Thromboprophylaxis in the intensive care unit: Focus on medical–surgical patients

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Critically ill patients in the medical–surgical intensive care unit are at high risk for deep venous thrombosis and pulmonary embolism, which comprise venous thromboembolism. Herein, we describe the prevalence, incidence, risk factors, clinical consequences, prophylaxis against venous thromboembolism in critically ill patients, and compliance with thromboprophylaxis. We focus primarily on medical–surgical intensive care unit patients, who represent the largest subgroup of critically ill patients. Despite the large and growing number of critically ill patients in our aging society, their high risk for venous thromboembolism, and the morbidity and mortality associated with this complication of critical illness, relatively few rigorous studies are available. Large, well-designed, randomized trials of thromboprophylaxis, powered to detect differences in patient-important outcomes, are required to advance our understanding and care of these vulnerable patients. Furthermore, because thromboprophylaxis is a common error of omission in hospitalized patients, redoubled efforts are needed to ensure that it is used in practice. (Crit Care Med 2010; 38[Suppl]:S76–S82)

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Venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication of critical illness (1, 2). Most thrombi are asymptomatic and are confined to the deep veins of the calf. However, with time, 20% to 30% of untreated calf vein thrombi extend proximally into the thigh, where, if untreated, they pose a 40% to 50% risk of PE (3). Early studies of the natural history of PE suggest that untreated PE has a mortality rate of at least 25% (4).

The contents of this article are drawn largely from publications on medical–surgical patients in the intensive care unit (ICU). Other contributions in this supplement address cancer patients and pregnant women. Readers are referred elsewhere for a focus on additional ICU subgroups such as neurosurgical populations.

DVT and PE: Common but Clinically Silent in the ICU

Although DVT has potentially serious consequences, it is almost universally unrecognized in patients admitted to the ICU. In an observational study of 100 critically ill medical patients, lower limb Doppler ultrasounds were performed twice weekly and at 1 wk after discharge from the ICU (5). In these patients, DVT detected using screening ultrasonography was present in 32% of those receiving no prophylaxis, in 40% of those receiving subcutaneous unfractionated heparin (UFH), and 33% of those receiving mechanical prophylaxis. Using the more sensitive invasive test of venography in a higher-risk group of trauma patients, DVT has been documented in 31% of patients receiving prophylaxis with enoxaparin and 44% of patients receiving UFH (6). These studies illustrate the high prevalence of DVT in critically ill patients, most cases of which are unsuspected, even when thromboprophylaxis is prescribed.

Concern about undiagnosed VTE in the medical–surgical ICU setting is underscored by studies showing that the majority of ultrasound-proven DVT present no findings on physical examination (5, 7). A prospective study using twice-weekly leg ultrasound scans identified proximal DVT in 25 of 261 (10%) patients during the ICU stay, and an additional four patients had DVT after ICU discharge (8). All but one of these DVT was clinically unsuspected and all occurred despite routine thromboprophylaxis. In a multicenter, prospective cohort study designed to determine whether the low-molecular-weight heparin (LMWH) dalteparin bioaccumulated in critically ill patients with impaired renal function, proximal DVT was detected in seven of 138 (6%) patients. Importantly, of 158 patients considered for this study, 15 (10%) were excluded because they had unsuspected DVT on a screening ultrasound performed at the time of ICU admission (9). In a randomized trial of UFH vs. the LMWH dalteparin in critically ill medical–surgical patients wherein twice-weekly ultrasound scans were performed to screen for proximal DVT, 11 of 129 (9%) of patients were identified to have lower limb DVT; none of these events were identified as a result of a clinician suspecting DVT (10).

