Low-molecular-weight heparin thromboprophylaxis in medical-surgical critically ill patients: A systematic review

Christine Ribic MD, MSc, Wendy Lim MD, FRCPC, MSc (Epid), Deborah Cook MD, FRCPC, MSc (Epid), Mark Crowther MD, FRCPC, MSc (Epid)

aDepartment of Medicine, McMaster University, Hamilton, Canada L8N 3Z5
bDepartment of Clinical Epidemiology, McMaster University, Hamilton, Canada L8N 3Z5
cDepartment of Biostatistics, McMaster University, Hamilton, Canada L8N 3Z5

Keywords:
Low-molecular-weight heparin; Thromboprophylaxis; Critically ill; Intensive care unit

Abstract

Purpose: The study aimed to systematically review the effect of low-molecular-weight heparin (LMWH) thromboprophylaxis in medical-surgical critically ill patients in the intensive care unit.

Methods: In duplicate and independently, we searched for relevant articles using MEDLINE and EMBASE; we also contacted experts and reviewed reference lists. For included studies, we abstracted data on study and patient characteristics, LMWH use, clinical outcomes (venous thromboembolism [VTE], bleeding, and mortality), laboratory outcomes (anti-Xa levels and thrombocytopenia), and methodological quality.

Results: We included 8 prospective cohort studies and 1 randomized trial, with a total of 629 patients. Eight studies (n = 406 patients) reported anti-Xa levels and only 3 studies (n = 240 patients) reported on at least one clinical outcome. Low-molecular-weight heparin does not appear to bioaccumulate based on repeated measurements of trough anti-Xa levels. Thrombocytopenia occurred in 9.3% of patients receiving LMWH; heparin-induced thrombocytopenia was not reported. In studies reporting clinical outcomes, the frequency of VTE in patients receiving LMWH ranged from 5.1% to 15.5%, bleeding complications ranged from 7.2% to 23.1%, and mortality ranged from 1.4% to 7.4%.

Conclusions: Low-molecular-weight heparin may be effective for thromboprophylaxis in medical-surgical critically ill patients, but no trials have compared LMWH against an alternative active strategy; thus, LMWH cannot be recommended routinely. Trials testing LMWH thromboprophylaxis are required, which examine patient-important end points such as the incidence and clinical consequences of VTE, bleeding, heparin-induced thrombocytopenia, and mortality.

© 2009 Elsevier Inc. All rights reserved.

1. Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common cause of hospital-acquired morbidity and mortality in critically ill patients admitted to the medical-surgical intensive care unit (ICU). Risk factors such as prolonged...
immobilization, recent surgery, hypercoagulability from acute-phase reactants, and vascular injury caused by invasive procedures increase the risk of VTE in this setting [1]. Based on systematic screening, cross-sectional studies estimate the prevalence of DVT to be 2% to 10% on admission to the ICU, whereas longitudinal studies estimate the incidence of DVT developing over the ICU stay ranging from 9% to 40% [2-5].

Anticoagulant thromboprophylaxis is the commonest approach to VTE prevention in medical-surgical critically ill patients. Surveys of stated practice, observational studies, and international registries indicate that unfractionated heparin (UFH) is most often prescribed [2-4,6-9]. Low-molecular-weight heparins (LMWHs) have also been examined in some recent observational studies in medical-surgical ICU patients [10,11]. Low-molecular-weight heparins provide anticoagulation through antithrombin-mediated inhibition of factor Xa, and to a lesser extent, factor IIa (thrombin). The high bioavailability and predictable anticoagulant effect of LMWHs have led to their increasing use for thromboprophylaxis in medical and surgical patients, particularly because LMWHs do not require regular laboratory monitoring or dose adjustments [12].

