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Case Report

Dabigatran Compared with Warfarin for Stroke Prevention in Patients with Atrial Fibrillation: An Evidence Based Case Report

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Background. Atrial fibrillation (AF) increases the risk of having stroke as high as five fold. Anticoagulant administration such as vitamin K antagonist has been used regularly to reduce the occurence of stroke. Despite the high efficacy, warfarin has several limitations, including a narrow therapeutic window, multiple food and drug interactions, and the need for frequent laboratory monitoring. Dabigatran, an oral thrombin inhibitor, displays some positive characteristics as the solution to warfarin's limitations.
Aim. To determine the efficacy of dabigatran compared to warfarin for stroke prevention in patients with atrial fibrillation.
Methods. A search was conducted on PubMed and Google. The selection of title and abstract was done using inclusion and exclusion criteria. Five original articles were found, but only one study was used. The selected study was critically appraised for its validity, importance and applicability.
Result. The administration of 150 mg of dabigatran was superior to warfarin with respect of stroke. The relative risk reduction was 36% in the 150 mg dabigatran group. The rate of stroke was 1.01% per year in the group that received 150 mg dabigatran, as compared with 1.57% per year in the warfarin group (relative risk 0.64; 95% confidence interval, 0.51 to 0.81, $p<0.001$). The administration of dabigatran increased the risk of gastrointestinal bleeding.
Conclusion. In patients with atrial fibrillation, dabigatran given at a dose of 150 mg, as compared with warfarin, was associated with lower rate of stroke. Dabigatran administration requires closed gastrointestinal monitoring.

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Keywords: Dabigatran, warfarin, stroke, atrial fibrillation

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Laporan Kasus

Dabigatran dibandingkan Warfarin untuk Pencegahan Stroke pada Pasien dengan Atrial Fibrilasi: Laporan Berbasis Bukti

Alvin Nursalim[1], Yoga Yuniadi[2]

Latar belakang. Atrial fibrilasi (AF) meningkatkan risiko terjadinya stroke sebanyak lima kali. Warfarin, golongan antagonist vitamin K, telah digunakan cukup lama untuk menurunkan kejadian stroke. Namun warfarin memiliki beberapa keterbatasan seperti ambang terapi yang sempit, berbagai interaksi obat dan diperlukannya pemantauan berkala. Dabigatran, antitrombin oral, memiliki beberapa keunggulan sebagai jawaban sebagai keterbatasan dari warfarin.
Tujuan. Menentukan efektivitas dabigatran dibandingkan warfarin untuk pencegahan stroke pada pasien dengan atrial fibrillasi.
Metode. Pencarian terstruktur dilakukan dengan menggunakan Pubmed dan Google. Setelah dilakukan penapisan judul dan abstrak dengan kriteria inklusi dan eksklusi, lima studi ditemukan, tetapi hanya satu studi yang digunakan penulis. Studi ini ditelaah dengan menggunakan kriteria yang mencakup *validity, importance,* dan *applicability* untuk menentukan derajat kegunaan dalam studi ini.
Hasil. Pemberian dabigatran sebanyak 150 mg menyebabkan penurunan risiko terjadinya komplikasi stroke pada pasien AF sebesar 36% dibandingkan warfarin. Kejadian stroke pada kelompok yang menerima 150 mg dabigatran sebesar 1.01% per tahun dibandingkan dengan 1.57% pada kelompok warfarin. (*relative risk* 0.64; 95% *confidence interval*, 0.51-0.81, p<0.001). Namun pemberian dabigatran meningkatkan risiko terjadinya perdarahan gatrointestinal.
Kesimpulan. Pemberian 150 mg dabigatran menurunkan risiko terjadinya stroke pada pasien AF dibandingkan pemberian warfarin. Namun pemberian dabigatran memerlukan pemantaun perdarahan gastrointestinal.

