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Is Dabigatran Non-inferior to Warfarin for the Prevention of Stroke in Those with Atrial Fibrillation?

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Abstract

OBJECTIVE: The objective of this systematic review is to determine whether or not dabigatran 150 mg twice daily is non-inferior to warfarin for the prevention of stroke in those with atrial fibrillation with similar rates of bleeding events.

STUDY DESIGN: Review of 3 English language primary studies. All three trials were randomized controlled trials which were blinded for those receiving dabigatran and un-blinded for those receiving warfarin.

DATA SOURCES: Articles were found using PUBMED and COCHRANE databases.

OUTCOME MEASURED: The primary outcomes of these studies were either incidence of stroke or systemic embolism and/or major bleeding events.

RESULTS: The RE-LY study determined that rates of stroke or systemic embolism were 1.11% per year in the group who received 150 mg of dabigatran twice daily and 1.69% per year in those who received dose adjusted warfarin (CI =95%; P=<0.0001). The incidence of major bleeding was 3.11% per year in those who received dabigatran 150 mg twice daily and 3.36% per year in the warfarin group (P=0.003). The RE-COVER study found that recurrent venous thromboembolism occurred in 2.4% of patients who received dabigatran and 2.1% of those who received warfarin (CI= 95%, P= <0.001). Incidence of major bleeding was found in 1.6% of patients in the dabigatran 150 mg group and a slightly higher percentage of 1.9% of those in the warfarin group (CI=95%). The PETRO study determined that in the 150 mg dabigatran group without aspirin, 9% of patients reported clinically relevant bleeding with zero thromboembolic events. In patients who received dose adjusted warfarin without aspirin, 5.7% of patients experienced clinically relevant bleeding with also no reported thromboembolic events (P=0.01).

CONCLUSION: The systemic review of all three randomized controlled trials indicates that dabigatran 150 mg twice a day is a safe, effective, and more convenient alternative to warfarin to prevent stroke in patients with atrial fibrillation.

KEYWORDS: Atrial fibrillation, dabigatran, warfarin, stroke.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting more than two million patients throughout the United States.[1] Each year, more than 300,000 new cases are diagnosed.[2] Atrial fibrillation comprises nearly $6 – 7 billion in direct medical expenditures and accounts for approximately 350,000 hospitalizations annually.[3] Research has shown that when comparing medical costs of a non-AF patient to an AF patient, total annual direct medical costs of those with AF are close to 5 times greater than that of those without the arrhythmia.[4] Medical costs in patients with this condition may be so high secondary to the nature and risks of the arrhythmia.

In episodes AF, the normal electrical impulses which are generated through the sinoatrial node become disorganized by electrical impulses that originate in other areas of the heart, possibly the pulmonary veins. This “chaotic” electrical activity results in the muscle of the atria fibrillating instead of producing a coordinated contraction of the chambers. Unbalanced conduction of the ventricles also produces an irregularly irregular ventricular rate. Atrial fibrillation can be acute, occurring in episodes lasting only minutes to weeks, or may be chronic, becoming permanent in nature.[5]

Many patients are asymptomatic during an episode of AF. Others may have more marked symptoms such as palpitations, syncope, chest pain, or shortness of breath. Atrial fibrillation is commonly diagnosed through a simple electrocardiogram which will show absence of P-waves and the presence of an irregularly irregular ventricular rate. Risk factors for developing AF include heart failure, hypertensive cardiovascular disease, coronary artery disease, valvular heart disease, and recent myocardial infarction.[6]

AF is commonly treated with medications to control heart rate and rhythm to revert the patient back to normal sinus rhythm. Some surgical or catheter based therapies can also be used. Because up to 5% of patients with chronic atrial fibrillation have at least one embolic episode per year, there is a need for these patients to be anticoagulated.[7] Currently, warfarin, a vitamin K antagonist, is the first line treatment being used for prophylactic anticoagulation in this population. However, due to increased risk of patient hemorrhage during usage, monthly laboratory monitoring and numerous drug and food interactions, a new oral anticoagulant drug is needed that has a similar or improved safety profile, as well as better convenience for patients who must be on lifelong anticoagulant therapy. Dabigatran is a new oral direct thrombin inhibitor that is being evaluated for the prevention of stroke in those patients with AF with a similar incidence of hemorrhage.

