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Extended-Duration Venous Thromboembolism Prophylaxis in Acutely Ill Medical Patients With Recently Reduced Mobility

A Randomized Trial

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Background: Extended-duration low-molecular-weight heparin has been shown to prevent venous thromboembolism (VTE) in high-risk surgical patients.

Objective: To evaluate the efficacy and safety of extended-duration enoxaparin thromboprophylaxis in acutely ill medical patients.

Design: Randomized, parallel, placebo-controlled trial. Randomization was computer-generated. Allocation was centralized. Patients, caregivers, and outcome assessors were blinded to group assignment. (ClinicalTrials.gov registration number: NCT00077753)

Setting: 370 sites in 20 countries across North and South America, Europe, and Asia.

Patients: Acutely ill medical patients 40 years or older with recently reduced mobility (bed rest or sedentary without [level 1] or with [level 2] bathroom privileges). Eligibility criteria for patients with level 2 immobility were amended to include only those who had additional VTE risk factors (age >75 years, history of VTE, or active or previous cancer) after interim analyses suggested lower-than-expected VTE rates.

Intervention: Enoxaparin, 40 mg/d subcutaneously (2975 patients), or placebo (2988 patients), for 28 ± 4 days after receiving open-label enoxaparin for an initial 10 ± 4 days.

Measurements: Incidence of VTE up to day 28 and of major bleeding events up to 48 hours after the last study treatment dose.

Results: Extended-duration enoxaparin reduced VTE incidence compared with placebo (2.5% vs. 4%; absolute risk difference favoring enoxaparin, −1.53% [95.8% CI, −2.54% to −0.52%]). Enoxaparin increased major bleeding events (0.8% vs. 0.3%; absolute risk difference favoring placebo, 0.51% [95% CI, 0.12% to 0.89%]). The benefits of extended-duration enoxaparin seemed to be restricted to women, patients older than 75 years, and those with level 1 immobility.

Limitation: Estimates of efficacy and safety for the overall trial population are difficult to interpret because of the change in eligibility criteria during the trial.

Conclusion: Use of extended-duration enoxaparin reduces VTE more than it increases major bleeding events in acutely ill medical patients with level 1 immobility, those older than 75 years, and women.

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* For a list of the EXCLAIM study investigators, see **Appendix 1** (available at www.annals.org).

Hospitalized medical patients have a high risk for venous thromboembolism (VTE) (1). Recent studies (2–4) suggest that 5% to 15% of medical patients who do not receive appropriate prophylaxis develop objectively confirmed deep venous thrombosis (DVT). Up to 75% of fatal pulmonary embolism cases occur in hospitalized medical patients (5), and VTE is associated with considerable long-term morbidity and substantial consumption of hospital resources (6).

Large clinical trials have demonstrated the benefits of short-term VTE prophylaxis in hospitalized acutely ill medical patients; these benefits are mostly attributable to reductions in asymptomatic VTE (2–4). On the basis of this evidence, guidelines recommend use of unfractionated heparin, low-molecular-weight heparin, or fondaparinux for medical patients with heart failure or severe respiratory disease or those who are confined to bed with 1 or more risk factors, such as cancer, previous VTE, or inflammatory bowel disease (1).

Extended-duration (4-week) prophylaxis has been shown to significantly reduce the incidence of VTE compared with a standard (1-week) regimen in high-risk surgical patients (7–10). However, studies have not assessed the efficacy and safety of extended-duration prophylaxis in acutely ill medical patients. We hypothesized that an extended-duration enoxaparin regimen similar to that evaluated in patients undergoing elective hip arthroplasty (7) would be beneficial for acutely ill medical patients at high risk for VTE (11). We designed a randomized clinical trial

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to assess the efficacy and safety of extended-duration enoxaparin compared with placebo, following a 6- to 14-day, clinically proven regimen for VTE prophylaxis (2, 11).

METHODS

This was an international, multicenter, parallel-group, double-blind trial (11). We conducted it according to standards of good clinical practice and in keeping with the Declaration of Helsinki and local regulations. The institutional review board at each site approved the trial. Participation required written informed patient consent.

Setting and Patients

We enrolled patients from 370 hospitals across 20 countries between February 2002 and March 2006 (**Appendix 1**, available at www.annals.org). We recruited patients with acute medical illness (for example, heart failure, respiratory insufficiency, or infection) who met previously reported eligibility criteria (11). In brief, patients were eligible if they were at least 40 years of age, had a life expectancy of at least 6 months, and had recently reduced mobility for up to 3 days. In addition, they had to be considered by the enrolling investigator as likely to have reduced mobility for at least 3 days after enrollment. We defined "reduced mobility" as requiring total bed rest or being sedentary without bathroom privileges (level 1 immobility) or with bathroom privileges (level 2 immobility). We subsequently amended the eligibility criteria as described in the Trial Monitoring and Amendment section.

Randomization and Interventions

Enrolled patients received open-label subcutaneous enoxaparin, 40 mg/d, for 10 ± 4 days; some completed open-label prophylaxis in the outpatient setting. Patients who successfully completed open-label prophylaxis were randomly assigned in a 1:1 ratio in a double-blind manner to receive either subcutaneous enoxaparin, 40 mg/d, or placebo for an additional 28 ± 4 days. The random assignment list was computer-generated in permuted blocks of 4, stratified by center, by a clinical research organization (Covance, Radnor, Pennsylvania); staff obtained allocation assignments at the time of treatment by using a telephone interactive voice-response system.

During hospitalization, authorized study personnel administered the study drug. In the outpatient setting, the study drug was administered by study staff, health care providers, or patients (who had successfully completed training in the proper administration technique).

Efficacy Outcomes

Our primary efficacy end point was VTE, defined as the composite of symptomatic or asymptomatic proximal DVT, symptomatic pulmonary embolism, or fatal pulmonary embolism, during the double-blind treatment period (28 ± 4 days after random assignment). Secondary end points were VTE incidence through 3 months (day 90 ± 10) and mortality at 1 month (day 28 ± 4), 3 months (day 90 ± 10), and 6 months (day 180 ± 10). We assessed all efficacy end points, except mortality, in randomly assigned patients who received at least 1 dose of the study treatment during the double-blind treatment period and had at least 1 interpretable ultrasonogram during the period or up to 7 days after (efficacy population).

We used bilateral compression ultrasonography or venography to evaluate patients with suspected DVT on the basis of symptoms during the double-blind treatment period. We used computed tomography or ventilation–perfusion lung scanning to evaluate suspected symptomatic cases of pulmonary embolism. When available, we used autopsy results to assess the presence of fatal pulmonary emboli. We counted each symptomatic event as a primary efficacy end point only if sufficient data were available for confirmation by central adjudication.

At the end of the double-blind treatment period, patients underwent bilateral ultrasonography of the lower extremities to identify asymptomatic proximal DVT. Locally trained and certified operators used a standardized B-mode compression ultrasonography protocol that required 10 scans at predefined segments of the femoral and popliteal veins. In addition, all scans were centrally read by reviewers at Bio-Imaging Technologies (Newtown, Pennsylvania), who were blinded to treatment assignment, clinical information, and the local interpretation of the scan. Discrepancies between local and central readings were centrally adjudicated in blinded sessions (**Appendix 2**, available at www.annals.org) (11).

Safety Outcomes

The primary safety end point was the incidence of major hemorrhagic complications, during and up to 48

Context

Four weeks of enoxaparin therapy reduces VTE incidence more than 1 week of treatment in surgical patients at high risk for VTE. The same has not yet been shown for medical patients.

Contribution

Adding 28 days of enoxaparin treatment to an initial 10-day course reduced VTE incidence more than it increased major bleeding events in female, older, or sedentary patients with acute medical illness.

Caution

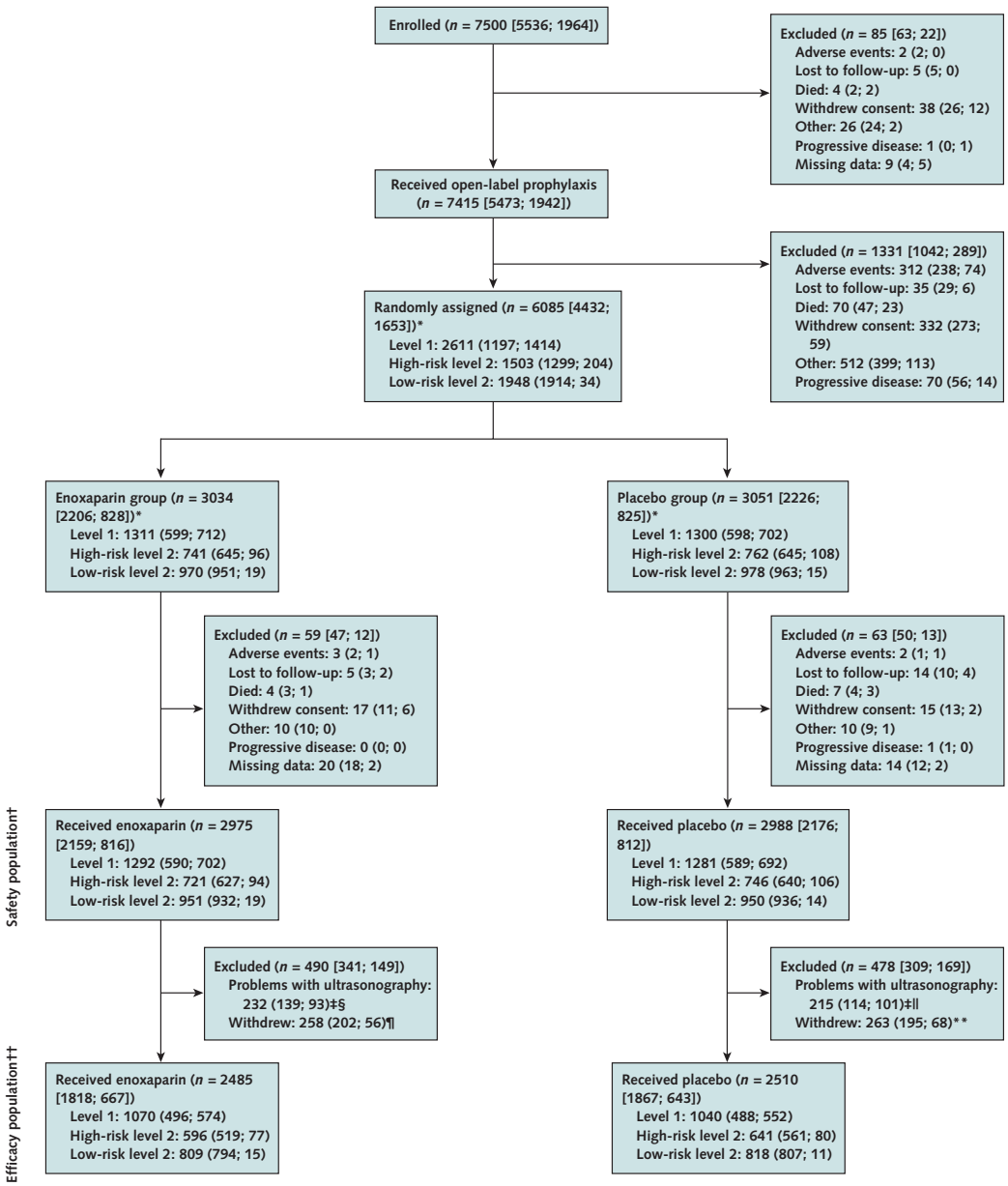
Trial eligibility criteria had to be modified after interim analyses suggested that extended-duration enoxaparin did more harm than good.