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Kata kunci: Dabigatran, warfarin, stroke, atrial fibrilasi

Clinical Scenario

Sixty five years old man was admitted to the hospital with palpitation since three days before hospital admission. The patient denied the same complaint before and had history of heart failure. The patient denied any history of chest pain, diabetes mellitus and gastrointestinal disease. From the physical examination BP: 150/90, temperature: 37°C, HR:

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irreguler. RR: 30x. There was no abnormality found in other physical examination. The doctor suspected the patient had atrial fibrillation which then confirmed by electrocardiography examination. The $CHADS_2$ score of this patient is two due to congestive heart failure and hypertension. After the administration of regular prescription for atrial fibrillation, the doctor faced a dilemmatic choice for the anticoagulant whether to administer warfarin, the popular drug he had been using for years or dabigatran, a new drug he just knew.

Introduction

Atrial fibrillation (AF) is the most common cardiac rhytm disorder and a powerful risk factor for stroke, independently increasing risk five-fold throughout all ages. The percentage of strokes attributable to AF increases steeply from 1.5% at 50 to 59 years of age to 23.5% at 80 to 89 years of age.[1]

Currently, Vitamin K antagonists (VKA) are commonly used to prevent stroke in AF patients. Until recently, VKA are the only orally active anticoagulants available. Warfarin, the most commonly used oral VKA, reduces the risk of stroke in patients with nonvalvular AF by 68%. Despite the high efficacy, warfarin has several limitations, including a narrow therapeutic window, multiple food and drug interactions, and the need for frequent laboratory monitoring. Due to its limitations, the therapeutic range is achieved in less than two-thirds of patients in clinical practice.[2] An orally effective anticoagulant, with less drug interaction and without the need for regular monitoring would be the answer to warfarin's limitations.

Dabigatran etexilate is an orally available prodrug that is converted to dabigatran, the active substrate. It is a reversible direct inhibitor of thrombin. Its half-life ($T_{1/2}$) is 14–17 hours and is excreted out through kidneys; thus, once or twice daily administration is enough.[3] Dabigatran has a rapid onset of action and does not need frequent monitoring.[4] Dabigatran does displays some positive characteristics, but whether its efficacy is equal or even better than warfarin need to be further investigated. This report is made to identify the efficacy of dabigatran compared to warfarin for stroke prevention in atrial fibrillation patients.

Clinical Question

Is dabigatran as effective as warfarin for stroke prevention in patients with atrial fibrillation?

Methods

Search strategy

PubMed,® and Google,® search was performed on November 2nd and 3rd 2011, using the keywords "dabigatran", "warfarin", "stroke" and "atrial fibrillation"along with its synonyms and related terms (Table 1). Searchstrategy, results, the inclusion and exclusion criteria are shown in a flowchart (Figure 1).

Selection

The first selection was based on title and abstract using inclusion criterias and exclusion criteria.. After selection, filtration and screening title abstract, one full-text article was available.

Table 1. Search strategy used in PubMed and Google (Conducted on November 2nd and 3rd 2011)

Database	Search terms	Results
Pubmed (2nd November 2011)	"dabigatran"[All Fields]) AND ("warfarin"[MeSH Terms] OR "warfarin"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields]) AND ("atrial fibrillation"[MeSH Terms] OR ("atrial"[All Fields] AND "fibrillation"[All Fields]) OR "atrial fibrillation"[All Fields])	26
Google (3rdNovember 2011)	Dabigatran Warfarin Atrial Fibrillation	43

Critical Appraisal

After the selection, critical appraisal was done using several aspects based on Center of Evidence-based Medicine, University of Oxford for therapy study (Table 2).

Result

The study conducted by Connolly SJ et al[5] is a phase III trial on 18,113 patients from 951 clinical centers in 44 countries. The study was a prospective, randomized, open-label, blinded-endpoint trial. Connolly SJ et al

