Prophylaxis Against Deep Vein Thrombosis in Critically Ill Patients With Severe Renal Insufficiency With the Low-Molecular-Weight Heparin Dalteparin

An Assessment of Safety and Pharmacodynamics: The DIRECT Study

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Background: Use of low-molecular-weight heparins is avoided in patients with renal insufficiency because of concerns about an excessive anticoagulant effect and increased bleeding risk. To challenge this premise, we evaluated if deep vein thrombosis (DVT) prophylaxis with dalteparin sodium confers an excessive anticoagulant effect in critically ill patients with severe renal insufficiency.

Methods: We conducted a multicenter, single-arm clinical trial of DVT prophylaxis with dalteparin sodium, 5000 IU once daily in critically ill patients with a creatinine clearance lower than 30 mL/min (to convert to milliliters per second, multiply by 0.0167). Bioaccumulation was defined by a trough anti-Xa level higher than 0.40 IU/mL, measured twice weekly. The pharmacodynamic properties of dalteparin were assessed by serial anti-Xa levels measured on days 3, 10, and 17.

Results: We enrolled 156 patients with a mean (SD) creatinine clearance of 18.9 (6.5) mL/min; 18 were excluded because they died or were discharged before testing (n=3) or had prevalent DVT (n=15). Of 138 patients included, the median (interquartile range [IQR]) dura-tion of dalteparin exposure was 7 (4-12) days. In 120 patients who had at least 1 trough anti-Xa level (427 total measurements), no patient had bioaccumulation (0%; 95% confidence interval [CI]: 0%-3.0%); the median (IQR) trough anti-Xa level was undetectable (<0.10 IU/mL [<0.10 to <0.10 IU/mL]). Based on serial measurements, peak anti-Xa levels were 0.29 to 0.34 IU/mL and trough levels were lower than 0.06 IU/mL. Deep vein thrombosis occurred in 7 of 138 patients (5.1%; 95% CI, 2.5%-10.1%); major bleeding occurred in 10 patients (7.2%; 95% CI, 4.0%-12.8%), all with trough anti-Xa levels of 0.18 IU/mL or lower.

Conclusion: In critically ill patients with severe renal insufficiency, DVT prophylaxis with dalteparin sodium, 5000 IU once daily, is not associated with an excessive anticoagulant effect due to drug bioaccumulation and is unlikely to contribute to bleeding.

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Group Information: Members of the committees and participating centers of the Canadian Critical Care Trials Group are listed on page 1811.

I N HOSPITALIZED MEDICAL AND surgical patients at increased risk for developing deep vein thrombosis (DVT), low-molecular-weight heparins (LMWHs) are effective agents to prevent DVT.[1] Critically ill patients admitted to an intensive care unit (ICU), like medical patients who have had an ischemic stroke or surgical patients who have had hip or knee arthroplasty, are at high risk for DVT; without anticoagulant prophylaxis, 20% to 40% will develop DVT,[2-4] and 10% will develop proximal DVT despite prophylaxis with unfractionated heparin (UFH).[3]

Clinicians typically use UFH for DVT prophylaxis in patients with renal insufficiency because its clearance is not affected by impaired renal function.[5] Indeed, experts usually advise caution regarding LMWH use in patients with renal insufficiency because its use might result in an excessive anticoagulant effect due to drug bioaccumulation, which predisposes to bleeding.[1,5-7] Patients with renal insufficiency are systematically excluded

from trials of LMWH assessing DVT prophylaxis,[8] limiting the applicability of prior trial results to this population. In patients at risk for DVT, LMWHs are an attractive prophylaxis option because, compared with UFH, they have superior efficacy in other high-risk populations[1] and a lower risk of heparin-induced thrombocytopenia (HIT),[9] an infrequent but serious adverse event.

