Warfarin versus Dabigatran: the Superior Option

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ABSTRACT

Background: Atrial fibrillation (AF) is an arrhythmia that increases the risks of blood clots, stroke, heart-failure. Oral antithrombotic and anticoagulation has been associated with the reduced formation of thrombus thus reducing the risk of AF related stroke. Novel oral anticoagulants (NOACs) were developed in response to the downfalls of Warfarin. The first of which was dabigatran, an oral prodrug, thrombin inhibitor.
Objective: The purpose of this study is to review the literature comparing warfarin and dabigatran on their efficacy (rates of stoke and systemic embolism), cost-effectiveness, and safety (events of major hemorrhage). Cost effectiveness was determined based on quality adjusted life-years (QALYs).
Methods: Medline (Ovid) was used as a database with the search terms: stroke, warfarin, dabigatran, and AF. Limited to English, full text, published from 1999-2016 six articles were then reviewed for their use in this abstract. Two fundamental studies were not revealed by the original search, but were sourced by all articles chosen and was therefore included. Eight articles were used.
Results: Dabigatran is prescribed in a 110 mg dose (D110) or a 150 mg dose (D150) twice daily. It was found that D110 had similar efficacy to warfarin but improved safety rates. D150 had decreased rates of stroke and systemic embolism compared to warfarin, but similar rates of major hemorrhage. In addition, Dabigatran safety may differ between sexes, Thirdly, NOACs are more expensive but more cost-effective than warfarin based on QALYs. D150 cost less than D110 per improvement in QALYs.
Conclusion: Both doses of dabigatran were found to be non-inferior to warfarin for safety and efficacy rates. D150 was superior in regards to efficacy rates. D110 was superior in regards to safety. D150 was superior to D110 and warfarin in cost-effectiveness. Future exploration into a tailored dose of Dabigatran and sex-differences.

INTRODUCTION

AF is an arrhythmia that increases the risks of blood clots, stroke, heart-failure. The Center for Disease Control estimate 2.7–6.1 million people in the United States have AF. Stroke as the leading cause of death and disability by the Public Health Agency of Canada; cost for health care and lost productivity due to premature death and long-term disability in 2000 was estimated to be $3.6 billion. Oral antithrombotic and anticoagulation has been associated with the reduced formation of thrombus thus reducing the risk of AF related stroke. Warfarin, a vitamin K antagonist, is the popular oral anticoagulant in the prevention of stroke but has downfalls. Warfarin was found to reduce the risk of stroke but increase the risk of hemorrhage. It is difficult to use, as it has many food and drug interactions and requires diligent monitoring. In response NOACs were developed, the first of which was Dabigatran Etexilate, an oral prodrug, competitive thrombin inhibitor. The prodrug is processed by a serum esterase to become dabigatran. Dabigatran has a rapid onset, is easy to use, and has few interactions. Its bioavailability is 6.8%, with a half-life of 12-17 hours it does not require regular monitoring.

RESEARCH QUESTION

Is Dabigatran or Warfarin more effective, safe, and cost-effective for the prevention of stroke in patients with AF?

