Venous Thromboembolism Prophylaxis in Critically Ill Patients

Anne G. McLeod, MD, MSc,a,b,*, William Geerts, MDa,c

KEYWORDS
• Venous thromboembolism • Thromboprophylaxis
• Prevention • Critical care

Venous thromboembolism (VTE) is a frequent but often silent complication of critical illness that has a negative impact on patient outcomes.1 The prevention of VTE is an essential component of patient care in the intensive care unit (ICU) setting, and is the focus of this review.

Critically ill patients present a number of important challenges with respect to VTE and its prevention. First, ICU patients have greater heterogeneity in their risk of thrombosis than do other hospitalized patient groups. Second, a clinical suspicion of possible VTE is very common (often daily) in these patients because of tachycardia, desaturation, patient anxiety, limb swelling, and fever. Third, symptoms and signs commonly associated with deep vein thrombosis (DVT) or pulmonary embolism (PE) are not reliable indicators of VTE in critical care patients.2,3 Fourth, ICU patients frequently have compromised cardiopulmonary function and, therefore, relatively small pulmonary emboli could have dire consequences. Autopsy studies have shown that PE is found in up to 25% of these patients and is sometimes the cause of their death.3 Finally, although critically ill patients often have multiple risk factors for VTE, they are frequently also at increased risk for bleeding because of recent surgery, trauma, intracranial or gastrointestinal bleeding, thrombocytopenia, and renal insufficiency. Despite these challenges, studies in trauma, surgery and acutely ill medical patients, as well as recently published studies in critical care patients, allow clinicians to provide effective and safe thromboprophylaxis.
Because clinical practice guidelines have recommended the routine use of thromboprophylaxis in critical care patients for more than 20 years, we review historical studies to understand the risk of VTE in patients not receiving pharmacologic or mechanical thromboprophylaxis. Autopsies in 436 critically ill patients in six studies detected PE in 7% to 27% of patients (mean 13%), and PE that caused or contributed to death was found in 0% to 12% (mean 3%) of these patients (Table 1). In the majority of patients with proven or fatal PE, there was no clinical suspicion of PE before death.

In an observational study of 100 critically ill medical patients, leg Doppler ultrasounds (DUS) were performed twice weekly during ICU admission and at 1 week after ICU discharge. Proximal DVT was detected in 32% of patients receiving no prophylaxis, 40% of patients receiving low-dose unfractionated heparin (LDUH), and 33% of those receiving mechanical prophylaxis. Only four prospective studies have assessed the incidence of DVT in critically ill patients who did not receive thromboprophylaxis (Table 2). In a study of 23 patients admitted to ICU with respiratory failure, Moser and coworkers found that 13% had DVT detected by fibrinogen leg scanning. Cade and colleagues detected DVT by fibrinogen leg scanning in 29% of patients in the placebo arm of a trial of 119 general ICU patients. Both studies are problematic because of poor characterization of patients, lack of follow-up, and the use of fibrinogen scanning for diagnosis. A study reported by Kapoor and colleagues in abstract form evaluated 390 medical ICU patients for DVT using DUS examinations every 3 days during their ICU admission. DVT was detected in 31% of patients not receiving thromboprophylaxis. The only ICU study to use routine contrast venography was conducted in mechanically ventilated patients treated for exacerbation of chronic pulmonary disease. DVT was diagnosed in 28% of patients in the placebo arm of this randomized trial; most of these were distal thrombi, with proximal DVT found in 8% of patients. In summary, screening of asymptomatic patients detected a prevalence of DVT in medical–surgical ICU patients not receiving thromboprophylaxis ranging from 13% to 31%. The clinical consequences of asymptomatic DVT detected by routine screening using any diagnostic method remain unclear. The presence of DVT, however, does significantly increase the risk of subsequent PE and it seems likely that this could contribute to adverse outcomes in patients with already compromised cardiopulmonary reserve.

