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New Age Anticoagulants: A Safer and More Effective Alternative to Warfarin?

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Abstract

Atrial fibrillation is the most common sustained heart rhythm in the United States with estimated prevalence rates of 8.8/100 (Wolf, Abbott, & Kannel, 1991). The largest risk for patients with atrial fibrillation is that of ischemic stroke from embolization of an atrial clot, thus the long standing treatment for this arrhythmia is aggressive anticoagulation. For decades this has been accomplished with the use of warfarin, however, the increased risk of hemorrhage combined with the inconvenience of weekly blood testing has prompted the development of potentially safer and more effective alternatives. A systematic review of the literature identified studies that examined the safety and efficacy of direct thrombin and factor Xa inhibitors compared with traditional warfarin therapy. It was found that the new anticoagulants reduce the incidence of stroke and thromboembolism without increasing the risk of major hemorrhage when compared to warfarin. This provides health care providers another option to safely anticoagulate patients diagnosed with non-valvular atrial fibrillation without the burden of PT/INR monitoring.

Introduction

- Atrial fibrillation is the most common sustained heart rhythm in the United States
- Largest risk for patients with atrial fibrillation is that of ischemic stroke from embolization of an atrial clot.
- Many food-drug and drug-drug interactions that can greatly influence the pharmacodynamics of warfarin leading to an extremely variable dose response curve, and a constant need for laboratory monitoring to ensure adequate anticoagulation
- Several large, phase III, randomized controlled trials that have investigated the safety and efficacy of these newer anticoagulants compared to traditional warfarin therapy

Statement of the Problem

- Warfarin has long been recognized as an effective therapy to prevent the occurrence of stroke and systemic embolism; however, the risk for bleeding, the variable dose-response curve, and the inconvenience of routine monitoring have prompted the development of safer, more effective alternatives.

Research Questions

- In patients with non-valvular atrial fibrillation, are the novel, oral anticoagulants a safer and more effective option for the prevention of stroke and systemic embolism?
- In patients that are anticoagulated with any novel anticoagulant, is there a reversal agent available in the event of major trauma, bleeding, or the need for surgery?
- Are novel anticoagulants a cost effective option compared to warfarin in patients with non-valvular atrial fibrillation?

Literature Review

- Primary end point of stroke or systemic embolism was lower with novel anticoagulants compared with warfarin
- Risk of death from any cause was lower with all novel anticoagulants than with warfarin
- Significant reduction in hemorrhagic stroke with novel anticoagulants compared to warfarin

Table 1. Main Study Characteristics

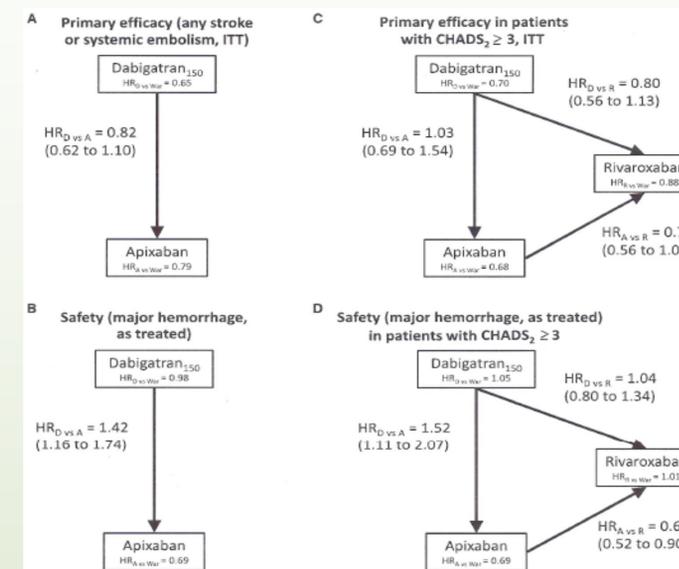
Study	Drug	No. of Patients	Masking	Test	Analysis (Primary Outcome)	Follow-up mo.
RE-LY	Dabigatran	12098	Open label	Noninferiority	ITT	300
ROCKET AF	Rivaroxaban	14264	Double blind	Noninferiority	ITT	20
ARISTOTLE	Apixaban	18201	Double blind	Noninferiority	ITT	10

Abbreviations: ARISTOTLE, Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; ITT, intention to treat; RE-LY, Randomized Evaluation of Long-Term Anticoagulant Therapy; ROCKET AF, An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation. ^a RE-LY trial included 18113 patients; there were 6015 patients excluded because they belonged to the low-dose study branch.

Table 2. Baseline Characteristics of the Patients

Characteristics	RE-LY		ROCKET AF		ARISTOTLE	
	Dabigatran	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin
Male (%)	63.2	63.2	60.3	60.3	60.5	65
Age (y)	71.5	71.6	73	73	70	70
Aspirin at entry (%)	38.7	40.6	36.3	36.3	31.3	30.5
Vitamin K antagonist at entry (%)			62.3	62.5		
Long-term vitamin K antagonist therapy (%)	50.2	48.6			57.1	57.2
Risk factors for stroke ≥3 (%)	32.6	32.1	87	86.9	30.2	30.2
Previous stroke, TIA, or both (%)	20.3	19.8				
Previous stroke, TIA, or embolism (%)			54.9	54.6	19.2	19.7
Hypertension (%)	78.9	78.9	90.3	90.8	87.3	87.6
Diabetes (%)	23.1	23.4	40.4	39.5	25	24.9
LVD or heart failure (%)	31.8	31.9	62.6	62.6	35.5	35.4

Abbreviations: ARISTOTLE, Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; LVD, left ventricular dysfunction; RE-LY, Randomized Evaluation of Long-Term Anticoagulant Therapy; ROCKET AF, An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients with Non-Valvular Atrial Fibrillation; TIA, transient ischemic accident



Discussion

- Currently no laboratory test to monitor the effects of any novel anticoagulant.
- In patients with renal insufficiency, half life of drug is lengthened
- No antidote to counteract the effects of direct thrombin or factor Xa inhibitors.
- All authors indicated the need for an adequately powered head to head study of direct thrombin inhibitors versus factor Xa inhibitors.
- Current literature indicates cost effectiveness but still many more questions than answers.

Applicability to Clinical Practice

- The issues of cost, safety, and efficacy must be continually investigated by researchers and evaluated by providers in order to optimize outcomes for any patients requiring anticoagulation.
- The use of any novel anticoagulant or warfarin is clearly better than the avoidance of any anticoagulation in patients with atrial fibrillation
- Consideration should be given to individual patients stroke and bleeding risk factors, potential financial burden, desired clinical effect, and patient/family concerns prior to initiation or alteration of anticoagulation.

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