Implication

Extended-duration enoxaparin seems to have a favorable benefit–risk ratio in high-risk subgroups of patients with acute medical illness.

—The Editors

Figure 1. **Study flow diagram.**



Numbers are reported for the total study population, followed by the number of patients enrolled before and after the eligibility criteria were amended.
* Includes 1 patient who did not receive enoxaparin during the open-label phase of the trial but received it during the double-blind phase and 23 patients (12 enoxaparin recipients and 11 placebo recipients; 22 preamendment [11 enoxaparin recipients and 11 placebo recipients], 1 postamendment [1 enoxaparin recipient]) for whom immobility classification data were missing or immobility-level classification was absent.
† Includes 22 patients (21 preamendment [10 enoxaparin recipients and 11 placebo recipients] and 1 postamendment [enoxaparin recipient]) who had missing immobility-level data or no immobility-level classification.
‡ Reasons include incompatible digital format, incomplete scans, and insufficient quality of scans.
§ No ultrasonography, reason not known, 65 (48; 17); evaluated outside of time window, 5 (4; 1); not sent for central reading, 43 (23; 20); not evaluable centrally, 100 (56; 44); not read centrally because of technical problems, 19 (8; 11).
‖ No ultrasonography, reason not known, 53 (38; 15); evaluated outside of time window, 2 (2; 0); not sent for central reading, 40 (20; 20); not evaluable centrally, 96 (44; 52); not read centrally because of technical problems, 24 (10; 14).
¶ Adverse event, 76 (60; 16); lost during follow-up, 6 (5; 1); died, 25 (17; 8); discontinued study participation, 61 (52; 9); progressive disease, 14 (11; 3); other, 76 (57; 19).
** Adverse event, 85 (70; 15); lost during follow-up, 13 (9; 4); died, 32 (20; 12); discontinued study participation, 56 (36; 20); progressive disease, 15 (15; 0); other, 62 (45; 17).
†† 21 patients were excluded from the immobility subgroups (20 preamendment [9 enoxaparin recipients and 11 placebo recipients] and 1 postamendment [enoxaparin recipient]) because immobility-level data were missing or immobility-level classification was absent.

Table 1. **Baseline Patient Characteristics at Baseline***

Variable	Preamendment		Postamendment		Total Population	
	Extended-Duration Enoxaparin (*n* = 2159)	Placebo (*n* = 2176)	Extended-Duration Enoxaparin (*n* = 816)	Placebo (*n* = 812)	Extended-Duration Enoxaparin (*n* = 2975)	Placebo (*n* = 2988)
Demographic characteristics						
Mean age (SD), *y*	67.8 (12.2)	67.2 (12.4)	68.1 (12.0)	68.2 (12.7)	67.9 (12.1)	67.5 (12.5)
Men, *n (%)*	1081 (50.1)	1076 (49.4)	386 (47.3)	401 (49.4)	1467 (49.3)	1477 (49.4)
Race or ethnicity, *n (%)*						
White	1678 (77.7)	1685 (77.4)	548 (67.2)	551 (67.9)	2226 (74.8)	2236 (74.8)
Black	156 (7.2)	155 (7.1)	43 (5.3)	49 (6.0)	199 (6.7)	204 (6.8)
Hispanic	282 (13.1)	301 (13.8)	109 (13.4)	106 (13.1)	391 (13.1)	407 (13.6)
Asian or Oriental	17 (0.8)	15 (0.7)	69 (8.5)	66 (8.1)	86 (2.9)	81 (2.7)
Multiracial	9 (0.4)	13 (0.6)	39 (4.8)	33 (4.1)	48 (1.6)	46 (1.5)
Other	17 (0.8)	7 (0.3)	8 (1.0)	7 (0.9)	25 (0.8)	14 (0.5)
Region of enrollment, *n* (%)†						
Europe	918 (42.5)	912 (41.9)	243 (29.8)	247 (30.4)	1161 (39.0)	1159 (38.8)
North America	806 (37.3)	813 (37.4)	164 (20.1)	165 (20.3)	970 (32.6)	978 (32.7)
Latin America	281 (13.0)	290 (13.3)	88 (10.8)	87 (10.7)	369 (12.4)	377 (12.6)
Africa, Asia, or the Middle East	17 (0.8)	19 (0.9)	309 (37.9)	303 (37.3)	326 (11.0)	322 (10.8)
Australia	137 (6.3)	142 (6.5)	12 (1.5)	10 (1.2)	149 (5.0)	152 (5.1)
Mean body mass index (SD), kg/m^2	28.9 (8.6)	29.0 (8.6)	28.3 (7.2)	27.9 (7.3)	28.7 (8.3)	28.7 (8.2)
Body mass index ≥30 kg/m^2, *n (%)*	743 (34.4)	764 (35.1)	275 (33.7)	244 (30.0)	1018 (34.2)	1008 (33.7)
Primary enrollment diagnoses, *n* (%)						
Acute infection without septic shock	760 (35.2)	794 (36.5)	217 (26.6)	211 (26.0)	977 (32.8)	1005 (33.6)
Acute respiratory insufficiency	692 (32.1)	666 (30.6)	213 (26.1)	234 (28.8)	905 (30.4)	900 (30.1)
Heart failure‡	329 (15.2)	350 (16.1)	217 (26.6)	214 (26.4)	546 (18.4)	564 (18.9)
Post–acute ischemic stroke	131 (6.1)	127 (5.8)	67 (8.2)	64 (7.9)	198 (6.7)	191 (6.4)
Acute rheumatic disorders	59 (2.7)	62 (2.8)	16 (2.0)	21 (2.6)	75 (2.5)	83 (2.8)
Active cancer	33 (1.5)	36 (1.7)	17 (2.1)	10 (1.2)	50 (1.7)	46 (1.5)
Fracture	10 (0.5)	12 (0.6)	10 (1.2)	5 (0.6)	20 (0.7)	17 (0.6)
Multiple diagnoses	10 (0.5)	4 (0.2)	11 (1.3)	8 (1.0)	21 (0.7)	12 (0.4)
Active inflammatory bowel disease	4 (0.2)	8 (0.4)	3 (0.4)	0 (0.0)	7 (0.2)	8 (0.3)
Other	131 (6.1)	117 (5.4)	45 (5.5)	45 (5.5)	176 (5.9)	162 (5.4)
Risk factors and immobility level, *n (%)*						
Level 1 immobility§‖	590 (27.3)	589 (27.1)	702 (86.0)	692 (85.2)	1292 (43.4)	1281 (42.9)
Level 2 immobility§¶	1559 (72.2)	1576 (72.4)	113 (13.8)	120 (14.8)	1672 (56.2)	1696 (56.8)
Age >75 y**	431 (27.6)	423 (26.8)	69 (61.1)	78 (65.0)	500 (29.9)	501 (29.5)
Cancer**	210 (13.5)	246 (15.6)	25 (22.1)	26 (21.7)	235 (14.1)	272 (16.0)
History of VTE**	109 (7.0)	116 (7.4)	16 (14.2)	17 (14.2)	125 (7.5)	133 (7.8)
Age >75 y	632 (29.3)	635 (29.2)	246 (30.1)	268 (33.0)	878 (29.5)	903 (30.2)
Active or previous cancer	296 (13.7)	329 (15.1)	99 (12.1)	93 (11.5)	395 (13.3)	422 (14.1)
History of VTE	143 (6.6)	154 (7.1)	57 (7.0)	48 (5.9)	200 (6.7)	202 (6.8)
Obesity (body mass index ≥30 kg/m^2)	743 (34.4)	764 (35.1)	275 (33.7)	244 (30.0)	1018 (34.2)	1008 (33.7)
Venous insufficiency	293 (13.6)	305 (14.0)	113 (13.8)	104 (12.8)	406 (13.6)	409 (13.7)
Hormone therapy	58 (2.7)	54 (2.5)	9 (1.1)	9 (1.1)	67 (2.3)	63 (2.1)
Chronic heart failure	488 (22.6)	493 (22.7)	266 (32.6)	277 (34.1)	754 (25.3)	770 (25.8)
Chronic respiratory failure	879 (40.7)	882 (40.5)	304 (37.3)	309 (38.1)	1183 (39.8)	1191 (39.9)
Chronic inflammatory disease	7 (0.3)	19 (0.9)	1 (0.1)	2 (0.2)	8 (0.3)	21 (0.7)
Family history of VTE	4 (0.2)	1 (0.0)	0	0	4 (0.1)	1 (0.0)
Thrombophilia	4 (0.2)	3 (0.1)	0	0	4 (0.1)	3 (0.1)
Previous medications, *n (%)*						
Antiplatelet or anti-inflammatory drugs	589 (27.3)	547 (25.1)	167 (20.5)	167 (20.6)	756 (25.4)	714 (23.9)
Antiplatelet drugs	151 (7.0)	155 (7.1)	55 (4.7)	50 (6.2)	206 (6.9)	205 (6.9)
Anti-inflammatory drugs	555 (25.7)	502 (23.1)	155 (19.0)	151 (18.6)	710 (23.9)	653 (21.9)

VTE = venous thromboembolism.
* Data are for the trial safety population of 5963 patients.
† Europe: France, Germany, Great Britain, Italy, Poland, Russia, and Spain. North America: Canada and the United States. Latin America: Argentina, Brazil, Colombia, and Mexico. Africa, Asia, or the Middle East: India, Israel, South Africa, and Tunisia.
‡ Modified New York Heart Association functional class III or IV.
§ We excluded 22 patients in the total safety population (21 preamendment [10 from the enoxaparin group and 11 from the placebo group] and 1 postamendment [from the enoxaparin group]) because of missing immobility-level data or absence of immobility-level classification.
‖ Total bed rest or sedentary without bathroom privileges.
¶ Total bed rest or sedentary with bathroom privileges.
** Patients in these subgroups could have >1 risk factor for VTE.

