Nonleg Venous Thrombosis in Critically Ill Adults
A Nested Prospective Cohort Study

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IMPORTANCE Critically ill patients are at risk of venous thrombosis, and therefore guidelines recommend daily thromboprophylaxis. Deep vein thrombosis (DVT) commonly occurs in the lower extremities but can occur in other sites including the head and neck, trunk, and upper extremities. The risk of nonleg deep venous thromboses (NLDTVts), predisposing factors, and the association between NLDTVts and pulmonary embolism (PE) or death are unclear.

OBJECTIVE To describe the frequency, anatomical location, risk factors, management, and consequences of NLDTVts in a large cohort of medical-surgical critically ill adults.

DESIGN, SETTING, AND PARTICIPANTS A nested prospective cohort study in the setting of secondary and tertiary care intensive care units (ICUs). The study population comprised 3746 patients, who were expected to remain in the ICU for at least 3 days and were enrolled in a randomized clinical trial of dalteparin vs standard heparin for thromboprophylaxis.

MAIN OUTCOMES AND MEASURES The proportion of patients who had NLDTVts, the mean number per patient, and the anatomical location. We characterized NLDTVts as prevalent or incident (identified within 72 hours of ICU admission or thereafter) and whether they were catheter related or not. We used multivariable regression models to evaluate risk factors for NLDTVt and to examine subsequent anticoagulant therapy, associated PE, and death.

RESULTS Of 3746 trial patients, 84 (2.2%) developed 1 or more non-leg vein thromboses (superficial or deep, proximal or distal). Thromboses were more commonly incident (n = 75 [2.0%]) than prevalent (n = 9 [0.2%]) (P < .001) and more often deep (n = 67 [1.8%]) than superficial (n = 31 [0.8%]) (P < .001). Cancer was the only independent predictor of incident NLDTV (hazard ratio [HR], 2.22; 95% CI, 1.06-4.65). After adjusting for Acute Physiology and Chronic Health Evaluation (APACHE) II scores, personal or family history of venous thromboembolism, body mass index, vasopressor use, type of thromboprophylaxis, and presence of leg DVT, NLDTVts were associated with an increased risk of PE (HR, 11.83; 95% CI, 4.80-29.18). Nonleg DVTs were not associated with ICU mortality (HR, 1.09; 95% CI, 0.62-1.92) in a model adjusting for age, APACHE II, vasopressor use, mechanical ventilation, renal replacement therapy, and platelet count below 50 × 109/L.

CONCLUSIONS AND RELEVANCE Despite universal heparin thromboprophylaxis, nonleg thromboses are found in 2.2% of medical-surgical critically ill patients, primarily in deep veins and proximal veins. Patients who have a malignant condition may have a significantly higher risk of developing NLDTVt, and patients with NLDTVt, compared with those without, appeared to be at higher risk of PE but not higher risk of death.

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Critically ill patients are at risk of venous thrombosis, and therefore guidelines recommend daily thromboprophylaxis.2,3 Deep vein thrombosis (DVT) commonly occurs in the lower extremities but can occur in other sites including the head and neck, trunk, and upper extremities. Nonleg deep venous thromboses (NLDVTs) refer to venous thromboses occurring in any deep vein other than the lower extremity. The risk of NLDVT, predisposing factors, and the association between NLDVTs and pulmonary embolism (PE) or death are unclear.

In a recent observational study, 862 patients in a surgical intensive care unit (ICU) were screened weekly for upper-limb DVTs. Despite standardized heparin thromboprophylaxis, 15% developed 1 or more upper-extremity DVTs.3 In a 6-month cross-sectional study of 5451 consecutive inpatients and out-patients who had ultrasonography-confirmed DVTs, Joffe et al4 found that the strongest risk factor for upper-extremity DVT was the insertion of a central venous catheter. The association between central venous catheters and upper-extremity DVT was also identified in 2 prospective studies, and cancer was found to be a strong predictor.5,6

Clinical consequences of NLDVTs are not well understood. One study showed that 2.6% of ICU patients who had upper-extremity DVTs identified by ultrasound duplex screening had embolization to the lungs during hospitalization.3 Another prospective cohort study of 27 consecutive non-ICU patients who were referred to a specialized thrombosis unit found that up to 36% of patients who had upper-extremity DVT may develop PE during a mean follow-up period of 2 years, despite anticoagulation for the first 3 months.7 Other investigators have reported that the rate of PE in patients who have upper-extremity DVTs is lower than in patients who have leg DVTs (9% vs 29%; P < .001).5 Finally, mortality associated with NLDVTs is comparable to that associated with leg DVTs.5,8,9 However, existing studies on the consequences of NLDVTs have focused mostly on upper-extremity DVTs in patients who are not critically ill.10

The objective of this study was to describe the frequency, anatomical location, risk factors, management, and consequences of NLDVTs in a large cohort of medical-surgical critically ill adults. Our a priori hypotheses were that both baseline and time-dependent variables would be associated with NLDVTs and that NLDVTs would not be associated with PE and ICU mortality.