OBJECTIVE

The objective of this systematic review is to determine whether or not dabigatran 150mg is non-inferior to warfarin for the prevention of stroke in those with atrial fibrillation with a similar safety profile. To date, there are few anticoagulant drugs, other than warfarin, that are approved to prevent stroke in patients with AF. Dabigatran is the first oral direct thrombin inhibitor that has been approved to compete with warfarin to prevent stroke in those with AF with similar frequency of bleeding.

METHODS

The three studies that are included in this review are randomized controlled trials comparing the efficacy of dabigatran 150 mg to dose adjusted warfarin for the prevention of stroke in those atrial fibrillation with similar incidence of hemorrhage.

Connolly et al. conducted the RE-LY study, a randomized controlled trial to assess the efficacy of dabigatran 150 mg versus warfarin. The trial was non-inferior, double blinded for those in the dabigatran group and unblinded for those in the warfarin group due to the need for adjusted INR levels. The study focused on 18,113 patients with atrial fibrillation documented on echocardiography with one of the following: previous stroke or TIA, left ventricular ejection fraction less than 40%, New York Heart Association Class II or higher, age of 75, or age of 64 – 74 with diabetes, hypertension, or coronary artery disease. The intervention addressed in the study included dabigatran 150 mg twice daily to prevent stroke or systemic embolism in those with atrial fibrillation. The comparison group was dose adjusted warfarin. The primary outcomes of this study were incidence of stroke or systemic embolism, with secondary efficacy endpoints consisting of major bleeding, hemorrhagic stroke, and mortality rate.

Shulman at el. conducted the RE-COVER study, a double blinded randomized controlled trial to determine the efficacy of dabigatran 150mg versus warfarin for the treatment of acute venous thromboembolism as well as rates of hemorrhage. This study included 2,539 patients 18 years of age or older who had acute, symptomatic, objectively verified proximal deep vein thrombosis of the legs or pulmonary embolism and for whom 6 months of anticoagulant therapy was considered to be an appropriate treatment. Dabigatran 150 mg twice daily, after a median of 9 days of initial parenteral anticoagulation, was the intervention addressed in this study. The comparison group was comprised of dose adjusted warfarin after initial parenteral anticoagulation. The primary outcome measured in this study was 6-month incidence of confirmed venous thromboembolism. Secondary outcomes were major bleeding events, acute coronary syndromes, other adverse events, and results of liver function tests.

Ezekowitz et al. conducted a similar randomized controlled trial which was double blind in respect to dabigatran, but open label regarding aspirin and warfarin. The population addressed in the PETRO study was patients with atrial fibrillation at high risk for thromboembolic events or AF with coronary artery disease plus 1 or more of the following: hypertension, diabetes, symptomatic heart failure, left ventricular dysfunction, or previous stroke or TIA. Dabigatran was administered at 50 mg, 150 mg, or 300 mg, twice daily with either no aspirin, 81 mg or 325 mg aspirin once daily. The dabigatran 150 mg dose twice daily without aspirin was the main focus for this review. These interventions were compared to dose adjusted warfarin. The primary outcome addressed was frequency of bleeding events and secondary outcomes were incidence of stroke and/or systemic thromboembolism.

These studies were found by the author using PubMed and Cochrane databases. The key words dabigatran, warfarin and atrial fibrillation were used in the literature searches to find articles that were published in English in peer-reviewed journals dated between 2007 – 2009. The articles were chosen if they were relevant, valid, and the outcomes of the studies were comprised of evidence that mattered to the patients (POEMS – Patient Oriented Evidence that Matters). The articles selected were those that met the following criteria: POEM, randomized controlled trial, a diagnosis of atrial fibrillation based upon electrocardiogram, or a primary outcome of stroke or major bleeding. Any studies not meeting these criteria were excluded from this review. P-values, number needed to treat (NNT), number needed to harm (NNH), relative risk reduction (RRR), absolute risk reduction (ARR), control event rate (CER), and experimental event rate (EER) were the statistics used and reported in the studies. Table 1 shows the demographics of the three studies included in this review.

