New insights on the role of direct thrombin inhibitors for the prevention of venous thromboembolism after major orthopaedic surgery

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Low-molecular-weight heparins (LMWH) have long been the mainstay for the prevention of venous thromboembolism (VTE) in high risk populations. Over the last decade, a number of new anticoagulant drugs have challenged the role of LMWH, in particular in the setting of major orthopaedic surgery. All of these new compounds are characterized by a selective inhibitory effect directed against a single target of the coagulation cascade, in most cases activated Factor X (FXa) and thrombin. Several phase III clinical trials published in the last 10 years compared at least five new anticoagulant agents with the LMWH enoxaparin in patients undergoing total hip replacement surgery (THR) and total knee replacement surgery (TKR). These agents include one parenteral, indirect, FXa inhibitor, fondaparinux; two oral, direct thrombin inhibitors, ximelagatran and dabigatran etexilate; and two oral, direct, FXa inhibitors, rivaroxaban and apixaban. With the exception of ximelagatran, which was withdrawn because of liver toxicity issues (1), three of these compounds are currently available for clinical use in patients undergoing THR and TKR in several countries (fondaparinux, dabigatran etexilate, rivaroxaban), and one is expected to receive regulatory approval in the European Union in the coming months (apixaban).

Although formal direct comparisons between new drugs are not available, some attempts have been made to compare the published results of these studies with the aim to identify which new molecule or which new class of drugs (thrombin inhibitors or FXa inhibitors) may be the best alternative to LMWH in this setting (2, 3). However, indirect comparisons across studies should be taken very cautiously because of the numerous differences in study designs, including the dosing regimens for the comparator enoxaparin, the timing of administration of the first dose of the study drugs, and the definitions of the outcome measures, among others. Nonetheless, despite all limitations of indirect comparisons, there is undoubtedly a general perception of a greater superiority of the FXa inhibitors over the standard of practice enoxaparin, and of a substantial equivalence of the thrombin inhibitors to the comparator LMWH in the prevention of VTE after major orthopaedic surgery. This was consistently shown by the results of the meta-analysis of the four randomized studies comparing fondaparinux with enoxaparin in patients undergoing THR, TKR and hip fracture surgery, where a 55.2% (95% CI 45.8%-63.1%) reduction in the incidence of total VTE, and a 57.4% (95% CI 35.6%-72.3%) reduction in the rate of proximal deep vein thrombosis (DVT) in favour of fondaparinux was documented (4). This was also shown by the results of the pooled analysis of the four studies comparing rivaroxaban with enoxaparin in patients undergoing THR and TKR, where a statistically significant reduction in the primary end-point of symptomatic VTE and all-cause mortality from 1.0% in the group treated with enoxaparin to 0.5% in the group treated with rivaroxaban was reported (5). On the other hand, the pooled analysis of the first three studies comparing dabigatran etexilate 220 mg once daily with enoxaparin found a substantial equivalence between the two drugs in both the rates of total VTE and of major VTE and VTE related mortality (6). In a recent systematic review and “adjusted indirect comparison” between rivaroxaban and dabigatran, rivaroxaban was found to be superior to dabigatran for the prevention of VTE after major orthopaedic surgery, although at the cost of a slight trend towards increased haemorrhage (3). This potential of FXa inhibitors to increase the risk of bleeding was also previously reported with fondaparinux in comparison with enoxaparin (4), but not with apixaban (7–9).

In this issue of Thrombosis and Haemostasis, Eriksson and colleagues present the results of a new clinical trial, RE-NOVATE II, which compared dabigatran etexilate 220 mg once daily with enoxaparin 40 mg once daily for 28–35 days in 2055 patients undergoing THR (10). As in the previous studies, the two compounds showed similar efficacy, with a similar incidence of the primary end-point, defined as a composite of total VTE and death from all causes. Bleeding rates were also similar between the two groups. However, for the first time, the RE-NOVATE II study showed a superiority of dabigatran etexilate over enoxaparin in the secondary efficacy outcome defined by the incidence of clinically relevant VTE (e.g. proximal deep vein thrombosis and non-fatal pulmonary embolism).

