The Efficacy of Dabigatran versus Warfarin for Stroke Prevention in Patients With Atrial Fibrillation: Systematic Review

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Conclusion: Now that it is approved by the FDA, dabigatran offers significant improvements in anticoagulation therapy for stroke and systemic embolism prevention in patients with atrial fibrillation. The fixed-dose will most likely make it easier and safer for patient to adhere to the prevention guidelines.

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The Efficacy of Dabigatran versus Warfarin for Stroke Prevention in Patients With Atrial Fibrillation: Systematic Review

A course paper presented to the College of Health Professions in partial fulfillment of the requirements of the degree of Master of Science

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Biography

[Redacted for privacy]

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[Redacted for privacy]
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Keywords: warfarin, atrial fibrillation, nonvalvular and dabigatran.
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INTRODUCTION

Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia and a risk factor for stroke and systemic embolism. It is described as the heart's atria quivering instead of beating effectively. Blood isn't pumped completely out of them, so it may pool and clot. If a piece of a blood clot in the atria leaves the heart and becomes lodged in an artery in the brain, a stroke result. Additionally, the prevalence of AF increases with age. According to Go, et al. (2001, p. 2370) "In 2000, it was estimated that approximately 2.3 million people in the United States suffer from atrial fibrillation. While the prevalence of atrial fibrillation is less than 1% in people younger than 55 years old, it rises to 9% in individuals over 80 years of age. The patient prevalence is likely to increase 2.5-fold during the next 50 years”. Consequently, the stroke rate and systemic embolism rates due to AF will also increase.

A stroke can result in serious disability or death. According to Chung and Caplan (2007, chap. 43) "there are two major types of stroke: ischemic stroke and hemorrhagic stroke. When a blood vessel that supplies blood to the brain is blocked by a blood clot, this is called an ischemic stroke. A blocked artery may happen in two ways.

- A clot may form in an artery that is already very narrow. This is called a thrombus. If it completely blocks the artery, it is called a thrombotic stroke.
- A clot may break off from somewhere in your body and travel up to the brain to block a smaller artery. This is called an embolism. It causes an embolic stroke."
A second major cause of stroke is bleeding in the brain. This is called a hemorrhagic stroke. It can occur when small blood vessels in the brain become weak and burst. Some people have defects in the blood vessels of the brain that make this more likely. The flow of blood that occurs after the blood vessel ruptures damages brain cells.” Similarly, a systemic embolism consists of an embolus that can lodge anywhere in the body and obstruct its blood flow causing an infract and tissue death.

Furthermore, Lin, Wolf, Kelly-Hayes, Beiser, Kase, Benjamin and D'Agostino (1996, p. 1760) concluded that, “strokes associated with AF tend to be more severe and are associated with higher mortality, greater disability, and higher healthcare costs”. Equally importantly, Lip and Boos (2006, p. 155) found that “comorbid factors such as hypertension, diabetes mellitus, congestive heart failure and prior stroke, all serve to increase the risk of stroke in AF, and the risks are cumulative.”

It has been established that warfarin is an effective drug to prevent stroke and systemic embolism in patients with AF. “Vitamin K antagonists (VKA) such as warfarin reduce the risk of stroke and systemic embolism in patients with AF by 68%” (Atrial Fibrillation, 1994). However, according to Nichol, et al. (2008, p. 62) “VKAs are cumbersome to use because of their delayed onset of action, differences in effects on the coagulation cascade, and multiple interactions with food and drugs that necessitate frequent laboratory monitoring. In clinical practice, patients receiving warfarin therapy spend approximately 50% to 60% of the time within the therapeutic range, and warfarin is often not used when clinically indicated.”
Thus, there is a need for new anticoagulant agents that are effective, safe, and convenient to use.

Dabigatran etexilate is an orally available reversible direct thrombin (factor IIa) inhibitor. Since thrombin enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of a thrombus. Both free and clot-bound thrombin, and thrombin-induced platelet aggregation are inhibited. In addition, this conversion is independent of cytochrome P-450, making drug-drug and drug-diet interactions less likely. It is also, predominantly excreted via a renal pathway, reducing hepatotoxicity.