Table 2. **Incidence of Primary Efficacy and Safety Outcomes**

End Point	Preamendment*			Postamendment		
	Extended-Duration Enoxaparin, *n/N (%)*	Placebo, *n/N (%)*	Absolute Risk Difference (CI), %†	Extended-Duration Enoxaparin, *n/N (%)*	Placebo, *n/N (%)*	Absolute Risk Difference (CI), %†
VTE‡§						
All	45/1818 (2.5)	78/1867 (4.2)	−1.70 (−2.86 to −0.55)	16/667 (2.4)	22/643 (3.4)	−1.02 (−2.85 to 0.80)
Level 1	12/496 (2.4)	30/488 (6.1)	−3.73 (−6.25 to −1.20)	13/574 (2.3)	17/552 (3.1)	−0.81 (−2.70 to 1.07)
Level 2	33/1313 (2.5)	47/1368 (3.4)	−0.92 (−2.21 to 0.36)	3/92 (3.3)	5/91 (5.5)	−2.23 (−8.16 to 3.69)
High-risk‖	18/519 (3.5)	31/561 (5.5)	−2.05 (−4.51 to 0.41)	3/77 (3.9)	5/80 (6.3)	−2.35 (−9.20 to 4.49)
Low-risk¶	15/794 (1.9)	16/807 (2.0)	−0.09 (−1.44 to 1.26)	0/15 (0.0)	0/11 (0.0)	–
Major bleeding events**						
All	19/2159 (0.9)	10/2176 (0.5)	0.42 (−0.07 to 0.91)	6/816 (0.7)	0/812 (0.0)	0.74 (0.15 to 1.32)
Level 1	5/590 (0.8)	2/589 (0.3)	0.51 (−0.37 to 1.38)	4/702 (0.6)	0/692 (0.0)	0.57 (0.01 to 1.13)
Level 2	14/1559 (0.9)	8/1576 (0.5)	0.39 (−0.19 to 0.98)	2/113 (1.8)	0/120 (0.0)	1.77 (−0.66 to 4.20)
High-risk‖	4/627 (0.6)	3/640 (0.5)	0.17 (−0.65 to 0.99)	2/94 (2.1)	0/106 (0.0)	2.13 (−0.79 to 5.04)
Low-risk¶	10/932 (1.1)	5/936 (0.5)	0.54 (−0.27 to 1.35)	0/19 (0.0)	0/14 (0.0)	0.00 (0.00 to 0.00)

VTE = venous thromboembolism.
* Data include outcomes that were not fully adjudicated at the time of interim analysis. The analysis using adjudicated data only found no significant difference between groups. See "Trial Monitoring and Amendment" in the Methods section for further details.
† For VTE end points in the total population, we report 95.8% CIs ($P < 0.042$) because of the α adjustment for the interim analysis. For all other end points, we report 95% CIs ($P < 0.050$).
‡ Assessed in the efficacy population (4995 patients). We excluded 21 patients from the immobility subgroups (20 preamendment [9 in the enoxaparin group and 11 in the placebo group] and 1 postamendment [from the enoxaparin group]) because of missing immobility-level data or absence of immobility-level classification.
§ One patient included in the placebo group of the preamendment and total populations experienced a VTE but had missing immobility-level data or absence of immobility-level classification.
‖ Patients with level 2 immobility and ≥1 of the following VTE risk factors: age >75 y, history of VTE, or active or previous cancer.
¶ Patients with level 2 immobility and none of the additional specified risk factors for VTE.
** Post hoc analysis performed by using a threshold hemoglobin decrease of ≥20 g/L for a major bleeding event. Assessed in the safety population (5963 patients), except for 22 patients (21 preamendment [10 from the enoxaparin group and 11 from the placebo group] and 1 postamendment [from the enoxaparin group]) whom we excluded because of missing immobility-level data or absence of immobility-level classification. **Appendix Table 3** (available at www.annals.org) describes the types of major bleeding events we observed.

hours after the double-blind treatment period, as determined by central adjudication with blinding to treatment assignment (**Appendix 2**). Secondary safety end points were the incidence of major and minor hemorrhagic complications, serious adverse events, and thrombocytopenia. We assessed safety end points and mortality in all randomly assigned patients who received at least 1 dose of study medication (safety population).

Hemorrhages were considered to be major if they were overt and associated with death; a decrease in hemoglobin level of at least 30 g/L or a transfusion of at least 2 units of packed red blood cells or whole blood; surgical intervention; or retroperitoneal, intracranial, or intraocular bleeding. In a post hoc analysis, we used a more stringent threshold hemoglobin decrease of 20 g/L, as used in other trials, to further assess major bleeding events.

Minor hemorrhages were those that were overt and did not meet the criteria for a major hemorrhage. These included epistaxis lasting more than 5 minutes or requiring intervention, ecchymosis or hematoma larger than 5 cm, hematuria not associated with urinary catheter trauma, subconjunctival or gastrointestinal hemorrhage, or wound hematoma. We obtained platelet counts at the end of both the open-label and double-blind treatment phases.

We defined adverse events as new illness, worsening of preexisting illness, study medication effects (including comparator), or a combination of these. Serious adverse events were those that resulted in death or persistent or substantial disability or incapability, were life-threatening or considered an important medical event, or required inpatient hospitalization or prolongation of existing hospitalization. Bleeding events and VTE were considered serious adverse events if they met the above criteria.

Trial Monitoring and Amendment

An independent data safety monitoring board (DSMB) (**Appendix 1**) conducted interim analyses of adjudicated efficacy and safety outcomes when 25%, 50%, and 75% of the target enrollment (4044 patients) had been recruited. For the final interim analysis, adjudicated efficacy data were available for 3056 of 3685 patients with evaluable ultrasonograms and adjudicated safety data were available for 4060 patients.

The final interim efficacy analysis found lower-than-assumed VTE rates, with no statistically significant difference between treatment groups (37 of 1526 [2.4%] in the enoxaparin group vs. 50 of 1530 (3.3%) in the placebo group; $P = 0.16$) after unblinding and an 8.67% chance of finding such a significant difference. The interim safety analysis also found a statistically significant increase in major hemorrhages associated with 1 treatment group (13 of 2020 [0.64%] in the enoxaparin group vs. 6 of 2040 [0.29%] in the placebo group; $P = 0.05$) after unblinding. On the basis of these analyses, the DSMB recommended that the study as designed be terminated. The DSMB also highlighted that event rates in patients with level 1 immo-

Table 2—Continued

Total Population		
Extended-Duration Enoxaparin, *n/N (%)*	Placebo, *n/N (%)*	Absolute Risk Difference (CI), %†
61/2485 (2.5)	100/2510 (4.0)	−1.53 (−2.54 to −0.52)
25/1070 (2.3)	47/1040 (4.5)	−2.18 (−3.80 to −0.57)
36/1405 (2.6)	52/1459 (3.6)	−1.00 (−2.31 to 0.31)
21/596 (3.5)	36/641 (5.6)	−2.09 (−4.50 to 0.31)
15/809 (1.9)	16/818 (2.0)	−0.10 (−1.48 to 1.28)
25/2975 (0.8)	10/2988 (0.3)	0.51 (0.12 to 0.89)
9/1292 (0.7)	2/1281 (0.2)	0.54 (0.04 to 1.04)
16/1672 (1.0)	8/1696 (0.5)	0.49 (−0.08 to 1.05)
6/721 (0.8)	3/746 (0.4)	0.43 (−0.37 to 1.23)
10/951 (1.1)	5/950 (0.5)	0.53 (−0.27 to 1.32)

bility were consistent with the study design assumptions, which suggested that the trial could be continued in this subgroup of patients. The steering committee requested further analyses to identify whether any patients with level 2 immobility had increased risk for VTE because such patients may also have had event rates consistent with initial hypotheses. The steering committee requested a blinded multivariate analysis on risk factors for VTE (performed by the sponsor because of limited DSMB resources). This analysis identified patients with level 2 immobility and age older than 75 years, previous VTE, or active or previous cancer as having increased VTE risk and event rates consistent with study design assumptions. The steering committee therefore issued a protocol amendment that changed the eligibility criteria to require patients with level 2 immobility to also have 1 or more of these risk factors (termed "high-risk level 2"). The DSMB reviewed the amended protocol and considered it a safe and feasible way to continue the study. Enrollment criteria for patients with level 1 immobility remained unchanged, and we continued to enroll patients with level 1 immobility during and after the protocol amendment process.

Statistical Analysis

Our original statistical assumptions are described elsewhere (11). In brief, we based our sample size calculation on an assumed VTE rate of 4.0% at day 28 in the placebo group after random assignment. With 80% power and a 2-sided type I error rate of 5%, we needed 4044 evaluable patients to show a 40% reduction in the VTE incidence with the extended-duration enoxaparin regimen; with an expected evaluability rate of 70%, we aimed to enroll 5800 patients. **Appendix 2** describes event rate assumptions and modified target enrollment after the protocol amendment.

All end points were assessed in 3 study populations: preamendment (patients enrolled before the level 2 eligibility criteria amendment), postamendment (patients enrolled after the eligibility criteria amendment), and total. We performed primary efficacy and safety analyses only on adjudicated events and assessed them in secondary analyses by immobility subgroup (level 1, level 2, high-risk level 2 [≥1 of 3 VTE risk factors], or low-risk level 2 [0 of 3 VTE risk factors]). We also assessed selected efficacy and safety end points in patients stratified by use of antiplatelet therapy for 1 or more days and performed interaction analyses to assess the impact of antiplatelet therapy on the observed treatment effect.

We compared incidence of VTE and bleeding between randomly assigned treatment groups by using chi-square and Fisher exact tests. We performed a time-to-event analysis for all-cause mortality by using a Cox proportional hazards model, with the treatment group as the only covariate; according to our visual inspection of the curves, the proportional hazards assumption was met. After correcting for the interim analysis, we set the critical *P* value at 0.042 for the final analysis of the primary efficacy end point in the total population and reported 95.8% CI values. For all other end points, a *P* value less than 0.05 was considered significant. We conducted formal tests of interaction between the study drug and age, sex, and immobility level and constructed forest plots for the primary efficacy end point. We did not conduct formal tests of interaction for the primary safety end point because there were too few events. We performed a sensitivity analysis for the primary efficacy end point, which included all patients who withdrew or were excluded from the study after random assignment. We used SAS, version 9.1 (SAS Institute, Cary, North Carolina), for all statistical analyses.