Serum anti-Xa levels can be used to measure LMWH activity and are used as a surrogate marker to quantify bleeding risk. When LMWH is used for thromboprophylaxis in orthopedic and abdominal surgery, the optimal range that produces effective anticoagulation without excessive bleeding is thought to be achieved with doses of heparin that result in a peak plasma factor Xa activity between 0.25 an 0.29 IU/mL during the first 3 postoperative days and between 0.33 and 0.37 IU/mL from days 4 to 10 [13].

Outside of the ICU setting, meta-analyses of randomized trials have shown the efficacy and safety of UFH thromboprophylaxis, and of LMWH thromboprophylaxis, compared with no anticoagulant thromboprophylaxis in medical and surgical patients [14,15]. However, no randomized trials have compared UFH vs LMWH in medical-surgical patients, and few studies have examined the efficacy of LMWH in the medical-surgical ICU. Although LMWH thromboprophylaxis has been shown to be more effective than UFH in trauma patients and in patients with spinal cord injuries, concerns remain about bioaccumulation, particularly among patients with renal impairment, potentially leading to hemorrhagic complications [16-19]. The objective of this systematic review was to examine the effect of LMWH thromboprophylaxis on clinical and laboratory outcomes in medical-surgical critically ill patients in the ICU.

2. Methods

2.1. Study identification

We searched for relevant studies using a detailed electronic search of the MEDLINE (1950 to February 2008 week 3) database. We examined reference lists from studies identified through the electronic search and from eligible studies; we also consulted with content experts.

2.2. Eligibility criteria

We included prospective cohort and randomized controlled trials that used LMWH for thromboprophylaxis in critically ill patients in medical, surgical, trauma, or mixed ICU settings and evaluated clinically relevant outcomes (VTE, bleeding, or mortality) or laboratory outcomes (anti-factor Xa levels or thrombocytopenia). We excluded study designs that were retrospective audits, surveys of stated practice, case reports, case series, pilot trials, and reviews. We also excluded studies that exclusively enrolled trauma or spinal cord injury patients given that LMWH has been evaluated in randomized trials in these populations [16,17]. Finally, we excluded studies published in languages other than English.

2.3. Study selection

In duplicate, 2 of us reviewed the titles and abstracts of the studies identified in the search and excluded studies not meeting eligibility criteria. If both reviewers agreed about eligibility, the article was included in the systematic review. Any disagreements between reviewers were resolved through discussion to reach consensus.

2.4. Data collection and quality assessment

A single reviewer abstracted data, including descriptive data (type of ICU, patient population) and methodological quality (randomization, concealment, blinding, confounders) from all studies.

2.5. Statistical analysis

We report agreement for included articles using raw agreement and κ. We present patient characteristics from the primary studies using mean and SD or median and interquartile