PREVALENCE OF VTE IN CRITICALLY ILL PATIENTS ON ADMISSION TO ICU

Some patients newly admitted to a critical care unit will already have unsuspected DVT. Among six case series, including 1164 patients who were screened for asymptomatic DVT on admission to ICU, DVT was found in 6.3%. The recently published PROTECT study identified proximal DVT on the initial DUS, performed within 2 days after admission, in 3.5% of patients. Clinicians should be aware that many patients admitted to ICU will have been exposed to high-risk situations for the development of VTE such as immobilization, surgery, cancer, and chronic illness and may arrive with thrombosis already present.

CLINICALLY SILENT VTE IN CRITICALLY ILL PATIENTS

Critically ill patients commonly have asymptomatic thromboembolic events. For example, in a study of 90 trauma patients with no clinical suspicion of PE, routine
Table 1
Autopsy studies of pulmonary embolism in critically ill patients

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>ICU Setting</th>
<th>Admissions to ICU</th>
<th>Deaths, n (% ICU admissions)</th>
<th>Autopsies, n (% deaths)</th>
<th>PE, n (% autopsies)</th>
<th>Fatal PE, a n (% autopsies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuhaus et al (1978)</td>
<td>Medical/surgical</td>
<td>617</td>
<td>102 (17)</td>
<td>66 (65)</td>
<td>18 (27)</td>
<td>8 (12)</td>
</tr>
<tr>
<td>Moser et al (1981)</td>
<td>Respiratory</td>
<td>34</td>
<td>16 (47)</td>
<td>10 (63)</td>
<td>2 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Pingleton et al (1981)</td>
<td>Respiratory</td>
<td>197</td>
<td>56 (28)</td>
<td>40 (71)</td>
<td>19 (23)</td>
<td>NR</td>
</tr>
<tr>
<td>Cullen and Nemeskal</td>
<td>Surgical</td>
<td>NR</td>
<td>Approx. 760</td>
<td>152 (23)</td>
<td>15 (10)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>(1986)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blosser et al (1998)</td>
<td>Medical-coronary</td>
<td>NR</td>
<td>132 (NR)</td>
<td>41 (31)</td>
<td>3 (7)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Willemsen et al (2000)</td>
<td>Surgical</td>
<td>2,969</td>
<td>384 (13)</td>
<td>127 (33)</td>
<td>10 (8)</td>
<td>4 (3)</td>
</tr>
</tbody>
</table>

a Pulmonary embolism causing or contributing to death.

Abbreviation: NR, not reported.

Table 2
Prospective studies evaluating the rates of DVT in unprophylaxed critical care patients

<table>
<thead>
<tr>
<th>Study Quality Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author (year)</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Moser et al(^6) (1981)</td>
</tr>
<tr>
<td>Cade(^{12}) (1982)</td>
</tr>
<tr>
<td>Kapoor et al(^{13}) (1999)</td>
</tr>
<tr>
<td>Fraisse et al(^{14}) (2000)</td>
</tr>
</tbody>
</table>

Note. Includes studies in which no prophylaxis was given and routine screening with an objective diagnostic test for DVT was used.

Abbreviations: COPD, chronic obstructive pulmonary disease; DUS, Doppler ultrasound; Fg LS, \(^{125}\)I fibrinogen leg scanning; NR, not reported; RCT, randomized clinical trial.

screening contrast CT detected PE in 24%. Further, ICU patients are often unable to report symptoms because of sedation and mechanical ventilation. They are also immobilized and recumbent, making leg swelling and pain less likely to be apparent. Although clinical predictive models to assess the probability of DVT and PE have been well validated in outpatient populations, the reliability of physical examination in critically ill patients has not been found to be helpful in detecting lower limb DVT. In the PROTECT trial, 8.6% of patients receiving LDUH or LMWH thromboprophylaxis developed DVT detected by DUS and none of these events were identified as a result of a clinical suspicion of DVT.

Given that critically ill patients may develop asymptomatic VTE and that routine screening is both time consuming and costly, a predictive laboratory test for VTE in these patients might be of considerable value. A prospective cohort study was conducted to evaluate the utility of using D-dimer and tests of molecular hypercoagulability as predictors of DVT in critically ill patients. Neither D-dimer testing, performed serially during ICU admission, nor tests of hypercoagulability (activated protein C resistance, prothrombin mutation, protein C, protein S, antithrombin, IgG anticardiolipin antibody, and lupus anticoagulant) were able to predict patients who had DVT detected by routine DUS.