In a formal prospective evaluation of the diagnostic properties of the history and physical examination for signs of DVT, we documented disappointing utility of the conventional approaches proven to be useful in ambulatory patients. In 239 medical–surgical ICU patients, we conducted twice-weekly screening compression ultrasonography as a reference standard for the presence of DVT. Con-
currently, a twice-weekly structured physical examination was performed by two independent trained research coordinators who were blinded to the ultrasound results (11). They recorded baseline and twice weekly the Wells criteria (12, 13), which have been shown to predict the likelihood of ambulant outpatients harboring DVT. Patients were classified according to two composite scores, both of which use the history and physical examination to stratify patients for their risk of DVT. Method 1 was a DVT risk stratification system of three categories, and method 2 was a DVT risk score. We matched controls with cases (9:1) based on duration of ICU stay. Cases and controls were then allocated to low-risk, moderate-risk, and high-risk strata for DVT. Using method 1, the area under the receiver operating curve was 0.57 (95% confidence interval [CI], 0.33–0.78; \( p = .01 \)). Using method 2, the area under the receiver operating curve was 0.59 (95% CI, 0.42–0.75; \( p = .02 \)). An area under the receiver operating curve of 1.0 indicates an ideal test, and area under the receiver operating curve of 0.50 indicates a test with no diagnostic utility. These data show that the history and physical examination for DVT are not useful in screening for lower limb DVT in critically ill patients. This lack of utility is not surprising; as a result of recumbency, ICU patients do not manifest unilateral leg swelling, and as a result of coma attributable to their condition or drugs, they cannot report leg pain.

Clinically unsuspected PE also remains a problem among critically ill patients. Mechanically ventilated patients with sudden episodes of hypotension, tachycardia, or hypoxemia may have undetected PE (14). PE may also contribute to difficulty weaning critically ill patients from mechanical ventilation (5). In one study, 13 of 34 (38%) critically ill patients with known DVT and no symptoms of PE had PE diagnosed by ventilation–perfusion scans (15). We posit that among ICU patients with impaired cardiopulmonary reserve, even a small PE might have severe or fatal consequences (16). In an autopsy study, PE was found after death in 59 of 404 (15%) hospitalized patients. In another study, PE was unsuspected in 14 of 20 (70%) patients who died of PE (17). In a 25-yr longitudinal study, 9% of patients had PE identified at autopsy; fully 84% of these pulmonary emboli were unsuspected before death (18). VTE remains one of the most common unsuspected autopsy findings in critically ill patients (19).

In summary, VTE in the ICU is more common than appreciated in practice. DVT and PE are difficult to diagnose by typical signs and symptoms useful in other hospitalized patients or outpatients. VTE therefore is often silent and clinically unsuspected in medical–surgical ICU patients.

**Clinical Consequences of VTE in the ICU**

From the observational study cited (8) in which 10% of ICU patients had proximal DVT diagnosed by twice-weekly ultrasonography, patients with and without DVT were directly compared. Those with DVT had a longer duration of mechanical ventilation (median, 9 vs. 6 days, \( p = .02 \)), duration of ICU stay (median, 17.5 vs. 9 days; \( p = .005 \)), duration of hospital stay (median, 51 vs. 23 days; \( p < .001 \)), and higher hospital mortality (30% vs. 38%; \( p = .04 \)) (8).

To avoid overestimates of the morbidity and mortality attributable to DVT that can be generated by crude comparisons, we hypothesized that using rigorous matching methods, DVT would be associated with a trend toward longer ICU stay, but that refined estimates of harm require a large study. Using three methods, we estimated duration of ventilation, duration of ICU stay, and ICU mortality in a single center study of 261 ICU patients, 26 of whom had DVT diagnosed by twice-weekly ultrasound scans (20). The “matched cohort method” matched patients with and without DVT using Acute Physiology and Chronic Health Evaluation (APACHE) II score (\( \pm 4 \)), age (\( \pm 10 \) yrs), medical vs. surgical admission diagnosis, duration of ICU stay, and multiple organ dysfunction (MOD) score 3 days before DVT. The “model-based matched cohort” method used Cox proportional hazards to match patients with and without DVT. The “regression method” derived estimates based on regression modeling in the population. All three of these methods suggested that proximal DVT diagnosed by screening ultrasound is associated with increased duration of ventilation (1–9 days) and increased duration of ICU stay (3–9 days). The mortality attributable to DVT or PE remains uncertain; wide confidence intervals underscore the need for a larger study to obtain more refined estimates. Some patients may die with DVT or PE, whereas others die of PE. The diverse reasons for death in an ICU patient, the lack of standardized approaches to ascertain cause-specific ICU mortality, and the global under-diagnosis of PE in the ICU make it very difficult to estimate attributed morbidity and mortality with DVT or PE in this setting.

