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RESEARCH

Primary and secondary prevention with new oral anticoagulant drugs for stroke prevention in atrial fibrillation: indirect comparison analysis

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Abstract

Objective To do an indirect comparison analysis of apixaban against dabigatran etexilate (2 doses) and rivaroxaban (1 dose), as well as of rivaroxaban against dabigatranetexilate (2 doses), for their relative efficacy and safety against each other, with particular focus on the secondary prevention population for stroke prevention in atrial fibrillation. A secondary objective was to do the same analysis in the primary prevention cohort.

Design Indirect treatment comparisons of phase III clinical trials of stroke prevention in atrial fibrillation, with a focus on the secondary prevention cohorts. A secondary analysis was done on the primary prevention cohort.

Data sources Medline and Central (up to June 2012), clinical trials registers, conference proceedings, and websites of regulatory agencies.

Study selection Randomised controlled trials of rivaroxaban, dabigatran, or apixaban compared with warfarin for stroke prevention in atrial fibrillation.

Results In the secondary prevention (previous stroke) subgroup, when apixaban was compared with dabigatran (110 mg and 150 mg twice daily) for efficacy and safety endpoints, the only significant difference seen was less myocardial infarction (hazard ratio 0.39, 95% confidence interval 0.16 to 0.95) with apixaban compared with dabigatran 150 mg twice daily. No significant differences were seen in efficacy and most safety endpoints between apixaban or dabigatran 150 mg twice daily versus rivaroxaban. Less haemorrhagic stroke (hazard ratio 0.15, 0.03 to 0.66), vascular death (0.64, 0.42 to 0.99), major bleeding (0.68, 0.47 to 0.99), and intracranial bleeding (0.27, 0.10 to 0.73) were seen with dabigatran 110 mg twice daily versus rivaroxaban. In the primary prevention (no previous stroke) subgroup, apixaban was superior to dabigatran 110 mg twice daily for disabling or fatal stroke (hazard ratio 0.59, 0.36 to 0.97). Compared with dabigatran 150 mg twice daily, apixaban was associated with more stroke (hazard ratio 1.45, 1.01 to 2.08) and with less major bleeding (0.75, 0.60 to 0.94), gastrointestinal bleeding (0.61, 0.42 to 0.89), and other location bleeding (0.74, 0.58 to 0.94). Compared with rivaroxaban, dabigatran 110 mg twice daily was associated with more myocardial infarction events. No significant differences were seen for the main efficacy and safety endpoints between dabigatran 150 mg twice daily and rivaroxaban, or in efficacy endpoints between apixaban and rivaroxaban. Apixaban was associated with less major bleeding (hazard ratio 0.61, 0.48 to 0.78) than rivaroxaban.

Conclusions For secondary prevention, apixaban, rivaroxaban, and dabigatran had broadly similar efficacy for the main endpoints, although the endpoints of haemorrhagic stroke, vascular death, major bleeding, and intracranial bleeding were less common with dabigatran 110 mg twice daily than with rivaroxaban. For primary prevention, the three drugs showed some differences in relation to efficacy and bleeding. These results are hypothesis generating and should be confirmed in a head to head randomised trial.

Introduction

Impressive phase III clinical trials against warfarin have been published for the novel oral anticoagulants—that is, the direct thrombin inhibitors (dabigatran) and the factor Xa inhibitors (for example, rivaroxaban, apixaban). All showed non-inferiority for the primary efficacy endpoint of stroke and systemic embolism; dabigatran 150 mg twice daily and apixaban achieved superiority over warfarin for this endpoint.[1] With regards to safety, dabigatran 110 mg twice daily and apixaban had significantly less major bleeding (by 20% and 31%) compared with warfarin.

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