Dabigatran Compared to Warfarin in the Reduction of Stroke Risk in Patients With Atrial Fibrillation

Thomas S. Haslam
Pacific University

Follow this and additional works at: http://commons.pacificu.edu/pa

Recommended Citation
Dabigatran Compared to Warfarin in the Reduction of Stroke Risk in Patients With Atrial Fibrillation

Abstract
Background: Atrial fibrillation (AF) is the most common cardiac arrhythmia. Presenting with a wide range of symptoms, this disease affects more than 2.66 million people in the United States. Arguably the most concerning complication faced by patients with AF, is the dramatically increased risk of stroke associated with this disease. Those with AF are five times more likely to suffer from a stroke than those without. This risk is partially mitigated by thinning the blood using anticoagulant medications. Warfarin, the most commonly used anticoagulant, has been available for over 60 years. Warfarin is effective, but dated compared to newer drugs of its class and associated with inherent difficulties in treatment. Dabigatran, a new anticoagulant that promises to be easier to administer, may reduce the risk of stroke even further than warfarin. Is dabigatran a better option than warfarin in reducing stroke in patients with AF?

Method: Exhaustive search of available medical literature was done using CINAHL, Medline-OVID, and Academic Research Premiere using the following search terms: dabigatran, warfarin, atrial fibrillation, and stroke. Relevant articles were assessed for quality using the GRADE criteria.

Results: Five studies met inclusion criteria and were included in this systematic review. A large, multicenter, prospective, open-label, randomized trial with blinded evaluations of outcomes with 18 113 participants compared two doses of dabigatran with warfarin. It was demonstrated that while both doses of dabigatran were noninferior, the higher of the two doses was superior to warfarin in reducing stroke and systemic embolism. Certain risks were increases with dabigatran, such as gastrointestinal bleeding. Subgroup analyses, also included in the review, demonstrated that dabigatran is superior to warfarin in reducing stroke, even in subgroups with previous anticoagulant therapy or history of stroke. An observational study with 290 participants revealed that dabigatran is an independent predictor of bleeding and thromboembolic events in patients undergoing RF ablation therapy for AF.

Conclusion: Dabigatran reduces the risk of stroke to a greater extent than warfarin in patients with AF. It is also associated with a higher risk of bleeding complications in certain patients. Caution should be taken when treating with dabigatran, but it is a superior option to warfarin in many patients whose benefits outweigh the risk.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

First Advisor
James Ferguson, PA-C

Second Advisor
Annjanette Sommers, PA-C

This capstone project is available at CommonKnowledge: http://commons.pacificu.edu/pa/424
Copyright and terms of use

If you have downloaded this document directly from the web or from CommonKnowledge, see the “Rights” section on the previous page for the terms of use.

If you have received this document through an interlibrary loan/document delivery service, the following terms of use apply:

Copyright in this work is held by the author(s). You may download or print any portion of this document for personal use only, or for any use that is allowed by fair use (Title 17, §107 U.S.C.). Except for personal or fair use, you or your borrowing library may not reproduce, remix, republish, post, transmit, or distribute this document, or any portion thereof, without the permission of the copyright owner. [Note: If this document is licensed under a Creative Commons license (see “Rights” on the previous page) which allows broader usage rights, your use is governed by the terms of that license.]

Inquiries regarding further use of these materials should be addressed to: CommonKnowledge Rights, Pacific University Library, 2043 College Way, Forest Grove, OR 97116, (503) 352-7209. Email inquiries may be directed to: copyright@pacificu.edu

This capstone project is available at CommonKnowledge: http://commons.pacificu.edu/pa/424
NOTICE TO READERS

This work is not a peer-reviewed publication. The Master’s Candidate author of this work has made every effort to provide accurate information and to rely on authoritative sources in the completion of this work. However, neither the author nor the faculty advisor(s) warrants the completeness, accuracy or usefulness of the information provided in this work. This work should not be considered authoritative or comprehensive in and of itself and the author and advisor(s) disclaim all responsibility for the results obtained from use of the information contained in this work. Knowledge and practice change constantly, and readers are advised to confirm the information found in this work with other more current and/or comprehensive sources.