Methods

The Prophylaxis for Thromboembolism in Critical Care Trial (PROTECT; clinicaltrials.gov Identifier: NCT00182143), was a multicenter, randomized, blinded, and concealed trial of unfractionated heparin vs the low-molecular-weight heparin dalteparin for thromboprophylaxis in 3746 medical-surgical ICU patients. PROTECT was approved by the research ethics committee at each study center, and written informed consent was obtained from all patients or their designated surrogates. The primary outcome was proximal leg DVT as determined by twice-weekly screening ultrasonography. Secondary outcomes (venous thromboses in other anatomical locations, PE, bleeding, heparin-induced thrombocytopenia, and hospital mortality) were clinically suspected (not identified by systematic screening) and, when necessary, confirmed. Diagnostic tests and management of confirmed venous thromboembolism (VTE) were at the discretion of the ICU team. Research coordinators collected data daily in the ICU regarding life support, diagnostic tests, drugs, devices, events, and exposures that modify the risk of, or define, thrombotic or bleeding events. Patients were followed up to hospital discharge to document vital status and VTE events. The methods and results of this trial have been described elsewhere.11,12

Data Classification and Adjudication Calibration Exercise

To accurately document all NLDVTs and pulmonary emboli in PROTECT, every thrombus reported on daily data collection forms was adjudicated in duplicate by an independent central committee comprising 4 physicians (F.L., L.M., P.D., and D.J.C.). Nonleg DVTs were defined by at least 1 noncompressible venous segment of a vein on ultrasonography. Pulmonary emboli were diagnosed when vascular filling defects appeared on computed tomographic angiograms or pulmonary angiograms or in the presence of an unmatched perfusion defect on ventilation-perfusion (V/Q) scans or if there were both a high pretest probability and nondiagnostic test result. To ensure that each adjudicator assessed these events consistently, we performed a calibration exercise in the first 6 months of the trial. Independently, and blinded to each other’s ratings, center, and study drug, all 4 adjudicators examined the clinical charts (including radiological reports) and case report forms of 20 patients considered by local research coordinators to have a nonleg thrombus. Venous thromboses were classified as deep or superficial and proximal or distal based on explicit anatomical criteria (Figure). Distinction between distal and proximal thromboses also reflects the convention that proximal compared with distal thrombi have a different natural history and greater risk of propagation. Agreement between adjudicators was measured using a weighted κ statistic (chance corrected agreement).13 A priori, we determined that satisfactory agreement after quadruplicate review (κ ≥ 0.8 or higher) would be required in the calibration exercise before proceeding with duplicate adjudication for the rest of the trial. After reviewing these 20 events to analyze discordance and recalibrate, adjudicators discussed reasons for disagreement. These included different understanding of the definitions for (1) prevalent vs incident, (2) proximal vs distal, (3) deep vs superficial, (4) catheter related, and (5) progressive thrombus. Thromboses diagnosed within the first 72 hours of ICU admission were reported as prevalent; those extending in both proximal and distal segments, as proximal; and those in deep and superficial segments, as deep. Thromboses were adjudicated as catheter related if a catheter had been present in the same or a contiguous venous segment during the 72 hours preceding thrombus detection. We included jugular thromboses as upper-extremity thromboses. Any thrombosis occurring outside the 4 extremities and pulmonary arterial vasculature were described as involving axial veins. Weighted κ values initially
Adjudication Process

After the calibration exercise, all further NLDVTs were adjudicated independently by 2 members of the 4-person central adjudication committee. Pairs of adjudicators were the principal investigator (D.J.C.) and one of the 3 other adjudicators (F.L., L.M., or P.D.) in random order, assigned after stratification by study drug (low-molecular-weight heparin vs unfractionated heparin). Adjudicators were blinded to one another’s ratings, to center, and to study drug. Disagreements were resolved by discussion and consensus.

