Factor Xa Inhibitors Versus Vitamin K Antagonists for Preventing Cerebral or Systemic Embolism in Patients With Atrial Fibrillation

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Atrial fibrillation (AF) is the most common type of arrhythmia in adults and becomes more common with increased age. Management of people with AF aims at preventing thromboembolic complications, and anticoagulant treatment with vitamin K antagonists (VKAs) has been the therapy of choice for many decades. A new class of anticoagulants, the factor Xa inhibitors, seems to have several pharmacological and practical advantages over VKAs, and some have recently been approved by regulatory authorities in the United States and Europe for stroke prevention in people with AF.

Objectives
The objectives of this study were to assess the effectiveness and safety of treatment with factor Xa inhibitors versus VKAs for the prevention of cerebral or systemic embolic events in people with nonvalvular AF.

Search Methods
We searched the trial registers of the Cochrane Stroke Group, the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE (all to June 2013). We also screened reference lists and contacted pharmaceutical companies, authors, and sponsors of relevant published trials.

Selection Criteria
We identified randomized, controlled trials that directly compared the effects of long-term treatment (>4 weeks) with factor Xa inhibitors and VKAs for the prevention of cerebral and systemic embolism in patients with AF. We included patients with and without a previous stroke or transient ischemic attack.

Data Collection and Analysis
The primary end point was the composite end point of all strokes (both ischemic and hemorrhagic) and noncentral nervous systemic embolic events compared with dose-adjusted warfarin (OR, 0.81; 95% CI, 0.72–0.91; Figure). All of the included studies (42,078 participants) reported the number of major bleedings. Treatment with a factor Xa inhibitor reduced the number of major bleedings compared with warfarin, but there was substantial heterogeneity (I²=81%), and the difference was not statistically significant (OR, 0.92; 95% CI, 0.63–1.34). The prespecified sensitivity analysis excluding an open-label study showed that treatment with a factor Xa inhibitor had an even more favorable effect on major bleedings, but moderate heterogeneity was still observed (I²=65%), and a random-effects analysis did not show a statistically significant decrease in the number of major bleedings in patients treated with factor Xa inhibitors (OR, 0.78; 95% CI, 0.57–1.05). The 1 trial accounting for a part of the observed heterogeneity was a study of idraparinux administered subcutaneously. Other sources of heterogeneity can be differences in baseline bleeding risks in the 2 largest trials of apixaban and rivaroxaban that we included in this review.

Data regarding intracranial hemorrhages (ICHs) were reported in 8 studies (39,638 participants). Treatment with a factor Xa inhibitor significantly decreased the number of ICHs compared with warfarin (OR, 0.56; 95% CI, 0.45–0.70). Again, we observed statistically significant heterogeneity (I²=60%).

Main Results
We included data from 42,084 participants included in 10 trials. All participants had a confirmed diagnosis of AF (or atrial flutter) and were deemed by the randomizing physician to be eligible for long-term anticoagulant treatment with a VKA (warfarin) with a target international normalized ratio of 2.0 to 3.0. The included trials directly compared dose-adjusted warfarin with apixaban, betrixaban, darexaban, edoxaban, idraparinux, or rivaroxaban. Four trials were double-masked, 5 were partially masked (ie, different doses of factor Xa inhibitor administered double-masked and warfarin administered openly), and 1 was open-label. Median duration of follow-up ranged from 12 weeks to 1.9 years.

The composite primary end point of all strokes (both ischemic and hemorrhagic) and noncentral nervous systemic embolic events was reported in 9 of the included studies (40,777 participants). Treatment with a factor Xa inhibitor significantly decreased the number of strokes and systemic embolic events compared with dose-adjusted warfarin (OR, 0.81; 95% CI, 0.72–0.91; Figure).
The sensitivity analysis excluding an open-label study with idraparinux showed that treatment with a factor Xa inhibitor still significantly reduced the number of ICHs compared with warfarin (OR, 0.51; 95% CI, 0.41–0.64), without any sign of statistical heterogeneity (I²=0%).

The number of patients who died from any cause was reported in 6 studies (38,924 participants). Treatment with a factor Xa inhibitor significantly reduced the number of all-cause deaths compared with warfarin (OR, 0.88; 95% CI, 0.81–0.97).

**Conclusions**

Factor Xa inhibitors significantly reduced the number of strokes and systemic embolic events compared with warfarin in patients with AF. Factor Xa inhibitors also reduced the number of major bleedings and ICHs compared with warfarin, but the reduction in major bleedings was not statistically significant, and the quality of the evidence was lower because of the observed heterogeneity.

**Applicability of Findings to Clinical Practice**

Overall, there is a small net clinical benefit of treatment with factor Xa inhibitors in people with AF because it leads to a reduction of strokes and systemic embolic events and also to a lower risk of bleedings (including ICHs) compared with dose-adjusted warfarin. There is currently no evidence to determine which factor Xa inhibitor is better for long-term
anticoagulant treatment of patients with AF because head-to-head studies of the different factor Xa inhibitors have not yet been performed.

**Future Research**

Future studies should aim to further determine the effects of long-term anticoagulation treatment with a factor Xa inhibitor after a prolonged follow-up (ie, beyond 2 years). More data regarding the effects of factor Xa inhibitors in people at low risk for thromboembolic events (ie, low CHA₂DS₂-VASc scores) are also needed because they were not enrolled in the included trials. Efforts should also be made to further identify blood tests to monitor the effect of factor Xa inhibitors and develop antidotes to counteract the anticoagulation effect when needed.

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This article is based on a Cochrane Review published in The Cochrane Library 2013, Issue 8 (see www.thecochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and The Cochrane Library should be consulted for the most recent version of the review.

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**Disclosures**

Dr Bruins Slot is employed by the Norwegian Medicines Agency and is a member of the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) and the Cardiovascular Working Party. The views expressed in this review are the personal views of Dr Bruins Slot and should not be understood or quoted as being made on behalf of or reflecting the position of the Norwegian Medicines Agency and the European Medicines Agency or one of its committees or working parties. Dr Berge has participated in an advisory committee meeting for Bayer Schering Pharma to discuss the results of the ROCKET AF (rivaroxaban) and received an honorarium and reimbursement of expenses related to this meeting.

**Reference**


**Key Words:** anticoagulation ■ atrial fibrillation ■ stroke
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