

# Preventing Stroke in Atrial Fibrillation: Warfarin vs. Factor Xa Inhibitors

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Warfarin has traditionally been used to prevent stroke in patients with atrial fibrillation. The advent of factor Xa inhibitors, however, has provided an alternative. This article evaluates the literature on factor Xa inhibitor use in patients with atrial fibrillation and discusses the general benefits and risks of this novel class of anticoagulants.

## INTRODUCTION

The heart is a muscular pump that circulates blood to the body. It accomplishes this through an electrical network that dictates the timing and nature of its contraction. Atrial fibrillation is an electrical abnormality whereby the heart beats irregularly and too quickly [1]. One consequence of atrial fibrillation is an increased tendency to form blood clots in the upper chambers of the heart [1]. These blood clots have the ability to break off and travel to the brain, where they can cause a stroke.

Patients with atrial fibrillation are at five times greater risk for stroke than similar aged individuals in normal sinus rhythm [2]. In order to prevent strokes, patients with atrial fibrillation are frequently anticoagulated with warfarin, a Vitamin K antagonist.

The decision to begin anticoagulation is usually based on a patient's CHADS<sub>2</sub> (history of congestive heart failure and/or moderate or severe systolic dysfunction; hypertension; age ≥ 75; diabetes mellitus; prior stroke, transient ischemic attack, or thromboembolism) score (Table 1) [3,4]. US guidelines recommend the initiation of warfarin therapy in pa-

tients with CHADS<sub>2</sub> scores of 2 or above, which correlates to an ischemic stroke rate of 4.2% per year (Table 2) [3,4].

**Table 1.** Calculation of CHADS<sub>2</sub> Score.

CHADS <sub>2</sub>	Score
C: Congestive heart failure	1
H: Hypertension	1
A: Age ≥ 75	1
D: Diabetes mellitus	1
S: Stroke, transient ischemic attack, or thromboembolism	2

**Table 2.** Ischemic Stroke Rate (%/year) by CHADS<sub>2</sub> Score.

CHADS <sub>2</sub> Score	Ischemic Stroke Rate (%/year)
0	0.6%
1	3.0%
2	4.2%
3	7.1%
4	11.1%
5	12.5%
6	13.0%

Currently, only 60% of patients with atrial fibrillation who meet criteria for anticoagulation take warfarin [5]. The main reasons cited for this low rate include fear of bleeding complications, difficulty dosing the medication, and the bothersome nature of frequent blood draws [5]. These associated difficulties were the impetus for trialing direct Xa inhibitors, which anticoagulate by blocking factor Xa in the coagulation cascade. Xa inhibitors were initially attractive for their ease of dosing (few drug and food interactions, standard dosing regimens) and for their convenience (no frequent blood draws) [5].

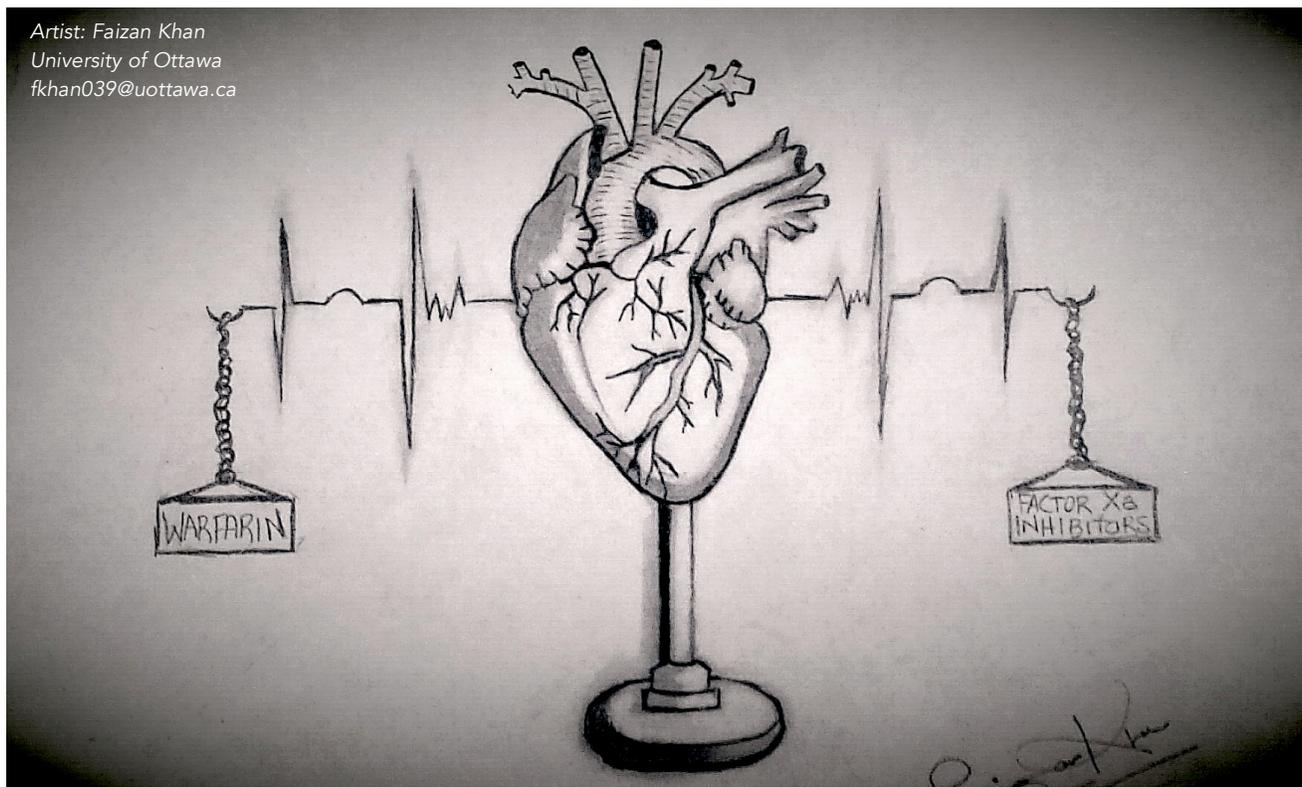
#### CLINICAL TRIALS: XA INHIBITORS VS. WARFARIN