In summary, DVT appears to confer a poor outcome in medical–surgical patients; less is known about the consequences of PE. Under-diagnosis of VTE and the dearth of large epidemiologic studies controlling for confounding factors preclude strong estimates of the attributed morbidity and mortality of VTE in the ICU setting.

**Evidence for VTE Prophylaxis in Medical–Surgical ICU Patients**

Patients in the medical–surgical ICU have unique characteristics that distinguish them from patients in various selected subgroups of ICU patients described. Medical–surgical critically ill patients have an increased risk of both VTE and bleeding. Critically ill patients have an increased risk of VTE because of their acute illness and frequent need for mechanical ventilation, sedation, and paralysis, and exposure to procedures such as surgery and central venous catheterization. The bleeding risk of medical–surgical ICU patients is high attributable to coagulopathy, thrombocytopenia, thrombocytopenia (drug induced by antitplatelet agents or not), and inadequate postoperative hemostasis. The choice of thromboprophylaxis depends on the balance of thrombotic and bleeding risk, which can change daily; thus, thromboprophylaxis prescriptions should be reviewed daily in the ICU. However, given the high prevalence of VTE, and its potential morbidity and mortality, VTE prophylaxis of some kind should be provided to all critically ill patients. Strategies to prevent VTE are of proven benefit in other populations, are widely available, and have a low risk of toxicity. The beneficial effect of subcutaneous UFH for the prevention of DVT has long been established (21). In two meta-analyses of trials enrolling >8000 general surgery patients, subcutaneous UFH resulted in a 60% to 70% relative risk reduction for both DVT and fatal PE (22, 23). Not surprisingly, the 8th American College of Chest Physicians (ACCP) Antithrombotic Consensus Conference recommends that on admission to the ICU, all patients should be assessed for their risk of VTE.
 Approximately 20% to 40% of patients admitted to the medical–surgical ICU will manifest severe renal insufficiency as indicated by a calculated creatinine clearance of <30 mL/min or the need for renal replacement therapy; clearly, this risk is anticipated on case mix. Concern that such patients may bioaccumulate LMWH, placing them at increased risk of bleeding, led us to address the safety of LMWH in critically ill patients. We performed two prospective observational studies. In the first single-center pilot study (30), we enrolled patients age 18 yrs or older, expected to stay ≥72 hrs, with a creatinine clearance ≥30 mL/min at ICU admission. The objectives were to detect bioaccumulation of dalteparin 5000 IU administered subcutaneously daily using trough anti-Xa levels (22–23 hrs after dose), and to examine the relationship between renal dysfunction and peak anti-Xa levels (4 hrs after dalteparin). We measured trough anti-Xa levels on 185 occasions in 19 patients; we measured peak anti-Xa levels on 113 occasions in 11 patients. We identified no bioaccumulation of LMWH in this study, as detected by trough anti-Xa levels. Most peak anti-Xa levels were in the conventional prophylactic range. The second multicentered prospective study of critically ill patients with severe renal insufficiency (creatinine clearance <30 mL/min) involved administration of dalteparin 5000 IU once daily subcutaneously for up to 30 days in the ICU (9). Our objectives were to determine whether dalteparin in ICU patients with severe renal insufficiency leads to bioaccumulation and anticoagulant-related bleeding, to determine the pharmacodynamic properties of dalteparin, and to determine rates and predictors of major bleeding and VTE in patients receiving dalteparin thromboprophylaxis. We defined bioaccumulation by trough anti-Xa levels >0.40 IU/mL, measured twice weekly 20 hrs after the previous dalteparin dose. We defined the pharmacodynamic properties of dalteparin by anti-Xa levels measured at 0, 1, 2, 4, 8, 12, 20, and 24 hrs after the previous dalteparin dose on day 3 ± 1, 10 ± 1, and 17 ± 1 of treatment. Daily, we recorded the incidence of major and minor bleeding and DVT, based on twice-weekly lower limb venous ultrasound testing. Of 156 patients enrolled, 18 were excluded because they died before testing (n = 3) or had prevalent DVT (n = 14) or PE (n = 1) within 48 hrs of enrollment. In 120 patients who had at least one trough anti-Xa level measured (454 total measurements), no patient had an anti-Xa level >0.40 IU/mL and the median trough anti-Xa level was <0.1 IU/mL (interquartile range 0.02–0.11 IU/mL).
Mechanical Prophylaxis in the ICU

