ORIGINAL ARTICLE

Dalteparin versus Unfractionated Heparin in Critically Ill Patients

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ABSTRACT

BACKGROUND

The effects of thromboprophylaxis with low-molecular-weight heparin, as compared with unfractionated heparin, on venous thromboembolism, bleeding, and other outcomes are uncertain in critically ill patients.

METHODS

In this multicenter trial, we tested the superiority of dalteparin over unfractionated heparin by randomly assigning 3764 patients to receive either subcutaneous dalteparin (at a dose of 5000 IU once daily) plus placebo once daily (for parallel-group twice-daily injections) or unfractionated heparin (at a dose of 5000 IU twice daily) while they were in the intensive care unit. The primary outcome, proximal leg deep-vein thrombosis, was diagnosed on compression ultrasonography performed within 2 days after admission, twice weekly, and as clinically indicated. Additional testing for venous thromboembolism was performed as clinically indicated. Data were analyzed according to the intention-to-treat principle.

RESULTS

There was no significant between-group difference in the rate of proximal leg deep-vein thrombosis, which occurred in 96 of 1873 patients (5.1%) receiving dalteparin versus 109 of 1873 patients (5.8%) receiving unfractionated heparin (hazard ratio in the dalteparin group, 0.92; 95% confidence interval [CI], 0.68 to 1.23; P=0.57). The proportion of patients with pulmonary emboli was significantly lower with dalteparin (24 patients, 1.3%) than with unfractionated heparin (43 patients, 2.3%) (hazard ratio, 0.51; 95% CI, 0.30 to 0.88; P=0.01). There was no significant between-group difference in the rates of major bleeding (hazard ratio, 1.00; 95% CI, 0.75 to 1.34; P=0.98) or death in the hospital (hazard ratio, 0.92; 95% CI, 0.80 to 1.05; P=0.21). In prespecified per-protocol analyses, the results were similar to those of the main analyses, but fewer patients receiving dalteparin had heparin-induced thrombocytopenia (hazard ratio, 0.27; 95% CI, 0.08 to 0.98; P=0.046).

CONCLUSIONS

Among critically ill patients, dalteparin was not superior to unfractionated heparin in decreasing the incidence of proximal deep-vein thrombosis. (Funded by the Canadian Institutes of Health Research and others; PROTECT ClinicalTrials.gov number, NCT00182143.)

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Venous thromboembolism is an important complication of critical illness. Patients in the intensive care unit (ICU) are at risk for venous thromboembolism because of their complex acute and chronic illnesses, as well as the need for life-support measures, sedation, analgesia and paralysis, central venous catheterization, and other procedures.[1,2]

Among four randomized thromboprophylaxis trials involving critically ill patients, the findings of two trials suggested a benefit of either unfractionated heparin[3] or low-molecular-weight heparin[4] over placebo, whereas two trials comparing low-molecular-weight heparin with unfractionated heparin had inconclusive results.[5,6] The primary objective of this multicenter, randomized study, called the Prophylaxis for Thromboembolism in Critical Care Trial (PROTECT), was to compare the effect of dalteparin, a low-molecular-weight heparin, with that of unfractionated heparin on the primary outcome of proximal leg deep-vein thrombosis in critically ill patients. Secondary outcomes included rates of pulmonary embolism, venous thromboembolism, bleeding, heparin-induced thrombocytopenia, and death.

Methods

Study Design

The trial was conducted in 67 ICUs in academic and community hospitals in Canada, Australia, Brazil, Saudi Arabia, the United States, and the United Kingdom. Recruitment began in May 2006 and, as projected, was completed in 4 years. The trial protocol is available with the full text of this article at NEJM.org.[7]

Patients

We enrolled patients who were at least 18 years of age, weighed at least 45 kg, and were expected to remain in the ICU for at least 3 days. Exclusion criteria were major trauma, neurosurgery or orthopedic surgery, need for therapeutic anticoagulation, heparin administration in the ICU for at least 3 days, contraindication to heparin or blood products, pregnancy, life-support limitation, or enrollment in a related trial. Research coordinators obtained written informed consent from all patients or their designated surrogates.