Table 1. Demographics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Connolly (2009) RE-LY	Double blind RCT with respect to dabigatran ; unblinded in respect to warfarin	18,113	Mean age 71	-Patients with AF documented on EKG with 1 of the following: -Previous stroke or transient ischemic attack -LFEV less than 40% -New York Heart Association Class II or higher -Age of 75 -Age of 64 – 74 with DM, HTN, or CAD	-Presence of severe valve disorder -Stroke w/in 14 days or severe stroke with in 6 mo before screening -Condition that increased risk of hemorrhage -CrCl <30 -Acute liver disease -Pregnancy	0	Dabigatran 150 mg BID
Schulman (2009) RE-COVER	Double blind RCT	2,550	55.0±15.8 Dabigatran 54.4±16.2 Warfarin	Patients 18 years of age or older who had acute, symptomatic, objectively verified proximal deep vein thrombosis of the legs or pulmonary embolism and for whom 6 months of anticoagulant therapy was considered to be an appropriate treatment	-Symptoms longer than 14 days - PE with instability -Other indication for warfarin -Unstable CV disease -High bleeding risk -Liver disease with AST > 2x upper limit -CrCl <30 -Pregnancy -Need for antiplatelet therapy -CI to heparin or contrast	5	Dabigatran 150mg BID
Ezekowitz (2007) PETRO	Double blind RCT in respect to dabigatran ; unblinded in respect to warfarin and ASA	502	70.9 ±7.9 years in patients with CAD 68.0 ±8.8 years in those without CAD	-Patients with AF at high risk for thromboembolic events -AF with CAD plus 1 of the following: -HTN, DM, symptomatic HF, LV dysfunction, previous stroke or TIA	-Mitral stenosis -Prosthetic heart valves -Cardioversion -Recent MI, stroke or TIA Coronary stent in last 6 mo -CI to anticoagulation -severe hemorrhage in last 6 mo -Renal impairment -Abnl liver function -Pregnancy -Investigation drug use in last 30 days	65	Dabigatran 50 mg, 150 mg, or 300 mg BID, with either no aspirin, 81 mg or 325 mg aspirin daily

OUTCOMES MEASURED

The outcomes of interest in the clinical trials varied according to each study. However, each study included outcomes, whether primary or secondary, that will be the focus of this review.

In the RE-LY study, the primary outcome measured was incidence of stroke or systemic embolism. The primary safety outcome was rate of major hemorrhage. Incidence of stroke was documented by sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery. The stroke was then categorized as ischemic, hemorrhagic, or unspecified. Occurrence of a systemic embolism was documented through imaging, surgery, or autopsy. Secondary outcomes consisted of major bleeding, hemorrhagic stroke, and mortality rate. Major bleeding or hemorrhage was documented by reduction in hemoglobin of at least 2g/L, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ.

In the RE-COVER trial, the primary study outcome was 6-month incidence of recurrent, symptomatic, objectively confirmed venous thromboembolism and related deaths. Symptoms suggestive of recurrent venous thromboembolism were evaluated with the use of the same diagnostic methods that had been used for the initial diagnosis. Secondary outcomes were major bleeding events, acute coronary syndromes, other adverse events, and results of liver function tests. Bleeding was defined as major if it was clinically overt and if it was associated with a decrease in hemoglobin of at least 2g/L, resulted in the need for transfusion of 2 or more units of red cells, if it involved a critical site, or if the bleeding was fatal.

In the PETRO study, the primary outcome addressed was frequency of bleeding events classified as fatal or life threatening retroperitoneal, intracranial, intraocular, or intraspinal

bleeding; or bleeding requiring surgery or transfusion of greater than 2 units associated with a reduction of hemoglobin greater than 2g/L. Secondary efficacy endpoints were incidence of stroke defined as acute onset of focal neurologic deficit of vascular origin lasting greater than 24 hours and/or systemic thromboembolism defined as an acute non-intracerebral or noncoronary vascular event.

RESULTS

All three randomized controlled trials evaluated the efficacy of dabigatran 150 mg twice daily to prevent stroke in patients in AF or measured rates of major and minor bleeding compared with dose adjusted warfarin.

