Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons

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CRD summary
This generally well-conducted review concluded that higher efficacy in prevention of symptomatic venous thromboembolism in new anticoagulants following total knee or hip replacement was associated with a higher risk of bleeding. This conclusion accurately reflects the evidence and is likely to be reliable.

Authors' objectives
To assess clinical outcomes for the use of new oral anticoagulants for prophylaxis against venous thromboembolism after total hip or knee replacement.

Searching
MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to April 2011. Clinical trial registries, relevant conference proceedings and websites of regulatory agencies were searched. The search strategy was available online. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) that compared rivaroxaban (10mg), dabigatran (220mg or 150mg) or apixaban (5mg) with enoxaparin in patients who underwent total hip or knee replacement were eligible for inclusion. Trials were required to assess an approved regimen for enoxaparin: 40mg once daily from 12 hours before surgery (Europe) or 30mg twice daily from 12 to 24 hours after surgery (North America). The primary outcome was symptomatic venous thromboembolism defined as deep vein thrombosis (DVT) or pulmonary embolism. Secondary outcomes were composites of total venous thromboembolism or all-cause mortality and of major venous thromboembolism or venous thromboembolism-related death. Major bleeding and clinically relevant non-major bleeding were also assessed.

Half of the included studies assessed rivaroxaban and a quarter each assessed dabigatran and apixaban. Most trials used the European enoxaparin regimen as comparator. Half of the trials were in patients who underwent total hip replacement and half of the trials were in patients who underwent total knee replacement. There was little variation in patient characteristics across the studies: mean ages ranged from 61 to 68 years and mean weight from 75kg to 84kg. Most patients were female.

Two reviewers independently selected the studies for inclusion.

Assessment of study quality
Study quality was assessed using the Jadad scale of up to five points for randomisation, blinding and treatment of withdrawals and drop-outs.

The authors did not state how many reviewers carried out the assessment.

Data extraction
Two reviewers independently extracted intention-to-treat data to enable calculation of relative risks (RR) and their 95% confidence intervals (CI). Risk differences and their 95% CI were calculated. Sponsors or principal investigators were contacted for missing outcome data.

Methods of synthesis
Pooled relative risks with 95% CI were calculated using DerSimonian and Laird random-effects meta-analyses. Statistical heterogeneity was assessed with $X^2$ and $I^2$. A sensitivity analysis was conducted with a Mantel-Haenszel fixed-effect model. Additional analyses were used to explore variables that included duration of thromboprophylaxis and use of alternative definitions on major bleeding. Subgroup analyses of trials in hip and knee replacement and the
different anticoagulants were carried out. Funnel plot analysis was used to assess the possibility of publication bias. Indirect comparisons between the new anticoagulants were carried out in addition to the direct comparisons with enoxaparin.

Results of the review
Sixteen RCTs (38,747 participants) were included in the review. All studies except one scored the maximum of 5 points on the Jadad scale and were judged to be at low risk of bias. One study scored three points because it was open-label. Follow-up ranged from 35-69 days to 90-100 days.

Patients treated with rivaroxaban had a statistically significantly lower risk of symptomatic venous thromboembolism than those given enoxaparin (RR 0.48, 95% CI 0.31 to 0.75; eight trials, I²=5%). No such significant benefit was seen with dabigatran (RR 0.71, 95% CI 0.23 to 2.12; four trials, I²=73%) or apixaban (RR 0.82, 95% CI 0.41 to 1.64; four trials, I²=40%). The heterogeneity in the dabigatran analysis was not explicable in terms of dose or otherwise. Inclusion of events that occurred during follow-up did not materially alter the results of the analyses.

The results of the secondary analyses that assessed impact on DVT and pulmonary embolism separately gave a more complex picture. Dabigatran was not associated with significant impact on either outcome but both rivaroxaban and apixaban reduced the rate of DVT but not of pulmonary embolism. Apixaban was associated with a numerical increase in cases of pulmonary embolism.

The impact on composite outcomes that included all-cause or thromboembolism-related mortality was similarly complex. Significant benefits were seen for rivaroxaban on both outcomes and for apixaban on the all-cause mortality composite outcome. Dabigatran showed trends towards higher rates of these composite outcomes that were significant for the 150mg dose on the all-cause mortality composite outcome. Full results were reported in the paper.

Rivaroxaban was associated with a statistically significantly increased risk of clinically relevant bleeding compared to enoxaparin (RR 1.25, 95% CI 1.05 to 1.49; eight trials, I²=5%). There was no difference between enoxaparin and dabigatran at either dose. There was a statistically significantly lower risk of clinically relevant bleeding with apixaban compared to enoxaparin (RR 0.82, 95% CI 0.69 to 0.98; four trials, I²=3%). Other secondary outcomes were reported in the review.

Indirect comparisons between the three new anticoagulants showed that rivaroxaban was associated with the lowest risk for symptomatic venous thromboembolism and apixaban had the lowest risk for clinically relevant bleeding. Net clinical outcomes did not differ between the treatments.

There was no evidence of publication bias. Sensitivity analyses did not materially effect the results of the direct comparison analyses except that author-defined criteria for major bleeding events made rivaroxaban appear statistically significantly superior to enoxaparin. Subgroup analyses showed no difference between knee and hip surgeries. A fixed-effect model made some of the differences between new anticoagulants in the indirect comparison statistically significant.

Authors' conclusions
Higher efficacy of the new anticoagulants was associated with a higher bleeding tendency. The new anticoagulants did not differ significantly from each other in efficacy and safety.

CRD commentary
The review question and inclusion criteria were clear. Two relevant databases and multiple other sources were searched without language restrictions, which reduced the risks that bias was introduced relevant studies were missed. The authors reported their methods to reduce reviewer bias and error for study selection and data extraction but not for validity assessment. The quality assessment used a composite score (generally considered unhelpful), but in this case all studies except one were considered to be high quality. The synthesis was appropriate and included assessment and exploration of heterogeneity.

The authors' conclusions fully reflected the results of this review of high-quality trials with a large number of patients and appear likely to be reliable.
Implications of the review for practice and research

**Practice**: The authors stated that uncertainty about the bleeding risk associated with new anticoagulant in higher-risk populations of standard clinical practice (such as elderly patients) emphasised the need for appropriate use according to product labelling to reduce this risk.

**Research**: The authors did not state any implications for further research.

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