Role of the Funding Source

This study was sponsored by sanofi-aventis (Paris, France), which also funded editorial support for the preparation of this article. The steering committee (**Appendix 1**) proposed the study design and was responsible for overseeing the conduct of the study and for reviewing and interpreting the data. The study protocol was developed and written by a clinical team at sanofi-aventis on the basis of the study design proposal. Staff at sanofi-aventis performed data management and statistical analysis. The steering committee developed the manuscript, with input from the sanofi-aventis clinical team and final authority from all coauthors.

RESULTS

Baseline Characteristics and Study Groups

Of 7500 initially enrolled patients (**Figure 1**), 7415 received open-label prophylaxis with enoxaparin (median duration, 8.0 days [interquartile range {IQR}, 6.0 to 10.0 days]) (**Figure 1**). Of 6085 patients who completed open-label therapy and were randomly assigned, 5963 received at least 1 dose of the study drug (median treatment duration, 27.0 days [IQR, 24.0 to 29.0 days] for the enoxaparin group vs. 28.0 days [IQR, 24.0 to 29.0 days] for the placebo group); these patients comprised our safety popula-

Table 3. **Incidence of the Individual Components of the Composite VTE End Point at Days 28 and 90**

End Point	Preamendment*			Postamendment		
	Extended-Duration Enoxaparin (n = 1818)	Placebo (n = 1867)	Absolute Risk Difference (CI), %†	Extended-Duration Enoxaparin (n = 667)	Placebo (n = 643)	Absolute Risk Difference (CI), %†
Day 28, *n* (%)‡						
Symptomatic VTE	4 (0.2)	22 (1.2)	−0.96 (−1.49 to −0.42)	1 (0.1)	2 (0.3)	−0.16 (−0.68 to 0.36)
Proximal DVT	44 (2.4)	73 (3.9)	−1.49 (−2.62 to −0.36)	16 (2.4)	22 (3.4)	−1.02 (−2.85 to 0.80)
Symptomatic	4 (0.2)	18 (1.0)	−0.74 (−1.24 to −0.25)	1 (0.1)	2 (0.3)	−0.16 (−0.68 to 0.36)
Asymptomatic	40 (2.2)	55 (2.9)	−0.75 (−1.77 to 0.28)	15 (2.2)	20 (3.1)	−0.86 (−2.61 to 0.89)
PE§	1 (0.1)	5 (0.3)	−0.21 (−0.47 to 0.05)	0	0	–
Symptomatic	0	4 (0.2)	−0.21 (−0.43 to −0.00)	0	0	–
Asymptomatic	1 (0.1)	1 (0.1)	0.00 (−0.15 to 0.15)	0	0	–
Fatal	0	1 (0.1)	−0.05 (−0.16 to 0.05)	0	0	–
Day 90, *n* (%)‡						
VTE	48 (2.6)	83 (4.4)	−1.81 (−3.00 to −0.61)	17 (2.5)	22 (3.4)	−0.87 (−2.72 to 0.97)
Symptomatic VTE	7 (0.4)	26 (1.4)	−1.01 (−1.62 to −0.40)	1 (0.1)	2 (0.3)	−0.16 (−0.68 to 0.36)
Proximal DVT	45 (2.5)	76 (4.1)	−1.60 (−2.74 to −0.45)	16 (2.4)	22 (3.4)	−1.02 (−2.85 to 0.80)
Symptomatic	5 (0.3)	21 (1.1)	−0.85 (−1.39 to −0.31)	1 (0.1)	2 (0.3)	−0.16 (−0.68 to 0.36)
Asymptomatic	40 (2.2)	55 (2.9)	−0.75 (−1.77 to 0.28)	15 (2.2)	20 (3.1)	−0.86 (−2.61 to 0.89)
PE§	3 (0.2)	7 (0.4)	−0.21 (−0.54 to 0.12)	1 (0.1)	0	0.15 (−0.14 to 0.44)
Symptomatic	2 (0.1)	5 (0.3)	−0.16 (−0.44 to 0.13)	0	0	–
Asymptomatic	1 (0.1)	2 (0.1)	−0.05 (−0.24 to 0.13)	1 (0.1)	0	0.15 (−0.14 to 0.44)
Fatal	0 (0.0)	2 (0.1)	−0.11 (−0.26 to 0.04)	1 (0.1)	0	0.15 (−0.14 to 0.44)

DVT = deep venous thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.
* Data include outcomes that were not fully adjudicated at the time of interim analysis. The analysis using adjudicated data only found no significant difference between groups. See "Trial Monitoring and Amendment" in the Methods section for further details.
† For VTE end points in the total population, we report 95.8% CIs ($P < 0.042$) because of the α adjustment for the interim analysis. For all other end points, we report 95% CIs ($P < 0.050$).
‡ Assessed in the efficacy population (4995 patients). We excluded 21 patients from the immobility subgroups (20 preamendment [9 in the enoxaparin group and 11 in the placebo group] and 1 postamendment [from the enoxaparin group]) because of missing immobility-level data or absence of immobility-level classification.
§ Includes asymptomatic PE events in 1 patient in the placebo group (who showed no clinical symptoms of VTE before death; PE was proven on autopsy) and 1 asymptomatic event in the enoxaparin group (detected after routine examination of a patient by using spiral computed tomography).

tion. Median treatment durations were similar in patients enrolled before and after the amendment (27.0 days [IQR, 24.0 to 29.0 days] vs. 28.0 days [IQR, 25.0 to 29.0 days] for both groups). Nine hundred sixty-eight patients withdrew from the study or had unevaluable ultrasonograms, which left 4995 patients in our efficacy population (median treatment duration, 28 days [IQR, 25.0 to 29.0 days] for both groups).

Baseline characteristics were well balanced between groups (**Table 1**). In both groups and trial periods, most patients had acute infection without septic shock, acute respiratory insufficiency, or heart failure (New York Heart Association class III or IV). The pre- and postamendment safety populations differed in some characteristics, most notably the proportion of patients with level 1 and level 2 immobility (preamendment, 1179 [27.3%] vs. 3135 [72.7%], respectively; postamendment, 1394 [85.7%] vs. 233 [14.3%]) (**Figure 1**).

Efficacy

Extended-duration enoxaparin significantly reduced VTE at 28 ± 4 days in the total efficacy population (61 events [2.5%] in the enoxaparin group vs. 100 events [4.0%] in the placebo group; absolute risk difference, −1.53% [95.8% CI, −2.54% to −0.52%]) (**Table 2**), an effect largely attributable to a decrease in symptomatic DVT (absolute risk difference, −0.60% [95.8% CI, −1.00% to −0.19%]) (**Table 3**). The effect was unchanged at 90 days, with an additional 4 events in the enoxaparin group and 5 events in the placebo group (absolute risk difference favoring enoxaparin, −1.57% [95.8% CI, −2.61% to −0.53%]), and was similar among the 324 patients with evaluable efficacy data who were also receiving antiplatelet agents (data not shown; P value for interaction = 0.32). Cumulative all-cause mortality did not significantly differ between groups at 30, 90, or 180 days (**Appendix Table 1**, available at www.annals.org). One patient in the placebo group died of a pulmonary embolism. Efficacy outcomes before and after the amendment are shown in **Tables 2** and **3** and **Appendix Table 1**.

Sensitivity analyses conducted for the primary efficacy end point suggested these findings were not dependent on the exclusion of unevaluable patients from the efficacy population (**Appendix 3**, available at www.annals.org).

Safety

The number of major hemorrhages at 30 days was significantly greater in the extended-duration enoxaparin group than the placebo group (25 events [0.8%] vs. 10 [0.3%] events; absolute risk difference, 0.51% [95% CI, 0.12% to 0.89%]), using a 20-g/L reduction in hemoglobin level as a threshold (**Table 2**). One patient in the

Table 3—Continued

Total Population		
Extended-Duration Enoxaparin (n = 2485)	Placebo (n = 2510)	Absolute Risk Difference (CI), %†
5 (0.2)	24 (1.0)	−0.75 (−1.19 to −0.32)
60 (2.4)	95 (3.8)	−1.37 (−2.37 to −0.37)
5 (0.2)	20 (0.8)	−0.60 (−1.00 to −0.19)
55 (2.2)	75 (3.0)	−0.77 (−1.69 to 0.14)
1 (0.0)	5 (0.2)	−0.16 (−0.34 to 0.04)
0	4 (0.2)	−0.16 (−0.32 to 0.00)
1 (0.1)	1 (0.1)	0.00 (−0.11 to 0.11)
0	1 (0.0)	−0.04 (−0.12 to 0.04)
65 (2.6)	105 (4.2)	−1.57 (−2.61 to −0.53)
8 (0.3)	28 (1.1)	−0.79 (−1.28 to −0.31)
61 (2.5)	98 (3.9)	−1.45 (−2.46 to −0.44)
6 (0.2)	23 (0.9)	−0.67 (−1.11 to −0.24)
55 (2.2)	75 (3.0)	−0.77 (−1.69 to 0.14)
4 (0.2)	7 (0.3)	−0.12 (−0.39 to 0.15)
2 (0.1)	5 (0.2)	−0.12 (−0.33 to 0.09)
2 (0.1)	2 (0.1)	0.00 (−0.16 to 0.16)
1 (0.0)	2 (0.1)	−0.04 (−0.18 to 0.10)

extended-duration enoxaparin group had hemorrhagic transformation of a stroke and died.

When we used the protocol definition of a major bleeding event (30-g/L reduction in hemoglobin level), the absolute difference in major hemorrhages at 30 days was slightly lower (0.44% [95% CI, 0.10% to 0.78%]) (**Appendix Table 2**, available at www.annals.org). Major hemorrhage rates were similar overall and across trial periods and immobility levels regardless of whether we used a 20-g/L or 30-g/L threshold (**Appendix Table 3**, available at www.annals.org).

Total bleeding events (major and minor) were also significantly increased in patients who received enoxaparin (absolute risk difference favoring placebo, 2.37% [95% CI, 1.26% to 3.48%]) (**Table 4** and **Appendix Table 4**). A higher proportion of the 411 patients (7%) who received antiplatelet agents for 1 day or longer experienced increases in major bleeding (9 [2.2%] vs. 18 [0.3%]; $P < 0.001$) and total bleeding events (32 [7.8%] vs. 270 [4.9%]; $P < 0.010$), but analyses revealed no statistically significant interaction between antiplatelet medication and treatment assignment for either outcome ($P = 0.54$ for major bleeding and 0.50 for total bleeding).

