Does a longer duration of oral factor Xa therapy increase the risk of bleeding or transaminitis?

From AM, Hoganson DD, Erwin PJ

CRD summary
This review found that oral factor Xa inhibitor anticoagulants (derivatives of oxazolidinone antibiotics) did not increase the risk of bleeding and reduced the risk of transaminitis (liver injury) compared with low-molecular weight heparin anticoagulants; these risks were not dependent on treatment duration. The authors’ conclusions are likely to be reliable in the context of the short-term evidence presented.

Authors’ objectives
To assess the risk of bleeding or transaminitis with longer duration of oral factor Xa inhibitor therapy compared with low-molecular weight heparin or vitamin-K antagonist therapy.

Searching
MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1988 to March 2010 with no restriction on type of journal or publication type; search terms were reported. Reference lists of recent reviews and Internet sources of registered trials were also searched.

Study selection
Randomised controlled trials (RCTs) that compared oral factor Xa inhibitors with low-molecular weight heparins or vitamin-K antagonists (with no restriction on particular participant populations) were eligible for inclusion in the review.

Eligible primary outcomes were any bleeding and transaminitis; transaminitis was defined as an on treatment alanine aminotransferase increase greater than three times the upper limit of normal. Secondary outcomes included non-surgical site bleeding, major bleeding, non-major bleeding, and on treatment elevation of alanine aminotransferase increase greater than three times the upper limit of normal plus total bilirubin increase greater than two times the upper limit of normal.

In the included trials, participants had deep vein thrombosis, or were undergoing knee or hip replacement or arthroplasty (repair). Oral factor Xa inhibitors included rivaroxaban (2.5mg to 40mg once or twice daily), apixaban (2.5mg to 20mg once or twice daily), betrixaban (15mg or 40mg twice daily), LY517717 (25mg to 150mg once daily) and YM150 (3mg to 60mg once daily). Control treatments were mostly enoxaparin (30 to 40mg once or twice daily delivered subcutaneously); it was combined with vitamin-K antagonist in two trials. One trial used heparin followed by vitamin-K antagonist as control. Treatment duration ranged from eight to 91 days.

Two reviewers independently selected studies for the review, with discrepancies resolved by consensus or by reporting the disputed data as missing or incomplete.

Assessment of study quality
The included trials were assessed for quality and individual quality components. They were scored as either criterion met, unclear, or criterion not met. Criteria included randomisation, description of allocation concealment, blinding of patients, blinding of healthcare workers, blinding of safety assessors, use of intention-to-treat analyses, and the proportion of participants included in the safety outcomes.

Two reviewers independently undertook quality assessment, with discrepancies resolved by consensus, or reporting the disputed data as missing or incomplete.

Data extraction
Data were abstracted on the risk of any bleeding or transaminitis; relative risks (RRs) and their 95% confidence intervals (CIs) were calculated. All data were stratified into two groups of short duration (shorter than one month of therapy) and long duration (longer than one month of therapy). Authors of included trials were contacted for missing data where necessary.

Two reviewers independently extracted data, with discrepancies resolved by consensus, or reporting the disputed data as missing or incomplete.

Methods of synthesis
 Trials were synthesised in meta-analyses using a Mantel-Haenszel random-effects model. Summary relative risks and 95% confidence intervals were calculated. Heterogeneity was assessed by the X² statistic and quantified by the I² value.

Subgroup analyses were undertaken by stratifying trials by drug duration and type of drug. Sensitivity analyses were undertaken by excluding data from phase II dose escalation trials and excluding non-clinically relevant dosages of oral factor Xa inhibitors.

Publication bias was assessed by visual evaluation of funnel plots.

Results of the review
 Seventeen RCTs (n=24,979 participants, range 178 to 4,541) were included in the review. All trials were randomised. Most trials had clear descriptions of allocation concealment. Almost all trials had drop-outs or withdrawals of over 5%. No trials used intention-to-treat analyses. One trial was triple blinded, five were double blinding, and the rest were single blinded, with most reporting blinded outcome assessment.

