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Is Dabigatran Superior to Warfarin in Treating Patients with Atrial Fibrillation?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not Dabigatran is superior to Warfarin in patients with atrial fibrillation.

STUDY DESIGN: Review of three English language primary studies published in 2007, 2009, and 2010.

DATA SOURCES: Three randomized control trials found using Cochrane Database.

OUTCOME(S) MEASURED: Outcomes measured were presence or absence of stroke or systolic embolism and intracranial hemorrhage. The absence of these events preserved neurologic function in patients with atrial fibrillation.

RESULTS: In both VKA-naïve and VKA-experienced patients, Dabigatran 150 mg was superior to Warfarin in both the prevention of stroke and systolic embolism and the prevention of intracranial hemorrhage. Thromboembolic events were most common in the group receiving Dabigatran 50 mg alone. When comparing Dabigatran and Warfarin without including previous VKA status, Dabigatran 150 mg is superior to Warfarin in prevention of stroke and systolic embolism, while Dabigatran 110 mg is noninferior. Hemorrhagic stroke rates were similar in both dose groups.

CONCLUSIONS: It is concluded that Dabigatran is superior to Warfarin in 150 mg dose and noninferior to Warfarin in 110 mg dose. Further research is warranted to determine other indications for treatment with Dabigatran.

KEY WORDS: Dabigatran, Warfarin, atrial fibrillation, stroke

INTRODUCTION

Atrial fibrillation is the most common chronic cardiac arrhythmia, affecting 10% of people over age 80 years. However, because atrial fibrillation is commonly asymptomatic, it is estimated that actual incidence rates may be double the reported rate[6]. It is estimated that the annual cost of treating atrial fibrillation is $26 billion[5]. About 350,000 hospitalizations, 5.0 million office visits, 276,000 ED visits and 234,000 OPD annually in the United States are attributed to atrial fibrillation[2].

Atrial fibrillation may occur without cardiac disease or in the presence of valvular heart disease, dilated cardiomyopathy, hypertension, or coronary heart disease. It may also have an acute, direct cause such as hyperthyroidism or alcohol intoxication. It is much more common in adults and very rare in children. Cases in children are typically due to congenital cardiac abnormalities such as WPW syndrome[6].

Atrial fibrillation is a condition in which there is rapid, irregular atrial activation with irregular ventricular response. The rate is usually between 120-160 bpm, but can be as high as >200 bpm[6]. The cause of atrial fibrillation remains commonly debated, but appears to be related to the complex interaction between the drivers of electrical impulse and the complex that potentiates the maintenance of wavelets of reentry[6]. Atrial fibrillation is significant clinically because it is related to the loss of atrial contractility, results in inappropriate fast ventricular response, and the loss of atrial contractility and emptying results in the risk of clot formation and subsequent thromboembolic events[6].

For many years, Warfarin was the gold standard treatment in prevention of thromboembolic events in patients with atrial fibrillation. Warfarin with an international normalized ratio (INR) of 2.0-3.0 has been recommended for patients with frequent or

sustained AF or with risk factors for thromboembolism. These risk factors include age > 65, history of congestive heart failure, diabetes mellitus, hypertension, left ventricular dysfunction, and left atrial enlargement[6].

Dabigatran is a direct thrombin inhibitor with a half-life of 12-17 hours. It does not require serum monitoring as Warfarin does. It was evaluated in a pilot trial of patients with atrial fibrillation with a goal of preventing venous thromboembolism. The results were found to be promising and Dabigatran was subsequently explored further as an alternative treatment for patients with nonvalvular atrial fibrillation[1].

OBJECTIVE

The objective of this selective EBM review is to determine whether or not Pradaxa (Dabigatran) is a more effective treatment of atrial fibrillation than Warfarin.

METHODS

The studies included in this selective EBM review involved patients over 65 years old with atrial fibrillation, LVEF<40%, heart failure, and some variation of CAD. Exclusion criteria included valvular disorders, kidney or liver dysfunction, pregnancy, and recent stroke. The intervention of Dabigatran 50, 110, 150, or 300 mg was compared against Warfarin titrated to a therapeutic INR level of 2.0-3.0. Outcome measured is preservation of neurologic function in patients with atrial fibrillation. This outcome is measured by rates of stroke or systolic embolism and intracranial hemorrhage in these patients. Studies compared are randomized controlled trials that are double-blinded with Dabigatran and open label with Warfarin out of necessity.

