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[Intervention Review]

Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation

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ABSTRACT

Background

Factor Xa inhibitors and vitamin K antagonists (VKAs) are now recommended in treatment guidelines for preventing stroke and systemic embolic events in people with atrial fibrillation (AF). This is an update of a Cochrane review previously published in 2013.

Objectives

To assess the effectiveness and safety of treatment with factor Xa inhibitors versus VKAs for preventing cerebral or systemic embolic events in people with AF.

Search methods

We searched the trials registers of the Cochrane Stroke Group and the Cochrane Heart Group (September 2016), the Cochrane Central Register of Controlled Trials (CENTRAL) (August 2017), MEDLINE (1950 to April 2017), and Embase (1980 to April 2017). We also contacted pharmaceutical companies, authors and sponsors of relevant published trials. We used outcome data from marketing authorisation applications of apixaban, edoxaban and rivaroxaban that were submitted to regulatory authorities in Europe and the USA.

Selection criteria

We included randomised controlled trials (RCTs) that directly compared the effects of long-term treatment (lasting more than four weeks) with factor Xa inhibitors versus VKAs for preventing cerebral and systemic embolism in people with AF.

Data collection and analysis

The primary efficacy outcome was the composite endpoint of all strokes and systemic embolic events. Two review authors independently extracted data, and assessed the quality of the trials and the risk of bias. We calculated a weighted estimate of the typical treatment effect across trials using the odds ratio (OR) with 95% confidence interval (CI) by means of a fixed-effect model. In case of moderate or high heterogeneity of treatment effects, we used a random-effects model to compare the overall treatment effects. We also performed a pre-specified sensitivity analysis excluding any open-label studies.

Main results

We included data from 67,688 participants randomised into 13 RCTs. The included trials directly compared dose-adjusted warfarin with either apixaban, betrixaban, darexaban, edoxaban, idraparinux, idrabiotaparinux, or rivaroxaban. The majority of the included data (approximately 90%) was from apixaban, edoxaban, and rivaroxaban.

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The composite primary efficacy endpoint of all strokes (both ischaemic and haemorrhagic) and non-central nervous systemic embolic events was reported in all of the included studies. Treatment with a factor Xa inhibitor significantly decreased the number of strokes and systemic embolic events compared with dose-adjusted warfarin in participants with AF (OR 0.89, 95% CI 0.82 to 0.97; 13 studies; 67,477 participants; high-quality evidence).

Treatment with a factor Xa inhibitor significantly reduced the number of major bleedings compared with warfarin (OR 0.78, 95% CI 0.73 to 0.84; 13 studies; 67,396 participants; moderate-quality evidence). There was, however, statistically significant and high heterogeneity (I^2 = 83%). When we repeated this analysis using a random-effects model, it did not show a statistically significant decrease in the number of major bleedings (OR 0.88, 95% CI 0.66 to 1.17). A pre-specified sensitivity analysis excluding all open-label studies showed that treatment with a factor Xa inhibitor significantly reduced the number of major bleedings compared with warfarin (OR 0.75, 95% CI 0.69 to 0.81), but high heterogeneity was also observed in this analysis (I^2 = 72%). The same sensitivity analysis using a random-effects model also showed a statistically significant decrease in the number of major bleedings in participants treated with factor Xa inhibitors (OR 0.76, 95% CI 0.60 to 0.96).

Treatment with a factor Xa inhibitor significantly reduced the risk of intracranial haemorrhages (ICHs) compared with warfarin (OR 0.50, 95% CI 0.42 to 0.59; 12 studies; 66,259 participants; high-quality evidence). We observed moderate, but statistically significant heterogeneity (I^2 = 55%). The pre-specified sensitivity analysis excluding open-label studies showed that treatment with a factor Xa inhibitor significantly reduced the number of ICHs compared with warfarin (OR 0.47, 95% CI 0.40 to 0.56), with low, non-statistically significant heterogeneity (I^2 = 27%).

Treatment with a factor Xa inhibitor also significantly reduced the number of all-cause deaths compared with warfarin (OR 0.89, 95% 0.83 to 0.95; 10 studies; 65,624 participants; moderate-quality evidence).

Authors' conclusions

Treatment with factor Xa inhibitors significantly reduced the number of strokes and systemic embolic events compared with warfarin in people with AF. The absolute effect of factor Xa inhibitors compared with warfarin treatment was, however, rather small. Factor Xa inhibitors also reduced the number of ICHs, all-cause deaths and major bleedings compared with warfarin, although the evidence for a reduction in the latter is less robust.

PLAIN LANGUAGE SUMMARY

Comparing two types of blood-thinning drugs, factor Xa inhibitors and vitamin K antagonists, to prevent blood clots in people with atrial fibrillation

Review question

We compared the benefits and harms of two types of so-called "blood-thinning" drugs (factor Xa inhibitors and vitamin K antagonists) in people with atrial fibrillation.

Background

People with atrial fibrillation, a condition that causes the heart to beat irregularly, are at an increased risk of getting blood clots. Such clots can block blood vessels and cause severe organ damage in the brain (stroke) or other organs. Various guidelines recommend that people with atrial fibrillation should be treated with "blood-thinning" drugs such as factor Xa inhibitors or vitamin K antagonists (e.g. warfarin) because these drugs can prevent the formation of blood clots. Serious side effects of these drugs are bleedings (e.g. into the brain) that can cause serious disability or even death.

Study characteristics

We searched various sources up to 29 August 2017 and included 13 studies that involved 67,688 people with atrial fibrillation who received either a factor Xa inhibitor or a vitamin K antagonist. All included people were adults and on average aged between 65 and 74 years. Approximately one-third were women.

Key results

We found that factor Xa inhibitors when compared with warfarin, which was used as comparator in all trials, reduced the number of strokes in people with atrial fibrillation. This reduction was, however, rather small. Factor Xa inhibitors also appeared to reduce the number of serious bleedings (including those into the brain) and the number of people dying from any cause compared with warfarin.

Quality of evidence

We considered the quality of evidence in our review as moderate to high. The studies that we included were generally large to very large. We found that the results from the larger studies were generally similar and this strengthened our findings. Finally, we are confident that we included all relevant studies in our review and did not miss any important studies.

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