Driven by the need to identify alternatives for DVT prophylaxis in critically ill patients with renal insufficiency, we challenged the premise that selected LMWHs bioaccumulate or contribute to bleeding in patients with impaired renal function. This reasoning was based on 3 considerations. First, existing data suggest that bioaccumulation occurs mainly in patients with renal insufficiency who receive therapeutic doses of LMWHs, which are 3- to 4-fold higher than those used for DVT prophylaxis.[1] Second, systematic reviews assessing LMWH use in patients with renal insufficiency found that administering prophylactic doses of LMWHs appear to be safe.[7,10] Third, preliminary observations suggest that dalteparin sodium, 5000 IU once daily, does not bioaccumulate in ICU patients with renal insufficiency.[11,12] The objectives of this study were (1) to determine if DVT prophylaxis with dalteparin in critically ill patients with severe renal insufficiency is associated with an excessive anticoagulant effect due to drug bioaccumulation and (2) to determine the incidence of DVT, bleeding, and HIT in such patients.

METHODS

STUDY DESIGN

The DIRECT (Dalteparin's Influence on the Renally Compromised: Anti-Ten-A) study was a multicenter, prospective, single-arm clinical trial assessing DVT prophylaxis with open-label dalteparin sodium, 5000 IU once daily, in critically ill ICU patients with severe renal insufficiency.

PATIENTS

Patients with the following inclusion criteria were enrolled: adults (age $\geq$18 years); body weight greater than 45 kg; expected ICU length of stay longer than 72 hours; and severe renal insufficiency, defined by a calculated creatinine clearance lower than 30 mL/min (to convert to milliliters per second, multiply by 0.0167) based on the Cockcroft-Gault formula.[13] Exclusion criteria were the following: ICU admission for longer than 2 weeks; orthopedic, cardiac, or neurological surgery within 3 months; active bleeding or high risk for bleeding; platelet count lower than $75 \times 10^3/\mu$L (to convert to $\times 10^9$/L, multiply by 1.0); international normalized ratio or activated partial thromboplastin time greater than 2 times the upper limit of normal; epidural catheter insertion within 12 hours; receipt of more than 2 doses of LMWH while in the ICU; need for therapeutic dose anticoagulation; prior adverse reaction to heparin; contraindication to blood products; bilateral leg amputation; pregnant or lactating woman; life expectancy less than 14 days or receiving palliative care; and prior enrollment in this study or enrollment in a concurrent study of antithrombotic therapy.

The research ethics boards of all participating sites—Canadian university-affiliated hospitals with closed mixed medical-surgical ICUs—approved the DIRECT study. Surrogate decision makers or patients provided written informed consent.

DALTEPARIN REGIMEN

Enrolled patients received open-label dalteparin sodium, 5000 IU once daily, administered by subcutaneous injection at 10:00 AM. This treatment was continued until ICU discharge or a maximum of 30 days, whichever came first. After ICU discharge or after 30 days, DVT prophylaxis was administered at the attending physician's discretion.

ANTI-Xa OUTCOMES

Trough Anti-Xa Levels

To assess for dalteparin bioaccumulation, we measured trough anti-Xa levels twice weekly (Mondays and Thursdays), 20 hours after the prior dalteparin dose. The first trough anti-Xa level was measured after a patient had received at least 1 dose of dalteparin. A priori, we defined bioaccumulation (excessive anticoagulant effect) of dalteparin prophylaxis in a patient by the presence of at least 1 trough anti-Xa level higher than 0.40 IU/mL.