The proportion of serious adverse events that led to death was 1.3% (39 of 2975 patients) in the extended-duration enoxaparin group and 1.5% (45 of 2988 patients) in the placebo group (**Table 4**). **Table 4** also shows the occurrences of other adverse events. We counted 13 cases of VTE and 20 major bleeding events (hemoglobin level decrease ≥20 g/L) as serious adverse events (**Appendix Table 5**, available at www.annals.org). Treatment-emergent adverse events that the investigator judged to be possibly related to study treatment were reported in 1.8% (54 of 2975) and 1.6% (49 of 2988) patients receiving extended-duration enoxaparin and placebo, respectively. The incidence of serious treatment-emergent adverse events that were possibly related to study treatment was 0.2% (5 of 2975 patients) in the extended-duration enoxaparin group and 0.2% (7 of 2988 patients) in the placebo group.

Subgroup Analyses

Tests of interaction in the total efficacy population revealed a statistically significant difference in primary efficacy outcome by sex ($P = 0.016$) and age ($P = 0.011$) (**Appendix Figure 1**, available at www.annals.org). Sex and age subgroups had distinct characteristics and did not substantially overlap; 35% of the women were older than 75 years, and women represented 59% of patients older than 75 years. We therefore assessed primary efficacy and safety end points by subgroups of sex and age and by immobility level (given the importance of immobility to the study design). **Table 5** presents primary efficacy and safety end points for age subgroups. We found statistically significant reductions in VTE with enoxaparin in women (absolute risk difference, −2.71% [95.8% CI, −4.15% to −1.28%]) but not men (−0.36% [95.8% CI, −1.79% to 1.07%]). Similarly, we found statistically significant increases in major bleeding events in women (0.66% [95% CI, 0.11% to 1.21%]) but not men (0.34% [95% CI, −0.20% to 0.89%]) (**Appendix Tables 5, 6,** and **7**, available at www.annals.org). Patients older than 75 years experienced statistically significant reductions in VTE with enoxaparin at all immobility levels (−4.25% [95.8% CI, −6.45% to −2.04%]) and a non–statistically significant increase in major bleeding events (0.24% [95% CI, −0.46% to 0.94%]). Patients 75 years or younger experienced no clear treatment benefit and some harm in both immobility groups (absolute risk difference for increase in major bleeding events, 0.62% [95% CI, 0.15% to 1.08%]).

DISCUSSION

Extended-duration prophylaxis with subcutaneous enoxaparin reduced the combined incidence of symptomatic or asymptomatic DVT, symptomatic pulmonary embolism, or fatal pulmonary embolism in acutely ill medical patients with level 1 immobility, those older than 75 years, and women, with increased rates of major bleeding events. The observed absolute differences in risk for VTE and major bleeding events suggest a favorable benefit-to-risk ratio in these patient subgroups, especially those older than 75 years. Our findings do not support the use of extended-duration prophylaxis for patients with level 2 immobility without any of the 3 specified risk factors for VTE. Mortality did not seem to differ between groups at any time point.

An interaction analysis identified patients older than 75 years and women as independent patient subgroups that may particularly benefit from extended-duration prophylaxis (**Table 5** and **Appendix Tables 6** and 7, available at

Table 4. **Incidence of Secondary Safety End Points and Adverse Events**

End Point	Preamendment*			Postamendment		
	Extended-Duration Enoxaparin (n = 2159)	Placebo (n = 2176)	Absolute Risk Difference (95% CI), %	Extended-Duration Enoxaparin (n = 816)	Placebo (n = 812)	Absolute Risk Difference (95% CI), %
Bleeding, *n* (%)						
All patients with bleeding†	157 (7.3)	98 (4.5)	2.77 (1.37 to 4.17)	29 (3.6)	18 (2.2)	1.34 (−0.29 to 2.96)
Patients with major bleeding events‡	19 (0.9)	10 (0.5)	0.42 (−0.07 to 0.91)	6 (0.7)	0 (0.0)	0.74 (0.15 to 1.32)
Major bleeding events						
Fatal	1 (<0.1)	0 (0.0)	0.05 (−0.04 to 0.14)	0 (0.0)	0 (0.0)	–
Intracranial	4 (0.2)	0 (0.0)	0.19 (0.00 to 0.37)	0 (0.0)	0 (0.0)	–
Intraocular	0 (0.0)	0 (0.0)	–	1 (0.1)	0 (0.0)	0.12 (−0.12 to 0.36)
Other	16 (0.7)	10 (0.5)	0.28 (−0.18 to 0.74)	5 (0.6)	0 (0.0)	0.61 (0.08 to 1.15)
Minor bleeding events	140 (6.5)	88 (4.0)	2.44 (1.11 to 3.77)	24 (2.9)	18 (2.2)	0.72 (−0.81 to 2.26)
Adverse events, *n* (%)						
Serious adverse events§	172 (8.0)	170 (7.8)	0.15 (−1.45 to 1.76)	44 (5.4)	48 (5.9)	−0.52 (−2.76 to 1.72)
Treatment-emergent adverse events‖	602 (27.9)	572 (26.3)	1.60 (−1.05 to 4.24)	146 (17.9)	161 (19.8)	−1.94 (−5.74 to 1.86)
Leading to discontinuation of study drug	82 (3.8)	114 (5.2)	−1.44 (−2.68 to −0.21)	23 (2.8)	23 (2.8)	−0.01 (−1.62 to 1.60)
Leading to death	23 (1.1)	34 (1.6)	−0.50 (−1.17 to 0.18)	16 (2.0)	11 (1.4)	0.61 (−0.63 to 1.85)
Thrombocytopenia (<50 000 × 10^9 cells/L)	6 (0.3)	8 (0.4)	−0.09 (−0.43 to 0.25)	1 (0.1)	1 (0.1)	0.00 (−0.34 to 0.34)
Heparin-induced thrombocytopenia	1 (<0.0)	0	0.05 (−0.04 to 0.14)	0	0	–

VTE = venous thromboembolism.
* Data include outcomes that were not fully adjudicated at the time of interim analysis. The analysis using adjudicated data only found no significant difference between groups. See "Trial Monitoring and Amendment" in the Methods section for further details.
† Includes major and minor bleeding events; these data used the post hoc criterion for major bleeding events of a threshold hemoglobin level decrease of 20 g/L. **Appendix Table 3** reports incidence of bleeding events with the original threshold criterion for major bleeding events.
‡ A threshold decrease in hemoglobin level of 20 g/L was incorporated as a post hoc criterion. **Appendix Table 3** reports incidence of major bleeding events with the original threshold criterion of a 30-g/L decrease in hemoglobin level. **Appendix Table 7** provides further details about the types of major bleeding events that occurred.
§ Includes 13 VTEs (1 in the enoxaparin group and 12 in the placebo group) and 20 major bleeding events (≥20-g/L decrease in hemoglobin level) (15 in the enoxaparin group and 5 in the placebo group). We also counted VTEs and major bleeding events as serious adverse events if they met the serious adverse event criteria (Methods section and **Appendix Table 4**).
‖ Adverse events that developed or worsened during the treatment or posttreatment periods and that investigators considered to be possibly related to the study medication. The total includes additional types of events that do not correspond to the listed subcategories.

www.annals.org). PREVENT (Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial) (12) also reported greater reductions in absolute risk for VTE in elderly patients who received low-molecular-weight heparin, compared with the overall population (3.8% vs. 2.19%, respectively). Previous studies (13) have demonstrated the effect of older age on VTE risk. Differential effects of anticoagulation therapy according to patient sex have also been reported in the context of VTE recurrence when oral anticoagulant therapy is discontinued after an unprovoked VTE; men have a higher risk for recurrence than women (14, 15).

The efficacy of short-term thromboprophylaxis in reducing the risk for VTE in acutely ill medical patients has been reported (2–4) and seems to be driven by a decrease in asymptomatic events. The use of asymptomatic proximal DVT as a clinical efficacy end point in phase 3 studies has been questioned. However, recent data link asymptomatic DVT in at-risk hospitalized medical patients with development of symptomatic VTE, the postthrombotic syndrome, and increased mortality; estimates (6, 16–18) suggest that approximately 34% of VTE-related deaths result from sudden pulmonary embolism in patients with no previous symptomatic VTE diagnosis. Although most confirmed VTEs in our study were asymptomatic proximal DVT diagnosed by ultrasonography, extended-duration prophylaxis was associated with a statistically significant decrease in the incidence of symptomatic VTE compared with placebo, which previous studies of short-term VTE prophylaxis in acutely ill medical patients did not show (2–4).

We also observed a statistically significant increase in the incidence of bleeding with extended-duration enoxaparin compared with placebo. The rates and absolute differences in major bleeding events observed in patients who received extended-duration enoxaparin are similar to the increased incidence associated with anticoagulant use in placebo-controlled trials of short-term prophylaxis (2–4), and they did not differ when we used a 30-g/L threshold decrease in hemoglobin level instead of a 20-g/L threshold as the criterion for major bleeding.

Our study has limitations. When we designed it, few data were available on the characteristics of acutely ill medical patients who would benefit the most from extended-duration prophylaxis. At the final interim analysis, we observed no significant between-group differences due to lower-than-expected VTE rates in patients with adjudicated data available. The subsequent eligibility criteria amendment focused enrollment on patients with increased VTE risk. This shift in eligibility during the trial means that although we report data for the total trial population,

Table 4—Continued

Total Population		
Extended-Duration Enoxaparin (*n* = 2975)	Placebo (*n* = 2988)	Absolute Risk Difference (95% CI), %
186 (6.3)	116 (3.9)	2.37 (1.26 to 3.48)
25 (0.8)	10 (0.3)	0.51 (0.12 to 0.89)
1 (<0.1)	0 (0.0)	0.03 (−0.03 to 0.10)
4 (0.1)	0 (0.0)	0.13 (0.00 to 0.27)
1 (<0.1)	0 (0.0)	0.03 (−0.03 to 0.10)
21 (0.7)	10 (0.3)	0.37 (0.01 to 0.74)
164 (5.5)	106 (3.5)	1.97 (0.91 to 3.02)
216 (7.3)	218 (7.3)	−0.04 (−1.35 to 1.28)
748 (25.1)	733 (24.5)	0.61 (−1.58 to 2.80)
105 (3.5)	137 (4.6)	−1.06 (−2.06 to −0.05)
39 (1.3)	45 (1.5)	−0.20 (−0.79 to 0.40)
7 (0.2)	9 (0.3)	−0.07 (−0.33 to 0.20)
1 (<0.0)	0	0.03 (−0.03 to 0.10)

our overall findings are no longer generalizable to the whole patient population. In particular, the postamendment population had a notably larger proportion of patients with level 1 immobility than the preamendment population. This may partly have resulted from the continued recruitment of patients with level 1 but not level 2 immobility, pending development and approval of the amendment. We cannot exclude the possibility that some enrolling investigators continued to follow this guidance of level 1–only recruitment after the amendment was issued. In addition, the increased proportion of patients recruited with level 1 immobility may have reflected the relative complexity of patient eligibility assessment, given that enrollment of patients with level 1 immobility did not require screening for additional VTE risk factors. However, despite the amendment's limitations, its implementation and the continuation of the trial allowed us to identify which acutely ill medical patients would and would not benefit from extended-duration prophylaxis.