Fig. 1 Flowchart of trials identified in the systematic review.
<table>
<thead>
<tr>
<th>Study (y)</th>
<th>Study design; patient enrollment</th>
<th>Type of ICU</th>
<th>Patients (n)</th>
<th>Patient diagnosis</th>
<th>Mean age (y); mean BMI</th>
<th>Illness severity or organ dysfunction</th>
<th>Creatinine (mg/dL); (mean ± SD)</th>
<th>Length of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Douketis (2008)</td>
<td>Prospective cohort; consecutive (multicenter)</td>
<td>MICU</td>
<td>138</td>
<td>Renal insufficiency</td>
<td>68.3 ± 15.5</td>
<td>APACHE II 27.6 ± 8.2</td>
<td>18.9 ± 6.5 mL/min</td>
<td>17 d</td>
</tr>
<tr>
<td>Rommers (2006)</td>
<td>Prospective cohort; Non-randomized, open parallel group</td>
<td>MSICU</td>
<td>14</td>
<td>Sepsis, neurotrauma, intoxication, pneumonia, multitrauma, COPD, perforated appendix, cerebral bleed</td>
<td>58 (32-85); 30.6 (22.5-37.9)</td>
<td>SOFA 4 (3-5)</td>
<td>71 (36-109)</td>
<td>24 h</td>
</tr>
<tr>
<td>Kani (2006)</td>
<td>Prospective cohort; consecutive (nonblinded)</td>
<td>MICU</td>
<td>10</td>
<td>Sepsis with renal insufficiency</td>
<td>72.9 ± 11.0</td>
<td>APACHE II 21.6 ± 11.1</td>
<td>2.7 ± 0.8; mean creatinine clearance 29.5 ± 6.42 mL/min</td>
<td>12 h</td>
</tr>
<tr>
<td>Jochberger (2005)</td>
<td>Prospective cohort; nonconsecutive</td>
<td>MICU</td>
<td>62</td>
<td>Multiple trauma, pulmonary, cardiac, infectious, neoplasm, orthopedic, other</td>
<td>63 ± 12; 25 ± 4.2</td>
<td>MODS 4.1 ± 2.1</td>
<td>1.35 ± 0.85</td>
<td>24 h</td>
</tr>
<tr>
<td>Rabbat (2005)</td>
<td>Prospective, cohort; consecutive</td>
<td>MSICU</td>
<td>19</td>
<td>Respiratory, cardiovascular, gastrointestinal, sepsis, neurologic</td>
<td>62.7 ± 13.2</td>
<td>APACHE II 23.5 ± 9.4</td>
<td>N/A</td>
<td>72 h or longer</td>
</tr>
<tr>
<td>Priglinger (2003)</td>
<td>Prospective cohort; consecutive</td>
<td>MSICU</td>
<td>29</td>
<td>Cardiac, pulmonary, gastrointestinal, sepsis, postoperative, CPR, hematologic, immunologic, endocrine</td>
<td>61.1 ± 16</td>
<td>APACHE II 20.4 ± 7, SAPS 49.1 ± 13</td>
<td>0.83 ± 0.25</td>
<td>5 d</td>
</tr>
<tr>
<td>Mayr (2002)</td>
<td>Prospective cohort; consecutive</td>
<td>MSICU</td>
<td>89</td>
<td>Multiple trauma, pulmonary, cardiac, infectious, sepsis, orthopedic, renal, other</td>
<td>58 (19-94)</td>
<td>MODS 3, BMI 24.7 (15.4-51.9)</td>
<td>N/A</td>
<td>24 h</td>
</tr>
<tr>
<td>Dorffler-Melly (2002)</td>
<td>Prospective case-control; consecutive (nonblinded)</td>
<td>ICU/GSW</td>
<td>45 (30 in ICU; 15 general surgery ward)</td>
<td>Medical sepsis, surgical sepsis, trauma, neurosurgery, cardiac surgery, orthopedic surgery, uncomplicated abdominal surgery</td>
<td>59.2 (54.3-63.5); 25.3 (23.1-28.0)</td>
<td>APACHE II 15.1 (13.2-16.9)</td>
<td>N/A; creatinine clearance &gt;30 mL/min</td>
<td>12 h</td>
</tr>
<tr>
<td>Fraisse (2000)</td>
<td>RCT; (double-blind, intention to treat)</td>
<td>MICU</td>
<td>223</td>
<td>Acute decompensated COPD</td>
<td>69.4 ± 7.7</td>
<td>SAPS 14.1 ± 3.6</td>
<td>N/A</td>
<td>Up to 21 ± 1 d</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; GSW, general surgery ward; MICU, medical intensive care unit; MODS, multiple organ dysfunction syndrome; MSICU, medical surgical intensive care unit; N/A, not available; RCT, randomized controlled trial; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

* Only applicable to observational studies.
range if data were skewed. Clinical heterogeneity of these studies precludes statistical pooling of the primary data.