In the RE-LY study a total of 18,113 patients were enrolled, all of which had a mean age of 71 years and a mean $CHADS_2$ score of 2.1 (the $CHADS_2$ score is a measure of the risk of stroke in which CHF, HTN, and age of 75 years or older, and DM are each given 1 point and previous stroke or TIA are each given 2 points).[8] The median duration of follow-up was 2.0 years with 99.9% of patients achieving complete follow-up. Rates of the primary outcome of stroke or systemic embolism were 1.11% per year in the group who received 150 mg of dabigatran twice daily and 1.69% per year in those who received dose adjusted warfarin. A confidence interval of 95% and a P-value of <0.0001 for non-inferiority was used for this data. The NNT was determined to be – 173, signifying that for every 173 patients treated with dabigatran, 1 less patient experienced stroke or hemorrhage compared with warfarin. The incidence of major bleeding was 3.11% per year in those who received dabigatran 150 mg twice daily and 3.36% per year in the warfarin group. The occurrence of hemorrhagic stroke was determined to be 0.38% per year in the warfarin group and 0.10% in the dabigatran group at a p-value of <0.0001. Mortality rate was found to be 3.64% per year with 150 mg of dabigatran

twice daily, whereas warfarin mortality was 4.13% per year at a p-value of 0.13. Major vascular events, major bleeding, and death comprised the net clinical benefit outcome. The rate of this outcome in the warfarin group was 7.64% per year and 6.91% per year in those given 150 mg of dabigatran at a CI of 95% and a p-value of 0.10 (Table 2). The NNH in this group was determined to be -400, thus, for every 400 patients treated with dabigatran, one less patient had an incidence of major bleeding, hemorrhagic stroke, or mortality compared to warfarin.

Table 2. Efficacy and Bleeding Outcomes of the RE-LY Study

Event	**Dabigatran 150 mg** N= 6076			**Dose Adjusted Warfarin** N= 6022		
	# of patients	%/year	P-value	# of patients	%/year	P-value
Stroke or systemic embolism	134	1.11	<0.0001	199	1.69	<0.0001
Major Bleeding	375	3.11	0.003	397	3.36	0.003
Hemorrhagic Stroke	12	0.10	<0.0001	45	0.38	<0.0001
Mortality Rate	438	3.64	0.13	487	4.13	0.13
Net clinical benefit	832	6.91	0.10	901	7.64	0.10

In the RE-COVER trial, a total of 2,564 patients were enrolled, with a total of 1,274 patients in the dabigatran 150 mg group and 1,265 in the warfarin group. Incidence of the primary outcome, recurrent venous thromboembolism, occurred in 2.4% of patients who received dabigatran and 2.1% of those who received warfarin at a CI of 95% and p-value of <0.001. The NNT in this group was 334. For every 334 people treated with dabigatran, 1 more person had an occurrence of confirmed venous thromboembolism, compared to warfarin. Incidence of major bleeding, which is of more concern for this review, was found in 1.6% of patients in the dabigatran 150 mg group and a slightly higher percentage of 1.9% of those in the

warfarin group. For every 334 people treated with dabigatran, one less person experienced major bleeding, acute coronary symptoms, and/or elevated liver function tests in comparison to warfarin. Sites of major bleeding for the dabigatran groups included gastrointestional (9 events), urogenital (5), intraarticular (1), intramuscular (1) or another site (6). For the warfarin group, major sites of bleeding included urogenital (6), gastrointestinal (5), intraarticular (4), intracranial (3), intramuscular (3), or another site (4). A total of 5.6% of patients who received dabigatran compared to 8.8% of patients who were given warfarin experienced major or clinically relevant non-major bleeding (Table 3).

