Oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis and cost-effectiveness analysis

Jonathan AC Sterne,[1]* Pritesh N Bodalia,[2,3] Peter A Bryden,[1] Philippa A Davies,[1] Jose A López-López,[1] George N Okoli,[1] Howard HZ Thom,[1] Deborah M Caldwell,[1] Sofia Dias,[1] Diane Eaton,[4] Julian PT Higgins,[1] Will Hollingworth,[1] Chris Salisbury,[1] Jelena Savović,[1] Reecha Sofat,[5,6] Annya Stephens-Boal,[7] Nicky J Welton[1] and Aroon D Hingorani[5,6]

[1]School of Social and Community Medicine, University of Bristol, Bristol, UK
[2]University College London Hospitals, NHS, London, UK
[3]Royal National Orthopaedic Hospital, NHS, London, UK
[4]AntiCoagulation Europe, Bromley, UK
[5]University College London, London, UK
[6]London School of Hygiene and Tropical Medicine, London, UK
[7]Thrombosis UK, Llanwrda, UK

*Corresponding author

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Scientific summary

Oral anticoagulants for venous thromboembolic disease and stroke

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Scientific summary

Background

Warfarin is an effective oral anticoagulant for stroke prevention in atrial fibrillation (AF), but anticoagulation is underused in clinical care. The risk of venous thromboembolic disease during hospitalisation can be reduced by low-molecular-weight heparin (LMWH): warfarin is the most frequently prescribed anticoagulant for treatment and secondary prevention of venous thromboembolism (VTE). Warfarin-related bleeding is a major reason for hospitalisation for adverse drug effects. The cost of warfarin is low, but therapeutic monitoring increases treatment costs. Novel oral anticoagulants (NOACs) have a more rapid onset and offset of action than warfarin, and more predictable dosing requirements.

Objectives

To identify the most effective, safe and cost-effective anticoagulant for stroke prevention in AF, and for primary prevention, treatment and secondary prevention of VTE.

Methods

We conducted four systematic reviews, with network meta-analyses (NMAs), of randomised controlled trials addressing (1) stroke prevention in AF (for which the search was run on 12 March 2014 and updated on 15 September 2014, and covered the period 2010 to September 2014), (2) primary prevention of VTE, (3) acute treatment of VTE and (4) secondary prevention of VTE (for all three of which the search was run on 19 March 2014, updated on 15 September 2014, and covered the period 2008 to September 2014). We extracted data on clinically relevant efficacy outcomes [stroke, symptomatic VTE, symptomatic deep-vein thrombosis (DVT) and symptomatic pulmonary embolism] and safety outcomes [major bleeding, clinically relevant bleeding (CRB) and intracranial haemorrhage], as well as myocardial infarction (MI) and all-cause mortality. We searched MEDLINE and PREMEDLINE In-Process & Other Non-Indexed Citations, EMBASE and The Cochrane Library, reference lists of published NMAs and trial registries. Two reviewers screened search results, extracted and checked data, and assessed risk of bias. For each outcome we analysed each direct pairwise comparison and performed NMAs to compare all interventions simultaneously.

We constructed discrete-time Markov models to evaluate cost-effectiveness of the different interventions included in the four networks. These synthesised evidence on a number of parameters (e.g. incidence of VTE and ischaemic stroke, relative treatment efficacy, adverse events, costs) to estimate the relative cost-effectiveness of treatment options. Model inputs were based on a variety of evidence sources, including routine data on drug costs and observational studies of long-term costs of, and quality of life with, AF and VTE. Model inputs on relative treatment efficacy and safety of anticoagulants were derived from the results of the NMAs.

Results

For stroke prevention in AF, apixaban (Eliquis®, Bristol-Myers Squibb, USA; Pfizer, USA) [5 mg twice daily (bd)] was ranked as being among the best interventions for a wide range of the outcomes evaluated, including stroke or systemic embolism (SE), MI, major bleeding, and all-cause mortality. Edoxaban (Lixiana®, Daiichi Sankyo, Japan) [60 mg od (once daily)] was ranked second for major bleeding and all-cause mortality. Except for all-cause mortality, outcomes for rivaroxaban (Xarelto®, Bayer HealthCare, Germany) (20 mg od) were ranked less highly than several other NOACs. The non-NOAC interventions {warfarin [international normalised

ratio (INR) 2–3] and antiplatelet therapy [aspirin/clopidogrel (Plavix®, Sanofi, USA) ≥ 150 mg od]} were ranked worst for stroke or SE, and were not among the best three interventions for any of the outcomes.