Table 5. **Incidence of Primary Efficacy and Safety End Points in Patient Age Subgroups, by Sex and Immobility Level**

End Point	Extended-Duration Enoxaparin, *n/N (%)*	Placebo, *n/N (%)*	Absolute Risk Difference (CI), %*
VTE at day 28†			
Age >75 y			
Women	9/400 (2.25)	34/446 (7.62)	−5.37 (−8.34 to −2.41)
Level 1	2/179 (1.12)	16/195 (8.21)	−7.09 (−11.39 to −2.78)
Level 2	7/220 (3.18)	18/250 (7.20)	−4.02 (−8.12 to 0.09)
Men	9/325 (2.77)	16/297 (5.39)	−2.62 (−5.86 to 0.63)
Level 1	3/120 (2.50)	8/119 (6.72)	−4.22 (−9.72 to 1.27)
Level 2	6/204 (2.94)	8/178 (4.49)	−1.55 (−5.52 to 2.42)
Age ≤75 y			
Women	14/837 (1.67)	23/801 (2.87)	−1.20 (−2.70 to 0.3)
Level 1	5/372 (1.34)	12/317 (3.79)	−2.44 (−4.94 to 0.05)
Level 2	9/460 (1.96)	10/478 (2.09)	−0.14 (−2.01 to 1.73)
Men	29/923 (3.14)	27/966 (2.80)	0.35 (−1.24 to 1.94)
Level 1	15/399 (3.76)	11/409 (2.69)	1.07 (−1.46 to 3.60)
Level 2	14/521 (2.69)	16/553 (2.89)	−0.21 (−2.25 to 1.84)
Major bleeding events‡			
Age >75 y			
Women	4/493 (0.8)	3/549 (0.5)	0.26 (−0.74 to 1.27)
Level 1	2/227 (0.9)	2/250 (0.8)	0.08 (−1.56 to 1.72)
Level 2	2/265 (0.8)	1/298 (0.3)	0.42 (−0.81 to 1.65)
Men	2/385 (0.5)	1/354 (0.3)	0.24 (−0.67 to 1.14)
Level 1	2/149 (1.3)	0/151 (0.0)	1.34 (−0.51 to 3.19)
Level 2	0/235 (0.0)	1/203 (0.5)	−0.49 (−1.46 to 0.47)
Age ≤75 y			
Women	10/1015 (1.0)	1/962 (0.1)	0.88 (0.24 to 1.52)
Level 1	3/446 (0.7)	0/406 (0.0)	0.67 (−0.09 to 1.43)
Level 2	7/564 (1.2)	1/550 (0.2)	1.06 (0.08 to 2.04)
Men	9/1082 (0.8)	5/1123 (0.4)	0.39 (−0.28 to 1.05)
Level 1	2/470 (0.4)	0/474 (0.0)	0.43 (−0.16 to 1.01)
Level 2	7/608 (1.2)	5/645 (0.8)	0.38 (−0.71 to 1.46)

VTE = venous thromboembolism.

* For VTE end points in the total population, we report 95.8% CIs ($P < 0.042$) because of the α adjustment for the interim analysis. For all other end points, we report 95% CIs ($P < 0.050$).

† Assessed in the efficacy population (4995 patients). We excluded 21 patients from the immobility subgroups because of missing immobility-level data or absence of immobility-level classification. Of these, 1 had VTE (a woman >75 years who received placebo).

‡ A threshold decrease in hemoglobin level of 20 g/L was incorporated as a post hoc criterion. **Appendix Table 6** reports incidence of major bleeding events with the original threshold criterion of a 30-g/L decrease in hemoglobin level. Assessed in the safety population (5963 patients). We excluded 22 patients from this analysis because of missing immobility-level data or absence of immobility-level classification; we observed no major bleeding events among these patients.

Another limitation is that we do not report the number of patients screened for inclusion. Although these data are important for assessing the generalizability of the observed results, we did not systematically capture them during our study. Finally, although our findings suggest that extended-duration VTE prophylaxis has a favorable balance of benefits and harms (17), decisions about the use of prophylaxis should depend on individual patient characteristics, preferences, and values (19, 20).

In conclusion, compared with placebo, extended-duration enoxaparin prophylaxis was associated with a reduction in the combined incidence of symptomatic or asymptomatic DVT, symptomatic pulmonary embolism, and fatal pulmonary embolism in acutely ill medical patients with level 1 immobility, those older than 75 years, and women. This risk reduction occurred in addition to that associated with short-term prophylaxis and was associated with levels of major bleeding events similar to those seen in previous studies of short-term VTE prophylaxis in medical patients (2–4). These findings, in addition to a patient's individual benefit–risk assessment and preferences, should assist physicians who are considering the use of extended-duration prophylaxis.

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Appendix 2: Supplementary Methodology

Central Adjudication of Efficacy and Safety End Points

A subcommittee of the steering committee performed adjudication of hemorrhages (presence or absence and severity), deaths (death characteristics and relation with treatment), and suspected VTE (including diagnostic tests, such as chest computed tomography, pulmonary angiography, venography, and ventilation–perfusion lung scan). The adjudication committees that assessed the efficacy and safety end points were blinded to treatment allocation but were aware of the period of the study when events occurred: open-phase, double-blind, or follow-up. A quorum of at least 3 members, including the chairperson, attended each adjudication meeting.

Event Rate Assumptions and Modified Target Enrollment After the Protocol Amendment

After the eligibility criteria were amended, we assumed that the placebo group in the higher-risk population would have a VTE rate of 5.2% at day 28 after random assignment. Given this increase in expected VTE rate, a type I error rate of 4.7% (adjusted following the interim analysis), and 80% power, we needed a reduced total of 3072 evaluable patients (1536 per treatment group) who met amendment criteria to show a 40% reduction in VTE incidence with the extended-duration enoxaparin regimen. Assuming an evaluability rate of 65%, we aimed to enroll 4730 patients who met the amendment criteria. Because we had already recruited 2883 patients with either level 1 or level 2 immobility (who were older than 75 years or had cancer, history of cancer, or history of VTE) at the time of the interim analysis and eligibility criteria amendment, we only needed an additional 1843 patients to achieve the revised target number of evaluable patients.

Appendix 3: Sensitivity Analyses Conducted for the Primary Efficacy End Point

We conducted sensitivity analyses to assess whether inclusion of all randomly assigned patients excluded from the efficacy population changed the primary efficacy end point result, assuming observed within-group event rates for missing patients and using the upper boundary of VTE incidence in the placebo group to determine the VTE incidence in the enoxaparin group required to yield a statistically nonsignificant difference. The difference in primary outcome remained statistically significant in both analyses, which suggests that the finding did not depend on the exclusion of the unevaluable patients.

Approximately 18% (1090 of 6085) of all randomly assigned patients were unevaluable and were therefore excluded from the primary efficacy analysis (including 122 patients who were randomly assigned but did not receive any prophylaxis during the double-blind phase and 968 patients who were randomly assigned, received treatment, but were excluded from the efficacy population for different reasons) (**Figure 1**). The unevaluable patients comprised 549 patients in the extended-duration enoxaparin group and 541 patients in the placebo group. Because we did not conduct the primary efficacy analysis on a true intention-to-treat basis, we subsequently performed a post hoc sensitivity analysis on all randomly assigned patients.

We performed 2 separate sensitivity analyses on the basis of 2 different key assumptions. The first analysis assumed that a similar rate of VTE would be observed in both patients who were included in the primary analysis of efficacy and those who were excluded (2.5% in the extended-duration enoxaparin group and 4.0% in the placebo group). On the basis of this assumption, we predicted a VTE rate of 76 of 3034 in the extended-duration enoxaparin group and 122 of 3051 in the placebo group, with a level of significance of $P < 0.001$.

In the second analysis, we assumed that the incidence rate of VTE in patients excluded from the primary efficacy analysis (549 and 541 patients in the enoxaparin and placebo groups, respectively) would range from the lower boundary (3%) to the upper boundary (5%) of the 95% CI in the placebo group and from 2% to 10% in the enoxaparin group, although the upper boundary of the 95% CI of observed VTE incidence in the enoxaparin group was only 3.1%. Assuming a VTE incidence rate of 5% in

the 541 patients in the placebo group (worst case), the VTE rate among the 549 patients in the enoxaparin group should be greater than 6.4% to obtain a nonsignificant difference between the groups ($P > 0.042$). Because the patients assessed for primary efficacy and those who were unevaluable (and therefore excluded from this assessment) were demographically similar, the likelihood of observing such results can be considered low.

Appendix Figure 2 shows changes in the *P* value according to the rates of VTE in the placebo group.

In conclusion, the strong significance of the treatment effect observed in the primary efficacy analysis would not have been affected by the inclusion of unevaluable patients.