Dabigatran was recently approved (at a dose of 150 mg BID) by the FDA to reduce the risk of stroke and systemic embolism in patients with AF. And in March 2011 a Focused Report of the American College of Cardiology Foundation/American Heart Association Task Force updated the 2006 Practice Guidelines to include Dabigatran as the first new oral anticoagulant to become available for clinical use in more than 50 years for the prevention of stroke and systemic embolism in patients with AF.

Purpose of the Study

This paper focuses on the current literature on preventive therapy for stroke and systemic embolism in patients with atrial fibrillation. It is a systematic review of the literature that examines the efficacy of dabigatran compared to warfarin therapy in patients with AF to prevent stroke and systemic embolism. This paper uses the Grading of Recommendations Assessment Development and Evaluation (GRADE) criteria to evaluate the strength of evidence for this research.
METHOD

An extensive review of the literature search was performed using the following database: Web of Science, MEDLINE and CINHAL. These databases were accessed through the Pacific University Library system. The following keywords were searched individually and in combination: “warfarin”, “atrial fibrillation”, “nonvalvular” and “dabigatran”. The search was limited to human subjects, the English language and full text articles. The initial results included 4 articles of which duplicates, descriptive reviews and letters to editors were excluded. Only randomized, controlled trials were reviewed. This resulted in two studies to review and include in the final analysis.

RESULTS

Dabigatran With or Without Concomitant Aspirin Compared With Warfarin Alone in Patients With Nonvalvular Atrial Fibrillation (PETRO Study) by Ezekowitz (2007)

The first study reviewed randomized 502 patients with non-valvular atrial fibrillation to dabigatran or warfarin. The median of length of diagnosis for atrial fibrillation was four 4 years but ranged from 0.05 to 30 years. All participants had, at least one additional risk factor for stroke (age over 75 years, prior transient ischemic attack (TIA) or stroke, documented coronary artery disease, hypertension requiring medical therapy, diabetes mellitus, symptomatic heart failure or ejection fraction <40%). Among the enrolled patients, 411 (81.9%) were male, with a mean age of 70.9 years and an average of three stroke risk factors.
Before the start of the study, all patients had been on vitamin K antagonist (VKA) therapy at least eight weeks, and had an INR of 2.0-3.0. This ensured that the baseline D-dimer was obtained under the condition of full anticoagulation. Subjects were then randomized into a 3 X 3 factorial distribution to receive either a combination of dabigatran (50 mg, 150 mg or 300 mg bid) and aspirin (0, 81 mg or 325 mg daily) or to receive adjusted-dose warfarin alone. While the dose of dabigatran was blinded, both warfarin and aspirin were open-label. Therapy lasted for 12 weeks.

The primary outcome was the frequency of bleeding events.

Classified as major or minor ... [which] assigned to the treatment the patient was receiving at the time of onset. Major bleeding was defined as fatal or life-threatening retroperitoneal, intracranial, intraocular, or intraspinal bleeding; or bleeding requiring surgery or transfusion of at least 2 units or associated with a decrease in hemoglobin of at least 2.0 g/L. Minor bleeding was further subdivided into clinically relevant or nuisance bleeding episodes. Clinically relevant bleeding was defined as skin hematoma that is more than 25 cm², spontaneous nose bleed of more than 5 minutes duration, macroscopic hematuria, spontaneous rectal bleeding, gingival bleeding for more than 5 minutes, any bleeding leading to hospitalization, any bleeding leading to transfusion of less than 2 units, or any other bleeding considered relevant by the investigator. (Ezekowitz, et al. 2007, p. 1421)

The patients taking 300 mg BID daily dabigatran along with aspirin had a major hemorrhage rate of 6.3% (4 of 64). The rate was statistically different compared with the group treated with dabigatran 300 mg twice daily without aspirin (0 of 105, p <0.02).
These patients were consolidated into a single group and proceeded to take 300 mg twice daily without aspirin. This significance persisted when clinically relevant and nuisance bleeding were added in (39.1% for 300 mg with aspirin compared to 13.3% without aspirin, \( p=0.0003 \)). The other disparity determined to have statistical significance was the low rate of total bleeding among the 50 mg dabigatran patients (regardless of aspirin use) compared to both the warfarin-using patients (6.5% versus 17.1%, \( p=0.044 \)) and the higher doses of dabigatran (17.8% for 150 mg and 21.9% for 300 mg; \( p \) of 0.01 and 0.0002, respectively).

