Systematic Review and Meta-Analysis

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Comparison of dabigatran and warfarin used in patients with non-valvular atrial fibrillation

Meta-analysis of random control trial

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Abstract

Background: Dabigatran is a kind of oral anticoagulant and there was little review only about dabigatran and warfarin used in patients with atrial fibrillation. This meta-analysis only assesses the dabigatran and warfarin used in patients with atrial fibrillation.

Design: Cochrane Library, PubMed, Clinical Trials.gov, CNKI, and WanFang databases were searched. The primary endpoint was the incidence of stroke and the second endpoints were the incidence of bleeding and embolic events.

Results: Six RCTs and 20086 patients were included in our meta-analysis. No significant difference was obtained between 110 mg dabigatran and warfarin on the endpoint of stroke (risk ratio (RR), 0.90; 95% confidence interval [CI], 0.71–1.12; $P = .34$; $I^2 = 0\%$) and embolic events p (RR, 0.89; 95% CI, 0.71–1.12; $P = .32$; $I^2 = 0\%$). However, the 110 mg dabigatran associated lower incidence of bleeding (RR, 0.81; 95% CI, 0.69–0.95; $P = .01$; $I^2 = 0\%$) compare with warfarin. When compared with 150 mg dabigatran, warfarin associated with lower rate of stroke (RR, 0.96; 95% CI, 0.83–1.12; $P = .62$; $I^2 = 0\%$) and embolic events (RR, 0.67; 95% CI, 0.53–0.86; $P = .001$; $I^2 = 0\%$) but similar in the incidence of bleeding (RR, 0.67; 95% CI, 0.53–0.86; $P = .001$; $I^2 = 0\%$).

Conclusion: No significant difference was obtained between 110 mg dabigatran and warfarin in the incidence of stroke and embolic events. However, the 110 mg dabigatran associated lower incidence of bleeding compare with warfarin. When compared with 150 mg dabigatran, warfarin associated with lower incidence of stroke and embolic events but similar in the incidence of bleeding.

Abbreviations: CI = confidence interval, RR = Risk ratio.

Keywords: atrial fibrillation, dabigatran, meta-analysis, warfarin

1. Introduction

Atrial fibrillation is the most common arrhythmic disease, and patients with atrial fibrillation tend to develop thrombus due to hemodynamic disturbances, resulting in a series of serious disabling and even fatal thromboembolic events and the non-valvular atrial fibrillation is a major cause of ischemic stroke.[1,2] Anticoagulant therapy is an important strategy in the comprehensive treatment for patients with atrial fibrillation. Warfarin is the most commonly used oral anticoagulant in clinical practice and reliable in preventing thromboembolism. Because of its narrow therapeutic window, frequent monitoring coagulation indicators and easy interaction with drugs and food which limits its further clinical application.[3] Dabigatran etexilate is a novel and synthetic direct thrombin inhibitor which is a prerequisite drug of dabigatran and a non-peptide thrombin inhibitor. After oral absorption by the gastrointestinal tract, it is converted in vivo to dabigatran with direct anticoagulant activity. Dabigatran binds to thrombin fibrin, preventing fibrinogen from splitting into fibrin. Thus blocking the coagulation cascade network of the last steps and thrombosis.[4] This meta-analysis is aim to analysis the efficacy and safety of dabigatran versus warfarin.

2. Method

Ethical approval was not necessary, because this work is a Meta-analysis.

2.1. Data source and literature search

A literature search of the Cochrane Library, PubMed, Clinical Trials.gov, CNKI, and WanFang databases were searched for RCTs. The search time was set from January 1990 through December 2017. The following keywords were used in search strategies and a sensitive filter for RCTs was also used: and in patients with "dabigatran", "warfarin", "atrial fibrillation", "diabetes foot", and "non-valvular". In addition, additional trials and information were reviewed according to the references listed in the selected trials.

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Table 1

Baseline characteristics of the included studies.