In our opinion, this finding has a great clinical relevance because it suggests that the reported superiority of FXa inhibitors over thrombin inhibitors may actually be the result of a higher efficacy in the prevention of initial clots forming in the distal vein system, with no difference between the two classes of drugs in the prevention of clots progression to more proximal sites and, thus, in the prevention of clinically relevant thrombosis. If we analyze the results of the individual studies comparing the new oral anticoagulant drugs with enoxaparin administered with the same...
regimen, that is 40 mg once daily started 12 hours prior to surgery, and in the same setting, that is patients undergoing THR, we can clearly observe a greater treatment effect with the FXa inhibitors when the outcome includes distal deep vein thrombosis, but a similar treatment effect among the new compounds when distal vein thrombosis is excluded (Tables 1 and 2) (9–13). The comparison of study designs proposed in Table 1 certainly highlights several major differences across studies which justify the different rates of events reported in each study and stress the need for a great caution when pooled analyses of aggregate

### Table 1: Description of phase III studies comparing the new anticoagulant drugs with enoxaparin* in the prevention of VTE in patients undergoing THR.

<table>
<thead>
<tr>
<th>Name of the study</th>
<th>Study drug (dose)</th>
<th>Timing first dose</th>
<th>Treatment duration</th>
<th>Primary outcome</th>
<th>Major VTE</th>
<th>Major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPHESUS (11)</td>
<td>Fondaparinux</td>
<td>6±2 hours</td>
<td>5–9 days</td>
<td>All DVT + PE</td>
<td>Proximal DVT-PE</td>
<td>Fatal bleed; bleed in a critical organ; leading to re-operation; overt bleeding with bleeding index of 2 or more (see original paper for more details)</td>
</tr>
<tr>
<td>RE-NOVATE II (12)</td>
<td>Dabigatran**</td>
<td>1–4 hours</td>
<td>28–35 days</td>
<td>All DVT + PE + death</td>
<td>Proximal DVT + PE</td>
<td>Fatal bleed; bleed in a critical organ; leading to re-operation; warranting treatment cessation; clinically overt associated with at least 2 g/dL fall in haemoglobin or leading to transfusion (2 or more units)</td>
</tr>
<tr>
<td>RECORD 1 (13)</td>
<td>Rivaroxaban</td>
<td>6–8 hours</td>
<td>35±4 days</td>
<td>All DVT + PE + death</td>
<td>Proximal DVT + PE + VTE death</td>
<td>Fatal bleed; bleed in a critical organ; leading to re-operation; clinically overt extra-surgical site bleed associated with at least 2 g/dL fall in haemoglobin or leading to transfusion (2 or more units)</td>
</tr>
<tr>
<td>ADVANCE 3 (9)</td>
<td>Apixaban</td>
<td>12–24 hours</td>
<td>32–38 days</td>
<td>All DVT + PE + death</td>
<td>Proximal DVT + PE + VTE death</td>
<td>Fatal bleed; intramuscular bleed with the compartment syndrome; bleed in the operated joint leading to re-operation; bleed in a critical site; clinically overt bleed associated with at least 2 g/dL fall in haemoglobin or leading to transfusion (2 or more units)</td>
</tr>
<tr>
<td>RE-NOVATE II (10)</td>
<td>Dabigatran**</td>
<td>1–4 hours</td>
<td>28–35 days</td>
<td>All DVT + PE + death</td>
<td>Proximal DVT + PE + VTE death</td>
<td>Fatal bleed; bleed in a critical organ; leading to re-operation; warranting treatment cessation; clinically overt associated with at least 2 g/dL fall in haemoglobin or leading to transfusion (2 or more units)</td>
</tr>
</tbody>
</table>

*Enoxaparin was started 12 hours prior to surgery and administered at the 40 mg once daily dose in all studies. Duration of treatment with enoxaparin was the same as for the study drug. ** 220 mg dose regimen. VTE, venous thromboembolism; THR, total hip replacement; DVT, deep-vein thrombosis; PE, pulmonary embolism.

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### Table 2: Results of phase III studies comparing the new anticoagulant drugs with enoxaparin in the prevention of VTE in patients undergoing THR.