Study Procedures

Using a centralized electronic system, local research pharmacists randomly assigned patients to receive either subcutaneous dalteparin (at a dose of 5000 IU once daily) or unfractionated heparin (at a dose of 5000 IU twice daily). Randomization was stratified according to center and type of admission (medical vs. surgical) with the use of undisclosed variable block sizes in a 1:1 ratio. Research pharmacists prepared identical syringes for subcutaneous injection of either dalteparin once daily plus placebo once daily (for parallel-group twice-daily injections) or of unfractionated heparin twice daily for the duration of the ICU stay. Patients, family members, clinicians, research personnel, ultrasonographers, and outcome adjudicators were all unaware of study-group assignments.

If major bleeding occurred, the study drug was withheld and subsequently restarted if appropriate. If the platelet count decreased to less than 50,000 per cubic millimeter or to less than 50% of the baseline value or if heparin-induced thrombocytopenia was otherwise suspected, an alternative anticoagulant agent[8] or mechanical prophylaxis was started. In such cases, an anti-PF4–polyanion enzyme immunoassay was performed locally, and the central reference laboratory at McMaster University performed a platelet ^{14}C-serotonin–release assay,[9] which, if positive, defined heparin-induced thrombocytopenia.

Research coordinators collected daily data on life-support measures, tests, drugs, devices, events, and exposures that modified the risk of or defined thrombotic or bleeding events. Patients were followed until the time of death in the hospital or discharge. Decisions about patient care, including management of suspected thromboembolism, were made at the clinicians' discretion.

Within 2 days after admission and then twice weekly, trained ultrasonographers assessed the proximal venous system in the leg at 1-cm intervals, documenting compressibility at six sites: common femoral, proximal, middle and distal superficial femoral, and popliteal veins and the venous trifurcation. Any partially or completely incompressible venous segment was classified as a deep-vein thrombosis. Wall thickening was not considered to be diagnostic of deep-vein thrombosis. If a venous segment was not well visualized, the test result was considered to be indeterminate.

OUTCOMES

The primary outcome was the incidence of proximal leg deep-vein thrombosis, defined as new-onset thrombosis detected 3 or more days after randomization. We defined deep-vein thrombosis that was diagnosed on the first screening ultrasonography as prevalent deep-vein thrombosis, reflecting a baseline characteristic. Patients with prevalent deep-vein thrombosis were included in the main analysis, but the thrombosis was not considered to be a primary outcome. Thromboses were considered chronic if a pretrial test showed a thrombus in the same or a contiguous venous segment. We defined a thrombus as catheter-related if a catheter had been present in the same or a contiguous venous segment within 72 hours before the diagnosis.

Secondary outcomes included any deep-vein thrombosis, pulmonary embolism, venous thromboembolism, death, and a composite of either venous thromboembolism or death. Additional secondary outcomes were major bleeding and heparin-induced thrombocytopenia.

We defined pulmonary embolism as definite (characteristic intraluminal filling defect on computed tomography of the chest, a high-probability ventilation–perfusion scan, or autopsy finding), probable (high clinical suspicion and either no test results or nondiagnostic results on noninvasive testing), possible (clinical suspicion and nondiagnostic results on noninvasive testing), or absent (negative or normal test results without reference to pretest probability) (for details, see the Supplementary Appendix at NEJM.org).[10]

We characterized bleeding according to site, severity, and consequences, using an instrument that has been validated in critically ill patients (for details, see the Supplementary Appendix).[11] Major bleeding was defined as hemorrhage occurring at a critical site (e.g., intracranial hemorrhage), resulting in the need for a major therapeutic intervention (e.g., surgery), causing hemodynamic compromise, requiring at least 2 units of red-cell concentrates, or resulting in death. Minor bleeding was defined as bleeding that did not fulfill the criteria for major bleeding (e.g., injection-site hematoma).

In formal calibration exercises during the first 6 months of the trial for the blinded adjudication of thrombotic and bleeding events, there was good agreement with respect to leg[12] and other[13] deep-vein thromboses, pulmonary embolism,[10] and bleeding[14] (kappa values, 1.00, 0.71, 0.82, and 0.81, respectively). Thereafter, we randomly assigned each outcome to two adjudicators (or four adjudicators in the case of pulmonary embolism) who were unaware of study-group assignments and of one another's assessments. Consensus was obtained for all outcomes with continued high levels of agreement throughout the trial.