Appendix Table 1. **All-Cause Mortality, by Immobility Level***

Time Point and Immobility Level	All-Cause Mortality		
	Extended-Duration Enoxaparin, *n/N (%)*	Placebo, *n/N (%)*	Hazard Ratio (95% CI)
Day 30			
Total	60/2975 (2.1)	65/2988 (2.2)	0.93 (0.65 to 1.32)
Preamendment	43/2159 (2.1)	47/2176 (2.2)	0.93 (0.61 to 1.40)
Postamendment	17/816 (2.1)	18/812 (2.3)	0.93 (0.48 to 1.80)
Immobility level			
Level 1	36/1292 (2.8)	43/1281 (3.4)	0.83 (0.53 to 1.29)
High-risk level 2†	18/721 (2.6)	11/746 (1.5)	1.70 (0.80 to 3.59)
Low-risk level 2‡	6/951 (0.7)	11/950 (1.2)	0.55 (0.20 to 1.48)
Day 90			
Total	148/2975 (5.2)	142/2988 (5.0)	1.04 (0.83 to 1.31)
Preamendment	105/2159 (5.2)	105/2176 (5.1)	1.01 (0.77 to 1.32)
Postamendment	43/816 (5.4)	37/812 (4.7)	1.14 (0.74 to 1.77)
Immobility level			
Level 1	82/1292 (6.6)	76/1281 (6.1)	1.06 (0.78 to 1.45)
High-risk level 2†	43/721 (6.3)	41/746 (5.9)	1.08 (0.71 to 1.66)
Low-risk level 2‡	23/951 (2.6)	25/950 (2.8)	0.92 (0.52 to 1.61)
Day 180			
Total	220/2975 (8.2)	204/2988 (7.7)	1.08 (0.89 to 1.31)
Preamendment	153/2159 (8.1)	150/2176 (7.8)	1.03 (0.82 to 1.29)
Postamendment	67/816 (8.5)	54/812 (7.5)	1.23 (0.86 to 1.75)
Immobility level			
Level 1	123/1292 (10.1)	105/1281 (9.2)	1.16 (0.89 to 1.50)
High-risk level 2†	63/721 (10.2)	57/746 (8.4)	1.15 (0.80 to 1.64)
Low-risk level 2‡	34/951 (4.1)	42/950 (5.3)	0.80 (0.51 to 1.26)

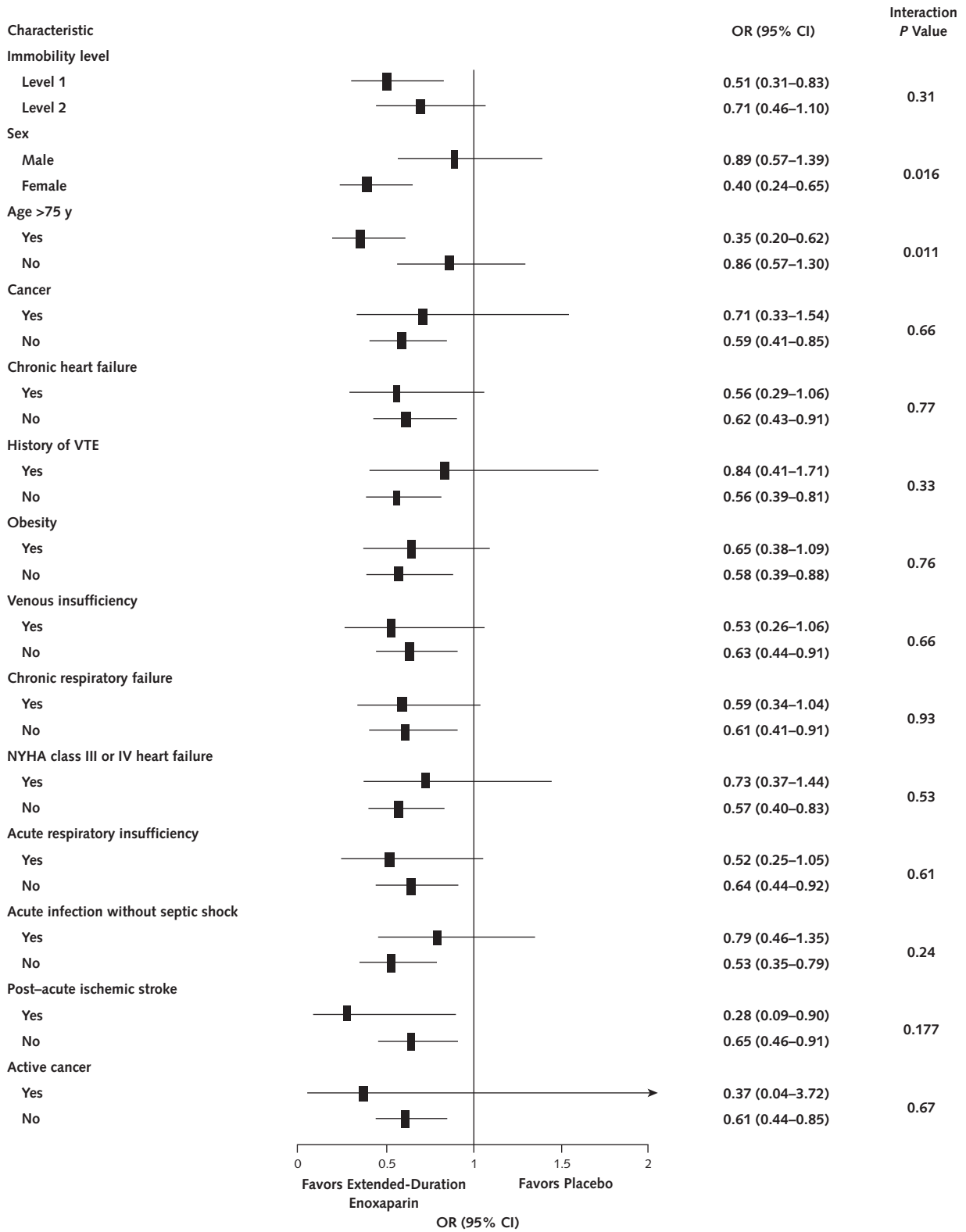
VTE = venous thromboembolism.
* We assessed mortality in the safety population and used Kaplan–Meier estimates to determine all-cause mortality rates.
† Patients with level 2 immobility and ≥1 of the following VTE risk factors: age >75 y, history of VTE, or active or previous cancer.
‡ Patients with level 2 immobility and none of the additional specified risk factors for VTE.

Appendix Table 2. **Incidence of the Primary Safety End Point, Using the Protocol-Defined Hemoglobin Decrease Threshold of 30 g/L**

Immobility Level	Major Bleeding Events*								
	Preamendment†			Postamendment			Total Population		
	Extended-Duration Enoxaparin, *n/N (%)*	Placebo, *n/N (%)*	Absolute Risk Difference (95% CI), %	Extended-Duration Enoxaparin, *n/N (%)*	Placebo, *n/N (%)*	Absolute Risk Difference (95% CI), %	Extended-Duration Enoxaparin, *n/N (%)*	Placebo, *n/N (%)*	Absolute Risk Difference (95% CI), %
All	16/2159 (0.7)	7/2176 (0.3)	0.42 (−0.01 to 0.85)	4/816 (0.5)	0/812 (0.0)	0.49 (0.01 to 0.97)	20/2975 (0.7)	7/2988 (0.2)	0.44 (0.10 to 0.78)
Level 1	4/590 (0.7)	0/589 (0.0)	0.68 (0.02 to 1.34)	2/702 (0.3)	0/692 (0.0)	0.28 (−0.11 to 0.68)	6/1292 (0.5)	0/1281 (0.0)	0.46 (0.09 to 0.84)
Level 2	12/1559 (0.8)	7/1576 (0.4)	0.33 (−0.22 to 0.87)	2/113 (1.8)	0/120 (0.0)	1.77 (−0.66 to 4.20)	14/1672 (0.8)	7/1696 (0.4)	0.42 (−0.11 to 0.96)
High-risk‡	4/627 (0.6)	3/640 (0.5)	0.17 (−0.65 to 0.99)	2/94 (2.1)	0/106 (0.0)	2.13 (−0.79 to 5.04)	6/721 (0.8)	3/746 (0.4)	0.43 (−0.37 to 1.23)
Low-risk§	8/932 (0.9)	4/936 (0.4)	0.43 (−0.29 to 1.16)	0/19 (0.0)	0/14 (0.0)	0.00 (0.00 to 0.00)	8/951 (0.8)	4/950 (0.4)	0.42 (−0.29 to 1.13)

VTE = venous thromboembolism.
* Assessed in the safety population (5963 patients). We excluded 22 patients in the total safety population (21 preamendment [10 from the enoxaparin group and 11 from the placebo group] and 1 postamendment [from the enoxaparin group]) because of missing immobility-level data or absence of immobility-level classification.
† Data include outcomes that were not fully adjudicated at the time of interim analysis. The analysis using adjudicated data only found no significant difference between groups. See "Trial Monitoring and Amendment" in the Methods section for further details.
‡ Patients with level 2 immobility and ≥1 of the following VTE risk factors: age >75 y, history of VTE, or active or previous cancer.
§ Patients with level 2 immobility and none of the additional specified risk factors for VTE.

Appendix Figure 1. **Relative risk for VTE across specific patient subgroups during the double-blind treatment period.**



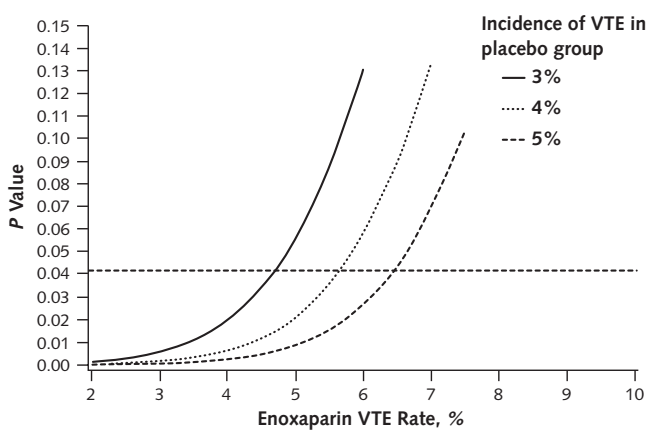
Assessed in the total efficacy population. NYHA = New York Heart Association; OR = odds ratio; VTE = venous thromboembolism.

Appendix Table 3. Causes of Major Bleeding Events

Major Bleeding Event	Preamendment, *n*		Postamendment, *n*		Total Population, *n*	
	Extended-Duration Enoxaparin*	Placebo	Extended-Duration Enoxaparin	Placebo	Extended-Duration Enoxaparin*	Placebo
Hemoglobin decrease ≥20 g/L†						
Gastrointestinal	9	7	1		10	7
Intracranial	4				4	
Fatal‡	1				1	
Hemothorax	1				1	
Pulmonary hemorrhage	1				1	
Subcutaneous	2				2	
Epistaxis	1				1	
Hematoma		2	1		1	2
Ecchymosis	1				1	
Leg hemorrhage, intermittent epistaxis, and intermittent abdominal ecchymosis			1		1	
Macroscopic hematuria or bladder-wall hematoma	1				1	
Hemoglobin decrease ≥30 g/L						
Gastrointestinal	8	7	1		9	7
Intracranial	4				4	
Fatal‡	1				1	
Hemothorax	1		1		2	
Pulmonary hemorrhage	1				1	
Subcutaneous	2				2	
Epistaxis						
Ecchymosis						
Macroscopic hematuria or bladder-wall hematoma	1				1	
Intraocular					1	
Hemoptysis					1	

* Two patients included in the extended-duration group of both the preamendment and total populations experienced 2 major bleeding events. One patient had a fatal intracranial bleeding event, and 1 patient experienced both an intracranial and a gastrointestinal bleeding event.
† Includes 1 patient in the placebo group with a hemoglobin decrease of ≥20 g/L at an undefined location.
‡ Hemorrhagic transformation of a stroke.