At a willingness-to-pay threshold of £20,000 per quality-adjusted life-year (QALY), all NOACs had positive expected incremental net benefit (INB) compared with warfarin (INR 2–3), suggesting that their use in AF may be a cost-effective use of UK NHS resources. Apixaban (5 mg bd) had the highest expected INB (£7533), followed by rivaroxaban (20 mg od) (£6365), edoxaban (£5279) and dabigatran (Pradaxa®, Prazaxa®, Pradax®, Boehringer Ingelheim GmbH, Germany) (£5279). Apixaban (5 mg bd) was the only NOAC for which the 95% confidence interval around INB was positive, suggesting that it is cost-effective compared with warfarin.

For primary prevention of VTE, we found little evidence that risk of symptomatic VTE, symptomatic DVT or symptomatic PE were lower for NOACs than for LMWH. We also found little evidence that risk of major bleeding or CRB is lower for NOACs than for LMWH. Warfarin was ranked with high probability as the best intervention for major bleeding events and LMWH [postoperative (post-op), standard dose] was ranked with high probability as best, or second-best, intervention for CRB. Neither the clinical effectiveness analysis nor the cost-effectiveness analysis (CEA) provided strong evidence that NOACs should replace post-op LMWH in primary prevention of VTE in patients undergoing hip or knee surgery.

For acute treatment of VTE, we found little evidence that NOACs reduced risk of symptomatic VTE, symptomatic DVT or symptomatic PE compared with warfarin or that the risk of any of these outcomes differed between licensed doses of NOACs. However, there was evidence that risk of major bleeding and CRB was lower with apixaban (5 mg bd) and rivaroxaban (15 mg bd then 20 mg od) than with warfarin (INR 2–3). There was a high probability that warfarin (INR 2–3) was ranked worst for major bleeding and CRB. There was a high probability that apixaban 5 mg bd was ranked best for major bleeding and CRB, and this intervention also had a high probability of being ranked best, or second best, for symptomatic DVT, symptomatic VTE and all-cause mortality. For a willingness-to-pay threshold of > £5000, apixaban 5 mg bd was the most cost-effective alternative to warfarin.

For secondary prevention of VTE, risk of symptomatic VTE and risk of symptomatic DVT were lower for all NOACS (at the doses included in the network) than placebo and aspirin. However, there was no clear evidence that risk of these outcomes differed between the NOAC interventions and warfarin. Risk of major bleeding and CRB was higher with warfarin and some NOAC interventions than placebo, but there was evidence that risk of these outcomes is lower with apixaban (2.5 mg or 5 mg bd) and dabigatran (150 mg bd) than warfarin. Aspirin had the highest expected net benefit for secondary prevention of VTE at willingness-to-pay thresholds of £20,000 and £30,000 per QALY. By contrast, all NOAC interventions had negative expected INBs at the £20,000 and £30,000 thresholds, indicating that they are not cost-effective compared with no pharmacotherapy.

Conclusions

Novel oral anticoagulants have advantages over warfarin in patients with AF. Of the available NOACs, apixaban 5 mg bd offers the best balance between efficacy and safety, and has the highest probability of being most cost-effective. NOACs offer no efficacy advantage over warfarin in the acute treatment of VTE, but have a lower rate of bleeding complications albeit at a higher cost. For a willingness-to-pay threshold of > £5000, apixaban 5 mg bd emerges as the most cost-effective alternative to warfarin. Neither the clinical effectiveness analysis nor the CEA provided strong evidence that NOACs should replace post-op LMWH in primary prevention of VTE in patients who are undergoing hip or knee surgery. If secondary prevention after 3–6 months of anticoagulation for a first episode of VTE is to be considered (this is not currently established practice), NOACs provide no advantage over aspirin 100 mg od.

The research needs identified by this review are for (1) calculations of the expected value of sample information, in order to clarify whether or not it would be justifiable to fund one more trial making direct comparisons between the most promising NOACs and NOAC doses, in situations typical of NHS clinical practice; (2) information on long-term rates of the main efficacy and safety outcomes among patients receiving anticoagulants for AF, for example from registries or health record data; (3) information on the role (if any) of therapeutic monitoring to enhance the safety and efficacy of NOACs; and (4) information on long-term adherence rates in patients receiving NOACs for AF.

Study registration

This study is registered as PROSPERO CRD42013005324, CRD42013005331 and CRD42013005330.

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