The first two large randomized controlled trials (RCTs) to compare Xa inhibitors to warfarin were “Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation” (ROCKET AF) and “Apixiban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation” (ARISTOTLE) [6,7].

ROCKET AF was a randomized, double blind, controlled trial performed between 2006 and 2010 that

compared oral rivaroxaban to warfarin for the prevention of stroke or systemic embolism in atrial fibrillation patients [6]. The trial enrolled 1,178 individuals with atrial fibrillation and moderate to high risk of stroke (CHADS<sub>2</sub> ≥2). The patients were randomized to receive once daily oral rivaroxaban or dose-adjusted warfarin. Results of the ROCKET AF study revealed a decreased incidence of stroke and systemic embolism in the rivaroxaban group when compared to the warfarin group (HR 0.79, CI 0.66–0.96). The rivaroxaban group also demonstrated a significant reduction in intracranial hemorrhage (0.5% vs. 0.7%, p=0.02) and fatal bleeding (0.2% vs. 0.5%, p=0.003) when compared to the warfarin group.

The ARISTOTLE trial (2006–2010, n=18,201) used the Xa inhibitor apixiban and was similar to ROCKET AF in design and outcomes measured [7]. ARISTOTLE demonstrated similar findings to those of ROCKET AF, with a reduced incidence of stroke and systemic embolism in the apixiban group when compared to the warfarin group (HR 0.79, CI 0.66–0.95), as well as reductions in major bleeding (HR 0.69, CI 0.60–0.80), hemorrhagic stroke (HR 0.51,



CI 0.35–0.75), and all-cause mortality (HR 0.89, CI 0.80–0.99). Neither study reported major side effects of the drugs beyond the bleeding described above.

One limitation of ROCKET AF was that the warfarin group had a therapeutic International Normalized Ratio (INR) only 55% of the time. Previous studies have demonstrated that a therapeutic range more than 58% of the time is required for warfarin anticoagulation to be considered superior to aspirin [8]. There was also a significant difference in number of prior myocardial infarctions between the rivaroxaban and warfarin groups [6]. The warfarin group exhibited a greater number of prior myocardial infarctions, suggesting the possibility of greater underlying cardiovascular disease burden. Both studies evaluated individuals at moderate-high risk for stroke—mean CHADS<sub>2</sub> for ROCKET AF and ARISTOTLE were 2.1 and 3.5, respectively—and so may not generalize to individuals with lower CHADS<sub>2</sub> scores. Pharmaceutical companies sponsored both ROCKET AF and ARISTOTLE, offering a potential source for bias in result interpretation.