3. Results

3.1. Study selection

Our search identified 111 published studies (Fig. 1). We excluded 92 studies after title and abstract screening and retrieved the remaining 19 studies for more detailed evaluation. Of these, 11 studies were excluded, one of which was a pilot trial reporting only feasibility data rather than clinical outcomes, 5 studies were excluded because they exclusively enrolled trauma or spinal cord injury patients, 2 were practice audits, and 3 were excluded because they were not published in English [20-30]. We identified one additional study in manuscript format through consultation with experts [31]. Therefore, we report on a total of 9 studies in this systematic review. Agreement on included studies was high, reflected in a raw agreement of 100% and $\kappa$ of 1.0.

3.2. Study and patient characteristics

We identified 1 randomized trial, 7 prospective cohort studies, and as well as 1 manuscript in press that fulfilled our eligibility criteria [10,11,31-37]. We present the characteristics of the included studies in Table 1. Individual study sizes ranged from 10 to 223 patients; a total of 629 patients were included. Patients were cared for in different types of ICUs: 4 medical, 4 mixed medical-surgical, and 1 surgical-trauma. The types of patients included were heterogeneous including those with medical or surgical sepsis, renal insufficiency, or acute decompensated chronic obstructive pulmonary disease.

3.3. Low-molecular-weight heparin thromboprophylaxis and outcomes reported

In Table 2, we present the LMWH type and dosing schedule, the comparison group (if any), the number of patients receiving LWMH, and the outcomes reported in all included studies. Various LMWHs were used: dalteparin (4 studies), nadroparin (2 studies), certoparin (1 study), and enoxaparin (2 studies) [10,11,31-37]. Dosing schedules varied from once-daily dosing in 8 studies to single-dose dalteparin in one study by Kani et al [10,11,31-37]. Most studies reported on anti-Xa levels, which were measured serially in 8 studies, and peak and trough anti-Xa levels were measured in 3 studies [10,11,31,33-37]. For clinical outcomes, 3 studies reported on rates of thrombosis and bleeding and 2 of those studies also reported mortality [31,32,36]. One study reported the incidence of thrombocytopenia [32].

<table>
<thead>
<tr>
<th>Study (y)</th>
<th>Thromboprophylaxis LMWH group (n)</th>
<th>Control Group (n)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Douketis (2008)</td>
<td>Dalteparin 5000 IU SC od</td>
<td>138 NA</td>
<td>Bioaccumulation (trough anti-Xa levels &gt;0.40 IU/mL), pharmacodynamics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(serial serum anti-Xa levels on days 3, 10, 17 at 0, 1, 2, 4, 8, 12, 20, 24 h)</td>
</tr>
<tr>
<td>Rommers (2006)</td>
<td>Dalteparin 2500 IU SC od</td>
<td>7 with edema</td>
<td>Anti-Xa levels at 0, 3, 4, 6, 8, 12, 24 h after administration</td>
</tr>
<tr>
<td>Kani (2006)</td>
<td>Dalteparin 5000 IU SC single</td>
<td>10 NA</td>
<td>Anti-Xa levels, clotting assay test at 2, 4, 6, 8 and 12 h after adminstration</td>
</tr>
<tr>
<td>Jochberger (2005)</td>
<td>Certoparin 3000 IU SC od or bid</td>
<td>32 (od dosing)</td>
<td>Anti-Xa levels at 4, 12, 16 and 24 h after administration</td>
</tr>
<tr>
<td>Rabbat (2005)</td>
<td>Dalteparin 5000 IU SC od</td>
<td>19 NA</td>
<td>Anti-Xa peak and trough levels, bleeding and thrombotic events</td>
</tr>
<tr>
<td>Priglinger (2003)</td>
<td>Enoxaparin 40 mg SC od</td>
<td>16 (ICU)</td>
<td>Anti-Xa levels at 0, 1, 3, 6, and 12 h after administration</td>
</tr>
<tr>
<td>Mayr (2002)</td>
<td>Enoxaparin 40 mg SC od</td>
<td>89 NA</td>
<td>Anti-Xa levels at 4, 12, and 24 h after administration</td>
</tr>
<tr>
<td>Dorfler-Melly (2002)</td>
<td>Nadroparin 2850 IU SC od</td>
<td>15 in ICU on vasopressors; 15 in ICU without vasopressors; 15 not in ICU and not on vasopressors</td>
<td>Mean plasma anti-Xa levels at 3, 6, 9, and 12 h after administration</td>
</tr>
</tbody>
</table>
| Fraisse (2000)      | Nadroparin adjusted for body weight; 3800 IU or 5700 IU SC od | 108 nadroparin 113 placebo | Incidence of DVT, hemorrhage, death | NA, not applicable; SC, subcutaneous; OD, daily; IU, international units.
3.4. Laboratory outcomes: anti-Xa levels

