Pfizer, and Leo Pharma; and has acted as a consultant for Bayer, Johnson & Johnson, and Portola. Dr. Schellong has received honoraria from Daiichi Sankyo, GlaxoSmithKline, Bristol-Myers Squibb, Bayer, Boehringer Ingelheim, and Sanofi; and has acted as a consultant for Daiichi Sankyo, Bayer, Boehringer Ingelheim, and Sanofi. Dr. Tapson has received research grants from Sanofi and Bayer; and previously acted as a consultant for Sanofi (now discontinued) and Janssen. Dr. Monreal has received research grant funding from Sanofi and Bayer; and has acted as a consultant for Bayer, Pfizer, and Daiichi-Sankyo. Prof. Samama has acted as a consultant for Sanofi, Bayer Healthcare, Eli Lilly and Daiichi Sankyo; member of advisory board/Steering Committee of Johnson & Johnson, Pfizer Laboratory, and MDS; and invited speaker for Sanofi, GlaxoSmithKline, Bayer Healthcare, and Boehringer Ingelheim. Dr. Chen was an employee of Sanofi at the time of this study but has no other relevant disclosures to declare. Dr. Deslandes is a current employee of Sanofi. Prof. Turpie has received honoraria from Bayer; Speakers’ Bureau fees for Pfizer, Johnson & Johnson, Sanofi, and GlaxoSmithKline; and has acted as a consultant for Bayer, Johnson & Johnson, and Astellas.