Statistical Analysis

Frequency and Anatomical Location of NLDVTs

We report the number and proportion of patients who had NLDVTs and the number and proportion of thromboses in each affected venous segment.

Risk Factors for NLDVTs

To examine risk factors for NLDVTs, we conducted a Cox proportional hazards multivariable analysis in which occurrence of incident NLDVTs was the dependent variable. We introduced 5 variables into the model simultaneously including 3 baseline factors (ie, Acute Physiology and Chronic Health Evaluation [APACHE] II score, body mass index, malignancy) and 2 time-dependent factors (treatment with vasopressors and with statins). These variables were identified as potential risk factors on the basis of previous studies and biologic plausibility.5,6,14 We defined malignancy as the presence of cancer within the last 5 years. We conducted a sensitivity analysis in which heparin-induced thrombocytopenia (diagnosed by serotonin-release assay) was also entered into the model. We used the same analytic method and the same 5 independent variables to examine risk factors for all nonleg thromboses (both deep and superficial). Post hoc, we build an additional multivariable model introducing a greater number of candidate predictors and selecting the final model using backward selection. The candidate predictors for this model included baseline factors (low-molecular-weight heparin vs unfractionated heparin as randomized, age [10-year increase], APACHE II [10-point increase], medical admission, end-stage renal disease, personal or family history of VTE, body mass index [10-point increase], cancer, and hospitalized for 1 week) and time-dependent factors (mechanical ventilation, vasopressors or inotropes, dialysis, central venous catheter, red blood cell transfusion, platelet transfusion, acetylsalicylic acid or thienopyridine, erythropoietin, and statin).

Consequences of NLDVTs

To describe the consequences of these NLDVTs, we report the number and proportion of patients with prevalent or incident NLDVTs who subsequently died, developed PE, or had therapeutic anticoagulation within 3 days of detection during the ICU or hospital stay. We compared these proportions with those in patients who did not have NLDVTs using the Fisher exact test.

To examine the impact of NLDVT on the occurrence of PE, we conducted a multivariable analysis using a Cox proportional hazards regression with PE as the dependent outcome. The independent variables in the model were heparin type, age, body mass index, treatment with vasopressors, prevalent or incident NLDVTs, and proximal leg DVTs. Post hoc, we conducted a sensitivity analysis using a model considering 2 baseline candidate risk factors and 5 additional time-dependent risk factors for PE, creating the model using backward selection. The additional potential predictors were renal replacement therapy in the preceding 3 days, invasive mechanical ventilation in the preceding 3 days, statins in the preceding 7 days, any central venous catheter in the preceding 3 days, a positive assay result for heparin-induced thrombocytopenia, APACHE II score, and personal or family history of venous thrombotic events. Age was removed from this model because it is included in the APACHE II score.

To examine whether proximal NLDVTs (prevalent or incident) influenced the risk of ICU mortality, we used a Cox proportional hazards model adjusted for the following variables: age, APACHE
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between May 2006 and June 2010, 3746 patients participated in the PROTECT trial in 67 ICUs in academic and community hospitals in Canada, Australia, Brazil, Saudi Arabia, the United States, and the United Kingdom. A detailed description of the participants, study protocol and interventions has been previously published.11

Of the 3746 patients, 84 (2.2%) enrolled were found to have 1 or more nonleg thromboses (superficial or deep, proximal or distal). Thirty-nine patients had more than 1 thrombosed segment. Overall, patients were 8 times more likely to have thromboses that were incident (n = 75 [2.0%]) than prevalent (n = 9 [0.2%]) (P < .001); 5 times more likely to have thromboses that were proximal (n = 76 [2.0%]) than distal (n = 15 [0.4%]) (P < .001); and twice as likely to have thromboses that were deep (n = 67 [1.8%]) than superficial (n = 31 [0.8%]) (P < .001). In 61 patients (1.6%), the diagnosis of incident thrombosis occurred in the ICU. In 47 of those 61 patients (1.3%), the thrombus involved a deep vein; the remainder were superficial thromboses. Forty patients (1.1%) had an incident catheter-related nonleg thrombosis, and in 34 of these patients (0.9%), the thrombosis involved a deep venous segment. These were not mutually exclusive categories (eg, a patient could have 2 nonleg VTEs—1 superficial and 1 deep). Catheters included centrally inserted (n = 2711) and peripherally inserted central catheters (n = 507); 506 patients had no central venous catheters. For 22 patients, daily data on intravenous catheters were missing.