The student author attests that this work is completely his/her original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.
Dabigatran Compared to Warfarin in the Reduction of Stroke Risk in Patients With Atrial Fibrillation

Thomas S. Haslam

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 2013

Faculty Advisor: James Ferguson, PA-C
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Thomas Haslam is a native of Utah where he majored in Behavioral Science and Health at The University of Utah. While completing his undergraduate degree, he worked as a clinical research team leader at the Comprehensive Arrhythmia Research and Management (CARMA) Center in Salt Lake City. Prior to attending college, Thomas served a full-time volunteer church mission in the Czech Republic and Slovakia, where he lived for over 2 years. He is married to his beautiful wife and a proud father of his son.
Abstract

**Background:** Atrial fibrillation (AF) is the most common cardiac arrhythmia. Presenting with a wide range of symptoms, this disease affects more than 2.66 million people in the United States. Arguably the most concerning complication faced by patients with AF, is the dramatically increased risk of stroke associated with this disease. Those with AF are five times more likely to suffer from a stroke than those without. This risk is partially mitigated by thinning the blood using anticoagulant medications. Warfarin, the most commonly used anticoagulant, has been available for over 60 years. Warfarin is effective, but dated compared to newer drugs of its class and associated with inherent difficulties in treatment. Dabigatran, a new anticoagulant that promises to be easier to administer, may reduce the risk of stroke even further than warfarin. Is dabigatran a better option than warfarin in reducing stroke in patients with AF?

**Method:** Exhaustive search of available medical literature was done using CINAHL, Medline-OVID, and Academic Research Premiere using the following search terms: dabigatran, warfarin, atrial fibrillation, and stroke. Relevant articles were assessed for quality using the GRADE criteria.

**Results:** Five studies met inclusion criteria and were included in this systematic review. A large, multicenter, prospective, open-label, randomized trial with blinded evaluations of outcomes with 18,113 participants compared two doses of dabigatran with warfarin. It was demonstrated that while both doses of dabigatran were noninferior, the higher of the two doses was superior to warfarin in reducing stroke and systemic embolism. Certain risks were increases with dabigatran, such as gastrointestinal bleeding. Subgroup analyses, also included in the review, demonstrated that dabigatran is superior to warfarin in reducing stroke, even in subgroups with previous anticoagulant therapy or history of stroke. An observational study with 290 participants revealed that dabigatran is an independent predictor of bleeding and thromboembolic events in patients undergoing RF ablation therapy for AF.

**Conclusion:** Dabigatran reduces the risk of stroke to a greater extent than warfarin in patients with AF. It is also associated with a higher risk of bleeding complications in certain patients. Caution should be taken when treating with dabigatran, but it is a superior option to warfarin in many patients whose benefits outweigh the risk.

**Keywords:** dabigatran, warfarin, atrial fibrillation, stroke
# Table of Contents

Biography ................................................................. 2
Abstract ................................................................. 3
Table of Contents ......................................................... 4
List of Tables ............................................................. 5
List of Abbreviations ..................................................... 5
Background ............................................................... 6
Method ..................................................................... 8
Results ..................................................................... 8
Discussion ............................................................... 16
Conclusion ............................................................... 22
References .............................................................. 23
Tables ..................................................................... 27
List of Tables

Table I: Characteristics of Reviewed Studies
Table II: Summary of Finding

List of Abbreviations

AF………………………………………………………………………...Atrial Fibrillation
VKA………………………………………………………………...Vitamin K Antagonist
GRADE………Grading of Recommendations, Assessment, Development and Evaluation
RE-LY……………..Randomized Evaluation of Long-Term Anticoagulant Therapy
INR………………………………………………………...International Normalized Ratio
D110………………………………………………………………...….Dabigatran 110 mg
D150………………………………………………………………...….Dabigatran 150 mg
RR…………………………………………………………………….………Relative Risk
CI…………………………………………………………………...….Confidence Interval
MI…………………………………………………………..……….Myocardial Infarction
TIA…………………………………………………………..….Transient Ischemic Attack
RF……………………………………………………………………….....Radiofrequency
FDA………………………………………………………..Food and Drug Administration
Dabigatran Compared to Warfarin in the Reduction of Stroke Risk in Patients With Atrial Fibrillation

BACKGROUND

Of the many arrhythmias that can affect the heart, atrial fibrillation (AF) is the most common. It has been estimated to account for one-third of all hospitalizations resulting from cardiac rhythm abnormalities.\(^1\) In the United States alone, approximately 2.66 million people suffer from this disease, a number that is expected to increase to more than 5.6 million by the year 2050.\(^2,\)\(^3\) As people grow older, their risk for developing AF also grows, with a 1.5-fold increase per decade of age.\(^1,\)\(^4\) Although some patients with AF may not complain of symptoms, it is common for those affected by this condition to experience palpitations, a rapid or irregular heartbeat, lightheadedness, extreme fatigue, shortness of breath, or chest pain.