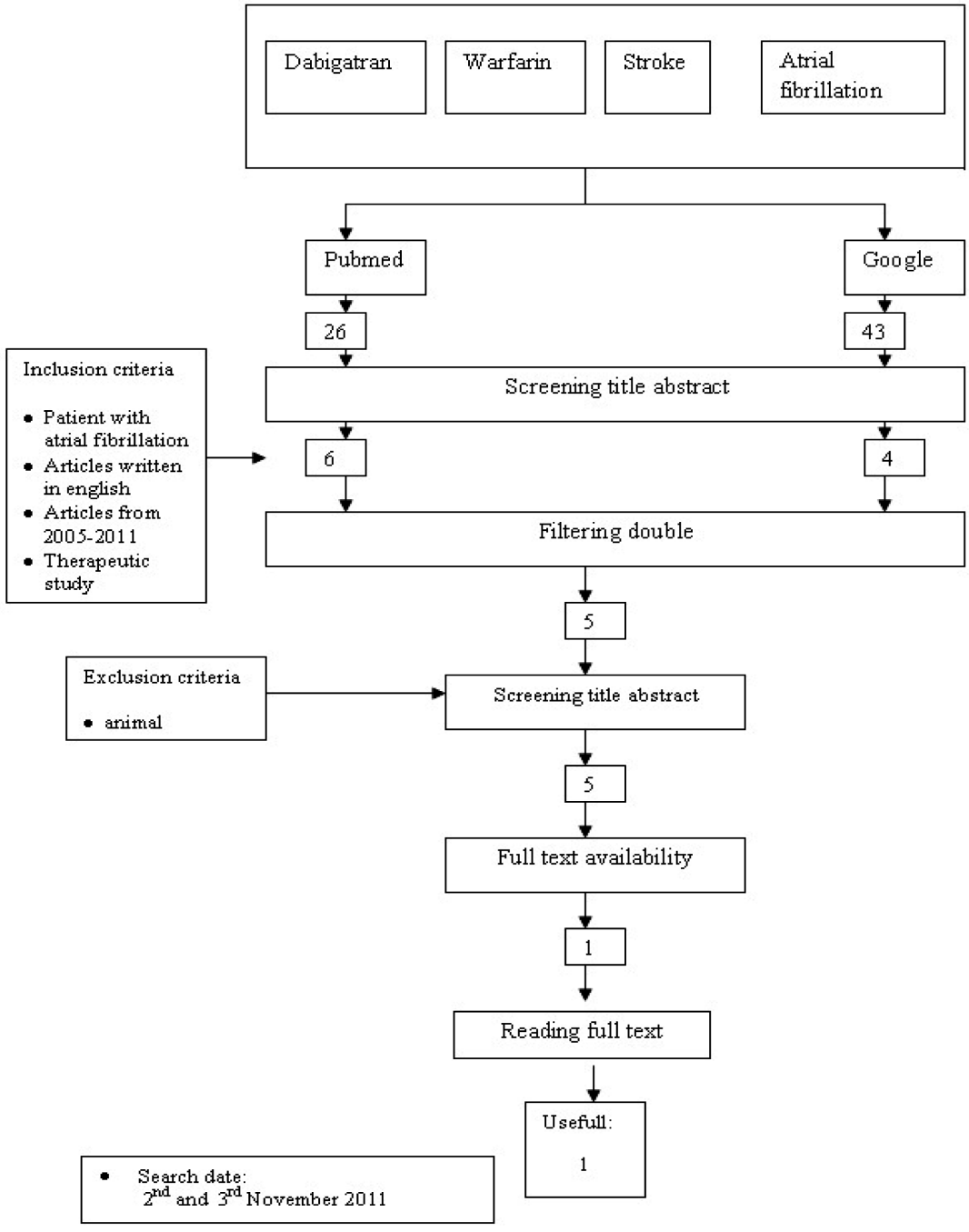

Figure 1. Flow Chart of Search Strategy

conducted a study to determine the efficacy of 110 mg and 150 mg of dabigatran compared to warfarin. Warfarin is given in tablets of 1, 3 or 5 mg and was adjusted locally to an international normalized ratio (INR) of 2.0-3.0.

In the first group, 110 mg of dabigatran is given to 6015 patients with atrial fibrillation. After a mean of 2 years follow-up, stroke occured in 171 patients receiving 110 mg of dabigatran compared to 185 patients in the warfarin group.The Control Event Rate (CER) was 3.1%, Experimental Event Rate (EER) was 2.8%, Relative Risk Reduction (RRR) was 9.7%, Absolute Risk Reduction (ARR) was 0.3% and Number Needed to Treat (NNT) was 333.The outcome of stroke was 1.44% per year in the 110 mg group, as compared with 1.57% in the warfarin group (relative risk 0.92; 95% confidence interval, 0.74 to 1.13). The meassurement of primary outcome in this tudy which include systemic embolism stated that the rates of primary outcome were 1.53% in the 110 mg of dabigatran and 1.69% in the warfarin group (relative risk 0.91; 95% confidence interval, 0.74-1.11)

In the second group, 150 mg of dabigatran is given to 6076 patients with atrial fibrillation. The outcome of stroke occured in 122 patients receiving 150 mg of dabigatran compared to 185 patients in the warfarin group. The CER was 3.1%, EER was 2%, RRR was 36%, ARR was 1.1% and NNT was 91. The outcome of stroke was 1.01% per year in the 150 mg dabigatran group, as compared with 1.57% in the warfarin group (relative risk 0.64; 95% confidence interval, 0.51-0.81).