In Table 3, we present results of the measured anti-Xa levels obtained using LMWH. Two studies examined anti-Xa levels in patients receiving, and not receiving, inotropes [10, 11]. In the first study, patients on vasopressors had lower mean anti-Xa levels compared with patients not receiving vasopressors [10]. In contrast, the second study found that

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Effect of LMWH on Laboratory Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory outcome</td>
<td>Method of prophylaxis</td>
</tr>
<tr>
<td>Mean plasma anti-Xa Level</td>
<td>Dalteparin</td>
</tr>
<tr>
<td>Douketis (2008)</td>
<td>Dalteparin</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Rommers (2006)</td>
<td>Dalteparin</td>
</tr>
<tr>
<td>Kani (2006)</td>
<td>Dalteparin</td>
</tr>
<tr>
<td>Jochberger (2005)</td>
<td>Certoparin</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabbat (2005)</td>
<td>Dalteparin</td>
</tr>
<tr>
<td>Mayr (2002)</td>
<td>Enoxaparin</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorffler-Melly (2002)</td>
<td>Nadroparin</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Xa activities</td>
<td>Enoxaparin</td>
</tr>
<tr>
<td>Priglinger (2003)</td>
<td></td>
</tr>
<tr>
<td>Mean anti-Xa AUC (0-24 h) (SD)</td>
<td>Dalteparin</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; AUC, area under the curve; IQR, interquartile range; SD, standard deviation; IU, international units.
there were higher anti-Xa levels in patients receiving 2 to 3 inotropes compared with 0 to 1 inotrope [11]. One study evaluated anti-Xa levels in patients with, and without, edema and found no significant difference [37]. There was no difference in anti-Xa levels in patients receiving once, compared with twice, daily dosing in one study [33]. Finally, anti-Xa activity clearance was lower in critically ill patients compared with medical patients in one study [35].

3.5. Laboratory outcomes: anti-Xa levels and renal insufficiency

Table 4 summarizes data from 3 studies on bioaccumulation of anti-Xa activity in patients with renal insufficiency [11,31,36]. All studies evaluated dalteparin. Two studies evaluated trough anti-Xa levels [31,36]. There was little or no evidence of bioaccumulation, defined by an anti-Xa level more than 0.04 IU/mL, in 427 trough measurements and only 3 of 185 measurements (1.6%) in critically ill patients with renal insufficiency [31,36]. Peak levels ranged from 0.30 to 0.42 IU/mL [11,36].

3.6. Laboratory outcomes: thrombocytopenia

One study reported on the incidence of thrombocytopenia, in which 17 patients developed platelet counts less than 100,000/mm³ or developed a 50% decrease compared with their baseline value [32]. The difference in thrombocytopenia in the nadroparin group vs placebo was not significant and occurred concomitantly with septic shock, ischemic vascular events, or with bleeding. Of the 10 events that occurred in the nadroparin group, 3 were considered to be serious by the critical events committee and 1 was considered possibly related to nadroparin.
3.7. Clinical outcomes: VTE