Perhaps more concerning than the above-mentioned symptoms, however, is the dramatically increased risk of stroke associated with AF. The effect of AF on the heart is characterized by disorganized electrical activity, which causes an irregular heartbeat. This altered heart rhythm causes the flow of blood through the heart to be disrupted, increasing the opportunity for thrombi to form. Research suggests that patients with AF are five times more likely to have a stroke than those without.\(^5\) Hart et al reported that one out of every six strokes occurs in a patient with AF.\(^6\) Additionally, a study by Marini et al concluded that AF is responsible for approximately 25% of all ischemic strokes.\(^7\)

To reduce the high risk of stroke, anticoagulants are administered to prevent blood from clotting within the heart. The most commonly used drug of this type today is warfarin, an oral vitamin K antagonist (VKA) introduced more than 60 years ago.\(^8\)
Warfarin, in preventing stroke, has been studied extensively and has been shown to reduce the risk in patients with AF by 64% compared to placebo. Warfarin has made dramatic changes in the lives of those with AF, becoming the trusted and preferred therapy in the prevention of stroke over the last several decades.

Although warfarin has been proven a successful treatment in the reduction of stroke for patients with AF, it is relatively aged in the realm of oral anticoagulant drugs. Even while taking warfarin, patients with AF remain at a much higher risk of stroke than those without the disorder. In addition, VKAs, like warfarin, present with unique challenges when administered as part of anticoagulant therapy. Patients on warfarin need frequent monitoring to ensure appropriate therapeutic effect, as there is wide variability in dose response and many interactions with foods and drugs. Poor patient compliance and a delayed onset of action are other factors that complicate warfarin therapy.

Dabigatran is a new anticoagulant, which was approved in the United States for use in patients with AF in October of 2010. A possibly superior alternative to warfarin, dabigatran may even further reduce the risk of stroke in patients with AF. This new drug is a direct thrombin inhibitor that promises to require less patient monitoring than that which is required by warfarin. The onset of action is much quicker with dabigatran and food or drug interactions are significantly decreases compared to warfarin, making administration easier and patient compliance more likely.

If dabigatran is more effective than warfarin in reducing the incidence of stroke in patients with AF, many lives could be preserved that may have otherwise been significantly impaired or lost. The question of whether dabigatran is more effective than
warfarin in reducing stroke for the population affected by AF is addressed in this systematic review.

METHODS

An exhaustive literature search of available research was done using CINAHL, Medline-OVID, and Academic Search Premiere using the following search terms: dabigatran, warfarin, atrial fibrillation, and stroke. Studies included in the systematic review were restricted to those written in English, as well as being peer-reviewed articles conducted on human participants. Studies were prioritized to include randomized controlled trials as well as prospective studies that include data directly comparing the efficacy of dabigatran versus warfarin in patients with atrial fibrillation. Sub-analyses of major studies comparing the two drugs were also included. Inclusionary criteria were established to limit articles to those published after 2008. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

RESULTS

The search resulted in 221 articles that contained all of the search fields entered. After screening for relevant articles, five were deemed of high relevance and validity, also meeting the required inclusionary and exclusionary criteria.
RE-LY Trial

The randomized evaluation of long-term anticoagulant therapy (RE-LY) trial, supported by a grant from Boehringer Ingelheim, is described by its designers as a phase 3, multicenter, prospective, open-label, randomized trial with blinded evaluations of all outcomes. The intent of the study was to compare the outcomes of two fixed doses of dabigatran to the currently accepted, and widely used, warfarin. The primary outcome measured was stroke or systemic embolism. The primary safety outcome was major hemorrhage, and secondary outcomes were stroke, systemic embolism, and death.

In this large study, 18,113 patients with AF were recruited from 951 centers in 44 countries and randomly assigned to one of three groups, balanced for demographic and prognostic equality. Eligibility for enrollment was limited to patients who had AF documented on electrocardiography at a screening, or within 6 months before the time of screening, and at least one risk factor for stroke. Patients were excluded if they had had a major stroke within 6 months or any stroke within 14 days before screening, a severe heart-valve disorder, a condition that increased risk of hemorrhage, liver disease, or were pregnant.