Several assumptions were made to interpret trough anti-Xa levels. First, we assumed that an anti-Xa level is a reliable measure of the anticoagulant effect of dalteparin. In support of this assumption, the anti-Xa level is approved by consensus groups to measure the anticoagulant effect of LMWHs.[14,15] Second, we assumed that an elevated trough anti-Xa level, reflecting an excessive anticoagulant effect, is a surrogate marker of bleeding risk,[16] reasoning that elevated levels of other markers of anticoagulant activity (eg, international normalized ratio, activated partial thromboplastin time) reflect an increased risk for bleeding with other anticoagulants (eg, warfarin, UFH).[14,15] Third, we assumed that a trough anti-Xa level higher than 0.40 IU/mL would reflect dalteparin bioaccumulation because in patients who receive a prophylactic dose of LMWH, the risk for bleeding increases with a trough anti-Xa level higher than 0.40 IU/mL,[16] whereas a trough anti-Xa level between 0.10-0.40 IU/mL is considered a safe level of anticoagulation[17] and a trough anti-Xa level of 0.20 IU/mL or lower occurs in patients with normal renal function.[18,19]

Serial Anti-Xa Levels

To assess dalteparin pharmacodynamics, we measured anti-Xa levels at 0 (baseline), 1, 2, 4, 8, 12, 20, and 24 hours after the prior dalteparin dose, with serial measurements targeted for days 3, 10, and 17 after the start of dalteparin therapy.

CLINICAL OUTCOMES

Deep Vein Thrombosis

Deep vein thrombosis was defined by a noncompressible vein segment on venous ultrasonography.[20] All patients underwent bilateral lower limb venous ultrasonography within 48 hours of study enrolment and twice weekly (Mondays and Thursdays) thereafter until ICU discharge or 30 days, whichever came first. A standard technique was used to assess for noncompressible vein segments that has high interrater reliability in ICU patients.[21] Screening for pulmonary embolism was not done, and if embolism was diagnosed, it was based on the results from objective diagnostic tests.[22,23]

Bleeding

Bleeding was defined as major if the patient had 1 or more of the following: (1) decrease in hemoglobin level of 2 g/dL or

greater (to convert to grams per liter, multiply by 10.0); transfusion of 2 units of red cells or more and no increase in hemoglobin level; spontaneous decrease in systolic blood pressure of 20 mm Hg or greater or heart rate increase of 20 beats/min or greater or decrease in systolic blood pressure of 10 mm Hg or greater while the patient was upright in the absence of another cause[24]; (2) bleeding at a critical site (eg, intracranial); or (3) bleeding at a wound site that required an intervention (eg, reoperation). Bleeding that did not satisfy these criteria was defined as minor.

Heparin-Induced Thrombocytopenia and Creatinine Clearance

All cases of suspected HIT were documented, and blood samples were processed at a central laboratory using a single serotonin release assay.[25] Creatinine clearance was measured at baseline and at the end of dalteparin administration.

PROCUREMENT AND PROCESSING OF BLOOD SAMPLES

Blood samples (1.0 mL) for anti-Xa measurements were drawn from an arterial catheter into a glass tube (Vacutainer; Becton-Dickinson, Franklin Lakes, New Jersey) containing 3.2% citrate. Blood samples were obtained after a 3- to 5-mL discard to avoid UFH contamination. Blood samples were centrifuged for 15 minutes at 1700g; the plasma was transferred to clean plastic tubes and centrifuged for 5 minutes at 1700g. Blood samples for trough anti-Xa levels were assayed in the laboratory of each clinical site: 10 sites used the Stachrom-Heparin assay (Diagnostica Stago, Asnieres-Sur-Seine, France); 1 site used the Spectrolyse Heparin Xa assay (Trinity Biotech, Wicklow, Ireland); and 1 site used the Electrochrome Beckman Coulter assay (Beckman Coulter Inc, Fullerton, California). Blood samples for serial anti-Xa levels were processed in local laboratories, stored at –70°C, then shipped to a central laboratory (Hemostasis Reference Laboratory, Hamilton, Ontario, Canada) for batch testing using the Stachrom-Heparin assay. To optimize the precision and reliability of serial anti-Xa measurements, a calibration curve for dalteparin was constructed using pooled platelet-poor plasma obtained from healthy volunteers.[26] All anti-Xa assays were performed by personnel who were unaware of patient characteristics.