STUDY OVERSIGHT

The trial was designed by the steering committee (see the Supplementary Appendix) and was approved by the research ethics committee at each study center. Funding was provided by the Canadian Institutes of Health Research, the Australian and New Zealand College of Anesthetists Research Foundation, and the Heart and Stroke Foundation of Canada. Study drugs were provided by Pfizer and by Eisai. Neither the funders nor the drug manufacturers played any role in the design or conduct of the trial or in the analysis or interpretation of the data. Members of the steering committee made the decision to submit the manuscript for publication. The authors all vouch for the accuracy and completeness of the data and the analyses.

STATISTICAL ANALYSIS

To detect a 30% reduction in the relative risk of proximal deep-vein thrombosis with the use of low-molecular-weight heparin, as compared with unfractionated heparin, from a baseline rate of 8%,[15,16] we determined that 1809 patients per group (total, 3618) would provide a power of 80% with the use of a two-sided alpha level of 0.05. We analyzed the primary outcome by means of the Haybittle–Peto method, using a P value of 0.001 for each of two interim analyses at one third and two thirds of projected total enrollment,[17,18] with adjustment for an overall type I error of 0.05, and with the final analysis conducted at an alpha level of 0.0495.

Data from patients were analyzed according to study-group assignment, with all patients (except those for whom consent was withdrawn) included in the intention-to-treat analysis. To compare the two study groups for incident outcomes, we used unadjusted Cox regression analysis and calculated hazard ratios and 95% confidence intervals, as prespecified in the trial

Table 1. Baseline Characteristics of the Intention-to-Treat Population.*

Characteristic	Dalteparin (N=1873)	Unfractionated Heparin (N=1873)
Age — yr	61.1±16.5	61.7±16.4
Female sex — no./total no. (%)	813/1865 (43.6)	801/1862 (43.0)
APACHE II score†	21.4±7.8	21.7±7.8
Body-mass index‡	28.3±8.1	28.2±7.3
Medical admission — no./total no. (%)§	1409/1873 (75.2)	1422/1873 (75.9)
Venous thromboembolism — no./total no. (%)		
Personal history	60/1865 (3.2)	60/1862 (3.2)
Family history	26/1865 (1.4)	30/1862 (1.6)
History of cancer — no./total no. (%)	82/1865 (4.4)	68/1862 (3.7)
Diagnosis on admission — no./total no. (%)¶		
Cardiovascular condition	166/1865 (8.9)	170/1862 (9.1)
Respiratory condition	855/1865 (45.8)	846/1862 (45.4)
Gastrointestinal condition	264/1865 (14.2)	256/1862 (13.7)
Renal condition	40/1865 (2.1)	25/1862 (1.3)
Neurologic condition	115/1865 (6.2)	114/1862 (6.1)
Sepsis	272/1865 (14.6)	277/1862 (14.9)
Metabolic condition	73/1865 (3.9)	71/1862 (3.8)
Other condition		
Medical	32/1865 (1.7)	33/1862 (1.8)
Surgical	48/1865 (2.6)	70/1862 (3.8)
Life support — no./total no. (%)		
Mechanical ventilation	1662/1862 (89.3)	1696/1862 (91.1)
Vasopressors	805/1862 (43.2)	872/1862 (46.8)
Dialysis		
Long-term	60/1865 (3.2)	58/1862 (3.1)
Any	125/1862 (6.7)	101/1862 (5.4)
Central venous catheterization	1543/1862 (82.9)	1580/1862 (84.9)

* Plus–minus values are means ±SD.
† The APACHE (Acute Physiology and Chronic Health Evaluation) II score ranges from 0 to 71, with higher scores indicating more severe disease.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Patients were stratified according to medical or surgical admission at the time of randomization. A surgical admission was defined as admission from the operating room or postoperative recovery room.
¶ The diagnoses in this category were mutually exclusive.

protocol.[7] We also conducted analyses adjusted for baseline characteristics. For venous thromboembolic events, the analyses were adjusted for scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II and status with respect to a personal or family history of venous thromboembolism, need for vasopressors, and end-stage renal failure.[15] For bleeding events, the analyses were adjusted for APACHE II scores and status with respect to end-stage renal failure.[19] For venous thromboembolic and bleeding events, data were censored at the time of death or discharge or at 100 days if patients were still hospitalized. We used the Wilcoxon rank-sum test to compare the duration of mechanical ventilation and of the stay in the hospital and ICU. All statistical tests were two-sided.