The three randomly assigned treatment groups consisted of dabigatran 110 mg (D110) bid, dabigatran 150 mg (D150) bid, or adjusted-dose warfarin. For those assigned to either group receiving dabigatran, the drug was administered, in a blinded fashion, in blank capsules containing either 110 mg or 150 mg to be taken two times each day. Warfarin was administered in an unblinded fashion in the third group, with the dose adjusted in each patient to achieve an international normalized ratio (INR) of 2.0 to 3.0,
monitored monthly. Immediately after randomization, follow-up visits were conducted at the following intervals: at 14 days, 1 and 3 months, and every 3 months from then forward for the remainder of the first year, and then every 4 months until the study concluded.  

The enrollment period occurred from December 22, 2005, until December 15, 2007, in which time all 18,113 patients were entered into the study. With all three treatment groups well balanced, the mean age of the patients was 71 years, with 63.6% being men. The final follow-up visits were conducted between December 15, 2008, and March 15, 2009. The average time of follow-up was 2 years. Complete follow-up was accomplished in 99.9% of patients, with only 20 patients lost to follow-up. No reason for loss was given.

In regards to the primary outcome, stroke or systemic embolism, both doses of dabigatran were shown to be noninferior to warfarin, but D150 was also superior. Stroke or systemic embolism occurred in 182 patients receiving D110 (relative risk [RR], 0.91; 95% confidence interval [CI] 0.74 to 1.11; P=0.34), 134 patients receiving D150 (RR, 0.66; 95% CI, 0.53 to 0.82; P<0.001), and 199 patients receiving warfarin.  

The rates of hemorrhagic stroke were significantly decreased with both doses of dabigatran versus warfarin (P<0.001). Rates in the warfarin group were 0.38% per year compared with 0.12% in the D110 group (RR, 0.31; 95% CI, 0.17 to 0.56; P<0.001) and 0.10% in the D150 (RR, 0.26; 95% CI, 0.14 to 0.49; P<0.001). For stroke of any type, D110 was noninferior, at 1.44% per year (RR, 0.92; 95% CI, 0.74 to 1.13; P=0.41), while D150 proved to be significantly superior at 1.01% per year (RR, 0.64; 95% CI, 0.51 to 0.81; P<0.001), compared to 1.57% per year in the warfarin group. The rates of ischemic
or unspecified stroke, compared to warfarin (1.20% per year), were positively and negatively affected, depending on the dose of dabigatran administered. The rate with D150 was improved, at 0.92% per year (RR, 0.76; 95% CI, 0.60 to 0.98; P=0.03) but the rate increased to 1.34% per year when D110 was administered (RR, 1.11; 95% CI, 0.89 to 1.40; P=0.35). 14

Rates of death from any cause were 4.13% per year in the warfarin group, compared with 3.75% per year in the D110 group (RR, 0.91; 95% CI, 0.80 to 1.03; P=0.13) and 3.64% per year in the D150 group (RR, 0.88; 95% CI, 0.77 to 1.00; P=0.051). These results were not statistically significant, however. The rate of major bleeding was 3.36% per year in the warfarin group, compared with 2.71% in the D110 group (RR, 0.80; 95% CI, 0.69 to 0.93; P=0.003) and 3.11% per year in the D150 group (RR, 0.93; 95% CI, 0.81 to 1.07; P=0.31). Although the rate of all types of major bleeding combined was reduced with dabigatran, the rate of major gastrointestinal bleeding was significantly increased in the D150 group (RR, 1.50; 95% CI, 1.19 to 1.89; P<0.001). 14

Rates of myocardial infarction (MI) increased in the dabigatran groups, as compared with the warfarin group. For warfarin, the rate of MI was 0.53% per year, while rates were 0.72% per year with D110 (RR, 1.35; 95% CI, 0.98 to 1.87; P=0.07) and 0.74% per year with D150 (RR, 1.38; 95% CI, 1.00 to 1.91; P=0.048). 14

The net clinical benefit outcome for the study consisted of major vascular events, major bleeding, and death. Combined, the rates for this outcome were 7.64% per year with warfarin, compared with 7.09% per year with D110 (RR, 0.92; 95% CI, 0.84 to 1.02; P=0.10) and 6.91% per year with D150 (RR, 0.91; 95% CI, 0.82 to 1.00; P=0.04). 14
According to the researchers of this study, the only adverse effect that was significantly more common with dabigatran, compared to warfarin, was dyspepsia. This occurred in 5.8% (348) of patients on warfarin, 11.8% (707) of patients receiving D110, and 11.3% (688) of patients receiving D150. The P value for both dabigatran groups versus warfarin was P<0.001.  

