Oral direct factor Xa inhibitors versus low-molecular-weight heparin to prevent venous thromboembolism in patients undergoing total hip or knee replacement: a systematic review and meta-analysis


CRD summary
This review concluded that compared with low-molecular-weight heparin, low doses of oral factor Xa inhibitors achieved a small absolute reduction in symptomatic deep vein thrombosis without the increase in bleeding associated with high doses. Despite problems with missing data these conclusions appear likely to be reliable.

Authors' objectives
To evaluate the benefits and harms of oral direct factor Xa inhibitors compared to low-molecular weight heparin (LMWH) in patients who underwent total hip or knee replacement.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to December 2011. The search strategy was reported. Abstracts of two haematology societies were searched from 2003 and 2004 up to 2011.

Study selection
Randomised controlled trials (RCTs) that assessed direct oral factor Xa inhibitors (including rivaroxaban, apixaban, edoxaban, YM150, TAK442, betrixaban and LY517717) in patients who underwent total hip or knee replacement were eligible for inclusion. Trials were required to use a comparator of any pharmacologic or nonpharmacologic thromboprophylactic intervention and report at least one of mortality at end of prophylaxis, mortality at during follow-up period, symptomatic deep vein thrombosis (DVT), nonfatal pulmonary embolism, major bleeding, intercranial bleeding and bleeding leading to reoperation.

Approximately half of the included trials were of patients who underwent knee replacement and half were of total hip replacement. Mean ages of patients ranged from 57.8 to 67.6 years. All trials employed mandatory venography for detection of asymptomatic DVT near the conclusion of treatment. Slightly more than half of the trials evaluated multiple doses of factor Xa inhibitors; eight of the other 10 trials assessed a low dose.

Two reviewers independently assessed the papers for inclusion; disagreements were resolved through discussion.

Assessment of study quality
Studies were assessed using the Cochrane risk of bias tool to assess studies as having a low, unclear or high risk of bias on criteria of randomisation, allocation concealment, blinding, selective reporting of data, incomplete outcome data and other factors. Confidence in estimates of treatment effects was assessed using the GRADE approach.

Two reviewers independently carried out the assessment. Disagreements were resolved through discussion.

Data extraction
Two reviewers independently extracted data on baseline characteristics of patients and intervention and comparator characteristics. Outcome data were extracted to enable calculation of odds ratios (OR) with 95% confidence intervals (CI).

Methods of synthesis
Trials were pooled using Peto odds ratios except for studies with zero events. A sensitivity analysis included trials with zero events. A further sensitivity analysis assumed that individuals with missing data had event risks of two or three times that of those with available data. An analysis that directly pooled risk differences was carried out. Numbers needed to treat were calculated.
The absolute effect on symptomatic DVT was estimated by applying the risk reduction from this meta-analysis to the baseline risk in a large cohort study. A priori subgroup analyses were used to assess the impact of Cochrane risk of bias (low versus unclear or high), intervention drug (rivaroxaban versus apixaban versus others), intervention drug dose (high versus intermediate versus low) and duration of prophylaxis (<14 days versus ≥14 days). Heterogeneity was assessed using the X² test and the I² statistic. A random-effects logistic regression model was used to investigate the risk of bleeding when low, moderate and high dose factor Xa inhibitors were considered as separate treatments. Publication bias was assessed using funnel plot analysis.

Results of the review
Twenty-two RCTs were included in the review. Follow-up ranged from less than 14 days in nine trials to 90 days in one trial; 12 trials had follow-up of between 30 and 70 days.

Risks of bias varied across criteria. The most common source of bias was incomplete outcome data, which was an issue for at least one assessed outcome in all except three trials; data on DVT and pulmonary embolism were missing for between 3% and 41% of patients. Overall the evidence was considered to be moderate quality.

There were no statistically significant differences between factor Xa inhibitors and LMWH in mortality at the end of treatment (OR 1.27, 95% CI 0.63 to 2.55; I²=0%) or at the end of follow-up (OR 0.95, 95% CI 0.55 to 1.63; I²=43%). There was no statistically significant difference between treatments in nonfatal pulmonary embolism.

There was a statistically significant benefit of reduced symptomatic DVT in patients treated with factor Xa inhibitors (OR 0.46, 95% CI 0.30 to 0.70; I² = 0%) which represented a reduction of three DVT (95% CI 1 to 5) events per 1,000 patients treated for one to five weeks. When the baseline risk from a large cohort study was used, factor Xa inhibitors were estimated to give a benefit of four (95% CI 3 to 6) fewer events per 1,000 treated patients.

Analyses of major bleeding events and bleeding leading to reoperation were not statistically significant but suggested the possibility of harm; analysis of absolute differences showed an increase of two (95% CI 0.98 to 1.65) major bleeding events per 1,000 patients treated for one to five weeks. Subgroup and regression analyses indicated that excess bleeding events resulted from high (OR 2.50, 95% CI 1.38 to 4.53) rather than low or intermediate doses of factor Xa inhibitors (no statistically significant difference) (test for interaction p=0.02).

There was asymmetry in the funnel plots for all outcomes except major bleeding but this may not indicate publication bias since the potentially missing studies would have favoured factor Xa inhibitors.

Authors’ conclusions
Compared with LMWH, lower doses of oral factor Xa inhibitors can achieve a small absolute reduction in symptomatic DVT without increased bleeding.

CRD commentary
The review question and inclusion criteria were clear. Several relevant databases and other sources were searched. Methods designed to reduce reviewer bias and error were reported for all stages of the review process. Risk of bias in included studies was assessed using a valid instrument.

The synthesis appeared appropriate and included assessment and exploration of sources of heterogeneity as well as an attempt to relate risk reductions to absolute risk. The problem of missing data was acknowledged by the authors.

The authors’ conclusions reflected the results of the review and appear likely to be reliable.

Implications of the review for practice and research
**Practice**: The authors stated that clinicians and patients should balance the benefits of convenience and the small reduction in thrombosis offered by factor Xa inhibitors against the cost and possibility that other adverse effects may emerge over the long term.

**Research**: The authors stated that the optimal pragmatic or practical trial of factor Xa inhibitors should have a design that determines a low risk of bias and a sample size large enough to detect differences in symptomatic events. Mandatory venography at the end of treatment should not be undertaken but clinical surveillance leading to testing for
DVT should be undertaken. Results should be reported for all randomised patients and data on components of composite outcomes should be reported.

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