Table 1: Demographics & Characteristics of Included Studies

Study	Type	# pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Connolly (2009)	RCT	18,113	>65	-Prev CVA/TIA -LVEF <40% >Class II HF sx within 6 months -Age >75 or 65-74 plus DM, HTN, or CAD	-valvular disorder -recent stroke -increased hemorrhage risk -CCl<30 ml/min -liver disease -pregnancy	0	Dabigatran 110 and 150 mg BID
Ezekowitz (2007)	RCT	18,113	>75	AF with CAD and at least 1 of: -HTN w/meds -DM -HF sx -LVEF<40% -Previous CIA/TIA -Age > 75	-mitral stenosis -prosthetic heart valve -planned cardioversion -MI within 1 month -Recent CVA/TIA -cardiac stent <6 months -GFR<30 mL/min -liver dysfunction -pregnancy -investigational drug use <30 days	0	Dabigatran 50, 150, or 300 mg alone or with 81 or 325 mg ASA
Wallentin (2010)	RCT	18,113	>65	-Previous CVA/TIA -LVEF<40% -Class II HF sx within 6 months -Age>75 or 65-74 plus HTN, DM, or CAD	-valvular disorder -recent stroke -increased hemorrhage risk -CCl<30 ml/min -liver disease -pregnancy	0	Dabigatran 110 and 150 mg

Data sources include PubMed and Cochrane databases. Searches were conducted using keywords “atrial fibrillation”, “Pradaxa”, and “Dabigatran” between 2011 and 2012. All articles were published in English between 2007 and 2010 and were selected

based on relevance to patients with atrial fibrillation. Statistics used include p-value, RRR, ARR, and NNT. Inclusion criteria included previous CVA/TIA, LVEF<40%, age > 65 and CAD. Exclusion criteria included valvular heart disorders, recent stroke, pregnancy, and kidney or liver dysfunction.

OUTCOMES

All outcomes were considered in relationship to patient preservation of neurologic function, the POEM that was addressed. Favorable outcomes included decreased rate of stroke and systolic embolism as well as decreased rates of intracranial bleeding. Unfavorable outcomes included increased rate of stroke, systolic embolism, or intracranial bleeding.

Stroke was defined as the sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery and characterized as ischemic, hemorrhagic, or unspecified. Intracranial hemorrhage consisted of hemorrhagic stroke and subdural or subarachnoid hemorrhage. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ, documented by means of imaging, surgery, or autopsy[1].

Outcomes were adjudicated by two investigators who were unaware of the treatment assignments. Transient ischemic attacks were further investigated to insure that they were not strokes. Questionnaires were routinely administered to participants in order to detect possible unreported events[1].

In the study comparing Dabigatran versus Warfarin in Vitamin K Naïve and Experienced patients, patients who are Vitamin K antagonist naïve or Vitamin K antagonist experienced were placed on treatments of either D110 (Dabigatran 110 mg)

twice per day, D150 (Dabigatran 150 mg) twice per day, or Warfarin titrated to an INR of 2.0-3.0. Rates of strokes or systolic embolism, intracranial bleeding, or life threatening bleeding were compared across these groups[4].

In the study Warfarin vs Dabigatran in patients with Atrial Fibrillation, Dabigatran was administered in a blinded fashion in doses of 110 or 150 mg while Warfarin was administered in an unblended fashion and titrated to an INR of 2.0-3.0. The primary study outcome was stroke, while the primary safety outcome was major hemorrhage[1].

In the study comparing Warfarin and Dabigatran with or without concomitant Aspirin, participants were randomized to receive blinded doses of 50, 150, or 300 mg Dabigatran twice daily alone or combined with 81- or 325- mg aspirin or open-label warfarin administered to achieve an INR of 2 to 3 for 12 weeks[3]. Rates of bleeding and thromboembolic events were recorded and compared between these groups.

RESULTS

In the study comparing Warfarin and Dabigatran in Vitamin K Naïve and Experienced patients, D110 and D150 were compared to Warfarin in patients that are VKA naïve and VKA experienced. In the D110 group, both VKA naïve and experienced patients had stroke and systolic embolism rates similar to Warfarin (RR=0.93, 95% CI, 0.7 to 1.25; P=0.65 and RR= 0.87; 95% CI, 0.66 to 1.15; P=0.32, respectively). However, there was a statistically significant decrease in stroke and systolic embolism in patients taking D150 versus Warfarin, in both VK naïve (RR=0.63; 95% CI, 0.46 to 0.87; P=0.005) and VK experienced patients (RR=0.66; 95% CI, 0.49 to 0.89; P=0.007).