Subgroup Analyses of the RE-LY Trial

Since the publication of the RE-LY trial in 2009, various researchers and teams have analyzed subgroups within the participants of the study, using the original data acquired by Connolly et al to undergo unique exploratory studies. These studies have served to validate the results of the RE-LY trial or to suggest new findings based on the data collected therein. The following are subgroup analyses of the RE-LY trial data.

VKA-naïve vs. VKA-experienced patients—This study, published in 2010 by Ezekowitz et al, aimed to determine whether the benefits of either dose of dabigatran were affected by previous VKA exposure. All participants in the RE-LY trial fit into one of two subgroups in terms of VKA exposure: VKA-naïve (≤62 days of lifetime VKA exposure, with 33% never prescribed a VKA) and VKA-experienced patients with AF. Warfarin, D110, and D150 were compared in balanced populations of these two subgroups.  

Stroke or systemic embolism rates in the D110 group were similar in both VKA-naïve and VKA-experienced groups compared with warfarin (RR, 0.93; 95% CI, 0.70 to 1.25; P=0.65 and RR, 0.87; 95% CI, 0.66 to 1.15; P=0.32, respectively). Interaction was not significant between the subgroups, at P=0.72. The rates for the D150 group were
significantly lower in both VKA-naïve and VKA-experienced groups compared with warfarin (RR, 0.63; 95% CI, 0.46 to 0.87; P=0.005 and RR, 0.66; 95% CI, 0.49 to 0.89; P=0.007, respectively). Interaction was not significant between the subgroups with D150 either, at P=0.84. With the primary outcome, among others, the results of the study concluded that previous VKA exposure does not influence the benefits of dabigatran at either dose compared with warfarin.  

**Previous TIA or stroke**—In this study conducted by Diener et al, the effects of dabigatran compared with warfarin are assessed in the subgroup of patients with previous transient ischemic attack (TIA) or stroke. Of the patients enrolled in the RE-LY trial, 3623 had a previous TIA or stroke. The rate of stroke or systemic embolism among those patients was higher than in those without (171 of 3 623 [2.38% per year] versus 348 of 14 489 [1.22% per year]; p<0.0001). Within the subgroup of patients who had previous TIA or stroke, there were 1195 patients were from the D110 group, 1233 from the D150 group, and 1195 from the warfarin group.

For the outcome of stroke or systemic embolism, the interaction between the subgroup with prior TIA or stroke, and those without, was non-significant for both the D110 and D150 groups (P for interaction=0.62 and P for interaction=0.34, respectively). The interaction was insignificant regarding stroke, by itself, in both the D110 and D150 groups as well (P for interaction=0.85 and P for interaction=0.28, respectively). There was no significant interaction found in any other outcome of the trial. The study concludes that the effects of D110 and D150 in patients with previous TIA or stroke are consistent with those in the other patients in RE-LY. The effect of dabigatran is not influenced by prior TIA or stroke.
**Stroke after cardioversion**—This study,\(^{18}\) by Nagarakanti et al, focused on the risk of stroke, post-cardioversion, in patients treated with dabigatran compared to warfarin, prior to cardioversion. A total of 1983 cardioversions were performed in 1270 patients during the course of the RE-LY trial: 647 in the D110 group, 672 in the D150 group, and 664 in the warfarin group. The majority of the cardioversions were electric: 85.6%, 81.9%, and 83.3% in D110, D150, and warfarin, respectively. The remainder were pharmacological, except for 2 in the D110 group, which were spontaneous.\(^{18}\)

Stroke or systemic embolism rates within 30 days of cardioversion were low among all three groups: 0.77% with D110, 0.30% with D150, and 0.60% with warfarin. Neither doses of dabigatran were significantly different than warfarin, with D110, \(P=0.71\), and D150, \(P=0.45\). Rates of major bleeding in all three groups were also low: 1.7% in D110, 0.6% in D150, and 0.6% in warfarin.\(^{18}\)

