Comparing Direct Factor Xa Inhibitors and Warfarin in the Prevention of Stroke in Patients with Atrial Fibrillation

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Introduction

Cerebrovascular accidents, also known as strokes, are currently the second leading cause of death worldwide with over 6 million deaths and another 5 million patients left with permanent disabilities.[1] While there are many factors associated with an increased risk of stroke, atrial fibrillation is the most prominent.[2] A risk assessment tool, called the $CHADS_2$ score, was created to assess the risk of stroke in patients with atrial fibrillation. A patient's overall score determines whether or not they receive anti-platelet (i.e. aspirin) or anti-coagulant (i.e. warfarin) therapy.[3]

Table 1: $CHADS_2$ stroke risk stratification

Condition	Points
C : congestive heart failure	1
H : blood pressure consistently > 140/90 (or hypertension treated with medication)	1
A : age ≥ 75 years	1
D : diabetes mellitus	1
S_2 : prior stroke, transient ischemic attack or thromboembolism	2

Overall Risk and Recommended Treatment		
$CHADS_2$ Score	**Risk**	**Anticoagulation Therapy**
0	Low	None or daily aspirin
1	Moderate	Daily aspirin or warfarin with INR 2-3
2 or more	High	Warfarin with INR 2-3

Table 1 displays the $CHADS_2$ risk assessment tool used to predict the risk of stroke in patient's with atrial fibrillation. Recommended anti-platelet or anti-coagulant therapy, corresponding to calculated risk, is also displayed.

While warfarin has been the mainstay of therapy for preventing stroke in patients with atrial fibrillation since 1954, there are many limitations to its use.[3] A new class of anticoagulants, the direct factor Xa inhibitors, have recently been approved by the FDA for preventing stroke in patients with atrial fibrillation. As compared to warfarin, these drugs are associated with a quicker onset of action, less drug and food interactions, and do not require coagulation monitoring or dose adjustments. The major disadvantages to the use of these drugs are that they are more expensive than warfarin and there are currently no known agents for drug reversal.[4,5,6]

With this research, we hope to define a new method of preventing stroke with the use of direct factor Xa inhibitors, while evaluating the overall efficacy, advantages and disadvantages as compared to that of warfarin.

Clinical Question

In middle-aged male and female patients with atrial fibrillation, is oral direct factor Xa inhibitor anticoagulant therapy as effective in preventing strokes and major bleeding events as compared to oral warfarin anticoagulant therapy?

Methods

Figure 1: Article Selection Criteria

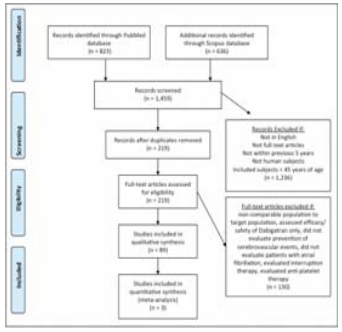

Figure 1 displays a PRISMA flow diagram that outlines the process used to select the 3 final studies to be included in the quantitative analysis.

Results

Table 2: Overview of studies used in quantitative analysis

	Study #1 Apixaban vs. Warfarin	Study #2 Edoxaban vs. Warfarin	Study #3 Rivaroxaban vs. Warfarin
Study Design	Randomized controlled double-blind, double-dummy		
Primary efficacy outcome	Rate of ischemic and hemorrhagic strokes, as well as systemic embolic event		
Primary safety outcome	Rate of intracranial hemorrhage, gastrointestinal bleeding, and major bleeding from another source		
Treatment groups	**Apixaban** (5 mg BID) n = 9,0120 **Warfarin** n = 9,081	**Low-dose edoxaban** (30 mg QD) n = 7,034 **High-dose edoxaban** (60 mg QD) n = 7,035 **Warfarin** n = 7,036	**Rivaroxaban** (20 mg QD) n = 7,131 **Warfarin** n = 7,133

Table 2 summarizes each of the studies used in the quantitative analysis. The dosages of warfarin in each of the studies was dose-adjusted to maintain a therapeutic INR of 2.0 – 3.0 throughout the duration of the study.

Discussion

Table 3: Meta-Analysis of Overall Stroke

Study	Intervention n/N	Control n/N	Relative risk (95% CI)	Weight (%)	Relative risk (95% CI)
Study #1	217/9,120	270/9,081		22.56%	0.80 (0.67 – 0.96)
Study #2					
High-dose	300/7,035	348/7,036		29.01%	0.86 (0.74 – 1.00)
Low-dose	392/7,034	348/7,036		29.01%	1.13 (0.98 – 1.30)
Study #3	183/7,081	233/7,090		19.42%	0.79 (0.65 – 0.95)
Total	1,092/30,270	1,199/30,243		100%	0.91 (0.84 – 0.99)

Table 3 displays the rate of overall stroke with treatment of direct factor Xa inhibitors versus warfarin. Overall stroke includes ischemic stroke, hemorrhagic stroke, and systemic embolism. The overall effect is considered non-significant if the symbol crosses the line of no effect (equal to 1).

Treatment with direct factor Xa inhibitors was associated with a statistically significant decreased rate of overall stroke, as compared to treatment with warfarin. Direct factor Xa inhibitors were also associated with a statistically significant decreased rate of hemorrhagic stroke, ischemic stroke, and systemic embolic events, as compared to treatment with warfarin (data not shown).

Table 4: Meta-Analysis of Major Bleeding

Study	Intervention n/N	Control n/N	Relative risk (95% CI)	Weight (%)	Relative risk (95% CI)
Study #1	432/9,088	581/9,052		29.23%	0.74 (0.66 – 0.84)
Study #2					
High-dose	424/7,012	533/7,012		26.77%	0.80 (0.70 – 0.90)
Low-dose	257/7,002	533/7,012		26.75%	0.48 (0.42 – 0.56)
Study #3	370/7,111	344/7,125		17.25%	1.08 (0.93 – 1.24)
Total	1,483/30,213	1,991/30,201		100%	0.75 (0.70 – 0.80)

Table 4 displays the rate of major bleeding with treatment of direct factor Xa inhibitors versus warfarin. Major bleeding includes intracranial, gastrointestinal, and major bleeding in other locations. The overall effect is considered non-significant if the symbol crosses the line of no effect (equal to 1).

Treatment with direct factor Xa inhibitors was associated with a statistically significant decreased rate of major bleeding events, as compared to treatment with warfarin.

Conclusion

- Direct factor Xa inhibitors are at least as effective, and in some cases more effective, than warfarin in preventing stroke and systemic embolism in patients with atrial fibrillation
- Direct factor Xa inhibitors are associated with significantly decreased rates of major bleeding events
- Apixaban is associated with the most significant reductions in rates of stroke and major bleeding events

Advantages: (of prescribing direct factor Xa inhibitors)
- Quicker onset of action than warfarin
- Less drug and food interactions as compared to warfarin
- Do not require coagulation monitoring
- Do not require dose adjustments

Disadvantages: (of prescribing direct factor Xa inhibitors)
- No known agent for drug reversal
- More expensive than warfarin

Table 6: Cost Comparison of Anticoagulant Therapies

Medication (tablets)	Cost per tablet
Warfarin (2 mg)	$2.15
Apixaban (5 mg)	$6.67
Edoxaban (60 mg)	$11.09
Rivaroxaban (20 mg)	$13.33

Ultimately, the decision to prescribe either a direct factor Xa inhibitor or warfarin to prevent the occurrence of stroke in patients with atrial fibrillation is as much a consideration of the patient's and clinician's comfort, as it is the overall efficacy and safety of the treatment.

References

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