Study	Sample size		Age		Male (%)		Therapy		Hypertension (%)		Diabetes mellitus (%)	
	T	C	T	C	T	C	T	C	T	C	T	C
PETRO Study 2007	166	70	70±8.1	69±8.3	82.3	94.3	Dabigatran 150 mg twice daily	Warfarin (INR of 2 to 3)	40.7	36.5	27	21.40
RE-LY Trial a 2016	4721	4718	72	72	64.8	65	Dabigatran 110 mg twice daily	Warfarin (INR of 2 to 3)	79.4	79.2	23.5	23.2
RE-LY Trial b 2016	4714	4718	72	72	64.5	65	Dabigatran 150 mg twice daily	Warfarin (INR of 2 to 3)	79.3	79.2	22.9	23.2
Yamaji 2014	106	203	60±8	62±8	75	75	Dabigatran 150 mg twice daily	Warfarin (INR of 2 to 3)	32	36	11	15
NCT 01136408 a	46	62	69.9±7.5	67.4±8.8	78.3	91.9	Dabigatran 110 mg twice daily	Warfarin (INR of 2 to 3)	/	/	/	/
NCT 01136408 b	58	62	68.3±9.1	67.4±8.8	91.4	91.9	Dabigatran 150 mg twice daily	Warfarin (INR of 2 to 3)	/	/	/	/
Su 2015	131	131	65.3±10.31	64.7±9.10	47.3	56.5	Dabigatran 110 mg twice daily	Warfarin (INR of 2 to 3)	/	/	/	/
Zuo 2015	90	90	65.87±4.88	63.63±5.61	55.5	54	Dabigatran 150 mg twice daily	Warfarin (INR of 2 to 3)	/	/	/	/

C = control, INR = international normalized ratio, T = treatment.

2.2. Study selection

Studies from the literature independently searched were screened by 2 investigators. When disagreements arose, a third investigator was consulted. Studies met the following inclusion criteria were included:

(1) RCTs conducted in humans;
(2) patients with non-valvular atrial fibrillation;
(3) full-text articles of controlled trials examining dabigatran versus warfarin;
(4) the incidence of stroke, bleeding and embolic events were reported.

The literature with the newest clinical data was included if there were duplicate studies from the same trial. Baseline characteristics of the included studies were showed in Table 1. Reviews, meta-analyses, editorials, observational studies, small-sample trials ($n < 50$), and studies in which it were not possible to assess the outcomes or lacked a control group were excluded.

2.3. Data extraction and quality assessment

Clinical data were extracted by 2 different authors independently using a standardized form, and a third investigator was consulted to resolve conflicting opinions. The following information was extracted from the included investigations: studies' names; year of publication; baseline characteristics including the total number of individuals, mean age and male percent. The incidences of the following endpoints were extracted: stroke, bleeding, and embolic events. Information including the method of blinding, random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other biases were collected to evaluate the quality of the included investigations.

2.4. Statistical analysis

Risk ratio (RR) and 95% confidence interval (CI) were used to report the difference in dichotomous outcomes. The Cochran Q test and I^2 statistic were used to assess the heterogeneity; a Cochran's $P < .10$ and an $I^2 > 50$ were considered to be significant heterogeneity. A fixed effect model was used in pooled analyses, whereas if there was significant heterogeneity, a random effect model will be used. Publication bias was assessed though Begg Test. Data analyses were performed by Review Manager (RevMan) software (version 5.1; The Cochrane Collaboration, Copenhagen, Denmark). The Begg Test used to evaluate the symmetry of the funnel plot was performed using STATA software (version 11.1; Stata Corp LP, College Station, TX). Also, sensitivity analysis was conducted by excluding each individual study through the STATA software.

3. Result

3.1. Search result

726 potentially relevant publications were identified and 98 full publications were reviewed, at last, 6 studies[5–10] met our selection criteria and were included as shown in Figure 1. In Appendix Table 1, http://links.lww.com/MD/C622, baseline characteristics of included studies were shown. We included 20086 participants in our meta-analysis (10032 for dabigatran and 10054 for warfarin). The quality assessment is detailed in Appendix Figure 1, http://links.lww.com/MD/C622 and 2, http://links.lww.com/MD/C622.

3.2. Clinical results

The incidence of stroke was the primary efficacy endpoint and the incidence of, bleeding and embolic events were the secondary endpoints. Subgroup analysis was conducted according to the dose of dabigatran that 1 subgroup is 110 mg dabigatran versus warfarin the other subgroup is 150 mg dabigatran versus warfarin.