Agreement among adjudicators on thrombus characteristics was excellent (overall pairwise weighted κ = 0.91).

Upper-Extremity Thromboses

Of 145 nonleg thrombosed venous segments, 137 (94.5%) originated in an upper extremity (Table 1). These were mostly proximal (n = 122 [89.1%]) and deep (n = 98 [71.5%]). Of the 137 thrombosed venous segments in the upper extremity, 89 (65.0%) were on the right, 48 (35.0%) were on the left, and the internal jugular was the most frequent site (21.4%). Overall, 70 of 137 (51.1%) of the thrombosed venous segments in the upper extremity were adjudicated as catheter related and 40 of the 3746 patients (1.2%) developed a catheter-related upper-extremity thrombus.

Other NLDVTs

In 7 patients (0.2%), NLDVTs occurred in axial veins. These were the portal (n = 2 [28.6%]), hepatic (n = 1 [14.3%]), splenic (n = 1 [14.3%]), and cerebral (n = 2 [28.6%]) veins and the vena cava (n = 2 [28.6%]) (Table 1).

Risk Factors for NLDVTs

Table 2 gives the characteristics of patients who had incident NLDVTs diagnosed in the ICU (n = 47) and of those who did not. Cancer was the only independent predictor of incident NLDVT in the first model (hazard ratio [HR] 2.22; 95% CI 1.06-4.65 [P = .03]). Baseline APACHE II scores, body mass index, and vasopressor or statin use were not independently associated with the occurrence of NLDVT (Table 3). A sensitivity analysis that included heparin-induced thrombocytopenia in the statistical model did not attenuate the strong association between cancer and NLDVT. Although heparin-induced thrombocytopenia was also associated with NLDVT, this relationship was not significant (HR, 4.35;
95% CI, 0.59-3.27 [P = .15]). In an additional post hoc sensitivity analysis, although an association with cancer remained statistically significant when all variables were kept in the model, only medical admitting diagnoses remained in the model after backward selection. This association suggested fewer NLDVTs in the context of medical admitting diagnoses (HR, 0.48; 95% CI, 0.25-0.90).

In the sensitivity analysis of predictors of any nonleg thromboses (either deep or superficial) diagnosed in the ICU (n = 61), we found a similar association between cancer and nonleg thrombosis, which was not statistically significant (HR, 1.96; 95% CI, 0.98-3.90 [P = .06]).

**Consequences of NLDVTs**

Both the management of NLDVTs and clinical outcomes in patients who had prevalent and incident NLDVTs are reported in Table 4. Regarding the therapeutic paradigm, 9 of the 67 patients (13.4%) with NLDVTs received therapeutic anticoagulation within 72 hours of diagnosis (within 3 days after the day of diagnosis). However, 55 were diagnosed in the ICU (8 prevalent and 47 incident), and information about anticoagulation was not collected for events diagnosed after ICU discharge. Of these 55 patients, 1 was discharged from the ICU and 1 died on day of diagnosis of first NLDVT. The remaining 53 patients had an NLDVT for which therapeutic anticoagulation could be captured in the PROTECT database.

Compared with patients who did not have NLDVTs, those who had NLDVTs were more likely to develop a PE (14.9% vs 1.9%; P < .001) and have a longer ICU stay (19 days [interquartile range [IQR], 10-33 days] vs 9 days [IQR, 6-15 days] [P < .001]) and hospital stay (39.5 days [IQR, 23-79 days] vs 21 days [IQR, 13-39 days] [P < .001]). Using a Cox proportional hazards model after adjusting for age, body mass index, type of prophylactic heparin, vasopressor use, and leg DVTs, the association between NLDVTs and PE remained statistically significant (HR, 11.83; 95% CI, 4.80-29.18 [P < .001]). A post hoc sensitivity analysis applied backward selection to select from the following list of variables: renal replacement therapy in the preceding 3 days, invasive mechanical ventilation in the preceding 3 days, statins in the preceding 7 days, any central venous catheter in the preceding 3 days, a positive assay result for heparin-induced thrombocytopenia, positive APACHE II score, and personal or family history of venous thrombotic events. The association between NLDVT and PE was unchanged (HR, 13.8; 95% CI, 5.8-32.6 [P < .001]).

