Review Article

Comparison of benefit between dabigatran and warfarin among patients with atrial fibrillation: A systematic review

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ABSTRACT

Warfarin is recognized as the standard antithrombotic agent for stroke prevention. However, new oral anticoagulant such as dabigatran constitutes huge improvement to compensate for the limitation of warfarin. A literature review was performed to compare and contrast the overall benefit of dabigatran and warfarin among patients with atrial fibrillation. We utilized HighWire as the data source for randomized controlled trials based on inclusion and exclusion criteria (from January 2007 to September 2013). Descriptive and quantitative information related to stroke and major bleeding were extracted from each trial. After a comprehensive screening of 298 search results, 17 studies which enrolled a total of 127,594 patients were included. Warfarin was found to have higher mean event rates for incidence of stroke, major bleeding, and net clinical benefit compared to dabigatran 110 mg and dabigatran 150 mg. Dabigatran 110 mg has higher rate of stroke and net clinical benefit than dabigatran 150 mg with less major hemorrhage. Overall, dabigatran had higher efficacy and safety profile than warfarin. Further research is required to determine the clinical feasibility of dabigatran in real-life practice.

Key words: Atrial fibrillation, dabigatran, prevention, stroke, warfarin

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmias, which affects about 2.0% of the general population.[1] It is characterized by an abnormal cardiac rhythm which is due to rapid or irregular electrical impulses in the upper chambers of the heart (atria).[2] As a result, blood cannot be effectively pumped into the lower chambers of the heart (ventricles) and this causes pooling of blood in the atrial appendages.[2] The incidence increases with age and is associated with the presence of structural heart disease.[3] AF is classified based on several defining characteristics such as electrocardiogram pattern, epicardial or endocavitary recordings, mapping of atrial electrical activity, or clinical features.[3] For effective diagnosis, clinicians should determine the frequency and duration of AF.[3] First detected AF can fall into either paroxysmal or persistent.[3] Recurrence and frequency of episodes are the main criteria to classify AF. If the episodes are two or more, then it is defined to be recurrent.[3] If the arrhythmia subsides automatically, it is classified as paroxysmal. However, those sustaining more than 7 days are defined as persistent AF.[3] Recovery of symptoms with pharmacological intervention or direct-current

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cardioversions does not change the classification.[3] Persistent AF usually leads to permanent AF where the cardioversion fails to treat the symptom.[3] One-third of patients with AF are asymptomatic.[1] The common symptoms include palpitations, dyspnea, fatigue, dizziness, and decreased exercise tolerance.[1] Early diagnosis of asymptomatic AF may lead to effective intervention and lower the risk of complications. The most serious complication of AF is stroke which is due to thromboembolism (TE). The incidence of stroke is more frequent among the elderly patients suffering from AF.[1] Clinically important TE has been reported by about 1–2% of patients within the 1st month after recovery from AF which lasts for more than 48 h.[1] Atrial thrombi can form after AF which in turns cause the disruption of blood flow.[1] Apart from stroke, AF may worsen heart failure and ischemic heart disease.[1] In addition, tachycardia and inefficiency of ventricular filling due to inactive atrial component are the two important symptomatic manifestations in many patients.[1] In some cases, patients can experience syncope. Treatment objectives in patients with AF include rate control, recovery of sinus rhythm, and prevention of TE.[3] These three strategies are not mutually exclusive.[3] Rate control strategy aims to correct the ventricular rate while rhythm control strategy involves the maintenance of normal sinus rhythm.[3] Antithrombotic therapy must be undertaken at all stages of AF to prevent TE and reduce the risk of stroke.[1]

