Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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VTE prophylaxis after hip or knee replacement: comparison of new oral anticoagulants

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A systematic review and meta-analysis of the newer oral anticoagulants apixaban, dabigatran etexilate and rivaroxaban has reached similar conclusions to NICE regarding direct comparisons with enoxaparin. The indirect comparisons between the drugs suggest differences in the risk of clinically relevant bleeding. However, these analyses have limitations and therefore may not resolve issues for local decision making about care pathways or about the choices made for and with individual patients.

Overview and current advice

NICE technology appraisals for apixaban\(^1\), dabigatran etexilate\(^2\) and rivaroxaban\(^3\) recommend these drugs (within their marketing authorisations) as options for the prevention of venous thromboembolic events in adults who have undergone elective total hip or total knee replacement surgery. This is reflected in NICE’s guidance on reducing the risk of venous thromboembolism (VTE) in people admitted to hospital\(^4\).

There are no published direct comparisons of these 3 drugs and the NICE appraisal committee for apixaban (the most recent NICE appraisal) concluded that it was not possible to estimate their relative effectiveness\(^1\). In its individual technology appraisals, NICE concluded that:-

- apixaban was more clinically effective than enoxaparin in preventing venous thromboembolic events with no statistically significant difference in bleeding risk\(^1\)
- dabigatran was not inferior to enoxaparin in preventing venous thromboembolic events with no statistically significant difference in bleeding risk\(^2\)
- rivaroxaban was at least as efficacious as enoxaparin in preventing venous thromboembolism but this was accompanied by a small increased risk of major bleeding\(^3\).
New evidence

This systematic review and meta-analysis is based on 16 previously published randomised controlled trials (RCTs) which compared each of these 3 anticoagulants with enoxaparin in people undergoing total hip or knee replacement. Twelve of these studies were included in the NICE technology appraisals for apixaban, dabigatran etexilate and rivaroxaban. Four of the studies included in this meta-analysis were excluded from the NICE technology appraisal for rivaroxaban because they were phase II trials. The authors considered only the effects on symptomatic VTE (a secondary outcome in the studies), whereas NICE also considered asymptomatic VTE (detected on venography). They also considered the risk of clinically relevant bleeding. This meta-analysis included studies which reflect the different doses of enoxaparin used in North America and in Europe: NICE’s evaluations mainly considered those studies which used the European dosing regimen.

The authors conducted traditional direct comparison meta-analyses of each drug with enoxaparin and also indirect, mixed treatment comparisons (MTCs), between the 3 anticoagulants. MTCs, sometimes called network meta-analyses, are used where data on direct comparisons from clinical trials are not available. Treatments are compared indirectly, for example, the effect of drug A compared with drug C is inferred statistically from the results of trials of drug A compared with drug B and drug B compared with drug C.

In the direct comparisons, neither apixaban (p=0.57) nor dabigatran (p=0.54) statistically significantly reduced the risk of symptomatic VTE compared to enoxaparin, although 95% CIs were comparatively wide. Rivaroxaban reduced the risk of symptomatic VTE to a statistically significant extent compared to enoxaparin (relative risk [RR] 0.48; 95% confidence interval [CI]: 0.31 to 0.75, \( p = 0.001\), 5 fewer events [95% CI 1 to 9 fewer] per 1000 people treated).

The direct comparison also found that the risk of clinically relevant bleeding was statistically significantly lower with apixaban than with enoxaparin (RR 0.82, 95% CI 0.69 to 0.98, \( p = 0.03\), 8 fewer events [95% CI 1 to 15 fewer] per 1000 people treated) but not statistically significantly different between dabigatran and enoxaparin (\( p = 0.21\)). However, rivaroxaban statistically significantly increased the risk of clinically relevant bleeding (RR 1.25, 95% CI 1.05 to 1.49, \( p = 0.01\), 9 extra events [95% CI 2 to 17 extra] per 1000 people treated).

In the indirect comparisons, the only statistically significant differences were in the risk of clinically relevant bleeding, which was less likely with apixaban than dabigatran (RR 0.73, 95% CI 0.57 to 0.94, 13 fewer events [95% CI 2 to 24] per 1000 people treated), and more likely with rivaroxaban than apixaban (RR 1.52, 95% CI 1.19 to 1.95, 18 extra events [95% CI 7 to 28] per 1000 people treated). There was no statistically significant difference between rivaroxaban and dabigatran with regard to clinically relevant bleeding (RR 1.12, 95% CI 0.87 to 1.44). Pairwise comparisons between the three drugs showed no significant differences with regard to symptomatic VTE.

The results from the direct comparisons are broadly similar to the conclusions of the NICE technology appraisals, except that NICE concluded that apixaban was more clinically effective than enoxaparin whereas this meta-analysis found no statistically significant difference. NICE concluded that there was no statistically significant difference in bleeding risk between apixaban and enoxaparin, whereas this meta-analysis found a lower risk of clinically significant bleeding with apixaban compared with enoxaparin. These differences may be because of the differences in doses of enoxaparin used in the studies and in outcomes considered. NICE also considered the cost-effectiveness of the options when it made its recommendations, whereas these authors did not. The meta-analysis authors note that their use of secondary outcomes from the included studies makes the results on symptomatic VTE exploratory in nature. Finally, it should be noted that the results of indirect comparisons are inferred statistically and these comparisons assume that the treatments, outcomes and populations studied in the included trials are similar.
The article starts with the premise that venous thromboembolism is responsible for the death of half a million people in Europe each year. The most recent National Joint Registry for England and Wales report states that, in 2011, there were about 165 thousand hip and knee replacement procedures. Mortality rates in the first 30 days after total hip or knee replacement were around 0.2% (although this did vary by both age and gender). The proportion of these deaths attributable to pulmonary embolism (PE) may be as low as 25% – 4. The proportion of these deaths attributable to pulmonary embolism (PE) may be as low as 25%.

This paper does provide an excellent analysis of available evidence and the authors give appropriate attention to the risk of clinically significant bleeding versus symptomatic venous thromboembolism as an endpoint, with the absolute risk of bleeding events being substantially greater. The authors correctly point out that the risk of bleeding increases with age and comorbidity – so will be understated in these trials of a younger, fitter population than that seen in clinical practice. Secondary to limitations in the original trials, the risk of wound complications was not assessed.

This paper adds to the current evidence base for understanding the place for using new oral anticoagulants in preventing venous thromboembolism. Implementing guidance requires translation from national guidance into the local pathway; and then for individual patients, a further translation is needed which takes into account both the characteristics of that individual patient but also their wishes, needs and values. Whilst the meta-analysis overall appears statistically robust, the paper provides little information on the characteristics and baseline risks of study participants. Without this it is difficult to apply the results to a presenting patient. This is further confounded as doses of enoxaparin within the studies included in the meta-analysis varied between 40 mg daily and 30 mg twice daily.
A key benefit of the new oral anticoagulants is that monitoring is not required and there are fewer interactions with other drugs; the downside is that there are no readily available reversing agents and experience is still accumulating about effectiveness and safety in various populations. Patients enrolled in many of the reviewed studies are likely to have demonstrated excellent adherence to their treatment regimen irrespective of the route of administration. In a real-world setting however, there might be significant differences in adherence between those patients taking treatments orally and those who have had their treatment injected.

Even with NICE guidance and additional reviews of current evidence such as this meta-analysis, local decision-makers and individual clinicians and their patients still face uncertainty in their decision-making about anticoagulation – as is the case with many new medicines.

About this Medicines Evidence Commentary

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