Risk of bleeding: There was no evidence of a significant difference in the overall risk of any bleeding between oral factor Xa inhibitor and low-molecular weight heparin/vitamin-K antagonist groups (RR 1.05, 95% CI 0.89 to 1.24; 17 RCTs). There were also no significant differences between groups for non-surgical site bleeding (RR 1.09, 95% CI 0.93 to 1.28; six RCTs), major bleeding (RR 0.94, 95% CI 0.64 to 1.37; 17 RCTs) or non-major bleeding (RR 1.00, 95% CI 0.88 to 1.15; 17 RCTs). Subgroup analyses by duration of treatment reported no difference in any of the risk of bleeding outcomes between groups. Subgroup analyses in trials that used the most clinically relevant drugs and dosages of oral factor Xa inhibitors found a significantly lower risk of any bleeding from apixaban 2.5mg twice daily compared with rivaroxaban 10mg daily. Subgroup analyses that compared the treatment in prophylaxis trials found no significant interaction between groups. Sensitivity analyses that removed of phase II trials found no evidence of a significant difference in any of the bleeding outcomes between groups; the overall risk of any bleeding was similar for clinically relevant drugs and dosages of oral factor Xa (combining apixaban 2.5mg twice daily and rivaroxaban 10mg daily) compared with control treatments. Moderate heterogeneity was found in the analysis of overall risk of any bleeding.

Risk of transaminitis: The overall risk of transaminitis as a primary outcome was significantly lower for patients who received oral factor Xa inhibitors compared with those who received low-molecular weight heparin or vitamin-K antagonists (RR 0.62, 95% CI 0.44 to 0.87; 15 RCTs), but there was no evidence of a difference between groups in the risk of transaminitis (defined as combined elevated alanine aminotransferase in combination with elevated bilirubin). Subgroup analyses showed that risks of transaminitis were similar in trials using short and long duration of treatment or trials using clinically relevant dosages of oral factor Xa inhibitors (apixaban 2.5mg twice daily versus rivaroxaban 10mg daily). Sensitivity analysis that removed phase II trials found a non-significant decreased risk of transaminitis (as a primary outcome) for oral factor Xa inhibitor therapy compared with control therapy (RR 0.70, 95% CI 0.47 to 1.03; number of studies not reported). Sensitivity analysis that was restricted to the most clinically relevant drugs and dosages (apixaban 2.5mg twice daily and rivaroxaban 10mg daily) found a significantly lower overall risk of transaminitis for oral factor Xa inhibitor therapy (RR 0.69, 95% CI 0.49 to 0.98; eight RCTs). Moderate heterogeneity was found in the analysis of overall risk of transaminitis.

Minimal evidence of publication bias was found for both primary outcomes.

Authors' conclusions

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The risk of bleeding with oral factor Xa inhibitors was similar to low molecular weight heparins, but risk of transaminitis was decreased. The risk of bleeding or transaminitis was not dependent on treatment duration.

CRD commentary
The review addressed a clear research question. Inclusion criteria appeared appropriate to the assessment of safety outcomes. A range of relevant sources were searched to identify studies. Attempts were made to find unpublished studies; funnel plots of the major outcomes were created to assess whether publication bias was likely. Appropriate methods were used to select studies and extract data.

An appropriate tool was used for quality assessment; the included trials were of good quality. Trials were heterogeneous with respect to design (including both phase II and phase III trials), participants (prevention of thrombosis and primary treatment for thrombosis) and interventions (a wide range of drugs and dosages of oral factor Xa inhibitors). However, subgroup and sensitivity analyses largely confirmed the overall results. The results were only generalisable to low-molecular weight heparin as the control therapy, as there were few trials that used vitamin K antagonists. Although stratification was performed to assess whether trial duration influenced the results, maximum duration was limited to three months. Synthesis of the trials and assessment of heterogeneity was appropriate, although both analyses of the primary outcomes had moderate to high heterogeneity, which was not further investigated or explained.

Although there was some unexplained clinical heterogeneity, the authors’ conclusions are likely to be reliable in the context of the short-term evidence presented.

Implications of the review for practice and research
Practice: The authors stated that long-term treatment with oral factor Xa inhibitors was likely to be safe but needed confirmation.

Research: The authors stated that more RCTs were required to assess the safety of long duration anticoagulation, particularly for the risk of bleeding.

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