In terms of intracranial bleeding, VKA-naïve (RR=0.27, 95% CI, 0.14 to 0.52; P<0.001) and VKA-experienced (RR=0.32; 95% CI, 0.18 to 0.56; P<0.001) patients taking D110 had lower rates of bleeding when compared with patients taking Warfarin.

When evaluating treatment effects of D150 versus Warfarin in VKA naïve patients, the RRR was 0.366%, ARR was 0.62% and NNT was 161. The D150 VKA naïve group had a stroke/systolic embolism rate of 1.07%, while the Warfarin group had 1.69% of patients experience stroke or systolic embolism. When evaluating the same groups for intracranial bleeding rates, 0.33% of the D150 group experienced intracranial bleeding, while 0.73 of the Warfarin group experienced intracranial bleeding. The RRR was 0.55% ARR was 0.40%, and NNT was 250.

Discontinuation of therapy was less common in VKA-experienced patients in the D110 and Warfarin groups. The discontinuation rates were similar between VKA naïve and experienced patients in the D150 group[1].

Table 2: Stroke, Systolic Embolism, and Bleeding Rates in Ezekowitz et al. 2010

	D110	D150	Warfarin
Stroke or systolic embolism			
VKA naïve	1.57%	1.07%	1.69%
VKA experienced	1.51%	1.15%	1.74%
Intracranial Bleeding			
VKA naïve	0.19%	0.33%	0.73%
VKA experienced	0.26%	0.32%	0.79%

In the study comparing Dabigatran vs Warfarin in patients with atrial fibrillation, stroke or systolic embolism occurred in 182 patients taking D110 (1.53% per year), 134

patients taking D150 (1.11% per year) and 199 patients taking Warfarin (1.69% per year). The 150 mg dose of Dabigatran was found to be superior to Warfarin (relative risk, 0.66; 95% CI, 0.53 to 0.82; P<0.001). Both D110 and D150 were noninferior to Warfarin.

Rates of hemorrhagic stroke were 0.38% per year in the Warfarin group. By comparison, the Dabigatran 110 mg group rates were 0.12% per year (relative risk with Dabigatran, 0.31; 95%CI, 0.17 to 0.56; P<0.001). The Dabigatran 150 mg hemorrhagic stroke rate was 0.10% per year (relative risk, 0.26; 95% CI, 0.14 to 0.49; P<0.001).

Dabigatran 150 mg reduced the systemic embolism or stroke risk when compared with Dabigatran 110 mg. It mainly reduced the risk of thrombus formation and ischemic stroke. Hemorrhagic stroke rates were similar in both dose groups. There was not a statistically significant difference in death rate between the two groups.

Evaluation of treatment effects concerning prevention of stroke and systolic embolism in the D150 group versus the Warfarin group showed an RRR of 0.34%, ARR of 0.58%, and NNT was 2. When evaluating treatment effects concerning hemorrhagic stroke in the same groups, RRR was 0.74%, ARR was 0.28%, and NNT was 357.

In terms of adverse events, dyspepsia was the only symptom that was significantly more common in subjects receiving Dabigatran in comparison with Warfarin. The Warfarin group reported dyspepsia at a rate of 5.8%, while the Dabigatran 110-mg and 150-mg groups reported dyspepsia at rates of 11.8% and 11.3%, respectively. Elevations of LFTs greater than 3 times the upper limit of normal range did not occur more frequently in either Dabigatran group than in the Warfarin group[3].

In the article comparing Warfarin versus Dabigatran with or without concomitant Aspirin, patients had a median of 3 risk factors for stroke. The primary outcome in this

particular study was major bleeding events. These events were limited to the group treated with Dabigatran 300 mg plus Aspirin (4 of 64). There was a statistically significant difference between bleeding rates in this group and bleeding rates in the group taking Dabigatran 300 mg alone (0 of 105, $p<0.02$). The frequency of bleeding in patients taking Dabigatran 50 mg was significantly less than the group taking Warfain with an INR between 2.0-3.0 ($p=0.044$). There were also differences in bleeding rates between the different Dabigatran doses. In the Dabigatran 300 mg group, 37 of 169 had bleeding events whereas in the 50 mg group, 7 of 107 had bleeding events ($p=0.0002$). In the Dabigatran 150 mg group, 30 of 169 had bleeding events when compared with 7 of 107 in the 50 mg group ($p=0.01$)[3].