Table 5 summarizes the clinical outcomes in these studies. Thromboembolic complications (DVT and PE) were seen in 45 (13.8%) of 326 patients in the studies that reported this outcome. The frequency of VTE in patients receiving LMWH ranged from 5.1% to 15.5% compared with 28.2% in patients who received placebo [32]. In the only randomized trial included in our review, 169 patients underwent contrast venography for evaluation of DVT [32]. There was a significantly lower incidence of venographically detected DVT in patients receiving nadroparin (13/84 patients, 15.5%) than in those receiving placebo (24/85 patients, 28.2%) [32]. The other 2 studies were prospective cohort studies evaluating LMWH in critically ill patients (without a comparison group), which used screening ultrasonography to detect DVT [31,36]. These studies reported asymptomatic proximal leg DVT in 5.1% to 15.5% of patients; most of the DVTs were in association with a femoral venous catheter.

3.8. Clinical outcomes: bleeding

Studies used variable definitions of bleeding. Overall bleeding, including both major and minor events, occurred in 55 (14.6%) of 378 patients in the studies that evaluated this outcome [10,32,37]. The frequency of bleeding in patients receiving LMWH ranged from 7.2% to 23.1% compared with 15.9% in patients receiving placebo in the randomized trial [32]. This trial reported 25 (6 major) episodes of bleeding using nadroparin and 18 (3 major) episodes in patients receiving placebo. Of the total bleeding events, 10 occurred in the study by Douketis et al, in which there was no association between major bleeding and detectable trough anti-Xa levels in the preceding 3 days according to univariate analysis [31]. The 2 patients who experienced bleeding in the study by Rabbat et al had trough anti-Xa levels below the detection threshold of the assay at the time of bleeding [36].

3.9. Clinical outcomes: mortality

Mortality was reported in 2 studies [31,32]. In the randomized trial comparing nadroparin vs placebo, there was no difference in mortality (7.4%) between the 2 groups; the other study using dalteparin with no comparison group reported a mortality rate of 1.4% [31,32].

4. Discussion

We identified one randomized trial and 8 observational studies that examined the effect of LMWH thromboprophylaxis in medical-surgical critically ill patients. We documented that there is inadequate research upon which to recommend that LMWH be used for thromboprophylaxis or used in preference to UFH. First, in total, fewer than 1000 medical-surgical ICU patients have been studied. Second, all studies used anti-Xa levels as a surrogate marker for LMWH anticoagulant effectiveness. Third, the risk-benefit ratio (balancing bleeding and thrombotic complications) of LMWH thromboprophylaxis is uncertain. Fourth, the clinical relevance of DVT prevention in terms of ICU-specific outcomes such as morbidity and mortality are unknown. Finally, no randomized trials have compared LMWH to an alternative thromboprophylactic agent.

Most of the data evaluating LMWH and critically ill patients are focused on serial measurements of anti-Xa levels, the interpretation of which has not been extensively studied. Although the pharmacokinetics of LMWH is predictable in most patient populations, this may not be the case in the critically ill. This is because critically ill patients often have concomitant conditions that may contribute to unpredictable anticoagulant responses, including organ dysfunction such as renal insufficiency, and they may have impaired cutaneous blood flow due to vasopressor dependency. We found that prophylactic enoxaparin was ineffective at achieving targeted anti-Xa levels in critically ill patients [10,33-35,37]. Increased body weight and multiple organ dysfunction were associated with a high probability of underdosing with enoxaparin [10,34]. Similarly, higher vasopressor requirements in critically ill patients were associated with below target anti-Xa levels in one small study [33]. Dorffler-Melly et al report that 15 critically ill patients receiving vasopressors had significantly lower anti-Xa levels than other patients, raising questions about inadequate protection from VTE using standard doses of prophylactic LMWH [10].