The major conclusion of the study was that rates of major bleeding and stroke within 30 days of cardioversion, in patients on either dose of dabigatran, are low and comparable to rates with warfarin.\(^{18}\)

**Dabigatran vs. Warfarin in Patients Undergoing Radiofrequency Ablation for AF**

This multicenter, observational study,\(^{19}\) published in March 2012, was designed to assess the risks of dabigatran, compared with warfarin, when used in patients with AF prior to undergoing radiofrequency (RF) ablation. Patients included in the study consisted of those who underwent RF ablation for drug-refractory, symptomatic AF at one of eight high-volume electrophysiology laboratories between January 2010 and July 2011. The mean age of the study population was 60 years, with 79% being male, and
57% having paroxysmal AF. The study was approved by a local institutional review board.¹⁹

The patient population was comprised of 290 patients with 145 patients in each of two groups, a dabigatran group and a warfarin group. The dabigatran group was made up of patients receiving D150 for at least 30 days prior to ablation. In the warfarin group, patients were receiving anticoagulation with warfarin for at least 30 days prior to ablation. The patients of each group were matched by age, sex, type of AF, and institution. Patients were excluded from the study if the INR was not between 2.0 and 3.5 at the time of the ablation procedure, or if the ablation was performed with the help of a remote navigation system. The ablation procedures were normalized by following standardized protocols.¹⁹

The primary safety outcome was a composite of bleeding and thromboembolic complications. Bleeding complications included hematomas, pericardial effusions, any bleeding requiring blood transfusions, and tamponade. Thromboembolic complications included stroke and TIAs after ruling out intracranial hemorrhage. All events occurring within 30 days of the RF ablation were included in the analysis.¹⁹

Of the 290 total patients, 32 (11%) had either bleeding or embolic complications. Of those, 29 (10%) had bleeding complications and 3 (1%) had thromboembolic complications. In the dabigatran group, 6% of patients had major bleeding complications (cardiac tamponade requiring drainage), as compared with 1% in the warfarin group (P=0.019). Total bleeding rate for the dabigatran group was 14%, as compared with 6% in the warfarin group (P=0.031). The rate of composite bleeding and embolic complications in the dabigatran group was 16%, as compared with 6% in the warfarin
group (P=0.009). The difference in all three of these complications between dabigatran and warfarin was statistically significant. The rate of embolic complications alone was non-significantly increased in the dabigatran group (2%), as compared with 0% in the warfarin group (P=0.25). 19

In univariable analysis of predictors of complication, the only predictors of bleeding were the use of dabigatran (p=0.031) and age older than 75 years (P=0.004). The only univariable predictors of the composite of bleeding and thromboembolic complications was also dabigatran (P=0.009) and age older than 75 (P=0.008). In multivariable logistic regression analysis including age older than 75, sex, AF type, and the use of dabigatran, the only independent predictors of bleeding or thromboembolic complications were dabigatran use (odds ratio, 2.76; 95% CI, 1.22 to 6.25; P=0.01) and age older than 75 (odds ratio, 3.82; 95% CI, 1.09 to 13.35; P=0.04). Dabigatran use was found to be an independent predictor of both bleeding complications (odds ratio, 2.34; 95% CI, 1.02 to 5.39; P=0.046) and composite of bleeding and thromboembolic events. 19

DISCUSSION

Although dabigatran is relatively new in the world of anticoagulant therapy, it appears to have compelling applications as an alternative to warfarin in the treatment of patients with AF.

Stroke or Systemic Embolism, and Stroke Alone

Strong evidence produced in recent years points to the fact that dabigatran has significant benefits, above that of warfarin, in reducing the risk of stroke for patients with
AF. The RE-LY trial, presumably the largest study conducted to date on the comparison of dabigatran and warfarin, demonstrated that, although warfarin is beneficial for AF patients, dabigatran is even better. The rate for patients in this cohort to experience a stroke or systemic embolism of any kind was 1.69% per year for those receiving warfarin. When that is compared to 1.11% per year for those receiving D150, it becomes easy to understand that this new drug has potential to improve the lives of those who suffer from this condition. Based on those rates, for every 1000 patients on anticoagulant warfarin therapy, 6 lives could potentially be preserved by switching to a therapy of D150. When stroke was considered by itself, D150 significantly reduced the rate per year, at 1.01%, compared with warfarin, at 1.57%. Based on the RE-LY trial data, D150 therapy is far superior to adjusted-dose warfarin to reduce the dramatic risk of stroke associated with AF.