**CLINICAL IMPACT OF VTE IN CRITICALLY ILL PATIENTS**

The presence of DVT or PE adversely affects morbidity and mortality in critically ill patients. In a prospective cohort study, a diagnosis of DVT was associated with longer duration of mechanical ventilation (median 9 vs 6 days, \( P = .03 \)), longer duration of ICU stay (median 17.5 vs 9 days, \( P = .005 \)), and longer duration of hospital stay (median 51 vs 23 days, \( P < .001 \)) compared with ICU patients without DVT. Although less is known about the impact of PE in this population, it seems likely, given the negative impact of PE on outcomes in other patient groups, that this would also be true for critically ill patients.

**RISK FACTORS FOR VTE IN CRITICALLY ILL PATIENTS**

Although the spectrum of diagnoses that result in admission to an ICU is wide, all critically ill patients are at increased risk of VTE. The vast majority will have at least one major risk factor for VTE and many will have multiple risk factors. These risk factors can be categorized into those that are present before admission to a critical care unit and those acquired during the ICU admission (Box 1). The relative contribution of each of these risk factors is unknown, but consideration of these risks is important in designating patients as moderate or high risk for VTE.

A number of studies have identified factors that were reported to predict an increased risk of VTE associated with an ICU admission, including increased age, APACHE (acute physiology and chronic health evaluation) score, recent surgery, sepsis, previous VTE, malignancy, major trauma, prolonged hospital stay preceding the ICU transfer, mechanical ventilation, use of paralytic drugs, insertion of a femoral vein catheter, and failure to use thromboprophylaxis. However, these studies were underpowered to determine independent predictors for thrombosis in ICU patients.

Cook and coworkers prospectively followed 261 medical–surgical ICU patients to determine the prevalence, incidence, and independent risk factors for proximal lower extremity DVT. Thromboprophylaxis was protocol driven and administered to all patients. The study found four independent DVT risk factors in the multivariable analysis. The two risk factors that were acquired before critical care admission were...
personal or family history of DVT (hazard ratio 4.0; 95% confidence interval (CI) 1.5–10.3) and dialysis-dependent renal failure (hazard ratio 3.7; 95% CI 1.2–11.1). The ICU-acquired risk factors were platelet transfusion (hazard ratio 3.2; 95% CI 1.2–8.4) and vasopressor administration (hazard ratio 2.8; CI 1.1–7.2; Table 3).1 Other studies have demonstrated that ICU patients who receive both LMWH and vasopressors have significantly lower anti-factor Xa activity than patients given the same dose of LWMH without vasopressors.28 It is proposed that vasopressor use contributes to poor efficacy of subcutaneous LMWH as a result of impaired peripheral perfusion and subsequent inadequate systemic bioavailability of the anticoagulant.

Several studies have identified central venous catheters, specifically femoral vein catheters, as significant risk factors for the development of VTE.22–26,29 Cook and colleagues1 also found that femoral vein catheterization was associated with lower extremity DVT but it was not an independent risk factor in the multivariable analysis. A small, unblinded randomized study of ultrasound-guided “low approach” femoral vein catheterization (10–15 cm below the inguinal ligament) in critical care patients, showed a significantly higher rate of DVT (13/40 vs 4/40; $P<.001$) with this approach compared to the classic insertion approach.30 In the PROTECT trial, catheter-related thrombosis occurred in 2.2% of patients receiving LMWH or LDUH.17

---

**Box 1**  
**Risk factors for critically ill patients**

Present Before the ICU Admission
- Increased age
- Previous VTE
- Trauma
- Surgery
- Malignancy
- Sepsis
- Immobilization: spinal cord injury, bedrest, stroke
- Estrogen: pregnancy, puerperium
- Cardiac or respiratory failure

Acquired During the ICU Admission
- Pharmacologic paralysis
- Mechanical ventilation
- Central venous lines, especially femoral vein catheters
- Surgical procedures
- Sepsis
- Renal dialysis
- Vasopressor use
- Platelet transfusion
- Use of recombinant factor VIIa

Risk factors for venous thrombosis in critically ill patients are many and varied. It is essential, however, to consider all critically ill patients to be at significant risk for VTE and to provide thromboprophylaxis routinely. Further studies are needed to help identify risk factors for the development of VTE despite the use of current thromboprophylaxis.