Traditional antiplatelet agents such as aspirin and antithrombotic agents such as warfarin (Vitamin K antagonist, and VKA) are usually indicated for the management of stroke prevention.[3] Aspirin is recommended in low-risk patients as prophylaxis while warfarin is suitable for patients at high risks of stroke.[3] In 2007, Hart *et al*. published a meta-analysis interpreting the efficacy and safety of antithrombotic agents (including VKAs) in patients with nonvalvular AF.[4] The data were extracted from 29 randomized controlled trials (RCTs).[4] On assessing six trials which compared VKA with placebo, adjusted-dose warfarin was shown to reduce relative risk (RR) of stroke by 64% (95% CI 49–74) versus placebo or control (53 events in 2396 patient-years vs. 133 events in 2207 patient-years).[4] For ischemic stroke alone, adjusted-dose warfarin achieves an RR reduction of 67% (95% CI 54–77).[4] Adjusted-dose warfarin was also found to have 26% (95% CI 3–43) reduction in all-cause mortality when to compare with placebo or control (110 vs. 143 deaths).[4] Despite the documented efficacy of VKAs in stroke prevention, there is evidence of increased risk of bleeding associated with anticoagulation therapy, ranging from minor bruising to serious bleeding events requiring transfusion and to the worst case scenario of fatal intracranial hemorrhage[1,5] Moreover, fluctuating dose–response relationship complicates the dosing regimen of warfarin.[5] Factors attributed to this phenomenon include genetic polymorphisms and environmental factors such as drug–drug and food–drug interactions.[5] Furthermore, warfarin has delayed onset and offset of action.[5] For high-risk individuals, warfarin has to be concurrently administered with intravenous heparin ("bridging therapy") for at least 4 days before therapy is initiated.[5] Apart from that, significant drug–drug and drug–food interactions also limit the application of warfarin in clinical context.[5] This is particularly challenging because AF often involves elderly patients who have issues of concomitant administration of multiple medications.[5] The narrow therapeutic window of warfarin (international normalized ratio [INR] of prothrombin times ranging between 2 and 3 in patients with AF is recommended) further restricts its usage.[4]

Therefore, alternative anticoagulants should be sought to address for issues of warfarin.[4] They should reduce stroke risk comparatively with lower risk of hemorrhage, enable fixed dosing, generate more predictable dose–response curve, produce quick onset and offset of action, have lower drug interaction potential and less dietary restriction, and require no dose titration and intensive laboratory monitoring. In this case, direct thrombin inhibitors such as dabigatran and Factor Xa inhibitors such as apixaban are the two new classes of agents that may replace warfarin in clinical setting.

Objective

A literature review was conducted based on RCTs, which compare and contrast the overall benefit of dabigatran and warfarin among patients with AF. This was done by:

- Examining the efficacy of both antithrombotic therapies
- Evaluating the safety of use of both antithrombotic therapies
- Interpreting the net clinical benefits of both antithrombotic therapies.

METHODOLOGY

Data sources and search strategy

We conducted a systematic literature search on HighWire database which covered the sources

from PubMed database for published articles dated from January 2007 to September 2013. The search strategy involved the use of the following search string: "warfarin" AND "atrial fibrillation" AND "dabigatran" AND "stroke prevention." Moreover, we manually screened through the reference lists of the available full-text articles and performed forward-tracking of the relevant articles in search of additional studies that fit our review objectives.

Inclusion and exclusion criteria

First, the type of population, choice of intervention and comparison, and primary outcome of the literature were determined.[6] The population to be investigated was patients with AF. Trials comparing head-to-head warfarin and dabigatran were included in the study. Finally, outcomes of interest were stroke and major bleeding which were explained in detail in the endpoint definition.

Only randomized controlled trials in the form of full-text articles or summary abstracts were selected.[6] However, cohort studies with large sample size (n = 50,000) were also considered. Furthermore, human studies presented in English language and population with additional high-risk factors of stroke such as previous stroke or transient ischemic attack (TIA) were also criteria of study inclusion for the review.

Apart from that, studies were excluded if they were (1) observational studies or case reports; (2) trials with no comparator (i.e., warfarin alone); and (3) patients with other coexisting condition such as chronic kidney disease, abnormal liver function, and pregnancy.

The assessment of the literature was done based on the primary and secondary outcomes defined during the literature search.

Endpoint definition

Primary endpoints

- Stroke, defined as a neurological deficiency, is characterized by an acute focal injury of the central nervous system (CNS) of a vascular origin which lasts for more than 24 h. It includes CNS infarction, ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage.[7] Likewise, TE is the umbrella term covering stroke, TIA, systemic or pulmonary embolism, and embolic complications to viscera and extremities[6]
- Major bleeding which involves fatal or life-threatening retroperitoneal, intracranial, intraocular, or intraspinal bleeding; subdural hematomas, or bleeding requiring surgery or transfusion of 2 U or associated with a decrease in hemoglobin of 2.0 g/L.[8]

Secondary endpoints

- Fatal or nonfatal adverse effects during treatment, excluding hemorrhage[6]
- All-cause death during treatment or follow-up.[6]

Data interpretation

Due to the complexity associated with the traditional analysis of RR and 95% confidence interval, mean event rate was calculated for the effects of warfarin and dabigatran (110 mg and 150 mg) in terms of TE (i.e., stroke), major bleeding, and net clinical benefit [Table 1]. In this review, event rate was the major determinant of outcome measure. Based on the