This benefit of D150 over warfarin was further analyzed in subgroup analyses of the RE-LY trial. Ezekowitz et al showed that whether or not patients have had prior exposure to VKA therapy is immaterial, reporting that the beneficial effects of dabigatran in reducing the risk of stroke or systemic embolism are superior to warfarin. Diener et al found that past history of TIA or stroke did not negatively affect the comparative benefit of D150 over warfarin. With the understanding that cardioversion treatment for patients in AF is a known risk factor for stroke or systemic embolism, Nagarakanti et al aimed to determine whether or not dabigatran use before the procedure increased risk. It was determined that rates of stroke or systemic embolism within 30 days of cardioversion were low and noninferior in any dose of dabigatran.
compared to warfarin. Dabigatran is, therefore, a reasonable alternative to warfarin in patients undergoing cardioversion.

Not all research has shown dabigatran to be a safe alternative to warfarin however, as some applications of the drug in AF therapy may actually increase the risk of harm to patients. The study by Lakkireddy et al\textsuperscript{19}, published in March 2012, found a discrepancy in the perceived benefit of dabigatran over warfarin that wasn’t reported in the RE-LY trial\textsuperscript{14}. This observational study found that D150 therapy before a patient undergoes RF ablation actually increases the risk of both thromboembolic (stroke or TIA) and bleeding complications within 30 days of the procedure. The multivariate regression analysis done to assess predictors of complications found D150 before RF ablation to be an independent predictor of bleeding or thromboembolic complications. This data, although new, and contrary to what was previously understood about the drug, lends great insight into the reality of dabigatran therapy. With RF ablation therapy becoming a more widely used intervention for AF that cannot be controlled with pharmacotherapy, caution should be given when considering dabigatran.\textsuperscript{21}

**Other Outcomes**

One of the most negative effects of warfarin therapy is the increased risk of bleeding, such as intracranial hemorrhage. Warfarin doubles the risk of intracranial hemorrhage compared to aspirin.\textsuperscript{9} The RE-LY trial\textsuperscript{14} found that the rate of this complication with either dose of dabigatran (D110 or D150) was less than a third of the rate with warfarin. This evidence further strengthens the case for dabigatran as an alternative to warfarin. For rates of all major bleeding complications, the D110 dose
resulted in a significant decrease, while the D150 rates were decreased, but not to a statistically significant degree, making both doses at least noninferior to warfarin, according to the RE-LY trial\textsuperscript{14}. This information is put into perspective by the results from Lakkireddy et al\textsuperscript{19}, which show a significant risk of bleeding complications with dabigatran over warfarin in patients undergoing RF ablation.

Due to the nature and results of the primary outcomes measured in the RE-LY trial\textsuperscript{14}, it is not surprising that rates of death were lower in both groups receiving dabigatran. The most significant decrease in mortality was the rate of death from vascular causes in the D150 group, which was approximately 15\% less than that in the warfarin group.

\textbf{Limitations of Studies}

Research to assess the effectiveness of dabigatran versus that of warfarin has inherent limitations that must be considered. Due to warfarin’s mechanism of action, therapy must be closely monitored in all patients receiving the drug. In the RE-LY trial\textsuperscript{14}, this requirement prevented the patients in the warfarin group, and the study administrators, from being blinded as to which treatment they received. The open-label use of warfarin increased the risk of bias in reporting. A blinded evaluation of outcome events was implemented in the study design in effort to reduce that risk. Risk of bias in the RE-LY trial\textsuperscript{14} was also a consideration due to it being funded by Boehringer Ingelheim, the manufacturer of dabigatran.

Regarding the subgroup analyses reviewed\textsuperscript{16-18}, it is important to understand that, although they tend to support the results of the RE-LY trial\textsuperscript{14} and offer new insights into
the use of dabigatran, these studies should be labeled as exploratory in nature, as the outcomes analyzed were not predetermined in the RE-LY trial.