Many other Xa inhibitors have been evaluated since ROCKET AF and ARISTOTLE. In 2013, a Cochrane Review was released pooling the major RCTs on the topic [9]. The review included 43,084 participants from ten RCTs that compared dose-adjusted warfarin to different Xa inhibitors, including apixiban, betrixaban, darexaban, endoxaban, idraparinux, and rivaroxaban for the prevention of stroke and other embolic events in atrial fibrillation patients. The mean CHADS<sub>2</sub> score of the study participants was 2.7 (range: 1.9–3.5), and the mean age ranged from 65 to 74 years. In the Cochrane group’s meta-analysis, it was found that Xa inhibitors significantly decreased stroke (OR 0.78, CI 0.69–0.89) and systemic embolic events (OR 0.53, CI 0.32–0.87) when compared to warfarin. They were also associated with fewer intra-cranial hemorrhages (OR 0.51, CI 0.41–0.64) and lower all-cause mortality (OR 0.88, CI .81–0.97).

## LIMITATIONS OF XA INHIBITOR ADOPTION

There are several limitations to the studies presented above. No studies to date compare the different Xa inhibitors directly against one another (e.g., apixiban vs. rivaroxaban), making it difficult to conclude if one Xa inhibitor is better than another [9]. Further, the majority of the large studies performed to date use either apixiban or rivaroxaban—85% of the data from the Cochrane Review was from studies that used either one of these two drugs. In fact, in sub-group analysis, the Cochrane Review found no significant reduction in stroke or systemic embolic events in any of the Xa inhibitors except apixiban and rivaroxaban. The longest follow-up time for studies included in the Cochrane analysis was 1.9 years, with some studies having follow-up of as little as 12 weeks. Finally, the studies conducted to date all include patients who both have and have not used warfarin before study enrollment, making it difficult to evaluate if prior warfarin status affects Xa inhibitor efficacy [9].

This last limitation was addressed in the “Endoxaban versus Warfarin in Patients with Atrial Fibrillation” (ENGAGE-AF) trial, which was a randomized, double blind trial comparing low- (30mg) and high-dose (60mg) endoxaban to dose-adjusted warfarin for the prevention of stroke or embolic events in patients with atrial fibrillation [10]. The trial enrolled 21,000 patients with atrial fibrillation and moderate to high risk of stroke (mean CHADS<sub>2</sub> 2.8) and had a mean follow-up time of 2.8 years. The study found that there was no difference in stroke/embolism rates between the high-dose endoxaban and warfarin groups in individuals with prior Vitamin K antagonist use (1.62% vs. 1.60%,  $p>0.05$ ), while there was a difference in Vitamin K antagonist naïve individuals (1.49% vs. 2.12%,  $p=0.03$ ). These results suggest that prior Vitamin K antagonist status may play a role in determining response to Xa inhibitors.

The clinical adoption of Xa inhibitors has been slow [11]. This can be attributed to a number of factors. Although the new Xa inhibitors are associated with a lower incidence of fatal bleeding and intracranial

hemorrhage, bleeding continues to remain a feared complication due to the lack of effective Xa inhibitor reversal agents. This is especially worrisome in certain populations, such as the elderly or those with gastrointestinal ulcers, where bleeding is particularly dangerous. The current mainstay of treatment for patients who present with acute bleeding on a Xa inhibitor is supportive care with fluid resuscitation, transfusions, source identification, and drug discontinuation [12]. The use of 4-factor prothrombin complex concentrate (PCC) was shown to normalize prothrombin time in human volunteers who received rivaroxaban, although no studies to date have evaluated the use of PCC in patients with acute bleeding [12]. There are certain additional populations in which factor Xa use is contraindicated. These groups include those with prosthetic heart valves (increases risk of thrombus on the valve), pregnant women (lack of clinical data), patients with renal insufficiency (Xa inhibitors have partial renal excretion), and those at the extremes of weight (affects dosing) [12].

Another issue that has slowed adoption of Xa inhibitors is medication adherence. Warfarin has a half-life of around 40 hr, which allows for patients to miss occasional doses without suffering from thromboembolic complications [12]. Xa inhibitors, in comparison, have a half-life of around 12 hr. This short half-life results in the rapid decline of the drug's antithrombotic effect if doses are missed [12]. Last, factor Xa inhibitors are expensive. Even with insurance, the copayments can be prohibitively high, increasing the likelihood of missed doses, splitting pills, and overall non-adherence [12,13].

## CONCLUSIONS

Studies to date demonstrate either superiority or noninferiority of Xa inhibitors to warfarin for the prevention of stroke in patients with atrial fibrillation. There are limitations to the data, however. In addition, there are many downsides to factor Xa

inhibitor use including the absence of an effective reversal agent, rapid decline of antithrombotic effect if doses are missed, and high cost. Taken together, these findings should prompt caution when considering the use of Xa inhibitors for the prevention of stroke in patients with atrial fibrillation.

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