<table>
<thead>
<tr>
<th>Name of the study</th>
<th>Primary outcome drug</th>
<th>Primary outcome enoxaparin</th>
<th>Treatment effect (%) (p value)</th>
<th>Major VTE study drug</th>
<th>Major VTE enoxaparin</th>
<th>Treatment effect (%) (p value)</th>
<th>Major bleeding study drug</th>
<th>Major bleeding enoxaparin</th>
<th>Difference (%) (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPHESUS (11)</td>
<td>37/908 (4.0%)</td>
<td>85/919 (9.0%)</td>
<td>–5.2 (&lt;0.001)</td>
<td>Prox DVT 6/922 (1%)</td>
<td>PE 2/1229 (0.2%)</td>
<td>–1.8 (0.0021)</td>
<td>0.0 (n.s.)</td>
<td>47/1140 (4.1%)</td>
<td>32/1133 (2.8%)</td>
</tr>
<tr>
<td>RE-NOVATE II (12)</td>
<td>53/880 (6.0%)</td>
<td>60/897 (6.7%)</td>
<td>–0.7 (n.s.)</td>
<td>–1.8 (n.s.)</td>
<td>0.0 (n.s.)</td>
<td>23/1146 (2.0%)</td>
<td>2/2224 (0.1%)</td>
<td>18/1154 (1.6%)</td>
<td>0.4 (n.s.)</td>
</tr>
<tr>
<td>RECORD 1 (13)</td>
<td>18/1595 (1.1%)</td>
<td>58/1558 (3.7%)</td>
<td>–2.6 (&lt;0.001)</td>
<td>4/1686 (0.2%)</td>
<td>33/1678 (2.0%)</td>
<td>–1.7 (&lt;0.001)</td>
<td>6/2209 (0.3%)</td>
<td>18/2224 (0.1%)</td>
<td>0.2 (n.s.)</td>
</tr>
<tr>
<td>ADVANCE 3 (9)</td>
<td>27/1949 (1.4%)</td>
<td>74/1917 (3.9%)</td>
<td>–2.5 (&lt;0.001)</td>
<td>10/2199 (0.5%)</td>
<td>25/2195 (1.1%)</td>
<td>–0.7 (0.01)</td>
<td>22/2673 (0.8%)</td>
<td>18/2659 (0.7%)</td>
<td>0.1 (n.s.)</td>
</tr>
<tr>
<td>RE-NOVATE II (10)</td>
<td>61/792 (7.7%)</td>
<td>69/785 (8.8%)</td>
<td>–1.1 (n.s.)</td>
<td>18/805 (2.2%)</td>
<td>33/794 (4.2%)</td>
<td>–1.9 (0.03)</td>
<td>14/1010 (1.4%)</td>
<td>9/1003 (0.9%)</td>
<td>0.5 (n.s.)</td>
</tr>
</tbody>
</table>

VTE, venous thromboembolism; THR, total hip replacement.
data are attempted. The finding that event rates for enoxaparin are highly variable across studies is therefore not surprising (Table 2). However, if only absolute differences between each study drug and the comparator are assessed, these appear to be comparable across all studies both for major VTE and major bleeding (Table 2). This is further confirmed when only proximal deep vein thrombosis is considered, with an absolute reduction of 1.5% and 1.8% in the RE-NOVATE I and II studies (10–12), and an absolute reduction ranging from 0.6% to 1.9% in the studies with the FXa inhibitors (9, 11, 13).

Taken together, the results of these studies strongly confirm the availability of effective and safe alternatives to standard treatment strategies. This is of particular relevance with the new oral anticoagulants, which offer practical advantages especially when treatment is required for an extended period of time.

A peculiarity of dabigatran etexilate consists in the possibility to adapt the dosage of the drug to the individual risk profile of the patient. Two dosages of dabigatran etexilate, 220 mg once daily and 150 mg once daily, are recommended for the prevention of VTE after THR and TKR, and two dosages, 150 mg or 110 mg (75 mg in the US), are currently recommended in North America for the prevention of stroke and systemic embolism in patients with atrial fibrillation following the results of the RELY study (14). If on the other hand the two higher dosages were proven to be effective in reducing the risk of major thromboembolic events in the study populations (10, 14), the two lower dosages appear as a very important resource to limit the risk of bleeding complications in fragile patients such as the elderly and patients with moderate insufficiency.

References