Changes in dosing occurred within the treatment period; investigators decreased dabigatran dosing to once daily in 12 patients, based on measurements of creatinine clearance and trough activated partial thromboplastin time (aPTT), and these patients were evaluated in their original dosing groups. Among patients in the warfarin group, INR was within range 57.2% of the time.

Some of the other outcomes at which the study looks include stroke and systemic embolism. “Stroke was defined as an acute onset of a focal neurologic deficit of vascular origin lasting for more than 24 hours. Systemic thromboembolism was defined as an acute nonintracerebral or noncoronary vascular event” (Ezekowitz et al. 2007, p. 1421). Overall there were only two thromboembolic events during the study, both of which occurred in patients taking dabigatran 50 mg twice daily (1.96%), one with the use of 81 mg of aspirin and one with no aspirin. One patient had a peripheral embolism to the toe and the other patient had a stroke and a renal infarction.

Overall, 38 patients discontinued treatment, all were dabigatran users; 4.7% of the 50 mg group, 5.3% of the 150 mg group and 8.9% of the 300 mg group stopped
treatment because of adverse outcomes. “29 due to adverse events, 3 withdrew consent; and 1 patient was not compliant with study medication.” (Ezekowitz et al. 2007, p 1421; Appendix, Table 1). Another patient returned for the final visit, but it was not possible to determine whether the patient was compliant with study medication. The patient was classified as discontinued. “The four remaining patients withdrew, one each as a result of percutaneous coronary intervention for coronary artery disease requiring clopidogrel, angiography planned before trial entry, difficulty with blood draws, and personal reasons” (Ezekowitz et al. 2007, p. 1421).

Dabigatran versus Warfarin in Patients with Atrial Fibrillation by Connolly et al. (2009)

The final study reviewed was the RE-LY study (Randomized Evaluation of Long-Term Anticoagulation TherapY) which enrolled 18,113 patients from 44 countries. These participants had “documented atrial fibrillation on electrocardiogram at the screening or within 6 months beforehand and at least one risk for stroke and systemic embolism (aged 75 years or older, prior TIA or stroke, hypertension, diabetes mellitus, coronary artery disease, ejection fraction less than 40% or heart failure in the last six months meeting the New York Heart Association class II or higher criteria)” and the listed criteria are referred to a CHADS2 score (Connolly, et al. 2009, p. 1140). The average age of the patients was 71 years and 63.6% were male. Half of the patients had received long term therapy with vitamin K antagonist. Twenty percent of these patients had history of TIA or stroke, while 79.9% reported hypertension and 16.6% had experienced a prior MI, with the mean CHADS2 score of 2.1. Patients were randomized to receive either a blinded dose of dabigatran (110 or 150 mg twice daily) or open-label
warfarin, with a target value of 2.0-3.0. Patients were followed for a median period of two years.

The primary outcome in RE-LY was defined as stroke or systemic embolism during the treatment period (Connolly et al. 2009, p. 1141). Stroke and systemic embolism are defined in the same way as in PETRO study. Dabigatran 110 mg twice daily was equivalent to warfarin for thromboembolic prophylaxis. With an event rate of 1.53% per year in this group, versus 1.69% per year in the warfarin group, the relative risk with 110 mg dabigatran therapy was 0.91 (95% CI, 0.74 to 1.11; p=.34), thus meeting the pre-specified non-inferiority criteria. Among patients taking 150 mg of dabigatran, the prophylactic effect surpassed non-inferiority, and demonstrated superiority to warfarin; the rate was 1.11% per year, versus 1.69% for the warfarin group, with a relative risk of 0.66 with this therapy (95% CI, 0.53 to 0.82; p < .001).