PATIENT AND STUDY MANAGEMENT

Patient management was at the discretion of the ICU team, which was blinded to all anti-Xa levels. Research coordinators who prospectively recorded bleeding and DVT outcomes during the study were unaware of anti-Xa levels. The ICU pharmacists were the only personnel aware of trough anti-Xa level results: in the event of a trough anti-Xa level higher than 0.40 IU, the pharmacist would instruct the ICU team to withhold the next dose of dalteparin.

A steering committee assumed overall responsibility for this study. An independent event adjudication committee reviewed all DVT, bleeding, and HIT outcomes. An independent data monitoring committee reviewed all trough anti-Xa levels and clinical outcomes after approximately 25, 50, 75, and 100 patients were enrolled and determined whether enrollment should continue or be suspended.

STUDY SAMPLE SIZE

Based on our hypothesis that dalteparin does not bioaccumulate and that the proportion of patients with a trough anti-Xa level higher than 0.40 IU/mL would be 10% or lower, we determined that a sample size of between 120 and 140 patients would exclude, based on the upper bound of the 95% confidence interval, more than 17% of patients with an elevated trough anti-Xa level (ie, 12 of 120 patients [10%] with an elevated anti-Xa level [95% confidence interval {CI}, 5.3%-16.8%] or 14 of 140 patients [10%] with an elevated anti-Xa level [95% CI, 5.2%-16.2%]).

STATISTICAL ANALYSIS

For all analyses, we present categorical data as number (percentage) and continuous data as mean (SD) or median (interquartile range [IQR]) if data were skewed. To assess for bioaccumulation of dalteparin, we determined the proportion (95% CI) of patients with at least 1 trough anti-Xa level higher than 0.40 IU/mL and the proportion of patients with at least 1 trough anti-Xa level of 0.10 IU/mL or higher (threshold of detectable anticoagulant effect). To assess for a possible association between bleeding and an excessive anticoagulant effect, we determined the proportion (95% CI) of patients with major bleeding, assessed trough anti-Xa levels in patients with major bleeding, and, using Cox proportional hazards regression analysis, we assessed a possible association between major bleeding and the presence of a detectable trough anti-Xa level ($\geq$0.10 IU/mL), which we used as a surrogate for an excessive anticoagulant effect. The pharmacodynamic profile of dalteparin was assessed based on the median (SD) anti-Xa levels at each time point during serial anti-Xa testing.[27] We determined the proportion (95% CI) of patients with DVT, pulmonary embolism, and HIT.

PATIENTS

We enrolled 156 patients with a mean (SD) creatinine clearance of 18.9 (6.5) mL/min. There were 15 patients excluded because DVT (n=14) or pulmonary embolism (n=1) was diagnosed within 48 hours of enrollment and 3 patients were excluded because of death (n=2) or discharge from the ICU (n=1) before venous ultrasound testing. Thus, the study population consisted of 138 patients who received at least 1 dose of dalteparin. The baseline characteristics are given in **Table 1**.

DALTEPARIN REGIMEN

The median (IQR) duration of DVT prophylaxis with dalteparin was 7 (4-12) days. Dalteparin was held for at least 1 day in 43 patients for a median (IQR) of 5 (1-10) days. In total, 301 doses of dalteparin were withheld. The reasons (percentage of all doses withheld) for withholding dalteparin included potential bleeding (38%); need for therapeutic anticoagulation (26%); suspected or confirmed HIT (20%); thrombocytopenia (11%); invasive procedure (10%); active bleeding (5%); dosing error (4%); and coagulopathy (1%). In some patients, there were multiple reasons for withholding dalteparin as per clinical practice; however, it was never withheld due to an elevated anti-Xa level.

