Addendum 1. Low molecular weight heparins for the treatment of Venous Thromboembolism

Background

Venous thromboembolism (VTE) is a common disease and a major health problem. The annual incidence rate was estimated to be 131.5 (95% CI, 130.2-132.9) per 100,000 persons in a recent study conducted in the United Kingdom (1), 104 (95% CI 95-114) per 100,000 persons in the United States (2), and 57 (95% CI 47-67) per 100,000 persons in Australia (3). VTE carries a relevant risk of morbidity and mortality, both in the short and long-term. With regard to the short-term risk, the case fatality rates at 28 days after a first lifetime VTE have been estimated to be 5% (95% CI 1-9%) after a so called “unprovoked” event, 7% (95% CI 2-13%) after VTE provoked by trauma, surgery or immobilization, and 25% (95% CI 15-36%) in patients with cancer (4). Short-term mortality is mainly driven by pulmonary embolism (PE). PE shows a wide spectrum of clinical presentations, ranging from asymptomatic incidental findings to fatal events. PE presenting with shock or hypotension is associated with the highest risk of mortality, exceeding 15% (5).

VTE is also associated with long-term clinical sequelae. First, the risk of recurrent VTE after withdrawal of anticoagulant treatment is high, being estimated around 30% after 8 years from the index event (6). Patients who experienced an unprovoked VTE event are at higher risk of recurrence as compared to those who had a VTE event associated with a major transient risk factor (9.8 versus 4.5 per 100 patient-years, respectively)(6-8). Second, in the long-term period after PE, some patients who do not undergo a complete recanalization of pulmonary arteries may develop chronic thromboembolic pulmonary hypertension (CTEPH). The incidence of symptomatic CTEPH is relatively low (less than 5% after 2 years from EP), but the associated morbidity and mortality are high, the latter being 50% after 5 years (9,10). Third, up to 30% to 50% of patients who had deep vein thrombosis (DVT) may suffer from
post-thrombotic syndrome (PTS), i.e. a cluster of symptoms (pain, cramps, heaviness, paresthesia, pruritus) and signs (pretibial edema, skin induration and hyperpigmentation, venous ectasia) which can have a significant impact on the quality of life, especially in severe form of PTS, when venous ulcers develop (11).

In order to prevent the short and long-term clinical consequences of VTE, anticoagulant therapy is the mainstay of treatment. During the acute phase, rapidly acting, parenterally administered anticoagulant drugs, such as unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) or fondaparinux should be administered. In addition, along with parenteral anticoagulants, the oral vitamin K antagonists (VKAs) are also early started during the acute phase, and then continued for the long-term secondary prevention of the disease. The acute phase parenteral anticoagulants are administered for at least five days and until the level of anticoagulation with the VKAs is adequate and stable (i.e. International Normalized Ratio (INR) > 2). More recently, the novel oral factor-Xa inhibitors rivaroxaban and apixaban have been approved for clinical use in both the the acute and long-term phases. On the other hand, the thrombin-inhibitor dabigatran has been approved for the long-term phase, after an initial course of LWMH in the acute phase.

**Comparison of UFH versus LMWH**

UFH was the first drug to be studied and became the standard treatment of VTE. UFH has the advantage of a rapid onset of action, but it requires frequent laboratory monitoring and dose titration. UFH is administered by continuous infusion or subcutaneously, requiring multiple injections per day. LMWH has a number of advantages over UFH, because it can be administered with once or twice daily injections at fixed, weight adjusted doses without the need for laboratory monitoring and because of its lower potential for heparin-induced thrombocytopenia.
In the 1990s, several randomized controlled trials (RCTs) evaluated the use of LMWH for the initial treatment of VTE (12-14). A systematic review and meta-analysis of studies comparing LMWH and UFH for the initial treatment of VTE was firstly conducted by the Cochrane Collaboration in 1999 and was recently updated in 2010 (15). This systematic review included 23 RCTs comparing fixed dose subcutaneous LMWH with adjusted dose intravenous or subcutaneous UFH in a total of 9587 VTE patients (15). LMWH was found to be associated with a statistically significant lower risk of recurrent VTE during the initial treatment (incidence of recurrent VTE 1.7% versus 2.4%; OR 0.68, 95% CI 0.48-0.97). This finding was confirmed also at 3 months follow-up (OR 0.71; 95% CI 0.56-0.90) and at the end-of follow-up (OR 0.70, 95% CI 0.57-0.85). Moreover, overall mortality was significantly reduced in patients treated with LMWH at the end of follow-up (4.4% versus 5.8%; OR OR 0.77, 95% CI 0.63-0.93). Finally, major bleeding during the initial phase of treatment was also significantly reduced with LMWH as compared to UFH, with an incidence of 1.1% versus 1.9%, respectively (OR 0.58, 95% CI 0.40-0.83).