Bleeding rates were a secondary outcome for the RE-LY study and were also defined the same as in the PETRO study. Major bleeding occurred in 2.71% of the dabigatran 110 mg group per year, in 3.11% of the dabigatran 150 mg group per year, and in 3.36% per year among warfarin users. This establishes a relative bleeding risk with dabigatran that is comparable to warfarin at the 150 mg dose (0.93; 95% CI, 0.81 to 1.07; p=.31) and superior to warfarin at 110 mg dose (0.80; 95% CI, 0.69 to 0.93; p =0.003) with intracranial bleeding were higher with warfarin treatment (0.74%) compared with the 110-mg (0.23%) and the 150-mg (0.30%) doses of dabigatran etexilate (p<.001 for both comparisons with warfarin; p=.28 between dabigatran etexilate doses). A risk reduction is seen in the category of life-threatening bleeding; here dabigatran 110 mg yields a relative risk of 0.68 (95% CI, 0.55 to 0.83; p<.001) and
dabigatran 150 mg a relative risk of 0.81 (95% CI, 0.66 to 0.99; \( p=0.04 \)). However, patients receiving dabigatran experienced more gastrointestinal bleeding (1.12% and 1.51% per year) compared to warfarin (1.02% per year) and this disparity reached statistical significance for the higher dabigatran dose (relative risk 1.50; \( p<0.001 \)).

For minor bleeding, dabigatran 110 mg established a relative risk of 0.79 versus warfarin (95% CI, 0.74 to 0.84; \( p<0.001 \)) and dabigatran 150 mg established a relative risk of 0.91 (95% CI, 0.85 to 0.97; \( p=0.005 \)).

A net clinical benefit was designed to combine major vascular events, major bleeding and death. By this measurement, the lower dose of dabigatran was equivalent to warfarin anticoagulation, while the higher dose dabigatran was slightly superior (relative risk of 0.91; \( p=0.04 \)).

Dyspepsia was the only adverse event that was significantly more common with dabigatran etexilate than with warfarin. It occurred in 348 patients out of 6,022 (5.8%) in the warfarin group, 707 patients out of 6,015 (11.8%) in the dabigatran etexilate 110-mg twice daily group, and 688 patients out of 6,076 (11.3%) in the dabigatran etexilate 150-mg twice daily group (\( p<0.001 \) for both comparisons). Elevations in the serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level of more than 3 times the upper limit of normal did not occur more frequently with dabigatran etexilate at either dose than with warfarin.
DISCUSSION

Atrial fibrillation is the most frequent cardiac arrhythmia and its prevalence is increasing with the aging population. Patients with atrial fibrillation are at increase risk of experiencing a stroke or systemic embolism event. Anticoagulation therapy is known to reduce these events and has been prescribed as prophylaxis for patients with atrial fibrillation. Unfortunately, warfarin was the only oral drug to do that. Even though, warfarin has proven its efficacy in lowering the risk of stroke and systemic embolism, it is not an ideal choice given the necessity of constant monitoring, to assess issues such as significant ADR and high affinity to interact with food and other drugs. Dabigatran is a newer oral, direct thrombin inhibitor that shows in this systemic review of these two studies the safety and superiority over warfarin which lead to its approval by the FDA and its incorporation into treatment guidelines for the American Heart Association, American College of Cardiology and European Society Cardiology.

The RE-LY study addressed stroke and systemic emboli prevention for patients with atrial fibrillation as its primary outcome in comparing two doses of the dabigatran with warfarin (Connolly et al. 2009). However, The PETRO study was more focused on bleeding prevention with higher doses of the dabigatran with and without aspirin versus warfarin (Ezekowitz et al. 2007). Minimal and non-reliable data was provided for prevention of stroke and systemic embolism in lower doses of dabigatran.

In the PETRO study a first attempt for evaluating the dosing of dabigatran and its safety on liver, blood and bleeding events with and without aspirin in patients with atrial fibrillation was made. The patients in the study were divided into 10 groups with different dosing regimen; this made it difficult to make a strong evaluation. Equally relevant was
the low number of participants and the short period of treatment exposure of only 12 weeks.

In contrast, the RE-LY study compared two doses of dabigatran (110mg and 150mg, twice daily) with warfarin. The study randomized a large population into three groups which made it more straightforward to interpret the results. Furthermore, the length of the study and the high rate of the follow up at 99.9% strengthen its reliability.

