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Efficacy and Safety of Factor Xa Inhibitors in the Prevention of Stroke in Patients with Atrial Fibrillation

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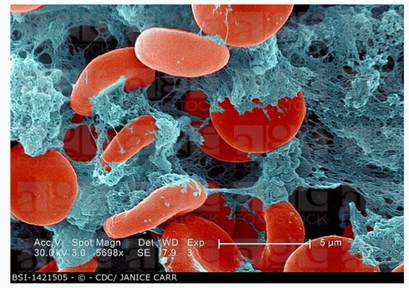

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INTRODUCTION AND BACKGROUND

Atrial Fibrillation (AF) is a cardiac arrhythmia defined as rapid and uncoordinated contractions of the cardiac atria; posing a significant risk for thrombosis formation due to blood stasis, with possible subsequent embolization and ischemic stroke[2]. AF is prevalent among older adults, posing a 1 in 4 (25%) lifetime risk for those over 40[3], and contributing to 15%-20% of all strokes[4]. Disability-Adjusted-Life-Years (DALY) is a metric developed to accurately describe the health burden of a particular disease, and accounts for both number of years of life lost due to premature death (YLL) and number of years of healthy life lost due to disability (YLD)[5]. Strokes are associated with an increased DALY score relative to other serious cardiovascular complications, such as myocardial infarction, as seen in Figure 1[5]. The comparatively high DALY score is due to the disability in survivors of stroke[5]. Due to the high incidence of stroke in patients with AF, and the high DALY associated with stroke, AF is a serious public health concern.

For the last 50 years standard prophylaxis to prevent ischemic stroke in persons with AF has been a vitamin K antagonist (VKA), such as warfarin. While VKA's have dramatically decreased the incidence of ischemic stroke is persons with AF, it has been associated with multiple adverse outcomes, such as massive bleeding due to supratherapeutic anticoagulation and ischemic stroke due to subtherapeutic anticoagulation. VKA administration is complicated by a variable dose response dependent on vitamin K intake and metabolism. It requires frequent laboratory evaluations necessitating complex and time-variable dosing schedules to achieve a narrow therapeutic window[1]. Factor Xa inhibitors (FXa inhibitors) are a new class of anticoagulant, and offer significant advantages over VKA such as simple once-daily dosing and therapeutic window reliability. The efficacy and safety profile of FXa inhibitors compared to VKA is a topic of current research and debate. If FXa inhibitors are found to be superior to VKA, this could change current management guidelines for AF prophylaxis.

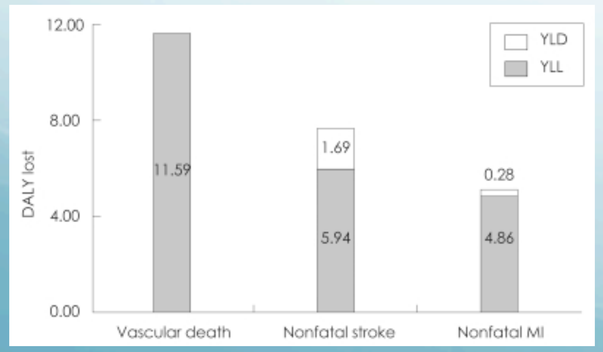

Figure 1: Comparison of DALY Lost Due to Nonfatal MI vs. Nonfatal Stroke [5]

RESULTS

CITATION	STUDY DESIGN	LEVEL OF EVIDENCE	SUMMARY/KEY FINDINGS
Bruins Slot KMH, Berge E (2013)	n = 40,777	Systemic Review (Level 1)	Xa inhibitors have decreased overall bleeding risk and a lower overall mortality than VKAs. Xa inhibitors have a decreased stroke incidence overall compared to VKAs.
Hori et al. (2012)	n = 1,280	Randomized Control Trial (Level II)	Rivaoroxiban is non-inferior to warfarin when comparing bleeding risk and shows a trend towards all-cause stroke reduction compared to warfarin.
Patel et al. (2011)	n = 14,139	Randomized Control Trial (Level II)	Rivaoroxiban and warfarin have similar risks of bleeds. Intercranial and fatal bleeds had a lower incidence with Rivaoroxiban (27 vs. 55)
Connolly et. al. (2013)	n = 508	Randomized Control Trial (Level II)	Betrixaban had a similar rate of bleeding compared to warfarin.
Granger et. al. (2011)	n = 18,201	Randomized Control Trial (Level II)	Apixiban was superior to warfarin in preventing stroke or embolism, caused less bleeding and resulted in lower mortality than warfarin.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Factor Xa inhibitors compared with vitamin K antagonists for prevention of stroke and other systemic embolic events in patient with atrial fibrillation