**PHARMACOLOGIC THROMBOPROPHYLAXIS STUDIES IN CRITICAL CARE**

Four randomized clinical trials of thromboprophylaxis in medical–surgical ICU patients have been completed using objective screening for DVT (Table 4). In 1982, Cade and coworkers randomized 119 general ICU patients to receive placebo or LDUH 5000 U subcutaneously twice daily. DVT, detected using fibrinogen leg scanning, was identified in 29% of patients in the placebo group and 13% of the treatment group, a relative risk reduction of 55% ($P < .05$). Bleeding rates in this study were not reported. Fraisse and colleagues compared the LMWH nadroparin to placebo in 223 patients requiring mechanical ventilation for chronic obstructive pulmonary disease (COPD) exacerbations; DVT was detected by routine venography in 28% of patients receiving placebo and 15% of LMWH recipients for a relative risk reduction of 45% ($P = .045$). No significant difference in bleeding was reported (3% and 6% in the placebo and nadroparin arms, respectively). Kapoor and coworkers reported, in abstract form only, a study of 791 medical ICU patients randomized to placebo or LDUH. Patients were screened for DVT using serial DUS; DVT was detected in 31% of patients receiving placebo and 11% of LDUH recipients ($P = .01$). Bleeding rates were not reported.

PROTECT is the only study to compare the effects of LMWH and LDUH for the prevention of VTE in medical–surgical ICU patients. It is important to be aware that trauma, orthopedic, and neurosurgery patients were not included in this trial. The investigators randomized 3764 patients in 67 centers in 6 countries to receive either

---

**Table 3**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Patients with DVT (%)</th>
<th>Patients without DVT (%)</th>
<th>Univariate Hazard Ratio (95% CI)</th>
<th>p Value</th>
<th>Multivariate Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal or family history of VTE</td>
<td>28.0</td>
<td>6.0</td>
<td>3.7 (1.4–9.3)</td>
<td>0.007</td>
<td>4.0 (1.5–10.3)</td>
<td>0.004</td>
</tr>
<tr>
<td>Thrombophilic disorder</td>
<td>12.0</td>
<td>2.8</td>
<td>3.8 (1.1–12.8)</td>
<td>0.03</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Chronic hemodialysis</td>
<td>16.0</td>
<td>6.0</td>
<td>3.3 (1.1–9.9)</td>
<td>0.03</td>
<td>3.7 (1.2–11.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Femoral venous catheter</td>
<td>56.0</td>
<td>38.4</td>
<td>2.0 (0.9, 4.6)</td>
<td>0.09</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Surgery</td>
<td>32.0</td>
<td>17.6</td>
<td>2.9 (1.1–7.8)</td>
<td>0.04</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Platelet transfusion</td>
<td>24.0</td>
<td>10.6</td>
<td>3.1 (1.2–7.9)</td>
<td>0.02</td>
<td>3.2 (1.2–8.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Vasopressor administration</td>
<td>36.0</td>
<td>19.9</td>
<td>3.0 (1.2–7.4)</td>
<td>0.02</td>
<td>2.8 (1.1–7.2)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Method of Diagnosis</th>
<th>Intervention</th>
<th>DVT, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>Experimental</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NR/NR</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Cade¹² (1982)</td>
<td>Fibrinogen leg scan daily for 4–10 days</td>
<td>Placebo</td>
<td>LDUH, 5000 U SC bid</td>
</tr>
<tr>
<td>Kapoor¹³ (1999)</td>
<td>DUS on admission and every 3 days</td>
<td>Placebo</td>
<td>LDUH, 5000 U SC bid</td>
</tr>
<tr>
<td>Fraisse¹⁴ (2000)</td>
<td>Weekly DUS and venography at day 21</td>
<td>Placebo</td>
<td>Nadroparin, Approx. 65 U/kg SC qd</td>
</tr>
<tr>
<td>PROTECT¹⁷ (2011)</td>
<td>DUS on admission and twice weekly</td>
<td>UFH 5000 U SC bid</td>
<td>Dalteparin, 5000 IU SC qd</td>
</tr>
</tbody>
</table>

Note. Results of randomized trials in which routine screening with an objective diagnostic test for DVT was used.