As a primary outcome of this systemic review, stroke and systemic embolism, in patients with atrial fibrillation, dabigatran 150 mg, twice daily, showed superiority in prevention compared with warfarin. At 110 mg, twice daily, dabigatran was non-inferior to warfarin. This is why the FDA approved only the 150 mg dosing.

In other outcomes including adverse reaction the two trials showed:

Intracranial hemorrhage: Dabigatran showed non-inferiority to warfarin. In the contrary, dabigatran 110 mg, twice daily, proved to lower the risk of intracranial hemorrhage compared to warfarin and was similar in the frequency of hemorrhagic event with dabigatran 150 mg, twice daily.

GI bleed: The high doses of dabigatran increase the risk of gastrointestinal bleed but not significantly more than did warfarin.

Coronary ischemic events: both dabigatran doses had an increased rate in myocardial events as compared to warfarin. It is known that warfarin is cardio-protective and reduce the risk of myocardial infarction. However, further study need to be conducted to determine the affect of dabigatran on cardiovascularity.

Dyspepsia: both studies demonstrated a higher discontinuation rate in patients taking dabigatran. Dyspepsia was a single major side effect that dabigatran had at all doses
across the board when compared to warfarin. It is probably related to the fact that “dabigatran capsules contain dabigatran-coated pellets with a tartaric acid core” to lower gastric pH and enhance dabigatran absorption (Stuart, et al. 2009. p. 1148). This affect needs to be explored and adjusted for in future research.

The Grading of Recommendations Assessment Development and Evaluation (GRADE) was used in this paper to evaluate the quality of evidence and strength of recommendations provided in this study.

- **High quality**— Further research is very unlikely to change our confidence in the estimate of effect
- **Moderate quality**— Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- **Low quality**— Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- **Very low quality**— Any estimate of effect is very uncertain (Guyatt et al. p 926)

All the trials in this review were randomized control trials, which are at a “high” type of evidence according to the GRADE criteria. The RE-LY study had stroke and systemic embolism as primary outcomes. However, it appears that the PETRO study had these outcomes as tertiary. But the outcomes were wholly consistent and the RE-LY study even modified their dosing based on the PETRO study giving further indicia of confidence in their early findings. This decision not to downgrade the evidence leaves a GRADE score of high for the combined outcomes.
In conclusion, dabigatran is the first oral anticoagulant approved by the FDA in the last 50 years albeit in one dosage. It showed as a safer and superior alternative to warfarin for stroke prevention in patients with atrial fibrillation. For patients and clinicians having difficulties keeping INR at 2.0-3.0 range (57% average) as well as newly diagnosed patients with atrial fibrillation, we recommend dabigatran as best initial anticoagulation therapy for stroke and systemic embolism prevention.
REFERENCES


### APPENDICES

**Table 1: Adverse events**

<table>
<thead>
<tr>
<th>Event</th>
<th>Dabigatran Dose (twice daily)</th>
<th>Warfarin to INR of 2–3 (n 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 mg (n 107)</td>
<td>150 mg (n 169)</td>
</tr>
<tr>
<td>Patients discontinuing with adverse events*</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Cardiovascular and peripheral embolic events†</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Major/clinically relevant hemorrhage</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal symptoms‡</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ALT/AST increased</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other symptoms§</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

* Some patients had more than 1 event.
† Cardiac failure, acute coronary syndrome, cerebrovascular accident, and peripheral emboli, including renal infarction.
‡ Abdominal pain, dyspepsia, and nausea.
§ Fatigue, dyspnea, visual disturbance, worsening dizziness, renal pain, and chest pain.

ALT  alanine aminotransferase; AST  aspartate aminotransferase.
# APPENDIX A

## Table 2: GRADE Table

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Quantity and type of evidence</th>
<th>Findings</th>
<th>Decrease GRADE</th>
<th>Increase GRADE</th>
<th>Grade of Evidence for Outcome</th>
<th>Overall GRADE of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran Vs Warfarin in patients with atrial fibrillation</td>
<td>Stroke prevention</td>
<td>2 RCT</td>
<td>Decreased stroke events</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>High</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td>Preventing systemic embolism</td>
<td>2 RCT</td>
<td>Decreased systemic embolism</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>High</td>
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</tbody>
</table>