Table 1: Event rate of warfarin and dabigatran for stroke, major bleeding, and net clinical benefit

Study	Stroke			Major bleeding			Net clinical benefit		
	W	D110	D150	W	D110	D150	W	D110	D150
Connolly *et al*.[9]	1.7	1.5	1.1	3.4	2.7	3.1	NA	NA	NA
Ezekowitz *et al*.[10]	1.7	1.6	1.1	3.6	3.1	3.3	NA	NA	NA
Diener *et al*.[11]	2.8	2.3	2.1	4.2	2.7	4.2	8.7	7.1	8.7
Hori *et al*.[12]	2.7	1.4	0.7	3.3	5.5	3.3	N.A	NA	NA
Pink *et al*.[13]	1.1	1.1	0.7	0.0	0.0	0.0	NA	NA	NA
Eikelboom *et al*.[14]	0.8	0.9	0.5	2.4	1.3	1.8	5.2	4.2	4.2
Healey *et al*.[19]	2.1	1.9	1.4	4.4	4.4	5.1	NA	NA	NA
Hart *et al*.[16]	0.6	0.8	0.3	0.6	1.7	0.6	NA	NA	NA
Hart *et al*.[17]	0.4	0.1	0.1	0.3	0.1	0.2	NA	NA	NA
Guo *et al*.[18]	NA	NA	NA	3.3	2.7	3.1	1.7	1.5	1.1
Flaker *et al*.[19]	1.8	1.7	1.1	3.9	2.9	3.1	NA	NA	NA
Gagne *et al*.[20]	2.7	2.1	1.9	4.6	3.8	4.9	NA	NA	NA
Douketis *et al*.[21]	0.6	0.5	0.5	4.6	3.8	5.1	NA	NA	NA
Zhu *et al*.[22]	3.1	2.5	1.4	3.8	2.2	2.2	9.7	8.4	6.5
Mean	0.6	0.5	0.4	1.2	0.9	1.1	0.7	0.6	0.5

D=Dabigatran, W=Warfarin, NA=Not available

incidence of each event in the specified study sample, percentage event rate was calculated or adopted from the results. Mean event rate was calculated latter to ease the comparison between warfarin and dabigatran.

Three out of 17 studies were excluded from the data interpretation due to the absence of data on dabigatran 110 mg (Ezekowitz *et al*., Lip *et al*.) and event rate (Eikelboom *et al*.).

RESULTS

Search results

The stepwise literature search process was illustrated in Figure 1. Initially, 298 entries were generated of which the title and abstract were screened as per the inclusion and exclusion criteria. From these, 235 were excluded because their content was out of the scope of the review. Full-text or abstract of the remaining 63 studies was further analyzed. Seventeen studies met the inclusion or exclusion criteria (15 full-text articles,[8-21,23] one conference abstracts,[24] and one letter to the editors).[22] Table 2 summarizes the relevant information retrieved from the selected trials.

Efficacy and safety of dabigatran versus warfarin

The primary efficacy outcome was stroke [Table 3] while the primary safety outcome was major bleeding [Table 4]. Likewise, net clinical benefit which was the composite of non-CNS systemic embolism, pulmonary embolism, hemorrhagic stroke, subdural bleeding, major extracranial bleeding, myocardial infarction, and death[12] was also compared in five studies [Table 5]. Data interpretation of endpoints and net clinical benefit of dabigatran and warfarin were shown in Table 1.