Appendix Figure 2. Changes in the *P* value, by VTE incidence in the placebo group.



The area below the horizontal dashed line represents the region of statistical significance. VTE = venous thromboembolism.

Appendix Table 4. Incidence of Major and Minor Bleeding Events

Patients	Incidence of Bleeding Events								
	Preamendment			Postamendment			Total Population		
	Extended-Duration Enoxaparin (n = 2159), n (%)	Placebo (n = 2176), n (%)	Absolute Risk Difference (95% CI), %	Extended-Duration Enoxaparin (n = 816), n (%)	Placebo (n = 812), n (%)	Absolute Risk Difference (95% CI), %	Extended-Duration Enoxaparin (n = 2975), n (%)	Placebo (n = 2988), n (%)	Absolute Risk Difference (95% CI), %
All patients with bleeding*	157 (7.3)	98 (4.5)	2.77 (1.37 to 4.17)	29 (3.6)	18 (2.2)	1.34 (−0.29 to 2.96)	186 (6.3)	116 (3.9)	2.37 (1.26 to 3.48)
Patients with major bleeding events†	16 (0.7)	7 (0.3)	0.42 (−0.01 to 0.85)	4 (0.5)	0 (0.0)	0.49 (0.01 to 0.97)	20 (0.7)	7 (0.2)	0.44 (0.10 to 0.78)
Major bleeding events									
Fatal	1 (<0.1)	0 (0.0)	0.05 (−0.04 to 0.14)	0 (0.0)	0 (0.0)	–	1 (<0.1)	0 (0.0)	0.03 (−0.03 to 0.10)
Intracranial	4 (0.2)	0 (0.0)	0.19 (0.00 to 0.37)	0 (0.0)	0 (0.0)	–	4 (0.1)	0 (0.0)	0.13 (0.00 to 0.27)
Intraocular	0 (0.0)	0 (0.0)	–	1 (0.1)	0 (0.0)	0.12 (−0.12 to 0.36)	1 (<0.1)	0 (0.0)	0.03 (−0.03 to 0.10)
Other	13 (0.6)	7 (0.3)	0.28 (−0.12 to 0.68)	3 (0.4)	0 (0.0)	0.37 (−0.05 to 0.78)	16 (0.5)	7 (0.2)	0.30 (−0.01 to 0.62)
Minor bleeding events	143 (6.6)	91 (4.2)	2.44 (1.10 to 3.79)	26 (3.2)	18 (2.2)	0.97 (−0.60 to 2.54)	169 (5.7)	109 (3.6)	2.03 (0.96 to 3.10)

* The total includes both major and minor bleeding events. Major bleeding event criteria included the original threshold criterion of a 30-g/L decrease in hemoglobin level. **Table 4** reports incidence of major bleeding events with the post hoc threshold criterion of a 20-g/L decrease in hemoglobin level. **Appendix Table 3** provides details about the types of major bleeding events that occurred.
† Criteria included a threshold decrease in hemoglobin level of 30 g/L.

Appendix Table 5. Primary Efficacy and Safety Outcomes Also Counted as SAEs

Outcome	Extended-Duration Enoxaparin, n			Placebo, n		
	Patients	Counted as SAEs	Total SAEs	Patients	Counted as SAEs	Total SAEs
VTE	61	1	216	100	12	218
Bleeding						
Hemoglobin decrease ≥20 g/L	20	15		7	5	
Hemoglobin decrease ≥30 g/L	25	15		10	7	

SAEs = serious adverse events; VTE = venous thromboembolism.

Appendix Table 6. Incidence of Primary Efficacy and Safety End Points, by Sex, Age, and Immobility Level

End Point	Extended-Duration Enoxaparin, *n/N (%)*	Placebo, *n/N (%)*	Absolute Risk Difference (CI), %*
VTE at day 28†			
Women	23/1237 (1.9)	57/1247 (4.6)	−2.71 (−4.15 to −1.28)
Level 1	7/551 (1.3)	28/512 (5.5)	−4.20 (−6.46 to −1.94)
Level 2	16/680 (2.4)	28/728 (3.8)	−1.49 (−3.36 to 0.38)
Men	38/1248 (3.0)	43/1263 (3.4)	−0.36 (−1.79 to 1.07)
Level 1	18/519 (3.5)	19/528 (3.6)	−0.13 (−2.45 to 2.19)
Level 2	20/725 (2.8)	24/731 (3.3)	−0.52 (−2.35 to 1.30)
Age >75 y	18/725 (2.5)	50/743 (6.7)	−4.25 (−6.45 to −2.04)
Level 1	5/299 (1.7)	24/314 (7.6)	−5.97 (−9.37 to −2.57)
Level 2	13/424 (3.1)	26/428 (6.1)	−3.01 (−5.91 to −0.11)
Age ≤75 y	43/1760 (2.4)	50/1767 (2.8)	−0.39 (−1.48 to 0.71)
Level 1	20/771 (2.6)	23/726 (3.2)	−0.57 (−2.34 to −1.19)
Level 2	23/981 (2.3)	26/1031 (2.5)	−0.18 (−1.57 to 1.22)
Major bleeding events‡			
Women	14/1508 (0.9)	4/1511 (0.3)	0.66 (0.11 to 1.21)
Level 1	5/673 (0.7)	2/656 (0.3)	0.44 (−0.34 to 1.21)
Level 2	9/829 (1.1)	2/848 (0.2)	0.85 (0.07 to 1.63)
Men	11/1467 (0.75)	6/1477 (0.41)	0.34 (−0.20 to 0.89)
Level 1	4/619 (0.6)	0/625 (0.0)	0.65 (0.01 to 1.28)
Level 2	7/843 (0.8)	6/848 (0.7)	0.12 (−0.71 to 0.96)
Age >75 y	6/878 (0.7)	4/903 (0.4)	0.24 (−0.46 to 0.94)
Level 1	4/376 (1.1)	2/401 (0.5)	0.57 (0.68 to 1.81)
Level 2	2/500 (0.4)	2/501 (0.4)	0.00 (−0.78 to 0.78)
Age ≤75 y	19/2097 (0.9)	6/2085 (0.3)	0.62 (0.15 to 1.08)
Level 1	5/916 (0.5)	0/880 (0.0)	0.55 (0.07 to 1.02)
Level 2	14/1172 (1.2)	6/1195 (0.5)	0.69 (−0.05 to 1.43)

VTE = venous thromboembolism.

* For VTE end points in the total population, we report 95.8% CIs ($P < 0.042$) because of the α adjustment for the interim analysis. For all other end points, we report 95% CIs ($P < 0.050$).

† Assessed in the efficacy population (4995 patients). We excluded 21 patients from the immobility subgroups because of missing immobility-level data or absence of immobility-level classification. Of these, 1 had VTE (a woman >75 years who received placebo).

‡ Assessed in the safety population (5963 patients). We excluded 22 patients because of missing immobility-level data or absence of immobility-level classification; we observed no major bleeding events among these patients. A threshold decrease in hemoglobin level of 20 g/L was incorporated as a post hoc criterion. **Appendix Table** 7 reports incidence of major bleeding events with the original threshold criterion of a 30-g/L decrease in hemoglobin level.

Appendix Table 7. Incidence of Major Bleeding in Patient Subgroups, Using the Protocol-Defined Hemoglobin Decrease Threshold of 30 g/L*

Subgroup	Incidence of Major Bleeding Events		
	Extended-Duration Enoxaparin, *n/N (%)*	Placebo, *n/N (%)*	Absolute Risk Difference (CI), %†
Age or sex			
Women	13/1508 (0.9)	2/1511 (0.1)	0.73 (0.23 to 1.23)
Level 1	4/673 (0.6)	0/656 (0.0)	0.59 (0.01 to 1.18)
Level 2	9/829 (1.1)	2/848 (0.2)	0.85 (0.07 to 1.63)
Men	7/1467 (0.5)	5/1477 (0.3)	0.14 (−0.32 to 0.60)
Level 1	2/619 (0.3)	0/625 (0.0)	0.32 (−0.12 to 0.77)
Level 2	5/843 (0.6)	5/848 (0.6)	0.00 (−0.73 to 0.73)
Age >75 y	5/878 (0.6)	2/903 (0.2)	0.35 (−0.24 to 0.93)
Level 1	3/376 (0.8)	0/401 (0.0)	0.80 (−0.10 to 1.70)
Level 2	2/500 (0.4)	2/501 (0.4)	0.00 (−0.78 to 0.78)
Age ≤75 y	15/2097 (0.7)	5/2085 (0.2)	0.48 (0.06 to 0.89)
Level 1	3/916 (0.3)	0/880 (0.0)	0.32 (−0.04 to 0.70)
Level 2	12/1172 (1.0)	5/1195 (0.4)	0.61 (−0.08 to 1.29)
Age and sex			
Age >75 y			
Women	4/493 (0.8)	1/549 (0.2)	0.63 (−0.24 to 1.50)
Level 1	2/227 (0.9)	0/250 (0.0)	0.88 (−0.33 to 2.10)
Level 2	2/265 (0.8)	1/298 (0.3)	0.42 (−0.81 to 1.65)
Men	1/385 (0.3)	1/354 (0.3)	−0.02 (−0.77 to 0.73)
Level 1	1/149 (0.7)	0/151 (0.0)	0.67 (−0.64 to 1.98)
Level 2	0/235 (0.0)	1/203 (0.5)	−0.49 (−1.46 to 0.47)
Age ≤75 y			
Women	9/1015 (0.9)	1/962 (0.1)	0.78 (−0.17 to 1.39)
Level 1	2/446 (0.4)	0/406 (0.0)	0.45 (−0.17 to 1.07)
Level 2	7/564 (1.2)	1/550 (0.2)	1.06 (0.08 to 2.04)
Men	6/1082 (0.6)	4/1123 (0.4)	0.20 (−0.36 to 0.76)
Level 1	1/470 (0.2)	0/474 (0.0)	0.21 (−0.20 to 0.63)
Level 2	5/608 (0.8)	4/645 (0.6)	0.20 (−0.74 to 1.14)

VTE = venous thromboembolism.

* Assessed in the safety population (5963 patients). We excluded 22 patients because of missing immobility-level data or absence of immobility-level classification; we observed no major bleeding events among these patients.

† For VTE end points in the total population, we report 95.8% CIs ($P < 0.042$) because of the α adjustment for the interim analysis. For all other end points, we report 95% CIs ($P < 0.050$).