Discussion

Connolly et al[5] conducted a study with 18,113 patients originated from 44 countries. This distribution can be a fair representative of race variability. The characteristics of the patients' baseline similar to the patient's age and gender presented in the clinical scenario. The mean age of patients in the 110 mg dabigatran, 150 mg dabigatran and warfarin group are 71.4± 8.6, 71.5±8.8 and 71.6±8.6 respectively.

Table 2. Critical Appraisal of the usefull articles based on criterias by Centre of Evidence Medicine University of Oxford[6]

Articles	Validity					Relevance					Result	Levels of evidence *
	Study design	Number of patients	Randomization	Similarity treatment and control	Blinding	Comparable treatment	Intention to treat	Domain	Determinant	Meassurement of outcome		
Connolly SJ et al5	+	18,113	+	+	+/-**	+	+	+	+	+	A	1B

Legend: + stated clearly in the article
- not being done
? not stated clearly

*Levels of evidence based on The Oxford Centre of Evidence-based Medicine

**Dabigatran was administered in a blinded fashion, while warfarin was administered in an unblinded fashion

Domain: Patients' mean age is 71 years old. Patients were eligible ifthey had atrial fibrillation documented on electrocardiography performed at screening or within 6 months beforehand.

Determinant: Administration of 110 mg and 150 mg of dabigatran (twice daily) and warfarin

Outcome: The occurence of stroke and systemic embolism

A: The administration of 150 mg of dabigatran was superior to warfarin in reducing the occurence of disabling stroke. (relative risk: 0.66; 95% confidence interval, 0.53 to 0.82; P<0.001) .

Most of the patients participated in this study are man (64.3%, 63.2% and 63.3% respectively). The mean $CHADS_2$ score was 2,1.

According to this study, the administration of 110 mg of dabigatran was equal to warfarin in preventing the occurence of stroke. There was no significant reduction of stroke in the 110 mg dabigatran group. In terms of major bleeding, the administration of 110 mg of dabigatran is associated with less major bleeding compared to warfarin.

The administration of 150 mg of dabigatran was superior to warfarin in the prevention of stroke. The relative risk reduction was 36%, the ARR was 1.1 % and the NNT was 91. The high NNT was tolerable since it is a prophylactic interventions that produce small effects in large numbers of patients and associated with critical diseases. TheNNT in this study can still be considered beneficial as a preventive meassure of stroke in AF patients.

The rate of life-threatening bleeding, intracranial bleeding and major or minor bleeding were higher with warfarin than with either the 110 mg or 150 mg dose of dabigatran. While the administration of 150 mg was associated with decreased risk of stroke and decreased risk of major bleeding, but the rate of gastrointestinal bleeding in this group increased. This phenomenon can be explained by the pharmakocinetics of dabigatran that requires low pH for it's absorbtion. Therefore, dabigatran capsules contain dabigatran-coated pellets with a tartaric acid core. This acid core contributes to the increasing acidity and increased incidence of dyspeptic symptoms in patients taking this drug.

Conclusion and recommendation

The administration of 110 mg of dabigatran, as compared with warfarin, was associated with similar rates of stroke and and lower rates of major bleeding; the 150 mg dose of dabigatran was associated with lower rates of stroke but with a similar rate of major bleeding. The administration of dabigatran must be accompanied by each patient's characteristic examnination, especially gastrointestinal disease. Since there was an increase of gastrointestinal bleeding with the increase of dabigatran dose, so gastrointestinal monitoring is recommended in all patients receiving dabigatran.This report can be translated into clinical practise. We recommend the administration of 150 mg for the patient in the clinical scenario above, with closed gastrointestinal monitoring.

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