* Proximal DVT.

Abbreviations: DUS, Doppler ultrasound; NR, not reported.

dalteparin 5000 IU once daily plus placebo once daily or LDUH 5000 U twice daily. Study prophylaxis was continued for the duration of the ICU admission. Screening for proximal DVT was conducted using DUS performed within 2 days of admission, twice weekly during the ICU stay, and as clinically indicated. Investigations for PE were also performed as clinically indicated. Prevalent DVT was identified at initial screening in 3.5% of the study patients. The two patient groups were well balanced; 76% of admissions were medical and 90% of patients required mechanical ventilation. APACHE II scores were 21 in both groups. Overall, 5.1% of patients receiving dalteparin and 5.8% of patients receiving LDUH developed proximal DVT ($P = .57$). Fewer patients developed the prespecified secondary outcome, PE, in the dalteparin group (1.3% vs 2.3%; $P = .01$), but hospital death did not significantly differ in the two groups. Major bleeding occurred in 5.5% of patients receiving dalteparin and 5.6% of those receiving LDUH. There were 50% fewer cases of heparin-induced thrombocytopenia in the dalteparin group. In this large trial, 5% of patients developed proximal leg DVT and 9% developed venous thrombosis in any location despite the use of thromboprophylaxis.

There are a number of reasons that LMWH should replace LDUH as routine anticoagulant thromboprophylaxis in critical care and other patient populations. Although LMWH and LDUH have similar efficacy in some patient groups, including general surgical and medical patients, LMWH is superior to LDUH in other patient groups (major trauma, orthopedic surgery, ischemic stroke). There are no significant differences in bleeding between these options while LMWH is associated with a 30-fold lower rate of heparin-induced thrombocytopenia compared with LDUH. As a result, no routine platelet count monitoring is required when patients receive LMWH. LDUH must be administered two or three times daily but most patients can be given LMWH once daily. As the cost of unfractionated heparin has increased substantially in recent years, there is no longer a major difference in cost between these agents. Finally, because LMWH can be used as thromboprophylaxis for almost all patients, the use of a single agent allows for standardization of prophylaxis across the hospital that should be associated with greater institution-wide adherence.

MECHANICAL THROMBOPROPHYLAXIS STUDIES IN CRITICAL CARE

Evidence is lacking to guide clinicians in the use of mechanical thromboprophylaxis for most patient populations, and there are no studies of mechanical thromboprophylaxis in the ICU setting. In some patient groups, mechanical prophylaxis is less effective than anticoagulant prophylaxis. The use of graduated compression stockings (GCS) or intermittent pneumatic compression (IPC) or both is recommended for use in patients with a contraindication to anticoagulant prophylaxis. Compliance with proper use of mechanical thromboprophylaxis is often poor, depriving patients of the protection this modality provides. A study of 137 patients who were prescribed either GCS or IPC found adherence in only 26% of the stocking patients and only 19% of the IPC patients.

Despite the use of inferior vena cava (IVC) filters as primary prophylaxis in many centers, there is no direct evidence of their effectiveness in this capacity. The only randomized trial of IVC filters was conducted in patients who were being treated for acute DVT. Patients who had filters inserted along with anticoagulation had fewer, mostly asymptomatic, PE but there was no reduction in death and there were significantly more recurrent DVTs than those who were anticoagulated alone. Of additional concern, in 2010, the FDA reported that they had received 921 reports of complications associated with IVC filters since 2005. The 8th ACCP Antithrombotic Guidelines recommend against the use of IVC filters for primary thromboprophylaxis.
in any patient group. Until further evidence is available, we believe that IVC filters should be limited to patients with acute proximal DVT and an absolute contraindication to therapeutic anticoagulation. In this context, only retrievable filters should be inserted, therapeutic anticoagulation should be started as soon as it is safe to do so, and the filter should be removed shortly after the patient starts treatment for their DVT. We do not believe that IVC filters should be used as primary prophylaxis or as an adjunct to anticoagulation in patients with VTE.