Patient or population: Patients with atrial fibrillation deemed eligible for long-term anticoagulant treatment
Settings: Hospital-based setting
Intervention: Factor Xa inhibitor[1]
Comparison: Dose-adjusted vitamin K antagonist[2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Warfarin	Factor Xa inhibitors				
Stroke and other systemic embolic events (Follow-up: 12 weeks to 1.9 years)	**32 per 1000**	**25 per 1000** (0 to 38)	**RR 0.82** (0.73 to 0.91)	40777 (9)	⊕⊕⊕⊕ **high**	Most data (84%) from studies with apixaban and rivaroxaban
All strokes (Follow-up: 12 weeks to 1.9 years)	**27 per 1000**	**20 per 1000** (0 to 26)	**RR 0.79** (0.69 to 0.89)	40749 (9)	⊕⊕⊕⊕ **high**	Most data (83%) from studies with apixaban and rivaroxaban
Major bleedings (Follow-up: 12 weeks to 1.9 years)	**46 per 1000**	**39 per 1000** (0 to 55)	**RR 0.90** (0.82 to 0.98)	42078 (10)	⊕⊕⊕◯ **moderate**[3]	Most data (87%) from studies with apixaban and rivaroxaban
Intracranial haemorrhages (Follow-up: 12 weeks to 1.9 years)	**11 per 1000**	**6 per 1000** (0 to 8)	**RR 0.56** (0.45 to 0.70)	39638 (8)	⊕⊕⊕⊕ **high**[4]	Most data (86%) from studies with apixaban and rivaroxaban
All-cause deaths (Follow-up: 12 weeks to 1.9 years)	**51 per 1000**	**45 per 1000** (0 to 66)	**RR 0.89** (0.82 to 0.97)	38924 (6)	⊕⊕⊕⊕ **high**	Most data (87%) from studies with apixaban and rivaroxaban

Figure 2: Summary of Findings for the Main Comparison[1]

METHODS

We performed a literature search of the Cochrane database and PubMed for patients with AF who received a factor Xa anti-coagulant versus those who received vitamin K antagonists for stroke prevention. Our search was limited to English language articles of human randomized controlled trials or systemic reviews published in the last 5 years. Some definitions and statistics from source documents were located by a standard Google search. Only full-text articles that were free of cost were used.

DISCUSSION / CONCLUSIONS

Factor Xa inhibitors are marginally safer and more efficacious than current vitamin K antagonists for the prevention of stroke in patients with AF. Systematic reviews and several double-blinded, randomized control trials have demonstrated that Xa inhibitors have reduced all cause mortality, severe bleeding including intracranial hemorrhages, embolic strokes, and systemic embolisms compared to conventional VKA therapy. Factor Xa inhibitors are statistically superior to VKA, but the data suggests that the number needed to treat is 369 patients to observe a clinical benefit over VKA therapy[1]. The high number needed to treat shows the advantage is marginal. That said, the pharmacodynamic and pharmacokinetic properties of factor Xa inhibitors allow for easier dosing and tighter therapeutic control compared to VKA. Xa inhibitors are easier for patients to take, require less laboratory testing, and are not as readily affected by variations of metabolism, diet and other drugs. Although the data shows that Xa inhibitors are only marginally better than VKA in terms of safety and efficacy, we postulate that the quality of life and ease of use for Xa inhibitors may be reason enough to encourage their use. Future studies are needed to elucidate which, if any, specific Xa inhibitors are better than others.

Recommendations:

1) Atrial fibrillation patients who meet current criteria for anticoagulant therapy should be treated with a factor Xa inhibitor.

2) Conduct further studies on the cost effectiveness and long term benefits of Xa inhibitors compared to VKA.

3) Further research is necessary to determine which, if any, factor Xa inhibitors are better than others.

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