An as-treated analysis and a per-protocol analysis were prespecified. The as-treated analysis included all patients except those who had

Table 2. Pharmacologic Cointerventions and Mechanical Thromboprophylaxis.*

Variable	Dalteparin (N=1862)	Unfractionated Heparin (N=1862)	P Value
Medication — no. (%)			
Stress-ulcer prophylaxis	1707 (91.7)	1701 (91.4)	0.77
Heparin for catheter patency	551 (29.6)	523 (28.1)	0.33
Acetylsalicylic acid	577 (31.0)	627 (33.7)	0.09
Thienopyridine antiplatelet agent	110 (5.9)	90 (4.8)	0.17
Statin	391 (21.0)	375 (20.1)	0.54
Erythropoiesis-stimulating agent	50 (2.7)	56 (3.0)	0.62
Mechanical prophylaxis — no. (%)†			
Antiembolic stockings			
Per protocol	327 (17.6)	310 (16.6)	0.49
Protocol violation	50 (2.7)	48 (2.6)	0.92
Pneumatic compression device			
Per protocol	201 (10.8)	212 (11.4)	0.60
Protocol violation	38 (2.0)	30 (1.6)	0.39
Days of mechanical prophylaxis — median (interquartile range)			
Antiembolic stockings	1 (1–2)	1 (1–2)	0.43
Pneumatic compression device	1 (1–3)	1 (1–3)	0.75
Central venous catheterization — no. (%)	1596 (85.7)	1626 (87.3)	0.16

* Listed are pharmacologic and mechanical cointerventions that might influence bleeding or thrombotic risk. Data on cointerventions were missing for 11 patients in each study group in the intention-to-treat analysis.

† Mechanical prophylaxis was considered to be in compliance with the protocol if a study drug was withheld for a prespecified reason (e.g., active major bleeding, high risk of major bleeding, or suspected or confirmed heparin-induced thrombocytopenia). Such prophylaxis was considered to be in violation of the protocol if it was used along with a study drug at any point during the study.

been excluded because consent was withdrawn, an incorrect randomization procedure was performed, or a study drug had not been administered.[7] The per-protocol analysis included only patients who were not treated for a prevalent venous thromboembolism, received a study drug for at least 2 days and had results on at least two tests for venous thromboembolism that were technically adequate. We conducted two sensitivity analyses,[7] with the first including any venous thromboembolism as an incident outcome if it occurred 2 or more days after randomization and the second including only venous thromboembolism that was clinically suspected and objectively confirmed. Three prespecified subgroup analyses were based on a priori classification of a patient's ICU admission as surgical versus medical, the presence or absence of vasopressor use, and the presence or absence of end-stage renal disease.[7]

RESULTS

PATIENTS

Of the 6034 patients who met the enrollment criteria, 4574 were approached for consent (Fig. 1 in the Supplementary Appendix). Consent was obtained for 3764 of these patients (82.3%) and was provided by substitute decision makers in 90.1% of cases. Consent was subsequently withdrawn for 18 patients. Of the 3746 patients in the intention-to-treat analysis, 1873 patients were assigned to receive dalteparin and 1873 to receive unfractionated heparin. No patients were lost to follow-up.

The baseline characteristics of the two study groups were similar. A total of 76% of the admissions were medical; 90% of the patients required mechanical ventilation, and 45% required vasopressors (Table 1). Prevalent proximal deep-vein thrombosis (i.e., identified at initial screening)

Table 3. Venous Thromboembolic Outcomes.

Outcome	Intention-to-Treat Analysis				As-Treated Analysis			
	Dalteparin (N=1873)	Unfractionated Heparin (N=1873)	Hazard Ratio (95% CI)	P Value	Dalteparin (N=1827)	Unfractionated Heparin (N=1832)	Hazard Ratio (95% CI)	P Value
	no. (%)				*no. (%)*			
Deep-vein thrombosis								
Proximal	96 (5.1)	109 (5.8)	0.92 (0.68–1.23)	0.57	94 (5.1)	108 (5.9)	0.91 (0.68–1.23)	0.54
Any	138 (7.4)	161 (8.6)	0.93 (0.72–1.19)	0.54	135 (7.4)	160 (8.7)	0.92 (0.72–1.19)	0.54
Pulmonary embolism								
Any	24 (1.3)	43 (2.3)	0.51 (0.30–0.88)	0.01	22 (1.2)	42 (2.3)	0.48 (0.27–0.84)	0.01
Possible	1 (<0.1)	4 (0.2)			1 (<0.1)	4 (0.2)		
Probable	5 (0.3)	11 (0.6)			4 (0.2)	10 (0.5)		
Definite	18 (1.0)	28 (1.5)			17 (0.9)	28 (1.5)		
Definite or probable	23 (1.2)	39 (2.1)	0.53 (0.30–0.92)	0.02	21 (1.1)	38 (2.1)	0.49 (0.28–0.88)	0.02
Any venous thromboembolism	154 (8.2)	186 (9.9)	0.87 (0.69–1.10)	0.24	150 (8.2)	184 (10.0)	0.87 (0.69–1.10)	0.24
Venous thromboembolism or death	530 (28.3)	589 (31.4)	0.89 (0.79–1.01)	0.07	511 (28.0)	575 (31.4)	0.89 (0.78–1.004)	0.06