Table 1. Clinical Characteristics of Enrolled Patients

Characteristic	Patients (N=138)
Age, mean (SD), y	68.3 (15.5)
Female, No. (%)	77 (55.8)
APACHE II score, mean (SD)	27.6 (8.2)
Surgical admission, No. (%)	36 (26.1)
Primary admission diagnosis, No. (%)	
Cardiovascular	15 (10.9)
Pulmonary	33 (23.9)
Gastrointestinal	26 (18.8)
Neurologic	6 (4.3)
Sepsis	31 (22.5)
Metabolic	6 (4.3)
Hematologic	16 (11.6)
Renal	2 (1.4)
Orthopedic	3 (2.2)
Renal classification, No. (%)	
Acute renal failure	85 (61.6)
Acute on chronic	32 (23.2)
Chronic renal failure	9 (6.5)
Chronic dialysis	12 (8.7)
CrCl at baseline, No. (%)	
<10.0 mL/min or chronic dialysis	13 (9.4)
10.0-14.9 mL/min	28 (20.3)
15.0-19.9 mL/min	37 (26.8)
20.0-24.9 mL/min	31 (22.5)
25.0-30.0 mL/min	29 (21.0)
CrCl, mean (SD), mL/min	18.9 (6.5)
CrCl at end of dalteparin administration, No. (%)	
<30.0 mL/min	87 (63.5)
30.0-39.9 mL/min	24 (17.5)
40.0-49.9 mL/min	12 (8.8)
≥50.0 mL/min	14 (10.2)
CrCl, mean (SD), mL/min	28.4 (17.3)
ICU length of stay, median (IQR), d	9 (5-15)
Management during ICU stay, No. (%)[a]	
Never underwent dialysis	76 (55.1)
Intermittent HD only	30 (21.7)
Continuous HD (includes SLED) only	10 (7.2)
Peritoneal dialysis only	3 (2.2)
Intermittent and continuous HD	17 (12.3)
Intermittent HD and peritoneal dialysis	1 (0.7)
Continuous HD and peritoneal dialysis	0
Intermittent HD, continuous HD, and peritoneal dialysis	1 (0.7)
ICU mortality, No. (%)	29 (21.0)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CrCl, creatinine clearance; HD, hemodialysis; ICU, intensive care unit; IQR, interquartile range; SLED, slow low-efficiency dialysis.

SI conversion factor: To convert creatinine clearance to milliliters per second, multiply by 0.0167.

[a] Of 138 patients included in this study, 45% required hemodialysis (intermittent or continuous) or peritoneal dialysis or a combination.

ANTI-Xa OUTCOMES

Trough Anti-Xa Levels

There were 427 trough anti-Xa levels measured in 120 patients; there were 18 patients in whom a trough anti-Xa level was not measured because it was not feasible. No patient (0%; 95% CI, 0%-3.0%) had bioaccumulation, defined by a trough anti-Xa level higher than 0.40 IU/mL, during the study. The median (IQR) anti-Xa level was undetectable (<0.10 IU/mL [<0.10 to <0.10 IU/mL]).

There were 334 trough anti-Xa levels (78%) in 113 patients that were undetectable (<0.10 IU/mL); 79 trough anti-Xa levels (19%) in 47 patients that were between 0.10 and 0.15 IU/mL; 9 trough anti-Xa levels (2%) in 7 patients that were between 0.16 and 0.20 IU/mL; and 5 trough anti-Xa levels (1%) in 4 patients that were higher than 0.20 IU/mL (0.21, 0.23, 0.26, 0.28, and 0.40 IU/mL). The number and timing of the detectable anti-Xa levels according to the duration of dalteparin treatment is given in **Table 2**.

Serial Anti-Xa Levels

Serial anti-Xa levels were measured in 109 patients after approximately 3 days after the start of dalteparin therapy, in 46 patients after approximately 10 days, and in 15 patients after approximately 17 days; 19 patients did not have serial anti-Xa testing done. Median (IQR) anti-Xa levels at 0, 1, 2, 4, 8, 12, 20, and 24 hours after a targeted 3, 10, and 17 days of dalteparin treatment is presented in **Table 3**. Peak levels were between 0.29 IU/mL and 0.34 IU/mL, and trough levels were below the lower limit of detection (<0.06 IU/mL) irrespective of the duration of treatment.

