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Abstract

Atrial fibrillation is a common cause for stroke. Vitamin K antagonists such as warfarin are an effective prophylactic medication to prevent stroke in patients with atrial fibrillation. Warfarin, however, has a narrow therapeutic index, reacts with certain foods, increases bleeding risks, and requires frequent monitoring. New medications have been developed to prevent clot formation while avoiding the negative effects of warfarin. The purpose of this study was to compare direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) versus warfarin in stroke prevention, safety, and cost.

The review of literature analyzed studies comparing warfarin and direct factor Xa inhibitors in patients with atrial fibrillation. Study outcomes included stroke prevention, bleeding risks, and cost. Analysis on antidote/reversal agents were also examined.

Direct factor Xa inhibitors decreased stroke compared with warfarin with an odds reduction of 0.81 and decreased intracranial hemorrhages with an odds reduction of 0.56 (Bruins & Berge, 2013). Direct factor Xa inhibitors were more cost effective, but with higher out of pocket expense. Direct factor Xa inhibitors have no reversal agent. Despite no antidote, research showed lower rates of fatal bleeding deaths associated with direct factor Xa inhibitor use compared to warfarin.

Introduction

Atrial fibrillation is a common abnormal heart rhythm leading to increased thrombus formation and stroke risk. Eckman (2016) states:

> Atrial fibrillation (AF) is the most common significant cardiac rhythm disorder and is also the most powerful common risk factor for stroke: about 15% of all strokes in the U.S. are attributable to AF. (p. 234)

Vitamin K antagonists have long been used as an effective prophylactic medication to prevent thrombus formation in patients with atrial fibrillation. According to Santarpia, Curcio, Sibilio, and Indolfi (2015), warfarin's "effectiveness is proven by 64% relative risk reduction of stroke compared with placebo, and it also shows superior results to aspirin and to aspirin plus clopidogrel" (p. 914). Warfarin, while effective at preventing thrombi, has several drawbacks associated with its use. The direct factor Xa inhibitors have been developed in an attempt to effectively anticoagulate patients while avoiding the negative aspects of warfarin.

Statement of the Problem

Warfarin is an effective anticoagulant but has several drawbacks to its use including a narrow therapeutic index, reaction with foods containing vitamin K, variable pharmacokinetics/pharmacodynamics and increased risk of intracranial hemorrhage. These factors led to the development of new medications such as the direct factor Xa inhibitors.

Research Questions

In patients with atrial fibrillation, do direct factor Xa inhibitors decrease the risk of stroke and bleeding, and are the direct factor Xa inhibitors cost effective when compared to warfarin? Are direct factor Xa inhibitors reversible?

Literature Review

An online database search of PubMed and Cochrane was performed for scholarly articles related to direct factor Xa inhibitor use versus warfarin in nonvalvular atrial fibrillation. Specific searches included efficacy of factor Xa inhibitors versus warfarin for stroke prevention, safety, cost, and reversibility.

Atrial fibrillation is a risk factor for stroke and a commonly used grading scale to assess stroke risk in atrial fibrillation is the CHA_2DS_2-VASc score.

Table 1: CHA_2DS_2-VASc Risk Score for assessing risk of stroke and for selecting antithrombotic therapy for patients with atrial fibrillation.

CHA_2DS_2-VASc Risk Score	
Heart failure or LVEF ≤ 40% 1	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke, transient ischemic attack, or thromboembolism	2
Vascular disease (previous myocardial infarction, peripheral artery disease, or aortic plaque)	1
Age 65–74 years	1
Sex category (ie, female sex)	1
Maximum score	9

Adjusted stroke rate according to CHA_2DS_2-VASc score

CHA_2DS_2-VASc Score	Patients (n=7329)	Adjusted stroke rate (%/year)
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7 %
9	14	15.2%

CHA_2DS_2-VASc score = 0: recommend no antithrombotic therapy

CHA_2DS_2-VASc score = 1: recommend antithrombotic therapy with oral anticoagulation or antiplatelet therapy but preferably oral anticoagulation.

CHA_2DS_2-VASc score = 2: recommend oral anticoagulation

Papadakis et al., 2015, p. 386

Stroke Prevention:

- Bruins and Berge (2013) completed a systematic review and found a statistically significant reduction of all types of strokes for the factor Xa inhibitors compared to warfarin (odds ratio 0.78, 95% CI 0.69 to 0.89).
- Granger et al. (2011) compared apixaban and warfarin in stroke prevention. Results demonstrated 1.60% had stroke or systemic embolism on warfarin compared to 1.27% on apixaban (hazard ratio for apixaban, 0.79, 95% CI, 0.66-0.95, P<0.001 for noninferiority, P=0.01 for superiority).
- Patel et al. (2011) compared rivaroxaban and warfarin in stroke prevention. Results demonstrated rivaroxaban had a stroke or systemic embolism occurrence rate of 1.7% per year compared to 2.2% on warfarin (hazard ratio for rivaroxaban group, 0.79, 95% CI, 0.66 to 0.96, P<0.001 for noninferiority).
- Giugliano et al. (2013) compared edoxaban and warfarin for stroke reduction and found high-dose edoxaban and warfarin had an equal ischemic stroke risk of 1.25% per year (hazard ratio 1.00, 95% CI, 0.83 to 1.19, P<0.97).