was present in 3.5% of those receiving dalteparin and 3.4% of those receiving unfractionated heparin. Throughout the trial, the rates of cointerventions with drugs or devices that influence bleeding or thrombotic risk were similar in the two groups (Table 2). Doses of a study drug were missed on 3.3% of study days, and the use of a nonstudy drug occurred on 1.0% of study days. The median duration of exposure to a study drug in both groups was 7 days (interquartile range, 4 to 12).

OUTCOMES

The primary outcome of incident proximal leg deep-vein thrombosis developed in 96 of 1873 patients (5.1%) assigned to receive dalteparin and in 109 of 1873 patients (5.8%) receiving unfractionated heparin (hazard ratio in the dalteparin group, 0.92; 95% confidence interval [CI], 0.68 to 1.23; P=0.57) (Table 3 and Fig. 1). Pulmonary embolism developed in significantly fewer patients assigned to receive dalteparin (24 patients, 1.3%) than in those assigned to receive unfractionated heparin (43 patients, 2.3%) (hazard ratio, 0.51; 95% CI, 0.30 to 0.88; P=0.01) (Table 3, and Fig. 2 in the Supplementary Appendix). The two groups did not differ significantly with respect to the rates of other deep-vein thromboses or any venous thromboembolism (Table 3, and Fig. 3 in the Supplementary Appendix). There was a trend toward a lower rate of the composite outcome of any venous thromboembolism or death for patients assigned to receive dalteparin (530 patients, 28.3%) than for those assigned to receive unfractionated heparin (589 patients, 31.4%), but this difference was not significant (hazard ratio, 0.89; 95% CI, 0.79 to 1.01; P=0.07).

Catheter-related thrombosis occurred in 44 patients (2.3%) assigned to receive dalteparin and in 39 patients (2.1%) assigned to receive unfractionated heparin (P=0.51). The results of leg ultrasonography were indeterminate in 4 patients (0.2%) assigned to receive dalteparin and 6 patients (0.3%) assigned to receive unfractionated heparin (P=0.52).

Major bleeding occurred in 103 patients (5.5%) assigned to receive dalteparin and 105 patients (5.6%) assigned to receive unfractionated heparin (hazard ratio, 1.00; 95% CI, 0.75 to 1.34; P=0.98) (Table 4). Heparin-induced thrombocytopenia was confirmed in 5 patients (0.3%) assigned to receive dalteparin and 12 patients (0.6%) assigned to receive unfractionated heparin (hazard ratio, 0.47;

95% CI, 0.16 to 1.35; P=0.16). Events that were defined as serious adverse events were reported for 7 patients (0.4%) assigned to receive dalteparin and 6 patients (0.3%) assigned to receive unfractionated heparin (P=0.76) (see the Supplementary Appendix). These events included major bleeding in 6 patients assigned to receive dalteparin and 5 patients assigned to receive unfractionated heparin, heparin-induced thrombocytopenia involving an arterial thrombus in 1 patient assigned to receive dalteparin, and a venous and intracardiac thrombus in 1 patient assigned to receive unfractionated heparin.

The results of the adjusted analyses and as-treated analyses were similar to those in the main analyses. The results of sensitivity analyses — one that included all outcomes after randomization as incident outcomes and one that included only clinically suspected venous thromboembolic outcomes — were also similar to the unadjusted results. The latter analyses showed that dalteparin was associated with significantly fewer clinically suspected pulmonary emboli (in 22 patients, 1.2%) than was unfractionated heparin (38 patients, 2.0%) (hazard ratio, 0.51; 95% CI, 0.29 to 0.90; P=0.02). The per-protocol analyses also had results similar to those of the main analyses, but the hazard ratio for the development of heparin-induced thrombocytopenia favoring dalteparin was significant (0.27; 95% CI, 0.08 to 0.98; P=0.046) (Table 1 in the Supplementary Appendix). The prespecified subgroup analyses identified no between-group differences in the rates of proximal deep-vein thrombosis (Table 2 in the Supplementary Appendix).