Based on the available evidence, the latest version of the the American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines on treatment of VTE calculated that LMWH, as compared to intravenous UFH, is associated with 10 fewer deaths from any cause per 1000 patients (from 2 fewer to 16 fewer), 15 fewer recurrent VTE events per 1000 patients (from 6 fewer to 23 fewer) and 5 fewer (from 8 fewer to 0 more) major bleeding episodes per 1000 patients (11). When compared to subcutaneous UFH, LWMH was found to be associated with a similar frequency of mortality, recurrent VTE and major bleeding (11).

Therefore, the ACCP guidelines recommend an initial treatment of acute VTE with parenteral anticoagulation (LMWH, fondaparinux, UFH) and suggests LMWH over intravenous or subcutaneous UFH (11).

Moreover, due to the favourable efficacy and safety profile of LMWH, along with the greater ease of use, several trials tested the possibility to manage patients with acute DVT at home.
The results of these studies suggest that home treatment is not associated with an increase in mortality, recurrent VTE or major bleeding and may be associated with improved outcomes (16). The ACCP guidelines recommend initial treatment at home over treatment in hospital in patients with acute DVT of the leg and whose home circumstances are adequate (11). Finally, data on the incidence of heparin associated thrombocytopenia in patients receiving heparin at therapeutic doses for VTE treatment have been recently meta-analyzed. The results show a trend towards a lower incidence of thrombocytopenia associated with LMWH as compared to UFH, although this difference was not statistically significant (0.6% versus 0.9%, respectively, RR 0.69, 95% CI 0.38-1.23) (17). More recently, the findings from the RIETE registry, on more than 24,000 patients diagnosed with acute VTE showed that the incidence of heparin associated thrombocytopenia was significantly higher in the UFH group (1.36%, 95% CI 0.79-2.17) than in the LMWH group (0.54%, 95% CI 0.44-0.64) (18).

Conclusions

In conclusion, based on the available evidence, LMWH shows a favourable efficacy and safety profile for the treatment of acute VTE. Moreover, LMWH is easy to administer, can be injected once daily and does not require to be titrated based on laboratory tests. Therefore, when compared to UFH, LMWH should be considered as the treatment of choice for the treatment of acute VTE in the majority of circumstances.
Table 1. Efficacy and safety of LMWH as compared to UFH

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Risk with UFH</th>
<th>Risk difference with LMWH (95% CI)</th>
<th>Relative risk (95% CI)</th>
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</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
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<tr>
<td>Intravenous</td>
<td>46 per 1000</td>
<td>10 fewer per 1000 (from 2 fewer to 16 fewer)</td>
<td>0.79 (0.66-0.95)</td>
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<tr>
<td>Subcutaneous</td>
<td>33 per 1000</td>
<td>3 more per 1000 (from 11 fewer to 25 more)</td>
<td>1.1 (0.68-1.76)</td>
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<td><strong>Recurrent VTE</strong></td>
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<tr>
<td>Intravenous</td>
<td>55 per 1000</td>
<td>15 fewer per 1000 (from 6 fewer to 23 fewer)</td>
<td>0.72 (0.58-0.89)</td>
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<tr>
<td>Subcutaneous</td>
<td>42 per 1000</td>
<td>5 fewer per 1000 (from 20 fewer to 19 more)</td>
<td>0.87 (0.52-1.45)</td>
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<tr>
<td><strong>Major Bleeding</strong></td>
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<tr>
<td>Intravenous</td>
<td>15 per 1000</td>
<td>5 fewer per 1000 (from 8 fewer to 0 more)</td>
<td>0.67 (0.45-1)</td>
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<tr>
<td>Subcutaneous</td>
<td>16 per 1000</td>
<td>4 more per 1000 (from 7 fewer to 30 more)</td>
<td>1.27 (0.56-2.9)</td>
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</tbody>
</table>

References