ANTICOAGULANT THROMBOPROPHYLAXIS IN CRITICALLY ILL PATIENTS WITH RENAL INSUFFICIENCY

Approximately one third of medical–surgical patients admitted to ICU have severe renal failure as defined by a calculated creatinine clearance of less than 30 mL/min. These patients are known to be at increased risk of VTE; however, because LMWH is dependent on renal clearance, there has been concern about bioaccumulation of this class of anticoagulants in patients with renal insufficiency. The DIRECT Study was conducted to assess the safety and pharmacodynamics of prophylactic dalteparin in patients with severe renal insufficiency. This multicenter trial assessed the bioaccumulation of dalteparin 5000 IU once daily, by measuring trough anti-factor Xa levels twice weekly and serial anti-factor Xa levels at 0, 1, 2, 4, 8, 12, 20, and 24 hours on days 3, 10, and 17 of ICU admission. No patient developed bioaccumulation as defined by an anti-factor Xa trough level of greater than 0.4 IU/mL over the course of his or her ICU stay. Major bleeding occurred in 10 of 138 patients (7.2%; 95%CI, 4.0%–12.8%). Because trough anti-factor Xa levels in these patients were 0.18 IU/mL or lower, it is unlikely that bioaccumulation of dalteparin contributed to bleeding. In addition, peak levels were 0.2 to 0.40 IU/mL, reflecting appropriate thromboprophylaxis levels. This study provides strong evidence that prophylactic dosing of dalteparin in patients with severe renal insufficiency is not associated with bioaccumulation and establishes that there is no indication for dose adjustment or anti-factor Xa levels routinely in these patients. The impact of renal insufficiency on prophylactic doses of LMWHs other than dalteparin is unclear and further studies are needed to clarify the need for dose reduction in the management of patients on these medications.

SCREENING FOR ASYMPTOMATIC DVT IN CRITICALLY ILL PATIENTS

As a result of the poor correlation between symptoms and signs of VTE in critically ill patients and the high rate of VTE, a number of studies, including PROTECT, have used serial DUS screening of asymptomatic patients to assess for DVT. This raises the question of whether this method should be used to screen all or a high-risk subset of critically ill patients for DVT. However, DUS is costly and time consuming, and the clinical importance of DVT detected by asymptomatic screening is unclear. Further, screening for asymptomatic DVT has not been shown to be effective in trauma or major orthopedic surgery patients and may cause harm because of possible false-positive results and due to resultant therapeutic anticoagulant therapy in the patients found to be positive. We believe that a randomized trial of the addition of routine screening DUS to an optimal prophylaxis regimen would be important, feasible, and ethical. In the meantime, long-term follow-up studies to assess the clinical impact of screening and economic analyses with modeling of reasonable outcomes may help guide this decision. Currently, we recommend that DUS screening be limited to patients at very high risk for thrombosis who cannot be reasonably prophylaxed (eg, patients with combined intracranial bleeding and leg injuries that preclude the use of both anticoagulant and mechanical prophylaxis).
SPECIAL CONSIDERATIONS FOR LMWH USE IN CRITICALLY ILL PATIENTS

Several studies have reported a lower plasma anti-factor Xa activity after LMWH administration in patients receiving vasopressors. In a small study of ICU patients with normal renal function and not receiving vasopressors, anti-factor Xa levels were measured after administration of dalteparin 2500 IU, subcutaneously daily in seven patients with peripheral edema and seven patients without. No significant differences were found. However, another small study documented lower anti-factor Xa activity in edematous compared to nonedematous trauma patients. The number of patients in each of these studies is small and further investigations are needed.