Venous thromboembolic events tended to occur much more frequently during the ICU stay than thereafter during hospitalization (Fig. 4, 5, and 6 in the Supplementary Appendix). Of 205 total proximal leg deep-vein thromboses, 182 developed in the ICU and 23 on the ward. Of 67 total pulmonary emboli, 47 developed in the ICU and 20 on the ward. Of 340 total venous thromboembolic events, 289 developed in the ICU and 51 on the ward. Of 67 patients with incident pulmonary emboli, 13 (19.4%) had prevalent proximal deep-vein thrombosis.

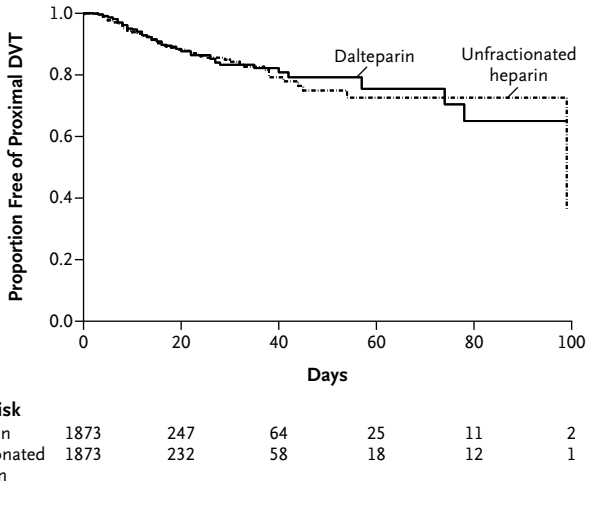

Figure 1. Kaplan–Meier Curves for the Time to Proximal Deep-Vein Thrombosis.

Freedom from proximal deep-vein thrombosis (DVT), the primary end point, over time is shown for patients assigned to receive either dalteparin or unfractionated heparin in the intention-to-treat population.

DISCUSSION

In this randomized trial involving critically ill patients receiving thromboprophylaxis, we found no significant differences in rates of proximal leg deep-vein thrombosis, the primary end point, between those receiving dalteparin and those receiving unfractionated heparin. The confidence interval around the hazard ratio for the primary end point was fairly wide, so it did not exclude either a 32% benefit or a 23% harm associated with dalteparin, as compared with unfractionated heparin. Thus, the result for the primary outcome was not clinically directive. Rates of venous thrombosis, venous thromboembolism, major bleeding, and death were similar in the two study groups. Dalteparin was associated with significantly fewer pulmonary emboli; the number of patients who would need to undergo prophylaxis with dalteparin rather than unfractionated heparin to prevent one pulmonary embolism was 100. Heparin-induced thrombocytopenia was rare, and in the per-protocol analysis, it occurred significantly less often in patients receiving dalteparin than in those receiving unfractionated heparin. However, caution is warranted in making inferences about nominally significant findings in secondary outcomes.

We selected dalteparin for this trial on the basis of preparatory research suggesting an absence of bioaccumulation of the drug in critically ill patients, including patients with renal