Bleeding Risks:

- Bruins and Berge (2013) found factor Xa inhibitors decreased intracranial hemorrhage when compared to warfarin (odds ratio 0.51, 95% CI, 0.41-0.64, I^2=0%). Factor Xa inhibitors decreased bleeding risks versus warfarin with high heterogeneity (odds ratio 0.89, 95% CI, 0.81-0.98, I^2=81%).
- Miller, Grandi, Shimony, Filion, and Eisenberg (2012) demonstrated the new oral anticoagulants reduced rates of intracranial hemorrhage (RR, 0.49, 95% CI, 0.36-0.66). Rivaroxaban had similar major bleeding risks while apixaban had less major bleeding risks when compared to warfarin (RR, 0.88, 95% CI, 0.71-1.09). Rivaroxaban was associated with higher gastrointestinal bleeding (RR 1.46, 95% CI, 1.19-1.78).
- Giugliano et al. (2013) demonstrated warfarin had a major bleeding occurrence rate of 3.43% per year while 60 mg edoxaban had major bleeding occurrence rate of 2.75% per year (hazard ratio, 0.80, 95% CI, 0.71-0.91, P<0.001). High-dose edoxaban was associated with higher rates of gastrointestinal bleeding (1.51% versus 1.23% in the warfarin group) (hazard ratio, 1.23, 95% CI, 1.02-1.50, P Value=0.03).

Cost:

- Amin et al. (2014) demonstrated cost savings with the direct factor Xa inhibitors apixaban ($493) and rivaroxaban ($358) for stroke prevention. In cost avoidance, excluding intracranial hemorrhage, apixaban saved $752 while rivaroxaban cost more than warfarin by $502.
- Out of pocket expenses depends on insurance coverage. With no insurance the cost of rivaroxaban is $347 for 20 mg tabs, $342 for 5 mg apixaban tabs, and $290 for 60 mg edoxaban tabs. The cost of warfarin is $13 for 5 mg tabs (Anticoagulants, 2015).

Reversibility:

- Despite no reversal agent Caldeira et al. (2015) completed a systematic review and meta-analysis comparing hemorrhage related deaths of the novel oral anticoagulants (NOACs) compared with warfarin. Results demonstrated the NOACs had a 47% odds reduction for fatal bleeds in patients with atrial fibrillation (odds reduction, 0.53, 95% CI, 0.42-0.68, I^2=0%, x^2=3.85, $P_{heterogeneity}$=0.43).

Discussion

Direct factor Xa inhibitors are efficacious at preventing both ischemic and hemorrhagic stroke. Apixaban is superior to warfarin in stroke prevention while rivaroxaban and edoxaban are non-inferior to warfarin. All three direct factor Xa inhibitors cause less intracranial hemorrhage. Apixaban had less bleeding risks associated with its use compared to warfarin. Rivaroxaban had similar bleeding rates as warfarin but increased gastrointestinal bleeding. Edoxaban demonstrated less overall bleeding risk when compared to warfarin except increased gastrointestinal bleeding in the high-dose form. No direct comparison studies of the direct factor Xa inhibitors have been performed. Out of pocket costs of the direct factor Xa inhibitors is high, however, direct factor Xa inhibitors provided an overall cost savings with reduced number of strokes and intracranial hemorrhages. The direct factor Xa inhibitors lack a reversal agent, however, the direct factor Xa inhibitors are associated with lower death rates when compared to warfarin.

Table 2:

Efficacy and Safety Randomized Trials Comparing NOACs and Warfarin in Patients With NVAF				
	RE-LY (dabigatran)	ROCKET-AF (rivaroxaban)	ARISTOTLE (apixaban)	ENGAGE AF-TIMI 48 (edoxaban)
No. of patients	18,113	14,264	18,201	21,105
Study population	Patients with NVAF $CHADS_2$ score ≥1 (mean 2.1) Mean age: 72 years	Patients with NVAF $CHADS_2$ score ≥2 (mean 3.5) Mean age: 73 years	Patients with NVAF $CHADS_2$ score ≥1 (mean 2.1) Mean age: 70 years	Patients with NVAF $CHADS_2$ score ≥2 (mean 2.8) Mean age: 72 years
Study design	Double-blind randomized, non-inferiority trial	Double-blind randomized, non-inferiority trial	Double-blind randomized, non-inferiority trial	Double-blind randomized, non-inferiority trial
Dosage	150 mg (110 mg) twice daily	20 mg (15 mg) once daily	5 mg (2.5 mg) twice daily	60 mg (30 mg) once daily
Control drug	Warfarin (INR 2–3) TTR 64%	Warfarin (INR 2–3) TTR 55%	Warfarin (INR 2–3) TTR 62%	Warfarin (INR 2–3) TTR 68.4%
Primary efficacy outcome	Stroke (ischemic or hemorrhagic) or systemic embolism	Stroke (ischemic or hemorrhagic) or systemic embolism	Stroke (ischemic or hemorrhagic) or systemic embolism	Stroke (ischemic or hemorrhagic) or systemic embolism
Principal safety endpoint	Major bleeding	Composite of major and non-major bleeding	Major bleeding	Major bleeding
Results	Efficacy of dabigatran 110 mg vs. warfarin (0.91; 95% CI, 0.74–1.11; P<0.001 for non-inferiority) Efficacy of dabigatran 150 mg vs. warfarin (0.66; 95% CI, 0.53–0.82; P<0.001 for superiority) Safety of dabigatran 110 mg vs. warfarin (0.80; 95% CI, 0.69–0.93; P=0.003) Safety of dabigatran 150 mg vs. warfarin (0.93; 95% CI, 0.81–1.07; P=0.31)	Efficacy of rivaroxaban 20 mg vs. warfarin (0.88; 95% CI, 0.74–1.03; P<0.001 for non-inferiority; P=0.12 for superiority) Safety of rivaroxaban 20 mg vs. warfarin (1.03; 95% CI, 0.96–1.11; P=0.44)	Efficacy of apixaban 5 mg vs. warfarin (0.79; 95% CI, 0.66–0.95; P<0.001 for non-inferiority; P=0.01 for superiority) Safety of apixaban 20 mg vs. warfarin (0.69; 95% CI, 0.60–0.80; P<0.001)	Efficacy of edoxaban 60 mg vs. warfarin (0.87; 97.5% CI, 0.73–1.04; P=0.08 for superiority Efficacy of edoxaban 30 mg vs. warfarin (1.13; 97.5% CI, 0.96–1.34; P=0.10 for superiority Safety of edoxaban 60 mg vs. warfarin (0.80; 95% CI, 0.71–0.91; P<0.001) Safety of edoxaban 30 mg vs. warfarin (0.47; 95% CI, 0.41–0.55; P<0.001)

ARISTOTLE, Apixaban for reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CI, confidence interval; ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48; NVAF, mon-valvular atrial fibrillation; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy trial; ROCKET-AF, Rivaroxaban Once-daily, oral direct factor Xa Inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation; TTR, mean percent of time in the therapeutic range. Other abbreviations as in Table 3.

Santarpia et al., 2015, p. 918

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Applicability to Clinical Practice

- Direct factor Xa inhibitors are effective in preventing stroke and have similar or reduced bleeding risks when compared to warfarin. Direct factor Xa inhibitors decrease the risk of intracranial hemorrhage.
- Direct factor Xa inhibitors have favorable pharmacokinetics and pharmacodynamics when compared to warfarin.
- Cost is a major concern with out of pocket expenses of direct factor Xa inhibitors far exceeding that of warfarin.
- Despite no reversal agent, direct factor Xa inhibitors cause less bleeding deaths when compared with warfarin.

Table 3:

	Rivaroxaban	Apixaban	Edoxaban
Target	Factor Xa	Factor Xa	Factor Xa
Oral bioavailability	80–100%	50%	62%
Time for peak effect	2–4 h	3–4 h	1–2 h
Plasm half-life	5–13 h	12 h	10–14 h
Metabolism/ elimination	Via CYP450, Via P-gp transporter/35% renal excretion	Via CYP450, Via P-gp transporter/27% renal excretion	Via CYP450, Via P Gp transporter/50% renal excretion
Drug interaction	Strong CYP3A4 and P-gp inhibitors: ↑↑↑ NOAC exposure *Azole-antimycotics - ketoconazole - itraconazole - voriconazole - posaconazole *HIV protease inhibitors *Dronedarone — Controindicated association	Strong CYP3A4 and P-gp inhibitors: ↑↑↑ NOAC exposure Azole-antimycotics - ketoconazole - itraconazole - voriconazole - posaconazole HIV protease inhibitors — Controindicated association	
	CYP3A4 inducers: ↓ NOAC exposure - rifampicin - phenytoin - carbamazepine - phenobarbital - *Hypericum perforatum* — Use association with caution	CYP3A4 inducers: ↓ NOAC exposure - rifampicin - phenytoin - carbamazepine - phenobarbital - *Hypericum perforatum* — Use association with caution	CYP3A4 inducers: ↓ NOAC exposure - rifampicin — Use association with caution
Dosage in NVAF	20 mg daily	5 mg twice daily	60 mg daily
Dose monitoring	–	–	–

CYP450, cytochrome P 450; CYP3A4, cytochrome P 450 3A4; INR, international normalized ratio; NOAC, non-vitamin K antagonist oral anti-coagulant; P-gp, P-glycoprotein.

	Warfarin/Phenprocoumon/Acenocoumarol
Target	Vitamin K epoxide reductase
Oral bioavailability	>90%/>90%/60%
Time for peak effect	48–72 h/72–96 h/36–48 h
Plasm half-life	36–42 h/120–200 h/8–14 h
Metabolism/ elimination	Via CYP450, Renal 90%/mainly hepatic/renal 60%, fecal 30%
Drug interaction	400 known interactions
Dosage in NVAF	According to INR (INR 2–3)
Dose monitoring	INR values

Santarpia et al., 2015, p. 917

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