In summary, critical illness, vasopressor use, and generalized edema may cause a reduction in anti-factor Xa levels in patients being prophylaxed with LMWH. However, the relationship between anti-factor Xa levels and the clinical effectiveness of LMWH remains uncertain. In a recent pharmacokinetic study, 72 ICU patients were randomized to a single dose of enoxaparin 40 mg, 50 mg, 60 mg, or 70 mg. Although anti-factor Xa levels correlated with the enoxaparin dose there was wide variability in the levels within each dose group. Further, 28% of the enoxaparin 40 mg, patients had no increase in their level compared with the pre-enoxaparin baseline. Another study demonstrated that peak anti-factor Xa levels below 0.2 U/ml, seen in half of the 54 ICU patients who were given enoxaparin 30 mg SC twice a day, were associated with more than three times higher DVT rate (37% vs 11%) than in the patients with higher peak levels. These studies, therefore, raises concerns about the appropriate LMWH dose in critically ill patients.

PRACTICAL RECOMMENDATIONS

Practical recommendations for the management of thromboprophylaxis in critical care patients are outlined in Fig. 1. All patients should be assessed on admission to the ICU and daily for their individual thrombosis and bleeding risks. Patients with active or high risk of clinically important bleeding should receive mechanical thromboprophylaxis with graduated compression stockings or intermittent pneumatic compression until their bleeding risk is reduced and anticoagulant thromboprophylaxis can be started. If mechanical devices are used, they must be properly fitted, applied to both legs and used continuously for almost 24 hours per day.

![Diagram](Fig. 1. Thromboprophylaxis in critical care patients.)
Many patients in ICU are considered to be at increased risk for bleeding because of oozing from IV sites, around urinary catheters, or with minor gastrointestinal bleeding. For most patients, minor bleeding is not a contraindication to anticoagulant thromboprophylaxis, which can be safely initiated. Anticoagulant thromboprophylaxis is unlikely to contribute to clinically significant bleeding, as has been demonstrated in several bleeding risk factor analyses.\textsuperscript{1,47,48} Even in patients with traumatic intracranial hemorrhage, there is evidence that early initiation of LMWH is not associated with an increased risk of rebleeding. For example, among 669 patients with traumatic intracranial hemorrhages, progression of the bleed was seen in 1.5% of patients who started LMWH within 72 hours with the same rate observed in patients who started after 72 hours.\textsuperscript{49}

There is evidence that the effectiveness of thromboprophylaxis decreases if its initiation is delayed. For example, in a study of pelvic trauma patients, delaying the start of LMWH prophylaxis for more than 24 hours after injury was associated with a sevenfold increase in DVT rate compared with starting within 24 hours.\textsuperscript{50} For most patients, LMWH can be started at the first dosing time after admission. If there is uncertainty about the patient’s bleeding risk on admission, mechanical prophylaxis can be started at this time or a brief period of observation can ensue. In both situations, the patient should be reassessed within the next 24 hours for anticoagulant prophylaxis or mechanical prophylaxis if bleeding concerns persist. Because the risk of both thrombosis and bleeding can change frequently in ICU patients, the use of thromboprophylaxis should be reviewed by the critical care team on a daily basis.

For patients at very high risk for VTE and in whom pharmacologic thromboprophylaxis cannot be used for at least several days, screening with bilateral proximal DUS may be considered although there is no direct evidence to support this approach and it might cause overall harm. Prophylactic IVC filters are not recommended in this (or any) patient population. Thromboprophylaxis should always be included as part of the ICU transfer orders.

Many critical care units admit a spectrum of patients including major trauma, neurosurgical, major orthopedic surgery, and cancer surgery patients in addition to general medical–surgical patients. Table 5 gives recommendations for thromboprophylaxis that include all of these patient groups. Patients deemed to be at usual or low risk for bleeding should be classified as moderate or high thrombotic risk based on the risk factors discussed previously such as personal or family history of VTE and end-stage renal disease. Patients with major trauma, spinal cord injury, major orthopedic surgery, or malignancy should be considered high risk and should receive LMWH and not LDUH.\textsuperscript{4}

<table>
<thead>
<tr>
<th>Bleeding Risk</th>
<th>Thrombosis Risk\textsuperscript{a}</th>
<th>Prophylaxis Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Moderate</td>
<td>LMWH 4000–6000 anti-factor Xa U SC qd (or LDUH 5000 U SC bid)</td>
</tr>
<tr>
<td>Low</td>
<td>High\textsuperscript{a}</td>
<td>LMWH 4000–6000 anti-factor Xa U SC qd</td>
</tr>
<tr>
<td>High</td>
<td>Moderate or high\textsuperscript{b}</td>
<td>GCS or IPC; convert to LMWH when bleeding risk decreases</td>
</tr>
</tbody>
</table>

\textsuperscript{a} High-risk patients include those who have had major trauma or spinal cord injury, major orthopedic surgery, or major surgery for cancer.