Nonleg DVTs were not associated with ICU mortality (HR, 1.09; 95% CI, 0.62-1.92 [P = .76]) in a model adjusted for age, APACHE II score, mechanical ventilation, treatment with vasopressors, renal replacement therapy, and platelet counts less than 50 × 10^9/L (Table 5). In sensitivity analyses that distinguished between superficial and deep NLDVTs (first sensitivity analysis) and adjusting for leg DVTs and PE (second sensitivity analysis), the association between NLDVTs and ICU mortality remained nonsignificant (data not shown).

**Discussion**

In a large international trial that compared unfractionated heparin and dalteparin for thromboprophylaxis, we found that ap-
Table 4. Management and Outcomes of NLDVTs: Univariable Analysis*

<table>
<thead>
<tr>
<th>Management/Outcome</th>
<th>NLDVT (n = 67)</th>
<th>No NLDVT (n = 3679)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE diagnosed on same day or after, No. (%)</td>
<td>8 (11.9)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>PE diagnosed ever, No. (%)</td>
<td>10 (14.9)</td>
<td>71 (1.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Therapeutic anticoagulation within 3 d of diagnosis, No. (%)</td>
<td>9 (13.4)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ICU mortality, No. (%)</td>
<td>14 (20.9)</td>
<td>574 (15.6)</td>
<td>.24</td>
</tr>
<tr>
<td>Hospital mortality, No. (%)</td>
<td>19 (28.4)</td>
<td>854 (23.2)</td>
<td>.31</td>
</tr>
<tr>
<td>ICU length of stay, median (IQR), d</td>
<td>19 (10-33)</td>
<td>9 (6-15)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hospital length of stay, median (IQR), d</td>
<td>39.5 (23-79)</td>
<td>21 (13-39)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: ICU, intensive care unit; IQR, interquartile range; NA, not applicable; NLDVT, nonleg deep vein thrombosis; PE, pulmonary embolism.

* In this table, we report unadjusted statistical comparisons of outcomes between patients who had NLDVTs and those who did not, using a t test for continuous outcome variables and a Fisher exact test for dichotomous outcomes. We report the number and proportion of patients with NLDVTs (both prevalent and incident) who had PE before the NLDVT or at any time, therapeutic anticoagulation within the first 3 days, mortality in ICU and in hospital, and length of ICU and hospital stay, unadjusted for other factors.

Table 5. Factors Associated With ICU Mortality: Multivariable Regression*

<table>
<thead>
<tr>
<th>Characteristic/Factor</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline characteristics</td>
<td></td>
<td></td>
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<tr>
<td>Age (10-y increase)</td>
<td>1.16 (1.09-1.23)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>APACHE II score (10-point increase)</td>
<td>1.23 (1.09-1.38)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time-dependent factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>1.05 (0.79-1.39)</td>
<td>.74</td>
</tr>
<tr>
<td>Vasopressors or inotropes</td>
<td>2.56 (2.13-3.08)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Any renal replacement therapy</td>
<td>1.29 (1.04-1.59)</td>
<td>.02</td>
</tr>
<tr>
<td>Platelet count &lt;50 × 10^9/L</td>
<td>2.30 (1.66-3.20)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NLDVT (includes both prevalent and incident)</td>
<td>1.09 (0.62-1.92)</td>
<td>.76</td>
</tr>
</tbody>
</table>

Abbreviations: APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; NLDVT, nonleg deep vein thrombosis.

* We report results of an adjusted analysis to examine the effect of NLDVT on ICU mortality and hospital mortality using a Cox proportional hazard multivariable model. The association of NLDVTs with ICU mortality was adjusted for 2 baseline factors (age and APACHE II score), and 5 time-dependent factors in the preceding 3 days (mechanical ventilation, treatment with vasopressors, renal replacement therapy, platelet counts less than 50 × 10^9/L, and NLDVT).

proximately 2% of patients had NLDVTs. Because the study protocol did not involve screening for nonleg thromboses, this rate of NLDVTs reflects only those patients who presented with clinical signs or symptoms that prompted a diagnostic investigation. We also found that patients who had a malignant condition have a high risk of developing an NLDVT during their stay in the ICU, in keeping with prospective registry studies that have shown that cancer is a dominant predictor of upper-extremity thromboses.2 However, a post hoc sensitivity analysis did not confirm this finding.

