Ximelagatran reduced venous thromboembolism more than warfarin after total knee replacement


Clinical impact ratings IM/Ambulatory care ★★★★★ Internal medicine ★★★★★★ Haematology ★★★★★

In patients having total knee replacement, is ximelagatran better than warfarin in preventing venous thromboembolism (VTE)?

CONCLUSION

In patients having total knee replacement, ximelagatran, 36 mg twice daily, was more effective than warfarin in preventing venous thromboembolism.

Abstract and commentary also appear in ACP Journal Club.

Commentary

The trial by Francis et al shows the superiority of 36 mg twice daily of ximelagatran over warfarin, both started after surgery, for prevention of VTE after total knee replacement surgery. However, as the greater efficacy came entirely from a decreased incidence of isolated (largely asymptomatic) calf vein thrombosis, the interpretation of these results deserves comment.

In most studies, comparing low molecular weight heparins (LMWHs), which have a rapid onset of action, and oral anticoagulants, which require 2–4 days to render an anticoagulant effect, the latter category of drugs has been less effective. Because both the study and the comparator drugs were started at the same time after surgery, I wonder whether the superiority of ximelagatran simply reflects the different onset of action of the 2 drugs. All that oral anticoagulants can do in this setting is prevent thrombus from growing. Indeed, both in this trial and in virtually all those assessing LMWHs, the incidence of proximal vein thrombosis and that of PE, when taken together, did not differ between patients receiving oral anticoagulants and those receiving heparin.

Despite this consideration, warfarin is problematic for VTE prophylaxis because of the need for laboratory monitoring and potential drug interactions, and LMWHs are the standard of care for the prevention of VTE after orthopaedic surgery. Although ximelagatran was shown to be more effective than enoxaparin in the EXPRESS study, it has not been compared with fondaparinux, a synthetic anti-Xa inhibitor that is more effective than enoxaparin for VTE prophylaxis after orthopaedic surgery. The ultimate comparison of efficacy in the prevention of VTE after orthopaedic surgery may be a head to head comparison between ximelagatran and fondaparinux.

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MAIN RESULTS

Fewer patients who received ximelagatran, 36 mg, had an occurrence of the composite primary endpoint than did patients who received warfarin (table). The ximelagatran 24 mg group did not differ from the warfarin group (table). Neither ximelagatran group differed from warfarin for the secondary composite endpoint of proximal DVT, PE, and all cause mortality (p values >0.10). Groups did not differ for bleeding (table).

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Source of funding: AstraZeneca.

Ximelagatran (X), 36 mg or 24 mg twice daily, vs warfarin after total knee replacement at 7–12 days*

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>X dose</th>
<th>Event rates</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite primary endpoint</td>
<td>36 mg</td>
<td>20.3% v 27.6%</td>
<td>26% (9.9 to 40)</td>
<td>14 (9 to 40)</td>
</tr>
<tr>
<td></td>
<td>24 mg</td>
<td>24.9% v 27.6%</td>
<td>9.8% (–8 to 25)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>36 mg</td>
<td>0.8% v 0.7%</td>
<td>18% (–61 to 26)</td>
<td>Not significant</td>
</tr>
<tr>
<td></td>
<td>24 mg</td>
<td>0.8% v 0.7%</td>
<td>20% (–61 to 270)</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

*Composite primary endpoint = venous thromboembolism, pulmonary embolism, and all cause mortality. Abbreviations defined in glossary; NNT, NNH, and CI calculated from data in article.