Table 3. Efficacy and Bleeding Outcomes of the RE-COVER Study

Outcome	**Dabigatran 150 mg twice daily (N=1274)**	**Warfarin (N=1265)**	**Confidence Interval**
Venous thromboembolism or related death	30 patients 2.4%	27 patients 2.1%	95%
Major Bleeding Events	20 patients 1.6%	24 patients 1.9%	95%
Major or clinically relevant non-major bleeding	71 patients 5.6%	111 patients 8.8%	95%

In the PETRO trial, 502 patients were randomized who had atrial fibrillation for a median duration of 4 years. The primary outcome was frequency of bleeding events. In the 150 mg dabigatran group without aspirin, 9% of patients reported clinically relevant bleeding with zero thromboembolic events. In patients who received dose adjusted warfarin without aspirin, 5.7% of patients experienced clinically relevant bleeding with also no reported thromboembolic events at a p-value of 0.01 (Table 4). The NNH for this study was -8 signifying that for every 8 patients treated with dabigatran without aspirin, 1 less patient experienced a bleeding event when compared to dose adjusted warfarin without aspirin.

Table 4. Major or clinically relevant bleeding episodes and thromboembolic events in PETRO

	Number of patients	Major Bleeding	Clinical Relevant plus Major Bleeding	Thromboembolic Events
Dabigatran 150 mg BID	100	0	9 (9%)	0
Warfarin	70	0	4 (5.7%)	0

Because in all three trials the data was dichotomous, the control event rate (CER), experimental event rate (EER), absolute benefit increase (ABI), relative benefit increase (RBI), number needed to treat (NNT) and number needed to harm (NNH) were each calculated. The CER is the percentage of patients who responded to the dose adjusted warfarin whereas the EER is the percentage who responded to the 150 mg dabigatran. The ABI is the increase of a good event as a result of dabigatran. The RBI is the proportional increase in the rates of good outcomes between the warfarin and dabigatran group. The results of number needed to treat and number needed to harm determines the number of people needed to be treated to prevent 1 event of stroke or embolic event or to cause 1 event of major hemorrhage. Table 5 represents this data that was calculated for all three of the trials described above.

Table 5. Treatment analysis for patients receiving dabigatran versus warfarin for prevention of stroke

Study	CER	EER	RBI	ABI	NNT and NNH
RE-LY	1.96% 3.36%	1.11% 3.11%	-34.3% -7.4%	-0.58% -0.25%	-173 (NNT) -400 (NNH)
RE-COVER	2.1% 1.90%	2.4% 1.60%	14.3% -15.8%	3.00% -3.00%	334 (NNT) -334 (NNH)
PETRO	17.1%	15.0%	-12.3%	-21.0%	-8 (NNH)

DISCUSSION

Dabigatran etexilate is a prodrug of dabigatran, a reversible competitive inhibitor of thrombin activity. Dabigatran is able to inhibit both free and clot bound thrombin, as well as inhibit thrombin's activation of platelets.[9] The drug requires no laboratory monitoring and carries

minimal drug and food interactions when compared with warfarin, making dabigatran an attractive alternative to patients and prescribers. The most common adverse events that have been associated with the use of dabigatran are bleeding and gastrointestinal symptoms including dyspepsia, nausea, diarrhea, abdominal pain, and gastrointestinal bleeding.[10] The RE-LY study demonstrated a statistically significant decrease in the rates of stroke and systemic embolism when compared with warfarin. The RE-COVER and PETRO study each exemplified the safety of dabigatran when compared to warfarin with a statistically significant decrease in major bleeding events.

All three studies presented in this review can be termed valid for many reasons. They were randomized controlled trials whose outcomes were presented as dichotomous data, and the studies were double-blinded in regards to the dabigatran group. There were also a minimal number of patients who were lost to follow-up. Because there was a small sample size of patients in the PETRO dabigatran 150 mg group, the results may have been skewed.

CONCLUSION

This review indicates that dabigatran 150 mg twice a day is a safe and effective alternative to warfarin to prevent stroke in patients with atrial fibrillation. In all three studies, dabigatran 150mg was found to be non-inferior to warfarin in respect to stroke prevention and incidence of bleeding. In the RE-LY study, dabigatran 150 mg was found to be superior when to compared to warfarin regarding rates of stroke and systemic embolism. Higher and lower doses of dabigatran have been investigated, however, results showed that the lower doses were not as effective in preventing stroke whereas higher doses had increased incidence of major bleeding rates. Future studies should compare the efficacy of dabigatran versus another new oral thrombin inhibitor, rivaroxaban, for the prevention of stroke in patients with AF.

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