In the study done by Lakkireddy et al\textsuperscript{19} regarding complications after RF ablation, a limitation to note was the sample size of 290 patients. Although it provides invaluable data concerning the safety of dabigatran, this number represents only a small fraction of the sample size in the RE-LY trial\textsuperscript{14}, and therefore more research with greater participation is warranted. This study was also observational, which is a limitation compared to a study that has been randomized and concealed. It is also possible that confounding variables, such as operator-specific techniques in the ablation procedures, were unaccounted for and affected the results.

**Clinical Application**

Given its limitations, the RE-LY trial\textsuperscript{14} was a large and well-designed study that revealed important information about dabigatran and its potential as a promising anticoagulant agent with the ability to save lives. The validity of the study was reinforced by the use of a dose gradient, not only comparing dabigatran with warfarin, but also comparing the effect of D110 with D150. It was clearly demonstrated that D150 has a superior ability to prevent stroke and systemic embolism than warfarin, while D110 proved to be noninferior. With the understanding that all anticoagulant therapy inherently raises the risk of bleeding, this comparison of D110 with D150 lends reason to believe that the dose could be adjusted to achieve a safe and desired effect in each unique patient, especially for those at higher risk of bleeding.

The subgroup analyses reviewed in this study serve to both support the evidence produced by the RE-LY trial\textsuperscript{14} and also provide clinicians with greater understanding of
the appropriateness as to when the drug should be administered. Though their data mainly serve to show the consistency of various subgroup results with the overall results of the original trial, this information can illuminate confusion when considering placing a subgroup patient on dabigatran. Knowing that dabigatran has the same effect on patients with differing medical histories increases its therapeutic value and will improve provider confidence in prescribing.

Dabigatran is not a flawless alternative to warfarin, however. Connolly et al\textsuperscript{14} of the RE-LY trial discovered that occurrence of dyspepsia is significantly increased in both doses of the drug compared to warfarin. Although this may not appear to be a major obstacle for some, it is reasonable to believe that this side effect could inhibit patient compliance if not tolerated or treated properly. Interestingly, the RE-LY trial\textsuperscript{14} also produced evidence that, even though rates of major bleeding were decreased as a whole, the rate of major gastrointestinal bleeding was significantly increased in the D150 group. This is a serious problem that warrants further investigation, as to ensure the safety of patients who might otherwise receive more harm than benefit from therapy. In a separate subgroup analysis of the RE-LY trial\textsuperscript{14}, focused solely on the risk of bleeding with dabigatran versus warfarin, it was determined that the D150 dose was associated with a significant increase in the rate of extracranial bleeding in patients 75 years and older.\textsuperscript{22}

On December 7, 2011, just over a year from the time dabigatran was approved in the United States for prevention of stroke in AF patients, the Food and Drug Administration (FDA) issued a safety warning\textsuperscript{23} in response to research that revealed warning signs of bleeding risk with dabigatran use. The FDA stated that they are evaluating reports of serious bleeding events in patients taking dabigatran, but that, at this
time, they believe that the drug provides an important health benefit when used as directed. This logic is supported by the net clinical benefit measured in the RE-LY trial 14, which is a measurement of the overall benefit and risk of dabigatran. Given the risks associated with this drug, Connolly et al reported that the net clinical benefit, while similar to warfarin in the D110 group, was significantly increased in the D150 group.

CONCLUSION

Dabigatran decreases the risk of stroke and systemic embolism in patients with AF to a greater extent than warfarin. It also carries with it a significant risk of bleeding, which in some cases is greater than the same risk with warfarin therapy. Though more research will surely provide greater insight into the application of dabigatran and its role in anticoagulant therapy, it is clear that, in many patients, this drug has the ability save lives at an increased rate than the current standard of care.

Great care and consideration should be taken when administering dabigatran, but when the benefits appear to outweigh the given risks, it is not only an appropriate alternative to warfarin, but a superior option to preserve the lives of those who suffer from this common arrhythmia.
References


Table I. Characteristics of Reviewed Articles and Summary of Findings

<table>
<thead>
<tr>
<th>Importance</th>
<th>Quality Assessment</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Studies</td>
<td>Design</td>
<td>Limitations</td>
</tr>
<tr>
<td>Stroke or Systemic Embolism</td>
<td>1</td>
<td>Prospective</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
<td>Prospective</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>2</td>
<td>Prospective</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>Prospective</td>
</tr>
</tbody>
</table>

*The RE-LY trial was not fully blinded, and therefore not upgraded because of observed dose-response gradient.