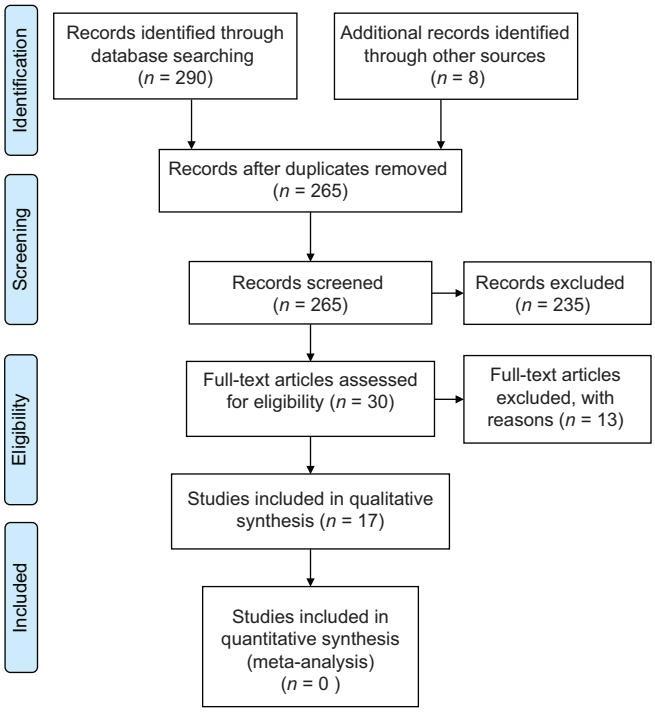

Figure 1: PRISMA flow diagram

Stroke

Mean incidence rate for stroke was calculated from 13 studies.[9-16,18,19,21,22,24] Warfarin had the highest mean event rate (0.6) followed by dabigatran 110 mg (0.5) and 150 mg (0.4).

Major Bleeding

Among 14 studies,[9-19,21,22,24,] warfarin caused the highest bleeding rate (mean event rate: 1.2) followed by dabigatran 150 mg (mean event rate: 1.1) and dabigatran 110 mg (mean event rate: 0.9).

Net clinical benefit

Among four studies,[11,17,21,24] warfarin had the highest mean event rate (0.7) followed by dabigatran 110 mg (0.6). Dabigatran 150 mg had the least net clinical benefit (0.5).

DISCUSSION

Based on the mean event rate calculated in the result, warfarin had the highest risk of stroke occurrence compared to dabigatran 110 mg and 150 mg. The results were supported by trials from Connolly *et al*., Parekh *et al*., Diener *et al*., and Hart *et al*. This suggested the relative inferiority in terms of stroke prevention by warfarin. Subgroup analysis of different doses of dabigatran showed that dabigatran 110 mg is a less effective oral anticoagulant than that of 150 mg, in which the result was coherent with that of Connolly *et al*. (RR: 1.16; 95% CI: 1.00–1.34; *P*: 0.052). In terms of major bleeding, warfarin was also associated with the highest risk of significant hemorrhage which limits its applicability in clinical setting (Oldgren *et al*., Healey *et al*., and Zhu *et al*.). On one hand, comparison between both doses of dabigatran revealed the fact that lower dose has higher safety profile than higher dose based on the observation of less hemorrhage events (Yang *et al*., Hart *et al*.). Apart from the efficacy and safety parameters, data analysis in terms of net clinical benefit, which is a combination of non-CNS systemic embolism, pulmonary embolism, hemorrhagic stroke, subdural bleeding, major extracranial bleeding, myocardial infarction, and death, also proposed that warfarin has less favorable clinical outcome with high-risk benefit ratio (Eikelboom *et al*.). In

Table 2: Description of anticoagulation studies

	Total number of patients	Patients treated with dabigatran	Dabigatran dosage	Patients treated with warfarin	Treatment duration	Key findings
Ezekowitz *et al*.[8]	502	432	50 mg BID in 105 150 mg BID in 166 300 mg BID in 161	70	12 weeks	Major bleeding events were limited to D300 plus aspirin while TE limited to D50
Lip *et al*.[23]	949	631	150 mg OD in 164 300 mg OD in 151 450 mg OD in 156 200 mg BID in 160	318	3-9 months	300 mg OD dose of D has same rate of stroke but lower bleeding risks than W
Connolly *et al*.[9]	18,113	12091	110 mg BID in 6015 150 mg BID in 6076	6022	2 years	D110 has similar rates of stroke but less major bleeding than W D150 is more effective for stroke prevention but same bleeding risk as W
Ezekowitz *et al*.[10]	9123	6030	110 mg BID in 3004 150 mg BID in 3026	3093	2 years	D at either dose has higher beneficial outcome than W in VKA-naïve patient*
Diener *et al*.[11]	3623	2428	110 mg BID in 1195 150 mg BID in 1233	1195	2 years	D110 is noninferior while D150 is superior in stroke reduction
Hori *et al*.[12]	326	218	110 mg BID in 107 150 mg BID in 111	108	1.3 years	Comparable stroke and bleeding profile with overall RE-LY study population (Connolly *et al*.)
Pink *et al*.[13]	18,113	12,091	110 mg BID in 6015 150 mg BID in 6076	6022	2 years	Both doses of D has positive benefit to harm ratio compared to W
Eikelboom *et al*.[14]	12,230	8141	110 mg BID in 4046 150 mg BID in 4095	4089	2 years	D110 was noninferior and D150 was superior to W for stroke prevention
Healey *et al*.[19]	7258	4828	110 mg BID 150 mg BID	2430	2 years	Both doses of D has lower rate of major bleeding than W in patient age >75 years old
Hart *et al*.[16]	1270	NA	110 mg BID 150 mg BID	NA	2 years	Both doses of D have low and comparable frequency of stroke and major bleeding than W
Hart *et al*.[4]	18,113	12,091	110 mg BID in 6015 150 mg BID in 6076	6022	2 years	Both doses of D have lower rate of intracranial hemorrhage than W
Guo *et al*.[18]	817	NA	110 mg BID 150 mg BID	60	1.9 years	Both doses of D have positive net clinical benefit compared to W
Flaker *et al*.[19]	5789	3859	110 mg BID in 1950 150 mg BID in 1909	1930	2 years	D110 provides comparable reduction in stroke with reduced bleeding compared to W D150 is superior in stroke prevention with similar major bleeding risks to W
Gagne *et al*.[20]	5882	3949	110 mg BID in 1968 150 mg BID in 1981	1933	2 years	D110 has similar rate of stroke but less bleeding than W D150 has lower rate of stroke with similar bleeding compared to W
Douketis *et al*.[21]	4591	3033	110 mg BID in 1487 150 mg BID in 1546	1558	2 years	D and W have similar rate of periprocedural bleeding
Eikelboom *et al*.[24]	18,113	12091	110 mg BID in 6015 150 mg BID in 6076	6022	2 years	Both doses of D have similar net clinical benefit, and they have better efficacy and safety profiles as compared to W
Zhu *et al*.[22]	2782	1856	110 mg BID in 923 150 mg BID in 933	926	2 years	D significantly reduces risk of stroke and major bleeding than W in Asians