For critical care units to consistently provide appropriate thromboprophylaxis, a formal policy, guideline or care map that is specific to the hospital is essential. The principles outlined in Box 2 can serve as a guide for such a policy. All ICU patients should be considered at risk for VTE and all patients should be provided anticoagulant or mechanical prophylaxis depending on bleeding risk. Consideration of specific prophylaxis should be individualized to each patient’s thrombotic and bleeding risks and this requires assessment on admission as well as daily reassessment. Mechanical prophylaxis should generally be restricted to patients with or at high risk for clinically important bleeding. Prophylaxis should generally not be interrupted for procedures or surgery. One strategy to reduce the temptation to hold anticoagulant prophylaxis for procedures is to provide the anticoagulant (usually a LMWH) in the evening; this will safely allow surgery or other procedures to be done the next morning without missing any doses. Prophylaxis should be included in postoperative and ICU transfer orders. Adherence to local prophylaxis guidelines should be supported with regular interactive education, preprinted order sets, reminders, and computer decision support systems. Compliance with thromboprophylaxis also requires periodic audits of adherence to the unit policy with feedback to frontline ICU staff. Unless optimal thromboprophylaxis is consistently at 100%, the audit results should be used for local quality improvement interventions. It is essential that all members of the critical care team (physicians, nurses, pharmacists, physiotherapists, respiratory therapists, and other health care professionals) be encouraged to take an active role in the implementation and daily assessment of VTE prevention and other key patient safety strategies.

SUMMARY

Considerable progress has been made in our understanding of VTE epidemiology, risk factors, and appropriate thromboprophylaxis in this challenging patient population. The use of anticoagulant thromboprophylaxis significantly decreases the risk of VTE in ICU patients. Prophylactic LMWH (or LDUH) can be safely administered to the majority of critically ill patients while those at high risk for clinically important bleeding should receive mechanical thromboprophylaxis until the bleeding risk decreases. Renal insufficiency is not a contraindication to the use of LMWH or LDUH. Despite appropriate thromboprophylaxis, proximal DVT still

<table>
<thead>
<tr>
<th>Box 2</th>
</tr>
</thead>
</table>

General recommendations for thromboprophylaxis in critical care patients

- Develop local evidence-based thromboprophylaxis policy and guidelines.
- Update guidelines as new evidence emerges.
- Consider all ICU patients to be at risk for VTE.
- Use thromboprophylaxis in all ICU patients.
- Individualize prophylaxis but select from a small number of options according to the local policy.
- Start thromboprophylaxis as soon as possible.
- Embed thromboprophylaxis into preprinted or computer order sets.
- Review thromboprophylaxis daily.
- Do not interrupt for procedures or surgery (qhs dosing).
- Consider a daily checklist of key ICU patient safety strategies (including thromboprophylaxis).
- Include in ICU transfer orders.
- Monitor and evaluate compliance with regular audits and provide feedback.
- Empower all health care professionals to play a role in thromboprophylaxis.
occurs in approximately 5% of ICU patients prophylaxed with LMWH or LDUH. Studies to identify risk factors for patients who fail appropriate thromboprophylaxis and ways to manage patients at high risk of bleeding and thrombosis are needed. The Agency for Healthcare Research and Quality (AHRQ) has ranked “the appropriate use of prophylaxis to prevent venous thromboembolism in patients at risk” the number one safety practice for hospitals. For health care providers in critical care units, the prevention of VTE must also be a high priority and should be a routine, daily consideration for every critically ill patient.

REFERENCES