Mechanical methods of prophylaxis are used in some critically ill patients who are either bleeding or are at high risk for bleeding. Nonpharmacologic approaches such as antiembolic stockings and pneumatic compression devices have not been evaluated in any trials in medical–surgical ICU patients.

Graduated compression stockings (or antiembolic stockings) are considered less effective than pharmacologic prophylaxis (32, 33). Their use is generally reserved for patients with a contraindication to pharmacologic prophylaxis. Pneumatic compression devices are similarly used for patients who have a contraindication to pharmacologic prophylaxis. A recent systematic review has documented that little is known about the effectiveness or safety of mechanical prophylaxis in medical–surgical ICU patients (34).

Inferior vena cava filters are widely used as prophylactic agents despite a singular lack of supporting trial data and, importantly, clear evidence that they increase the acute risk of recurrent DVT in patients in whom they are inserted after an initial DVT (35). The 8th ACCP Antithrombotic Consensus Conference guidelines recommend against the use of inferior vena cava filters as a primary thromboprophylaxis strategy (32). The only widely accepted indication for an inferior vena cava filter is for the prevention of PE in patients with a leg DVT who have a coincident and absolute contraindication to anticoagulant therapy such as active bleeding. Use of inferior vena cava filters for other indications, such as PE prophylaxis in trauma patients or as an adjunct to pharmacologic treatment in patients with large proximal DVT, is neither evidence-based nor generally regarded as safe and effective (36).

Anticoagulant thromboprophylaxis is very unlikely to cause major bleeding, as several bleeding risk factor analyses have shown (8, 9). Despite this, many patients in the ICU are perceived to have a high risk for bleeding and thus pharmacologic prophylaxis is withheld. Major or fatal bleeding is, in fact, very rare in the ICU, whereas VTE is relatively more common. Thus, the risk-to-benefit ratio generally favors use of anticoagulant thromboprophylaxis, and only patients with active, major bleeding or patients at high risk for serious re-bleeding (such as those with a very recent intracranial hemorrhage) should be considered to have an absolute contraindication to pharmacologic prophylaxis (32). Patients with HIT or suspected HIT are generally considered to have a contraindication to heparin; thus, an alternate HIT-safe anticoagulant is needed in these situations. Thrombotic and bleeding risks are dynamic and should be evaluated daily in ICU patients with respect to thromboprophylaxis.

In summary, anticoagulant thromboprophylaxis is likely more effective than mechanical approaches, but no randomized trials have compared them directly in medical–surgical ICU patients. A growing number of HIT-safe anticoagulants are available for suspected or confirmed HIT.

Thromboprophylaxis Compliance in Medical–Surgical ICU Patients

Several prospective, single-center utilization reviews of VTE prophylaxis provide evidence on how well thromboprophylaxis is applied in practice. Prophylaxis was prescribed in 33% of 152 medical ICU patients in one study (37), and in 61% of 100 medical ICU patients in another (5). In contrast, in a medical–surgical ICU in which a clinical practice guideline was in place, VTE prophylaxis was prescribed for 86% of 209 patients (38). In another study of medical–surgical ICU patients, after excluding patients receiving therapeutic anticoagulation and for whom heparin was contraindicated, 63% of 96 patients received UFH thromboprophylaxis (39).