*VKA-naïve is defined as a total lifetime use of a VKA of<62 days. D=Dabigatran, W=Warfarin, BID=Twice daily, OD=Once daily, NA=Not available, TE=Thromboembolism, VKA=Vitamin A antagonist

general, the incidence of major bleeding was higher than thromboembolic events in all treatment groups, suggesting the high inherent adverse effect of both warfarin and dabigatran despite attaining therapeutic efficacy. However, we were unable to determine the significance of the result generated because we did not perform statistical analysis on the significance of each mean event rate. To summarize, warfarin is less beneficial than dabigatran based on our findings. Further exhaustive statistical interpretation is required to confirm on the significance of the findings.

Warfarin has been established as the primary antithrombotic agent in relation to the treatment protocol of AF in patient with pronounced risk of stroke or TE.[3] For instance, ACTIVE-W trial provided

Table 3: Comparison of primary efficacy endpoint (stroke)

Study or subgroup	Number of event/event rate	Relative risk (confidence interval) *P*		
		110 mg D versus W	150 mg D versus W	150 mg D versus 110 mg D
Ezekowitz *et al*.[8]	D: 1/1.7% in 50 mg BID 0/0% in 150 mg, 300 mg BID W: 0/0%	NA	NA	NA
Connolly *et al*.[9]	D: 182/1.53% in 110 mg BID 134/1.11% in 150 mg BID W: 199/1.69%	0.91 (0.74-1.11) <0.001	0.66 (0.53-0.82) <0.001	0.73 (0.58-0.91) 0.005
Ezekowitz *et al*.[10]*	D: 89/1.57% in 110 mg BID 61/1.07% in 150 mg BID W: 97/1.69%	0.93 (0.70-1.25) 0.65	0.63 (0.46-0.87) 0.005	NA
Diener *et al*.[11]	D: 55/2.32% in 110 mg BID 51/2.07% in 150 mg BID W: 65/2.78%	0.84 (0.58-1.20) NA	0.75 (0.52-1.08) NA	NA
Hori *et al*.[12]	D: 2/1.38% in 110 mg BID 1/0.67% in 150 mg BID W: 4/2.65%	0.52 (NA) NA	0.25 (NA) NA	NA
Pink *et al*.[13]	D: 1.12% in 110 mg BID 0.68% in 150 mg BID W: 1.09%	NA	NA	NA
Eikelboom *et al*.[14]	D: 0.9% in 110 mg BID 0.5% in 150 mg BID W: 0.8%	1.08 (0.60-1.95) NA	0.63 (0.32-1.23) NA	NA
Healey *et al*.[19]	D: 87/1.89% in 110 mg BID 69/1.43% in 150 mg BID W: 101/2.14%	0.88 (0.66-1.17) 0.81	0.67 (0.49-0.90) 0.81	0.76 (0.55-1.04) 0.65
Hart *et al*.[16]	D: 5/0.77% in 110 mg BID 2/0.30% in 150 mg BID W: 4/0.60%	1.28 (0.35-4.76) 0.7087	0.49 (0.09-2.69) 0.4048	0.39 (0.07-1.98) 0.2351
Hart *et al*.[17]	D: 14/0.12% in 110 mg BID 11/0.09% in 150 mg BID W: 46/0.39%	0.30 (0.16-0.54) 0.001	0.23 (0.12-0.45) 0.001	0.78 (0.35-1.70) NS
Flaker *et al*.[19]	D: 1.72% in 110 mg BID 1.14% in 150 mg BID W: 1.80%	0.96 (0.69-1.35) NA	0.64 (0.43-0.93) NA	NA
Gagne *et al*.[20]	D: 82/2.12% in 110 mg BID 74/1.88% in 150 mg BID W: 101/2.68%	0.79 (0.59-1.05) NA	0.70 (0.52-0.95) NA	NA
Douketis *et al*.[21]	D: 7/0.5% in 110 mg BID 7/0.5% in 150 mg BID W: 10/0.6%	0.73 (0.28-1.92) 0.53	0.71 (0.27-1.85) 0.48	NA
Zhu *et al*.[22]	D: 44/2.50% in 110 mg BID 25/1.39% in 150 mg BID W: 53/3.06%	0.81 (0.54-1.21) 0.56	0.45 (0.28-0.72) 0.09	NA