We found more PE in patients who had NLDVTs than in those who did not. On average, 1 in 7 patients who had NLDVTs developed a PE during their hospital stay. In comparison, we previously documented that 1 in 12 patients who had a proximal leg DVT have a PE during their hospital stay.34 The apparently higher risk of developing a PE among patients who had an NLDVT compared with a leg DVT could be explained by the greater propensity to therapeutically anticoagulate patients who have lower-extremity DVTs, thereby attenuating the risk of thrombus propagation. However, whether systemic anticoagulation improves outcomes in patients who have NLDVTs and prevents PE remains unknown. It is also plausible that healthcare providers did not pursue the diagnosis of PE as aggressively in patients who already had a clear indication for therapeutic anticoagulation (leg DVT). Another possibility is that clinically evident NLDVTs may constitute more unstable thromboses more prone to embolize than leg DVTs found by screening ultrasonography. Despite the association of NLDVTs with PE, we did not find that NLDVTs were associated with increased mortality, although this study was underpowered to show this association.

Strengths of this study include the calibration exercise to adjudicate NLDVTs, which resulted in high diagnostic agreement. This was followed by randomized, blinded, and duplicate adjudication to ensure validity of the outcome assessment and consistency across events and over the duration of the trial. As a result, we developed a sensible, reproducible nomenclature for venous segments and important characteristics of venous thromboses for this study and future studies. A second strength is that thromboembolic events included in this study were not identified by screening but were largely clinically suspected and objectively confirmed, thereby representing thromboses that are most likely to be clinically relevant. Third, we did not standardize management of these thromboses, which replicates real-world practice. Fourth, we conducted Cox proportional hazard multivariable analyses to identify risk factors and consequences of NLDVTs, adjusting for confounders. We avoided overfitting the models, keeping in mind the number of events comprising the dependent variable and ensuring a minimum of 10 events for every independent variable category introduced in the model.21 Finally, these results are from an international thromboprophylaxis trial (PROTECT) that was conducted in 67 centers in 6 countries, which enhances the generalizability of the findings.
Limitations of this study include the relatively small number of NLDVTs, which necessitated limiting the number of possible predictors we could consider. The frequency of NLDVTs that we observed in this study is less than the 15% reported in a recent observational study in which 862 surgical ICU patients were screened for upper- and lower-extremity DVTs. This difference is likely explained by the use of screening, which invariably leads to higher thrombosis rates than in studies like ours, which reports clinically suspected and objectively confirmed thromboses, and as such, probably underestimate the true incidence of NLDVTs. Identification of NLDVTs is likely to increase, given the growing use of bedside ultrasoundography. Second, the absence of systematic screening for NLDVTs in our study precludes careful distinction between prevalent and incident thrombi. Third, the association between NLDVT and PE could be valid, but because there was no protocolized screening for NLDVT nor PE, we cannot rule out potential detection bias. Intensivists may have pursued a diagnosis of PE more often among patients with an NLDVT. Fourth, our regression does not incorporate information on central venous catheters in patients who did not have venous thromboses, so we could not analyze the impact of catheter insertion as a risk factor using regression analysis. Instead, catheter-related nonleg thrombi was adjudicated accordingly if the catheter had been in situ in the same or contiguous segment within the previous 72 hours. We found that catheter-related thromboses occurred in 52.1% of nonleg thrombi in this study, a proportion that corresponds to findings in other studies. Finally, follow-up was limited to hospital discharge. Accordingly, the long-term impact of NLDVTs, including postthrombotic syndrome and late PE is unknown.

Conclusions

Despite universal heparin thromboprophylaxis, nonleg thromboses are found in 2.2% of medical-surgical critically ill patients, primarily in deep veins and proximal veins. Patients who have a malignant condition may have a significantly higher risk of developing NLDVT, and patients with NLDVT, compared with those without, appeared to be at higher risk of PE but not higher risk of death.
Upper Extremity Deep Vein Thrombosis
A Call to Arms

Greg Maynard, MD, MSc, SFHM

Lamontagne et al14 present findings in this issue of JAMA Internal Medicine from a study focused on the epidemiology, management patterns, and clinical consequences of nonleg venous thrombosis. This prospective cohort study is nested in a large international trial (Prophylaxis for Thromboembolism in Critical Care Trial, aka, PROTECT) randomizing medical-surgical intensive care unit (ICU) patients to either unfractionated heparin or dalteparin for thromboprophylaxis. Of the 3746 patients, 84 (2.2%) experienced a total of 145 nonleg venous thromboses. Most thrombotic segments (94.5%) occurred in the upper extremity, and most thrombi occurred in the more clinically important deep vein thrombosis (UEDVT) literature is therefore appropriate and provides valuable perspective on potential implications for clinical practice, while highlighting the many questions left unanswered about this important entity.