Association Between Bleeding and Trough Anti-Xa Levels

Of 10 patients with major bleeding, 4 had detectable trough anti-Xa levels during dalteparin prophylaxis: 1 patient had 3 detectable trough anti-Xa levels (0.10, 0.11, and 0.12 IU/mL); the second patient had 3 detectable trough anti-Xa levels (0.10, 0.10, and 0.13 IU/mL); the third patient had 2 detectable trough anti-Xa levels (0.10 and 0.18 IU/mL); the fourth patient had 1 detectable trough anti-Xa level (0.10 IU/mL). Using univariate regression analysis, we found no association between major bleeding and a detectable trough anti-Xa level in the preceding 3 days (hazard ratio, 0.76; 95% CI, 0.15-3.81).

CLINICAL OUTCOMES

Seven patients (5.1%; 95% CI, 2.5%-10.2%) developed DVT, which was asymptomatic and involved the proximal leg veins in all patients. In 6 patients, DVT occurred in association with a femoral vein catheter. No patient developed pulmonary embolism. Ten patients (7.2%; 95% CI, 4.0%-12.8%) developed major bleeding, 2 of whom died with bleeding. Two patients (1.4%; 95% CI, 0.4%-5.1%) with prior exposure to UFH had serologically confirmed HIT. Mean (SD) creatinine clearance at baseline and at the end of dalteparin prophylaxis was 18.9 (6.4) and 28.4 (17.3), respectively.

COMMENT

In critically ill patients with severe renal insufficiency who receive, on average, 7 days of DVT prophylaxis with dalteparin sodium, 5000 IU once daily, we found that this treatment does not result in an excessive anticoagulant

Table 2. Trough Anti-Xa Levels According to the Duration of Dalteparin Treatment

	Study Day (From Date of Study Enrollment) of Trough Anti-Xa Measurements				
Variable	1-3	4-6	7-9	10-12	>12
Proportion of all trough anti-Xa levels ≥0.10 IU/mL, No./total No. (%)	13/67 (19.4)	26/149 (17.4)	19/55 (34.6)	11/63 (17.5)	24/93 (25.8)
Proportion of patients with at least 1 trough anti-Xa level ≥0.10 IU/mL, No./total No. (%)	13/63 (20.6)	25/103 (24.3)	19/54 (35.2)	11/48 (22.9)	16/37 (43.2)
Trough anti-Xa levels ≥0.10 IU/mL, median (IQR)	0.10 (0.10-0.13)	0.10 (0.10-0.14)	0.10 (0.10-0.13)	0.10 (0.10-0.12)	0.11 (0.10-0.13)

Abbreviation: IQR, interquartile range.

Table 3. Serial Anti-Xa Levels at 0, 1, 2, 4, 8, 12, 20, and 24 Hours After a Targeted 3, 10, and 17 Days of Dalteparin Treatment[a]

	Median (IQR) Anti-Factor Xa Levels		
Hours After Dalteparin Administration	After 3 Days of Dalteparin Prophylaxis (n=102)	After 10 Days of Dalteparin Prophylaxis (n=46)	After 17 Days of Dalteparin Prophylaxis (n=15)
0 (Before treatment)	<0.06 (<0.06-<0.06)	<0.06 (<0.06-<0.06)	<0.06 (<0.06-0.08)
1	0.16 (0.10-0.26)	0.20 (0.11-0.29)	0.23 (0.19-0.25)
2	0.28 (0.19-0.40)	0.29 (0.18-0.39)	0.32 (0.25-0.38)
4	0.29 (0.20-0.42)	0.35 (0.24-0.43)	0.34 (0.27-0.45)
8	0.19 (0.11-0.30)	0.23 (0.09-0.31)	0.17 (0.10-0.27)
12	0.09 (<0.06-0.15)	0.11 (<0.06-0.18)	0.10 (<0.06-0.29)
20	<0.06 (<0.06-0.06)	<0.06 (<0.06-0.06)	<0.06 (<0.06-0.11)
24	<0.06 (<0.06-<0.06)	<0.06 (<0.06-<0.06)	<0.06 (<0.06-0.06)