*Result of previously VKA naïve patient. D=Dabigatran, W=Warfarin, BID=Twice daily, NA=Not available, NS=Nonstatistically significant

evidence that antiplatelet agent was inferior to warfarin, suggesting the potential benefit to give warfarin in patients with coagulation disorder.[25] In spite of excellent anticoagulation effect, warfarin was known to be leading into serious hemorrhage complications. To illustrate, there was significantly higher incidence of intracranial bleeding with warfarin (0.74%) compared with dabigatran (110 mg: 0.23%, 150 mg: 0.30%) in the RE-LY trial. This could be attributed to the different mechanism of action of both antithrombotic agents. Tissue factor (TF) is a transmembrane receptor for factor VIIa which has substantial concentration in the brain for additional hemostatic protection.[26,27] The formation of TF-VIIa complexes as a result of interaction between activated coagulation factor VII and TF is the key initiator for cellular coagulation. Warfarin broadly inhibits carboxylation of coagulation factors II, VII, IX, and X, resulting in diminished production of factor VIIa and the subsequent suppression of TF VIIa-mediated thrombosis.[14] By comparison, dabigatran may preserve the hemostatic mechanisms in the brain by selectively inhibiting thrombin.[14] This leads to less risk of intracranial bleeding observed in the RE-LY trial. However, TF is also found in reasonably high concentration at the site of atherosclerotic

Table 4: Comparison of primary safety endpoint (major bleeding)

