

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

Karsten M.H. Bruins Slot, MD, PhD; Eivind Berge, MD, PhD

Anticoagulant treatment is recommended for the prevention of stroke and systemic embolic events in people with atrial fibrillation. Factor Xa inhibitors have practical advantages over vitamin K antagonists and are increasingly being used in clinical practice.

Objectives

We wanted to assess the effectiveness and safety of treatment with factor Xa inhibitors versus vitamin K antagonists for the prevention of cerebral or systemic embolic events in people with atrial fibrillation.

Search Methods

We updated our Cochrane review published in 2013 by performing a new search of the trials registers of the Cochrane Stroke Group (September 2016), the Cochrane Central Register of Controlled Trials (August 2017), MEDLINE, and EMBASE (both April 2017). We also used outcome data from marketing authorization applications submitted to regulatory authorities in the United States and Europe.

Selection Criteria

We identified randomized, controlled trials that directly compared the effects of long-term treatment (>4 weeks) with factor Xa inhibitors and vitamin K antagonists for the prevention of cerebral and systemic embolism in people with atrial fibrillation.

Data Collection and Analysis

The primary end point was the composite end point of all strokes and systemic embolic events. 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, we also used a random effects model and performed a prespecified sensitivity analysis excluding open-label studies.

Main Results

We included data from 68 688 participants enrolled in 13 trials.¹ The included trials directly compared dose-adjusted

warfarin with either apixaban, betrixaban, darexaban, edoxaban, idraparinux, idrabiotaparinux, or rivaroxaban. Median follow-up ranged from 12 weeks to 2.8 years.

The composite primary end point of all strokes and noncentral nervous systemic embolic events were reported in all of the included studies (67 477 participants). Treatment with a factor Xa inhibitor significantly decreased the number of strokes and other systemic embolic events compared with dose-adjusted warfarin (OR, 0.89; 95% CI, 0.82–0.97; Figure).

Treatment with a factor Xa inhibitor also significantly reduced the number of major bleedings compared with warfarin (OR, 0.78; 95% CI, 0.73–0.84), but there was substantial heterogeneity ($I^2=83%$). The prespecified sensitivity analysis excluding one open-label study with idraparinux gave a similar result (OR, 0.75; 95% CI, 0.69–0.81) and moderate heterogeneity was still observed ($I^2=72%$). The random effects analysis showed a statistically significant decrease in the number of major bleedings in patients treated with factor Xa inhibitors (OR, 0.76; 95% CI, 0.60–0.96).

Data on intracranial hemorrhages were reported in 12 studies (66 259 participants). Treatment with a factor Xa inhibitor significantly reduced the number of intracranial hemorrhages compared with warfarin (OR, 0.50; 95% CI, 0.42–0.59). We observed statistically significant, moderate heterogeneity ($I^2=55%$). The sensitivity analysis excluding the open-label study showed similar results with low heterogeneity ($I^2=27%$).

The number of patients who died from any cause was reported in 10 studies (65 624 participants). Treatment with a factor Xa inhibitor significantly reduced the number of all-cause deaths compared with warfarin (OR, 0.89; 95% CI, 0.83–0.95).

Authors' Conclusions

Factor Xa inhibitors reduced the number of strokes and systemic embolic events compared with warfarin in people with atrial fibrillation. Factor Xa inhibitors also reduced the number of major bleedings, intracranial hemorrhages, and all-cause deaths, but the evidence for the reduction in major bleedings is of lower quality because of the higher heterogeneity for this end point.

Received April 10, 2018; final revision received April 20, 2018; accepted May 4, 2018.

From the Department of Medicine, Oslo University Hospital, Norway.

This paper is based on a Cochrane Review published in *The Cochrane Library* 2018, Issue 3 (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.

Correspondence to Karsten M.H. Bruins Slot, Department of Medicine, Oslo University Hospital, Kirkeveien 166, Oslo 0407, Norway. E-mail kbriunsslot@yahoo.no

(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.118.021521.)

© 2018 American Heart Association, Inc.

Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.118.021521

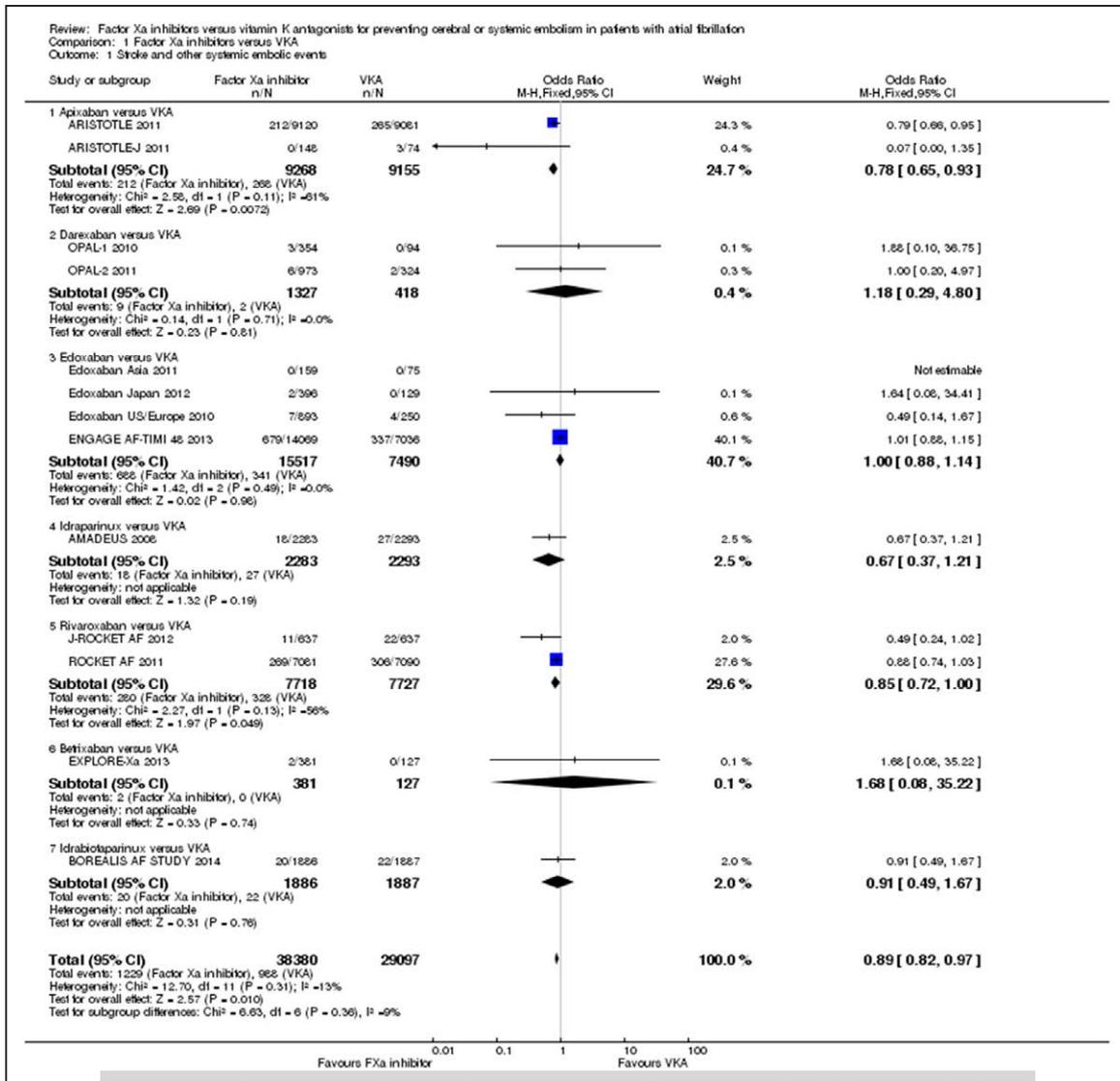


Figure. Comparison of factor Xa inhibitors versus warfarin for prevention of stroke and other systemic embolic events. CI indicates confidence interval; and VKA, vitamin K antagonist.

Applicability of Findings to Clinical Practice

Overall, there is a net clinical benefit of treatment with factor Xa inhibitors in people with atrial fibrillation, as it leads to a small reduction of strokes and systemic embolic events and a more pronounced reduction of bleedings (including intracranial hemorrhages) compared with dose-adjusted warfarin. There is currently no evidence to determine which factor Xa inhibitor is better for long-term anticoagulant treatment as direct comparisons of the different factor Xa inhibitors have not yet been performed.

Future Research

Future studies could aim to determine the effects of anticoagulation with a factor Xa inhibitor during longer-term follow-up and in people with a very low risk for thromboembolic events (ie, low CHA₂DS₂-VASc scores).

Sources of Funding

Supported by the South-Eastern Norway Regional Health Authority, Norway.

Disclosures

Dr Bruins Slot is currently employed by F. Hoffmann-La Roche (Roche Norge AS). The data included in this review are based on research which has been done independently of F. Hoffmann-La Roche. 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 F. Hoffmann-La Roche. Dr Berge chaired a symposium organized by Bayer in August 2017 and received payment for this work, after the review had been submitted to the Cochrane Stroke Group. This was in breach of Cochrane's Conflicts of Interest policy but has been discussed with the Funding Arbiters, who have agreed to allow publication of the updated review.

References

1. Bruins Slot KMH, Berge E. Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation. *Cochrane Database Syst Rev.* 2018;(3):CD008980. doi: 10.1002/14651858.CD008980.

KEY WORDS: atrial fibrillation ■ factor Xa inhibitors ■ stroke ■ vitamin K antagonists

Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Factor Xa Inhibitors Versus Vitamin K Antagonists for Prevention of Cerebral or Systemic Embolism in Patients With Atrial Fibrillation Karsten M.H. Bruins Slot and Eivind Berge

Stroke. published online June 4, 2018;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2018 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://stroke.ahajournals.org/content/early/2018/05/31/STROKEAHA.118.021521.citation>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Stroke* is online at:
<http://stroke.ahajournals.org/subscriptions/>