Table 4. Other Outcomes.*

Outcome	Intention-to-Treat Analysis				As-Treated Analysis			
	Dalteparin (N=1873)	Unfractionated Heparin (N=1873)	Hazard Ratio (95% CI)	P Value	Dalteparin (N=1827)	Unfractionated Heparin (N=1832)	Hazard Ratio (95% CI)	P Value
	no. (%)				*no. (%)*			
Bleeding								
Major	103 (5.5)	105 (5.6)	1.00 (0.75–1.34)	0.98	100 (5.5)	105 (5.7)	0.98 (0.73–1.31)	0.88
Any	244 (13.0)	247 (13.2)	1.01 (0.84–1.21)	0.93	236 (12.9)	247 (13.5)	0.98 (0.81–1.18)	0.83
Heparin-induced thrombocytopenia	5 (0.3)	12 (0.6)	0.47 (0.16–1.35)	0.16	5 (0.3)	12 (0.7)	0.47 (0.16–1.37)	0.17
Death								
In intensive care unit	284 (15.2)	304 (16.2)	0.97 (0.82–1.15)	0.71	268 (14.7)	293 (16.0)	0.95 (0.79–1.13)	0.53
In hospital	414 (22.1)	459 (24.5)	0.92 (0.80–1.05)	0.21	396 (21.7)	446 (24.3)	0.90 (0.78–1.04)	0.15
	median (interquartile range)				*median (interquartile range)*			
No. of days of invasive mechanical ventilation	6 (3–12)	6 (3–12)	NA	0.49†	6 (3–12)	6 (3–13)	NA	0.43†
No. of days in intensive care unit	9 (6–15)	9 (6–16)	NA	0.26†	9 (6–16)	10 (6–16)	NA	0.18†
No. of days in hospital	21.5 (13–39)	21 (13–41)	NA	0.51†	22 (13–39)	21 (13–41)	NA	0.47†

* NA denotes not applicable.
† This P value was calculated with the use of the Wilcoxon rank-sum test.

failure.[19,20] We suspect a class effect for low-molecular-weight heparins,[21] but given the particular molecular-weight profile of dalteparin, we cannot be sure that our findings are not unique to this drug. In the per-protocol analysis, the significant reduction in heparin-induced thrombocytopenia in the dalteparin group suggests a possible class effect of low-molecular-weight heparin, since enoxaparin was also shown to reduce this adverse drug reaction in a randomized, controlled trial,[22] and certoparin reduced the risk of antibody formation in another trial.[23]

Our results might have been different if the study enrollment had been larger or if we had used different drugs or doses. Although no trials have directly compared the use of unfractionated heparin in twice-daily and thrice-daily regimens, an indirect comparison suggests an increased rate of major bleeding with the thrice-daily regimen.[24] In a recent meta-analysis of studies in which twice-daily unfractionated heparin, thrice-daily unfractionated heparin, and low-molecular-weight heparin were compared with one another or with an inactive control, both twice-daily and thrice-daily regimens of unfractionated heparin had similar effects on the rates of deep-vein thrombosis, pulmonary embolism, major bleeding, and death.[25]

We used screening compression ultrasonography,[26,27] a procedure that has limitations, to detect deep-vein thrombosis. Classic signs and symptoms of deep-vein thrombosis do not develop in comatose, recumbent, critically ill patients, and systematic studies indicate that neither clinical examination[28] nor serial measurement of biomarkers[29] is useful for diagnosing deep-vein thromboses in the ICU. Though screening ultrasonography is safe, noninvasive, readily available, and recommended for research in this field,[30] it detects largely asymptomatic deep-vein thromboses. Deep-vein thrombosis of the leg is considered important because emboli are believed to arise from these veins,[31] rendering such thrombosis a surrogate outcome for pulmonary embolism. Pulmonary emboli are clinically important to the extent that they cause hemodynamic compromise or severely impaired gas exchange, thereby increasing morbidity and mortality among patients with poor cardiopulmonary reserve. We found that patients with pulmonary embolism had a substantially longer duration of mechanical

ventilation and a longer duration of stay in the ICU and hospital, as well as higher rates of death, than did patients without pulmonary embolism (data not shown).

The reduced rate of pulmonary embolism with dalteparin in this trial was identified in a relatively small number of events, resulting in wide confidence intervals around the observed effect. However, blinded adjudication with the use of objective definitions, reproducibility of these assessments, and consistency across prespecified analyses strengthen the inferences. Although all trends in venous thromboembolic outcomes favored dalteparin, the significant reduction in the rate of pulmonary embolism in the dalteparin group was not accompanied by a corresponding significant decrease in the rate of proximal deep-vein thrombosis. Possible explanations include embolism from other sites (e.g., upper limbs, pelvis, or distal leg, for which we did not screen), an effect of dalteparin on the propensity of leg thrombi to embolize, new-onset thrombus formation in pulmonary arteries during critical illness, and insensitivity or nonspecificity of proximal ultrasonography in asymptomatic patients.[32]

In summary, among critically ill patients with medical or surgical admissions, dalteparin, as compared with unfractionated heparin, did not decrease the incidence of proximal deep-vein thrombosis. It is possible that in a larger trial, such a difference might have been detected. There was a significant reduction in the secondary end point of pulmonary embolism in the dalteparin group.

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