In contrast to the potential underdosing of LMWH in critically ill patients is that of overdosing due to bioaccumulation of LMWH in the setting of renal insufficiency. The prevalence of renal insufficiency among critically ill patients ranges widely depending on case mix [38]. Douketis et al [31] found no evidence of LMWH bioaccumulation when dalteparin was given for thromboprophylaxis in 120 critically ill patients with severe renal insufficiency (defined as creatinine clearance [CrCl] of <30 mL/min), with no anti-Xa levels greater than 0.04 IU/mL. The study by Rabbat et al [36] also examined dalteparin in critically ill patients and found only a small proportion of patients having trough anti-Xa levels above their prespecified level of 0.10 IU/mL, suggesting no evidence of LMWH bioaccumulation. Similarly, Kani et al found that mean anti-Xa levels were comparable in those with moderate (CrCl 30-50 mL/min) compared with severe (CrCl < 30 mL/min) renal insufficiency with no evidence of bioaccumulation [11]. However, the results of this study are very limited because only a single dose of LMWH was administered, and bioaccumulation is more likely to occur only after repeated dosing.
Only 3 studies reported on relevant clinical outcomes (rates of VTE, bleeding, and mortality) [31,32,36]. Conclusions from these studies are limited because most studies were prospective cohort studies without a comparison group and given the small sample sizes that lead to imprecise estimates. Nonetheless, VTE was observed relatively frequently (approximately 14%) suggesting that this is a common complication of critical illness, which occurs despite use of anticoagulant thromboprophylaxis. Bleeding complications also occurred relatively frequently (approximately 15%), suggesting that thromboprophylaxis must be carefully weighed in these patients. Thrombocytopenia is a recognized complication of LMWH therapy (particularly heparin-induced thrombocytopenia) but this was not reported in any of these studies, so inferences are not possible for this outcome. The degree to which these adverse events are underestimated is difficult to ascertain because of underreporting; therefore, conclusions regarding the efficacy and safety of LMWH for medical-surgical ICU patients are limited.

Strengths of this systematic review include the duplicate comprehensive search strategy, explicit inclusion and exclusion criteria, and evaluation of the methodological quality of included studies. Study selection was conducted independently and in duplicate, and agreement was high. We abstracted and reported data according to outcomes presented in each study.

Limitations to the data in this systematic review include the focus on laboratory end points (particularly anti-Xa levels) rather than on patient-important end points. Although we examined the effect of LMWH on clinical outcomes as reported by the primary study investigators, few studies examined the strength of association between LWMH exposure and clinical outcomes using statistical analysis, or adjusted for other confounding variables. The type of LMWH was variable, and it is uncertain whether the pharmacokinetic properties, efficacy, and safety profile are the same for all LMWHs. However, there is little evidence that LMWHs, when used at “standard doses,” have differential efficacy [39]. Participants included medical, surgical, and trauma patients, which may differ in their baseline risks of thrombosis and bleeding, and their responses to LMWH. The comparison groups also varied; critically ill patients were examined with and without edema, vasopressor dependence, or compared with non-critically ill patients. Consequently, these diverse study populations, objectives, and designs precluded statistical pooling of study results. Because none of these studies were randomized trials evaluating the effect of LMWH thromboprophylaxis against active alternatives, no recommendations regarding the optimal prophylactic strategy can be made in this population.

In conclusion, little research exists upon which to make evidence-based thromboprophylaxis recommendations for LMWH in medical-surgical ICU patients. Based on data from anti-Xa levels, LMWH in standard prophylactic doses does not appear to bioaccumulate but may be inadequate to prevent VTE. Large rigorous clinical trials are required to address the role of LMWH in this population, with respect to efficacy, safety, and overall risk-benefit, focusing on patient-important outcomes.

Acknowledgments

This study was not funded. Dr Ribic has no conflicts of interest to declare. Dr Lim has received an unrestricted educational grant from Leo Pharma and is on the speaker’s bureau and received honoraria from Leo Pharma and Pfizer. Dr Cook has received LMWH study drug from Pfizer for a thromboprophylaxis trial. Dr Crowther’s conflicts of interest are pending.

References

Low molecular weight heparin thromboprophylaxis in medical-surgical ICU