Abbreviation: IQR, interquartile range.
[a] The lower limit of detection was an anti-Xa level lower than 0.06 IU/mL.

effect from drug bioaccumulation. In support of this conclusion, no patient had bioaccumulation (trough anti-Xa level >0.40 IU/mL) and trough anti-Xa levels were undetectable (<0.10 IU/mL) or minimal (0.10-0.20 IU/mL) in 99% of measurements. Furthermore, dalteparin had a "rapid rise and gradual fall to baseline" pharmacodynamic profile, typical of drugs that do not bioaccumulate. Finally, dalteparin prophylaxis was unlikely to contribute to major bleeding, since all patients with such bleeding had undetectable (<0.10 IU/mL) or minimal (0.10-0.18 IU/mL) trough anti-Xa levels, and an association between detectable trough anticoagulant levels and major bleeding was lacking (hazard ratio, 0.76; 95% CI, 0.15-3.81). Taken together, these findings challenge the premise that DVT prophylaxis with LMWHs should be avoided in patients with renal insufficiency, including patients with severe renal insufficiency.

We also evaluated clinical outcomes relevant to patients who are receiving DVT prophylaxis, since patients with renal insufficiency are at high risk for both DVT and bleeding.[28,29] The incidence of proximal leg DVT (approximately 5%) is consistent with findings from previous studies in critically ill patients who received DVT prophylaxis.[3] However, 6 of 7 cases of DVT occurred in association with a central vein catheter, which suggests the need for careful clinical monitoring and, possibly, screening for DVT in such patients. The incidence of major bleeding (approximately 7%) is considerably higher than that reported in other DVT prophylaxis trials[1] but likely reflects the disease burden in critically ill patients

and is consistent with findings from other studies assessing bleeding rates in such patients who receive anticoagulants.[3]

Our study is novel in that it assessed bioaccumulation and the pharmacodynamics of LMWH exclusively in patients with severe renal insufficiency. Our findings are consistent with a pilot study involving 19 critically ill patients with moderate to severe renal insufficiency (creatinine clearance <50 mL/min), in which we found no detectable trough anticoagulant effect (anti-Xa level <0.10 IU/mL) 23 hours after administration of dalteparin sodium, 5000 IU once daily.[12] Although LMWHs have been widely studied for the prevention and treatment of DVT and in patients with an acute coronary syndrome, these trials excluded patients with severe renal insufficiency.[1,30,31]

Others have investigated the potential for dalteparin bioaccumulation in patients with renal insufficiency. Kani and associates[32] studied 10 critically ill patients with moderate to severe renal insufficiency (mean creatinine clearance, 29.5 mL/min) who received dalteparin sodium, 5000 IU once daily, and had undergone serial anti-Xa testing. Although there was no dalteparin bioaccumulation, the clinical applicability of this study is limited because patients received only one dose of dalteparin. Tincani and associates[33] assessed DVT prophylaxis with dalteparin in 109 elderly patients (mean age, 83 years) with renal insufficiency. Although there was no evidence of dalteparin bioaccumulation after 6 days of treatment, only 24 patients had severe renal insufficiency, and selected patients received a lower dose of dalteparin sodium (2500

IU once daily) instead of the 5000-IU once-daily dose that is recommended for DVT prophylaxis.