In a 1-day, cross-sectional, multicenter utilization review of Canadian surgical ICU patients whose procedure was no more than 1 wk earlier, UFH was used predominantly (40). Two methods of VTE prophylaxis were prescribed for 20 of 89 (23%) patients. Prophylaxis with UFH or LMWH was significantly less likely for postoperative ICU patients requiring mechanical ventilation compared to patients weaned from mechanical ventilation later in their ICU course (odds ratio [OR], 0.36; p = .03). Use of intermittent pneumatic compression devices was significantly associated with current hemorrhage (OR, 13.5; p = .02) and risk of future hemorrhage (OR, 19.3; p = .001).

In a 1-day, bi-national, cross-sectional utilization review of medical ICU patients in France and Canada (41), we found that among 1222 patients (65% of whom were mechanically ventilated), heparin VTE prophylaxis was administered to 64% pa-
tients, similarly between the two countries. Excluding patients with contraindications to heparin and those receiving therapeutic anticoagulation, 92% of medical ICU patients appropriately received either UFH or LMWH prophylaxis. Independent predictors of any type of heparin prophylaxis were invasive mechanical ventilation (OR, 2.4; 95% CI, 1.4–4.3) and obesity (OR, 3.1; 95% CI, 1.1–8.8). LMWH was less likely to be prescribed for patients with renal failure (OR, 0.1; 95% CI, 0.0009–0.9) or those receiving antiemetic stockings (OR, 0.4; 95% CI, 0.1–0.9), and much more likely to be prescribed in French ICUs (OR 9.2; 5.0–16.9); however, among patients receiving LMWH, high doses were more likely to be prescribed in Canadian ICUs (OR, 8.7; 95% CI, 2.0–37.6). Patients who were pregnant or postpartum (OR, 7.7; 95% CI, 1.3–44.3), had neurologic failure (OR, 2.1; 95% CI, 1.3–3.4), or were Canadian (OR, 3.0; 95% CI, 2.1–4.4) were most likely to receive mechanical VTE prophylaxis (with antiembolic stockings or pneumatic compression devices), whereas those who were already receiving heparin were less likely to receive mechanical prophylaxis (OR, 0.5; 95% CI, 0.3–0.7).

Even among patients who ultimately have VTE, many may not have received any antecedent prophylaxis (42). A study of 14 Swiss hospitals enrolled 567 consecutive patients with acute VTE and hospitalization within the previous 30 days. Prophylaxis was used in only 329 (58%) patients within 30 days before the VTE event. Among medical patients, 146 of 306 (48%) received prophylaxis, and among surgical patients, 183 of 261 (70%) received prophylaxis (p < .001). There was an indication for prophylaxis in 86% medical patients and 83% of surgical patients. However, among the patients with an indication, only 52% of the medical patients and 76% of the surgical patients received prophylaxis (p < .001). Admission to the ICU (OR, 3.28; 95% CI, 1.94–5.57), recent surgery (OR, 2.28; 95% CI, 1.51–3.44), bed rest >3 days (OR, 2.12; 95% CI, 1.45–3.09), obesity (OR, 2.01; 95% CI, 1.03–3.90), previous DVT (OR, 1.71; 95% CI, 1.31–2.24), and previous PE (OR, 1.54; 95% CI, 1.05–2.26) were independent predictors of prophylaxis. Interestingly, cancer, age, acute heart failure, and acute respiratory failure were not predictive of prophylaxis.

Neurosurgical patients are a prototypical population in which to examine bleeding risk aversion, because anticoagulant thromboprophylaxis may increase the risk of devastating bleeding in these patients. In a self-administered questionnaire on the use and timing of anticoagulant thromboprophylaxis in different neurosurgical subgroups, Canadian neurosurgeons and intensivists differed widely as to what was prescribed and when (43). Physicians’ willingness to use anticoagulant prophylaxis was generally directly related to their assessment of baseline risk of thromboembolism and inversely related to their assessment of the baseline risk of bleeding. These findings underscore opportunities for future prognosis studies on the risks of VTE and hemorrhage, as well as randomized trials on the timing, strategies, risks, and benefits of thromboprophylaxis in different ICU subgroups.