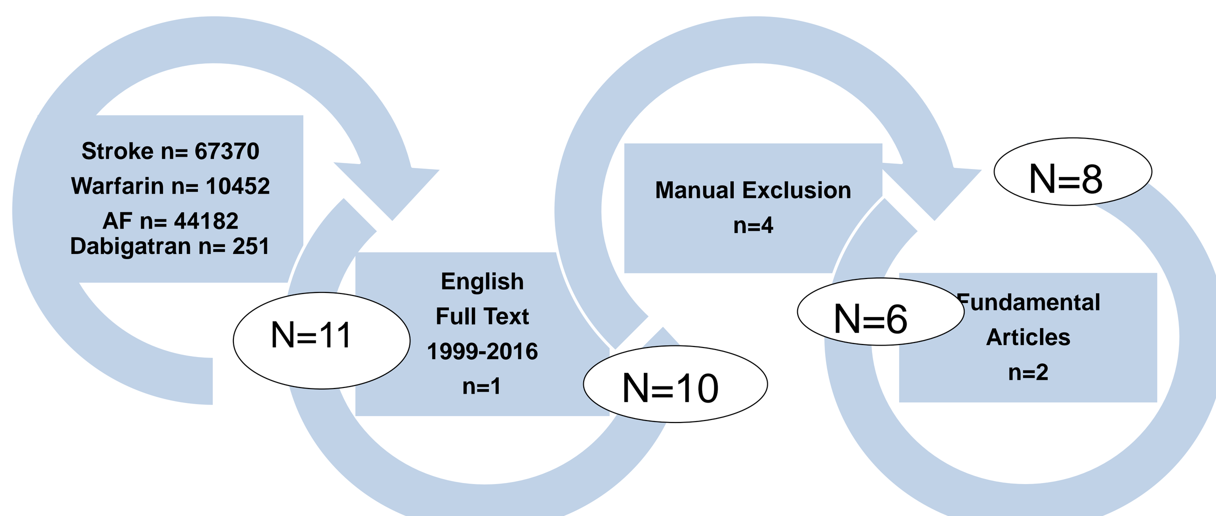

Figure 1. Flowchart showing the process of article selection. After searching the key words and applying the inclusion and exclusion criteria, a total of eight articles were used

METHODS

Search Strategy

The database used was Medline (Ovid).
The key words searched were: Stroke and warfarin and dabigatran and atrial fibrillation, resulting in 11 articles.

Inclusion Criteria

Inclusion criteria were: written in the English language, full text, published from 1999-2016, resulting in ten articles

Exclusion Criteria

Four articles were then manually excluded because: one focused solely on an elderly Chinese population, another for it focused on the clinical features of ischemic stroke in cessation of Dabigatran, another for it focused on interleukin-6 and C-reactive protein, and the final was excluded because it focused on a population who had an elective surgery.
Two fundamental study was not revealed by the original search, but was sourced by all articles chosen and was therefore included. A total of eight articles were used.

RESULTS

Article	Type of Study	Number of Participants	Risk of Stroke (efficacy)	Risk of Hemorrhage (safety)	Cost-Effectiveness
Avgil-Tsadok et al. (2016)	Cohort	• N= 63,110 • Dabigatran=15,918 • Warfarin=47,192 • 67.3% being elderly patients	• Similar risk between Dabigatran and Warfarin users regardless of dose in patients (HR 1.05, 95 % CI: 0.93, 1.19)	• Dabigatran= lower rates of intracranial haemorrhage (HR 0.60, 95 % CI: 0.47–0.76) • Dabigatran= higher rates of gastrointestinal bleeding in ≥75 years (HR 1.30 95 % CI: 1.14–1.50)	N/A
Seeger et al. (2015)	Sequential Cohort	• N=19,189 per group • Mean age: 68 years • 36 % female	• Dabigatran= greater stroke prevention in age 75+ (HR = 0.57; 0.33 to 0.97) or with < 6 months of use (HR = 0.51; 0.19 to 1.42).	• Dabigatran = lower rates of major bleeds among patients aged < 55 (HR = 0.51; 0.30 to 0.87), and with CHADS2 < 2 (HR = 0.58; 0.44 to 0.77).	N/A
Villines et al. (2015)	Cohort	• N=12,793 per group • mean age 74	• Dabigatran= fewer strokes (adjusted hazard ratio [95 % confidence intervals] 0.73 [0.55–0.97])	• Dabigatran= fewer major intracranial (0.49 [0.30–0.79]), urogenital (0.36 [0.18–0.74]) and other (0.38 [0.22–0.66]) bleeding • Dabigatran= frequent lower GI bleeding events (1.30 [1.04–1.62]) • Similar = Major bleeding (0.87 [0.74–1.03]) and major GI bleeding (1.13 [0.94–1.37])	N/A
Avgil Tsadok, PhD et al. (2015)	Cohort	• N= 63110 • 31 786 women (50.4%) • 31 324 men (49.6%).	• Dabigatran = lower risk in both sexes, lower risk of stroke in women treated with the 150-mg dose (HR, 0.79; 95% confidence interval, 0.56–1.04),	• Dabigatran = lower risk of bleeding in men (P for interaction=0.008)	N/A
Singh et al. (2015)	Meta-analysis of the four randomized trials	• N=5	N/A	N/A	• NOACs more expensive, found to be more cost-effective than warfarin based on QALYs. • D150 cost less than D110 per improvement in QALYs
Nagarakanti M.D. et al. (2015)	Cohort	• N= 18,113	• Similar: D110 and D150 compared to warfarin were similar (p [nonsignificant) in hypertensive and normotensive patients	• Dabigatran: reduction of intracranial hemorrhage (in both hypertensive and non-hypertensive patients). • Similar: D110 and D150 compared to warfarin in major bleeds (p [nonsignificant) in hypertensive and normotensive patients	N/A
Connolly M.D. et al. (2009)	RCT	• N=18,113	• D110 = similar rates of stroke • D150=lower rate of stroke	• D110= lower rates of major hemorrhage. • D150 =Similar rates of major hemorrhage	N/A
Eikelboom MBBS. et al. (2011)	RCT	• N=18,113	N/A	• D110 =a lower risk of major bleeding in patients aged <75 years (1.89% versus 3.04%; *P*0.001) • D110= similar risk in ages ≥75 years (4.43% versus 4.37%; *P*0.89; *P* for interaction 0.001) • D150=lower risk of major bleeding in those aged <75 years (2.12% versus 3.04%; *P*0.001) • D150= higher risk of major bleeding in those aged ≥75 years (5.10% versus 4.37%; *P*0.07; *P* for interaction 0.001).	N/A