There are 2 considerations relating to the study population that may affect the generalizability of our findings. First, 62% of patients had acute renal failure, in whom renal function may improve as interventions to restore renal function are initiated. In our study population, renal function improved overall during the study period (mean creatinine clearance, 18.9-28.4 mL/min), and this may have contributed to the lack of dalteparin bioaccumulation. However, renal function remained severely impaired (creatinine clearance <30 mL/min) in 64% and moderately impaired (creatinine clearance 30-50 mL/min) in 26% of patients at the end of the study, as given in Table 1. From a practical perspective, decisions about DVT prophylaxis in patients with impaired renal function take place at presentation. Our aim was to include a spectrum of patients representing a typical clinical population with impaired renal function, which, we believe, has greater generalizability than if we had limited our study to patients with less dynamic, end-stage renal disease. Nonetheless, caution should be used in applying our findings to patient subgroups, especially dialysis-dependent patients. Second, the bioavailability of LMWHs in critically ill patients may be theoretically less than in noncritically ill patients because of inotrope administration and subcutaneous edema, which may affect pharmacokinetic properties.[34-36] However, peak anti-Xa levels in this study were 0.20 to 0.40 IU/mL, which is consistent with prophylactic levels of anticoagulation observed in hospitalized medical and surgical patients and suggests adequate bioavailability of dalteparin.[17,37]

There are other potential study limitations. First, the study design precludes inferences about the efficacy and safety of dalteparin for DVT prophylaxis compared with other prophylaxis strategies, although this is being addressed in a randomized trial (the PROTECT [Prophylaxis of Thromboembolism in Critical Care] Trial[11]) comparing UFH and dalteparin in critically ill patients. Second, we studied dalteparin and cannot comment on the applicability of our findings to other LMWHs. Smaller LMWH fractions (enoxaparin) are cleared primarily by the kidney, whereas larger LMWHs (dalteparin and tinzaparin) have greater clearance by nonrenal mechanisms.[14,15] Previous studies have suggested that enoxaparin, especially when given in therapeutic doses, may bioaccumulate in patients with severe renal insufficiency.[7,38] Third, dalteparin administration was interrupted in 43 patients because of central venous catheter insertion and other reasons, which reflects how LMWH is used in the critical care setting. Finally, 3 assays were used to measure trough anti-Xa levels (same assay in 10 of 12 centers), with the potential for interassay variability in anti-Xa levels.[39] However, in a preplanned analysis in 10 patients who had 80 anti-Xa levels measured by 3 different assays, there was high interassay correlation ($r = 0.98$) in anti-Xa levels (Rita Selby, MD, oral communication, August 2007).

Strengths of this study include the comprehensive assessments of bioaccumulation and pharmacodynamics of dalteparin prophylaxis, clinical outcomes (bleeding, DVT, and HIT), and renal function in a well-defined patient population with severe renal insufficiency. Through daily screening in the ICU, consecutive eligible patients were enrolled, thereby minimizing the potential for selection bias that might occur in an observational study. To avoid biased interpretation of bleeding and thrombotic events, the critical care team and research coordinators were blinded to trough and serial anti-Xa levels. Furthermore, laboratory personnel measuring anti-Xa levels were unaware of patient characteristics and renal function.

Our study has implications for clinical practice. Our findings challenge the premise that selected LMWHs should be avoided in patients with severe renal insufficiency when administered for DVT prophylaxis. Furthermore, although we studied critically ill patients, we believe our findings may be generalizable to noncritically ill patients with severe renal insufficiency and to patients with mild to moderate renal insufficiency, in whom there may have been concerns about administering LMWHs because of potential bioaccumulation.

In conclusion, in critically ill patients with severe renal insufficiency, DVT prophylaxis with dalteparin is not associated with an excessive anticoagulant effect due to drug bioaccumulation and is unlikely to contribute to bleeding. Dalteparin sodium, 5000 IU once daily, appears to be a reasonable option for DVT prophylaxis in patients with severe renal insufficiency.

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