Efficacy and safety outcomes of oral anticoagulants and antiplatelet drugs in the secondary prevention of venous thromboembolism: systematic review and network meta-analysis


CRD summary
This review of 12 randomised controlled trials found that oral anticoagulants (dabigatran, rivaroxaban, apixaban and vitamin K antagonists) and antiplatelet agents (acetylsalicylic acid) were associated with a reduced recurrence of venous thromboembolism compared with placebo or observation. This finding is likely to be reliable but comparisons of individual treatments may be misleading given uncertainties inherent in the available evidence base.

Authors' objectives
To compare the efficacy and safety of oral anticoagulants (dabigatran, rivaroxaban, apixaban and vitamin K antagonists) and antiplatelet agents (acetylsalicylic acid) for the secondary prevention of venous thromboembolism (VTE).

Searching
MEDLINE (1950 to present), EMBASE (1980 to present) and Cochrane Central Register of Controlled Trials (CENTRAL) were searched using specified search terms. There were no language restrictions. Publications from potentially relevant journals and references of included studies and narrative reviews were searched by hand.

Study selection
Randomised controlled trials of patients receiving anticoagulants, antiplatelet drugs or placebo or observation for secondary prevention of VTE were eligible for inclusion provided they reported a prespecified primary or secondary outcome. VTE was objectively confirmed, symptomatic and treated for a minimum of three months with anticoagulants. Primary outcome measures were recurrent VTE and major bleeding episodes (detailed definitions provided in the manuscript). Secondary outcome included fatal recurrent VTE and fatal bleeding episodes.

Active treatments were compared to placebo or observation by one or two randomised controlled trials. There were direct comparisons of active treatments: standard adjusted dose Vitamin K antagonists with low intensity Vitamin K antagonists; standard adjusted dose Vitamin K antagonists with dabigatran 150mg twice daily; and apixaban 2.5mg twice daily with apixaban 5mg twice daily. The last was a three-arm trial including placebo. All studies were randomised controlled trials. Eight out of 12 trials enrolled more than 400 patients (median 780). Where reported, most patients had unprovoked VTE (high risk of recurrence). The median follow-up period was 14.3 months (range six to 37.2 months). There was a high proportion of male participants. Mean age was between 53 and 68 years.

Two reviewers assessed eligibility.

Assessment of study quality
Study quality was assessed using the Cochrane collaboration risk of bias tool.

Two reviewers assessed study quality.

Data extraction
Data were extracted (based on intention-to-treat) to enable calculation of odds ratios and associated 95% confidence intervals.

Two reviewers independently extracted data.

Methods of synthesis
Bayesian network meta-analyses and direct, frequentist, pairwise meta-analyses were conducted for all outcomes. Bayesian analysis was based on a binomial model using a random-effects network with informative priors for heterogeneity considering different drugs and doses independently and as exchangeable classes. Odds ratios and
associated credible intervals were calculated with outcomes re-expressed as risk differences. Where there were no events, the authors used a 0.5 imputation. Sensitivity analyses were conducted using fixed-effect and random-effects models with vague priors and excluding ximelagatran (withdrawn from the market) from the network.

Results of the review
Twelve randomised controlled trials were included; 11,999 patients were evaluated for efficacy and 12,167 for safety. All the trials were judged to be at low risk of bias.

All treatments reduced the risk of recurrent venous thromboembolism compared with placebo or observation. Vitamin K antagonists at a standard adjusted dose (target international normalised ratio 2.0-3.0) showed the greatest reduction in risk of recurrent VTE (OR 0.07, 95% CrI 0.03 to 0.15) and acetylsalicylic acid showed the greatest risk of recurrent VTE (OR 0.65, 95% CrI 0.39 to 1.03; two RCTs). Risk of major bleeding was higher with a standard adjusted dose of vitamin K antagonists (OR 5.24, 95% CrI 1.78 to 18.25) than with placebo or observation. Details for other agents were reported.

Fatal recurrent venous thromboembolism and fatal bleeding were rare. Sensitivity analyses and direct comparisons were generally consistent with the bayesian analyses (details reported).

Authors’ conclusions
Oral anticoagulants (dabigatran, rivaroxaban, apixaban and vitamin K antagonists) and antiplatelet agents (acetylsalicylic acid) were associated with a reduced recurrence of venous thromboembolism compared with placebo or observation. Reductions in risk were less pronounced for acetylsalicylic acid than the other agents included in the analysis. Vitamin K antagonists given at a standard adjusted dose were associated with the greatest risk reduction in recurrent venous thromboembolism but also the greatest risk of major bleeding.

CRD commentary
This review addressed a clearly defined question and utilised appropriate methods to minimise bias in the acquisition, selection and appraisal of evidence.

The authors’ conclusions reflect the evidence presented but the reliability of the findings are moderate to low because of uncertainties inherent in the evidence base. As the author’s acknowledged, applicability of the findings to all patients with VTE was questionable as the randomised controlled trials on which the analysis was based were likely to have excluded patients with more severe disease status. Most of the linkages in the network were based on individual trials (maximum two) so the estimates of heterogeneity were imprecise and uncertain. Any biases related to reporting, trial conduct or trial publication could have a profound effect on network geometry with potentially important impacts on the conclusions.

The authors acknowledged other uncertainties related to the problems of assuming exchangeability between studies (variable follow-up and lack of individual patient data). They also highlighted the lack of direct comparisons, need for longer follow-up and problems with low power associated with sparse data particularly with (relatively) rare adverse events. Thus although the conclusion that oral anticoagulants were effective compared to placebo or standard care was likely to be reliable, conclusions regarding relative effectiveness were probably unreliable, particularly where the ratio of benefits to harms was concerned.

Implications of the review for practice and research
Practice: The authors stated that acetylsalicylic acid use for secondary prevention of recurrent VTE may be valuable in patients with arterial disease and at low to moderate risk of recurrent VTE. Acetylsalicylic acid could be an attractive option to doctors and patients over vitamin K antagonists for the prevention of recurrent arterial and venous events, given its simplicity and ease of use. Individual patient risk factors require consideration when making recommendations.

Research: The role of acetylsalicylic acid as a secondary preventative agent remained unclear; further studies were needed to establish the benefit to harm profile. Direct comparisons of different treatments and access to individual patient data were also required. Larger studies of longer duration including assessments of cost-effectiveness were required.
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