Study or subgroup	Number of event/event rate	Relative risk (confidence interval) *P*		
		110 mg D versus W	150 mg D versus W	150 mg D versus 110 mg D
Ezekowitz *et al*.[8]	D: 0 in all doses W: 0	NA	NA	NA
Lip *et al*.[23]	D: 0/0.0% in 150 mg OD, 300 mg OD 3/1.9% in 450 mg OD 2/1.3% in 200 mg BID W: 2/0.6%	NA	NA	NA
Connolly *et al*.[9]	D: 322/2.71% in 110 mg BID 375/3.11% in 150 mg BID W: 397/3.36%	0.80 (0.69-0.93) 0.003	0.93 (0.81-1.07) 0.31	1.16 (1.00-1.34) 0.052
Ezekowitz *et al*.[10]*	D: 176/3.11% in 110 mg BID 190/3.34% in 150 mg BID W: 205/3.57%	0.87 (0.72-1.07) 0.19	0.94 (0.77-1.15) 0.55	NA
Diener *et al*.[11]	D: 65/2.74% in 110 mg BID 102/4.15% in 150 mg BID W: 97/4.15%	0.66 (0.48-0.90) 0.15	1.01 (0.77-1.34) 0.51	NA
Hori *et al*.[12]	D: 8/5.53% in 110 mg BID 5/3.33% in 150 mg BID W: 5/3.31%	0.79 (NA) NA	1.06 (NA) NA	NA
Pink *et al*.[13]	D: 0.0188% in 110 mg BID 0.0220% in 150 mg BID W: 0.0290%	NA	NA	NA
Eikelboom *et al*.[14]	D: 1.3% in 110 mg BID 1.8% in 150 mg BID W: 2.4%	0.55 (0.37-0.83) 0.06	0.75 (0.52-1.08) 0.003	NA
Healey *et al*.[19]	D: 204/4.43% in 110 mg BID 246/5.10% in 150 mg BID W: 206/4.37%	1.01 (0.83-1.23) <0.001	1.18 (0.98-1.42) <0.001	1.17 (0.97-1.40) 0.80
Hart *et al*.[16]	D: 11/1.70% in 110 mg BID 4/0.60% in 150 mg BID W: 4/0.60%	2.82 (0.90-8.82) 0.0617	0.99 (0.25-3.93) 0.9865	0.35 (0.11-1.09) 0.0585
Hart *et al*.[17]	D: 10/0.08% in 110 mg BID 24/0.20% in 150 mg BID W: 36/0.31%	0.27 (0.12-0.55) 0.001	0.65 (0.39-1.10) 0.10	2.4 (1.1-5.0) 0.02
Guo *et al*.[18]	D: 2.68% in 110 mg BID 3.13% in 150 mg BID W: 3.33%	NA	NA	NA
Flaker *et al*.[19]	D: 2.87% in 110 mg BID 3.14% in 150 mg BID W: 3.88%	0.74 (0.57-0.94) 0.4367	0.81 (0.64-1.03) 0.3421	NA
Gagne *et al*.[20]	D: 147/3.80% in 110 mg BID 188/4.86% in 150 mg BID W: 172/4.61%	0.82 (0.66-1.03) NA	1.05 (0.86-1.30) NA	NA
Douketis *et al*.[21]	D: 57/3.8% in 110 mg BID 78/5.1% in 150 mg BID W: 72/4.6%	0.83 (0.59-1.17) 0.28	1.09 (0.80-1.49) 0.58	NA
Zhu *et al*.[22]	D: 39/2.22% in 110 mg BID 39/2.17% in 150 mg BID W: 66/3.82%	0.57 (0.39-0.85) 0.07	0.57 (0.38-0.84) 0.008	NA

*Result of previously VKA naïve patient. D=Dabigatran, W=Warfarin, BID=Twice daily, NA=Not available

plaque.[26,27] This explains why warfarin appears to be more beneficial than dabigatran in reducing risk of myocardial infarction in the RE-LY trial.

However, warfarin is recognized to have a narrow therapeutic index with highly variable inter- and intra-individual anticoagulant response; therefore, it is necessary to regularly monitor INR and adjust the doses accordingly.[28] Certain factors such as potential drug–drug and drug–food interaction and genetic deficiency of certain enzymes involved in the metabolism of warfarin may lead to slow onset and offset of action. These further complicate the dosing regimen and limit the use of warfarin in clinical setting.[28] Therefore, a new oral anticoagulant with predictable pharmacokinetic and pharmacodynamics

Table 5: Comparison of net clinical benefit between dabigatran and warfarin

Study or subgroup	Number of event/event rate	Net clinical benefit (confidence interval) *P*		
		110 mg D versus W	150 mg D versus W	150 mg D versus 110 mg D
Diener *et al*.[11]	D: 169/7.12% in 110 mg BID 214/8.70% in 150 mg BID W: 204/8.73%	0.81 (0.66-1.00) 0.17	1.01 (0.84-1.23) 0.17	NA
Eikelboom *et al*.[14]	D: 4.2% in 110 mg BID 4.2% in 150 mg BID W: 5.2%	0.80 (0.62-1.02) 0.27	0.81 (0.63-1.03) 0.01	NA
Guo *et al*.[17]	D: 1.54% in 110 mg BID 1.12% in 150 mg BID W: 1.67%	−0.85 (−2.56-−0.12) NA	0.25 (−0.01-1.9) NA	NA
Eikelboom *et al*.[24]*	NA	−0.92 (−1.74-−0.21) 0.02	−1.08 (−1.86-−0.34) 0.01	−0.16 (−0.80-0.43) 0.60
Zhu *et al*.[22]	D: 147/8.36% in 110 mg BID 116/6.47% in 150 mg BID W: 167/9.65%	0.85 (0.68-1.06) 0.39	0.66 (0.52-0.83) 0.004	NA