Regarding mechanical prophylaxis, utilization is based more on unit tradition than data generated in ICU populations, as Australian nurses reported in a recent self-administered survey (44).

Although more randomized trials of VTE prophylaxis in medical–surgical critically ill medical patients would better inform practice, these trials are not enough. Additional trials testing the effectiveness of implementation strategies designed to change clinician behavior and improve thromboprophylaxis prescribing are also needed. For example, there are no randomized trials in the ICU setting comparing different thromboprophylaxis implementation strategies such as distribution of educational material, educational meetings, educational outreach visits, computer reminders, or individual audit and feedback (45). Also, there is little original research on the feasibility, acceptability, and cost of implementation strategies in thrombosis research. One systematic review by Tooher et al (46) showed how almost any intervention had a positive influence on thromboprophylaxis prescribing in the hospital setting. Whereas multifaceted approaches have been shown to improve thromboprophylaxis in the ICU (47), the most cost-effective approaches remain to be elucidated, which is a field ripe for future health services research.

Just as knowing the research evidence about health care interventions that prevent morbidity and mortality does not ensure that it is used in practice, knowing the research evidence about effective behavior change strategies does not ensure that they are used as implementation strategies. Therefore, one of the most important issues in closing the loop on safety initiatives is taking a scientific approach to evaluating whether the behavior change strategies are indeed being applied, and whether they are achieving the desired patient outcome. This feedback is only possible with rigorous surveillance, audits, and other observational studies. Recognizing this health services priority, the 8th ACCP Antithrombotic Consensus Conference recommends that every hospital develop a formal strategy that addresses the prevention of VTE (grade 1A) (24).

Another strategy that could help to improve thromboprophylaxis through increased awareness is participation in VTE registries. In the DVT-FREE Registry, 5451 patients with DVT in 183 US centers were recruited over 4 mos. Of 2726 inpatients with DVT, only 1147 (42%) received prophylaxis within 30 days of the diagnosis (48). The International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) showed that only 38% of hospitalized medical patients received some form of thromboprophylaxis (49). A registry of VTE events in the ICU setting could offer insight into current practice by further emphasizing the need for more effective implementation strategies and profiling the problem of VTE in general.

In summary, the utilization of thromboprophylaxis is generally low, even for patients who are at high risk for VTE, representing a field in need of local knowledge translation efforts and collaborative health services research.

CONCLUSIONS

In summary, VTE is a common and largely unrecognized complication of critical illness associated with adverse patient outcomes. There is a large body of evidence that pharmacologic prophylaxis reduces the risk of DVT and PE in patients who are not critically ill. Evidence about the effectiveness of thromboprophylaxis in the critically ill is limited but suggests efficacy similar to that seen outside the ICU. In medical–surgical ICU patients, the thrombotic and bleeding consequences of UFH vs. LMWH are unknown, and this trade-off is the subject of current randomized trials. LMWH is associated with less VTE than UFH in trauma and orthopedic patients. Graduated compression stockings and pneu-
matic compression devices have not been studied in the general medical–surgical ICU; mechanical thromboprophylaxis is thus limited to selected patients with contraindications to heparin such as active major bleeding or potential for major bleeding. There is no evidence in this population to support the prophylactic use of inferior vena cava filters in patients who do not have PE. Further trial data are required to guide optimal use of anticoagulant and mechanical prophylaxis in medical–surgical critically ill patients. Also, given the well-documented poor uptake of thromboprophylaxis, studies are also warranted to inform us about the most cost-effective implementation strategies to ensure optimal prevention against this common threat to patient safety. An editorial 10 yrs ago stated that the medical–surgical ICU was “the last frontier for prophylaxis” (50). Hopefully, the next decade will herald new data and unequalled attention to thromboprophylaxis in vulnerable medical–surgical ICU patients.

REFERENCES