Two patients had systemic thromboembolic events in this study. Both of the participants received the 50 mg dose of Dabigatran[3].

When considering the treatment effects of Dabigatran 150 mg alone versus Warfarin alone, the RRR was 0.12%, ARR was 2.1% and NNT was 48. In the 150 mg Dabigatran group, 15% of patients had either bleeding or thromboembolic events. In the Warfarin group, 17.1% experienced either one of the major outcomes in this study.

Table 3: Rates of bleeding and thromboembolic events in patients receiving Dabigatran alone or combined with aspirin versus Warfarin alone.

Dabigatran dose BID	Aspirin dose	#pts	Bleeding events (major)	Thromboembolic events	Total
50	0	59	0	0	2 (2.4%)
50	81	21	0	1 (4.8%)	2 (9.5%)
50	325	27	0	1 (3.7%)	3 (11.1%)
150	0	100	0	9 (9%)	15 (15%)
150	81	36	0	2 (5.6%)	8 (22.2%)
150	325	33	0	2 (6.1%)	7 (21.2%)
300	0	105	0	6 (5.7%)	14 (32.4%)
300	81	34	1 (2.9%)	5 (14.7)	11 (32.4%)
300	325	30	3 (10%)	6 (20%)	14 (46.7%)
Warfarin	0	70	0	4 (5.7%)	12 (17.1%)

More patients discontinued treatment in the Dabigatran group than in the Warfarin group due to adverse events. The most common adverse event reported was gastrointestinal discomfort such as nausea, vomiting, or diarrhea while taking Dabigatran. Most of the adverse symptoms were mild and did not require discontinuation of treatment[3].

DISCUSSION

One of the most serious complications of Warfarin therapy has been an increased risk for intracranial hemorrhage, especially hemorrhagic stroke. Dabigatran offers a two-thirds reduction in risk for intracranial hemorrhage, without increasing the risk for thromboembolic events[1].

A factor contributing to the benefits of Dabigatran may be the twice-daily dosing and shorter half-life. This enables the drug to have more stable anticoagulant effects throughout the day. This offers a large benefit in comparison to the difficult to control anticoagulant effects of Warfarin. Warfarin broadly inhibits coagulation, inhibiting factors II, VII, IX, and X as well as protein C and S. By contrast, Dabigatran selectively inhibits thrombin, which may enable the drug to prevent thrombosis while maintaining other aspects of coagulation and potentially preventing major bleeding[1].

A limiting factor for patients with atrial fibrillation is the cost of Dabigatran compared to the cost of Warfarin. Because the majority of patients treated for atrial fibrillation are >65 years old, the majority of them receive Medicare benefits. When Dabigatran was first released, the cost for Medicare patients was around $250 per month, while the cost of Warfarin was about $4 per month. Since its release, Dabigatran is now covered under Medicare Part D and costs $25-$40 per month. While it remains more

expensive than Warfarin, it is now considered to be much more affordable and patients are able to weigh the increased cost against potential other benefits such as decreased stroke risk and the lack of serum monitoring.

A possible limitation of this study is the open-label administration of Warfarin, preventing it from being completely double-blinded. This was necessitated by the INR monitoring associated with Warfarin treatment. However, the evaluation of outcome events remained blinded. Therefore, the risk for bias was significantly reduced.

CONCLUSIONS

Based on these three studies, it is concluded that Dabigatran is superior to Warfarin in the treatment of patients with atrial fibrillation. Dabigatran 110-mg and 150-mg groups consistently had lower rates of stroke and intracranial hemorrhage when compared with the Warfarin group. Therefore, neurologic function was preserved more frequently in the Dabigatran groups. Future research is warranted to evaluate whether or not Dabigatran is superior to Warfarin in preventing deep venous thrombosis (DVT) and subsequent pulmonary embolism (PE). To date, Warfarin remains the treatment of choice because Dabigatran does not have this indication for treatment.

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