*The results were shown in terms of ischemic stroke equivalents prevented per 100 patient years of treatment. D=Dabigatran, W=Warfarin, BID=Twice daily, NA=Not available

profile signifies huge improvement to the current anticoagulation therapy. Dabigatran, a potent direct thrombin inhibitor, is given as an orally available prodrug (dabigatran etexilate). Peak plasma concentration follows 0.5–2 h after administration, leading to rapid onset of action observed. This feature coupled with the simple twice daily dosing offers an ideal alternative for prevention of stroke. In the RE-LY trial, about one-third less risk of intracranial hemorrhage without change in efficacy against thromboembolic occurrence was found in dabigatran compared with warfarin. Overall, it is seen that the main benefits of dabigatran are the immediate onset of action and low risk of intracranial hemorrhage which is perhaps the prime concerns while using anticoagulants among AF patients. All these may advocate the superiority of dabigatran when compared with warfarin.

The main problem associated with dabigatran is the absence of antidote to reverse its antihemostatic effect.[16] This could bring a worse prognosis than warfarin in terms of major hemorrhage. Besides, patient may not be able to tolerate gastrointestinal symptoms presented as a common adverse effect of dabigatran. In the RE-LY trial, rate of discontinuation due to dyspepsia in dabigatran (110 mg: 11.8%; 150 mg: 11.3%) was almost double than that in warfarin (5.8%).[9] In addition, the incidence of gastrointestinal bleeding increased with the higher dabigatran dose with the exception of lower rate at other sites.[9] Generally, lower pH is favorable for the absorption of dabigatran. Hence, dabigatran capsules are formulated to contain dabigatran-coated pellets with a tartaric acid core.[9] This acidity may explain the common dyspeptic symptoms and gastrointestinal hemorrhage associated with dabigatran. In contrast, unabsorbed warfarin does not have bleeding concern because warfarin needs to be metabolized by hepatic enzymes to exert an anticoagulant effect.[19] Moreover, there was an increase of about 10% in mean serum creatinine in patient taking dabigatran in the trial conducted by Lip *et al*.[23] The inhibition of active renal tubular creatinine secretion via human organic cation transporter 2 protein may be contributing to the increased serum creatinine observed.[23] However, this is unlikely to be a real issue given its modest magnitude.[23] In terms of cost-effectiveness, high dose dabigatran (150 mg) was shown to be inferior (≤42,386 per quantity adjusted life years gained) compared with warfarin in patients whose INR is well managed or in centers that achieve good INR control.[13]

There are several strengths and limitations pertaining to this review. Strength of this review is the inclusion of RCT as the main types of study to generate the findings. Based on the topic, the effect of two interventions (exposure of warfarin and dabigatran) observed in a defined context (patients with AF) would be discussed. Therefore, RCT is preferred because it provides the strongest evidence for concluding net benefit of particular intervention. Next, large sample size of all trials in this review signifies high generalizability and reproducibility of the results. Then, consistent and similar adjudication of endpoints by medical experts was also emphasized in every trial. After that, homogeneity of data was observed in both endpoints.

Nonetheless, there are several important limitations which might compromise the quality of the review. First, most trials included were subgroup analysis of RE-LY trials. Inadequate independent trials in recent years had led to the decision to include subgroup

analysis in our findings. Consequently, our analysis might be limited by the similarity in RCT data. Second, the comparison of treatment effects might be limited by the low event rates observed across the trials. This was resolved by implementation of mean event rate in the interpretation of data. Third, there was absence of complete statistical data, especially *P* value of the endpoints in some studies. This resulted in inadequacy of information to verify the significance of data exhibited, and subsequently, a sound conclusion on the comparison could not be drawn. Therefore, results from our review should be interpreted as hypothesis and should be confirmed with comprehensive statistical interpretation.

CONCLUSION

Dabigatran (110 mg and 150 mg) was shown to have lower rate of thromboembolic complications and major bleeding than warfarin in patient with AF, suggesting the positive benefit profile of dabigatran in clinical setting. Hence, among patients where warfarin is not appropriate as the first choice, dabigatran can be an alternative. However, clinical significance of dabigatran is doubtful among population of low socioeconomic profile.

Alternatively, rate of hemorrhagic complication in warfarin could be reduced through professional counseling on drug–drug and drug–food interactions, precaution in taking the medication, and importance of adherence. There was also recommendation to compare warfarin and dabigatran in real world setting, especially at clinic operated by pharmacist focusing on warfarin as the mainstay of prevention of TE. In short, further prospective and RCTs are still required to confirm on the significance of these findings.

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Conflicts of interest
There are no conflicts of interest.

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