DISCUSSION

Efficacy:

•Dabigatran is similar or has a better protective effect than Warfarin at reducing stroke rates in patients with AF.
•**Dosage**: D110 has a similar rate of stroke compared to Warfarin. D150 has a lower rate of stroke. No difference in effect in study by Avgil-Tsadok et al.(2016) due to nature of cohort.
•**Age**: Dabigatran has greater stroke prevention in patients aged 75+ than Warfarin.
•**Sex**: protective factor for both sexes lowering the risk of stroke. D150 was observed to lower risk more in women however, it can be argued that they have a higher baseline risk of stroke which may act as a confounding variable.

Cost Effectiveness:

•NOACs more expensive, but more cost-effective than Warfarin based on QALYs.
•D150 cost less than D110 per improvement in QALYs.

Safety:

•Dabigatran has a similar risk to Warfarin or reduces risk of major hemorrhage
•**Dosage**: D110 showed lower rate of bleed than both Warfarin and D150. D150 had a similar rate of bleed to Warfarin in article by Connolly M.D. et al. (2009).
•**Age**: Two articles specified that Dabigatran showed greatest reduction in rate of bleeds in patients less than 55 and 75 than Warfarin.
•**Sex**: Dabigatran presents lower bleeding risk in men than in Warfarin
•Higher rates of gastrointestinal bleeding are noted with Dabigatran than Warfarin. Mechanism behind the bleed in the studies is not well understood.
•Increased risk of major bleeds for hypertensive patients
•Results are as expected since Dabigatran is a new prodrug that is meant to treat mishaps of Warfarin.

Limitations:

•Only one data base used limited to English with no articles published prior to 1999.
•We did not differentiate between the key terms valvular and non-valvular AF in our search
•The selective attrition of participants: due to nature of progressive disease leading to death
•The risk of confounding variables : AF burden (subtypes and severity of AF), faulty treatment adherence, over the counter use of aspirin, comorbidities (renal disorders, could modify or confound the effect of anticoagulants, etc.), observed heterogeneity between subgroups, inadequate propensity score analysis, and study duration (2 years).

Contextualization and Future Research:

•Further research is needed for patient tailored dosing and sex tailored dosing.
•Investigation into Dabigatran and Warfarin sites of bleeding is warranted

CONCLUSION

- Dabigatran was associated with improved efficacy measures: decreased rates of stroke.
- Dabigatran was associated with improved safety measures: decreased rates of intracranial hemorrhage
  - but some instances of increased rates of gastrointestinal hemorrhage
- Overall dabigatran was found to be more cost effective than warfarin per QALY
- Dabigatran is the superior option based on efficacy, safety and cost-effectiveness, when compared to Warfarin

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