3.3. Incidence of stroke

There are 3 RCTs including 4 group data that 19313 patients reported the incidence of stroke, with 9656 patients randomized to Dabigatran and 9657 patients randomized to Warfarin. There is no difference existed in Dabigatran 110 mg versus Warfarin subgroup (RR, 0.90; 95% CI, 0.71–1.12; $P = .34$; $I^2 = 0\%$; Fig. 2) considered the incidence of stroke, whereas, Dabigatran associated with lower incidence of stroke in Dabigatran 150 mg (RR, 0.69; 95% CI, 0.54–0.87; $P = .002$; $I^2 = 0\%$; Fig. 2) and overall analysis compare with Warfarin (RR, 0.79; 95% CI, 0.67–0.93; $P = .005$; $I^2 = 1\%$; Fig. 2).

3.4. Incidence of bleeding

There are 5 RCTs including 7 group data that 19587 patients reported the incidence of bleeding, with 9836 patients randomized to Dabigatran and 9751 patients randomized to Warfarin. There are no difference existed in Dabigatran 150 mg subgroup versus Warfarin (RR, 0.96; 95% CI, 0.83–1.12; $P = .62$; $I^2 = 0\%$; Fig. 3) considered the incidence of bleeding, whereas, Dabigatran associated with lower incidence of bleeding in Dabigatran 110 mg (RR, 0.81; 95% CI, 0.69–0.95; $P = .01$; $I^2 = 0\%$; Fig. 3) and

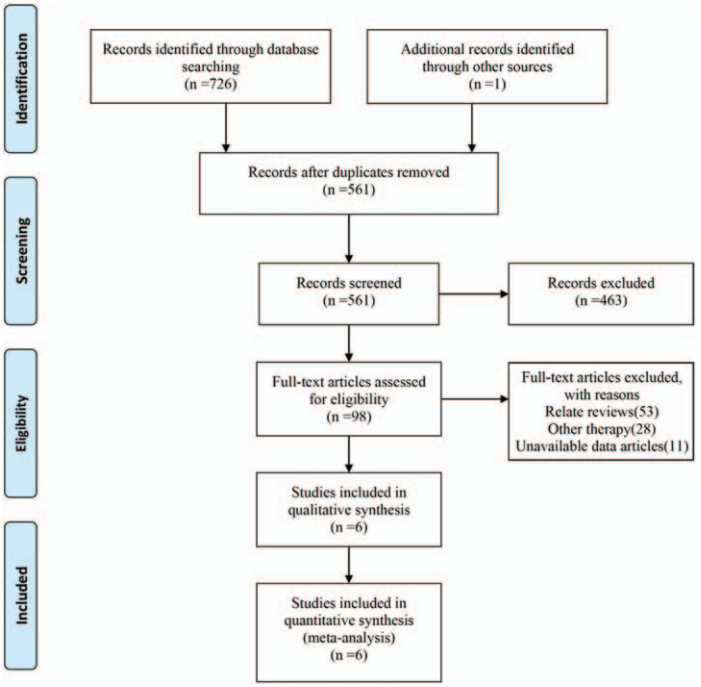

Figure 1. Flow chart of literature retrieval and selection.

overall analysis compare with Warfarin (RR, 0.89; 95% CI, 0.79–0.99; $P = .03$; $I^2 = 0\%$; Fig. 3).

3.5. Incidence of embolic events

There are 4 RCTs including 6 group data that 19547 patients reported the incidence of embolic events, with 9766 patients randomized to Dabigatran and 9771 patients randomized to Warfarin. There is no difference existed in Dabigatran 110 mg versus Warfarin subgroup (RR, 0.89; 95% CI, 0.71–1.12; $P = .32$; $I^2 = 0\%$; Fig. 4) considered the incidence of embolic events, whereas, Dabigatran associated with lower incidence of embolic events in Dabigatran 150 mg (RR, 0.67; 95% CI, 0.53–0.86; $P = .001$; $I^2 = 0\%$; Fig. 4) and overall analysis compare with Warfarin (RR, 0.78; 95% CI, 0.66–0.92; $P = .003$; $I^2 = 0\%$; Fig. 4).

3.6. Sensitivity and publication bias analysis

Sensitivity analysis was conducted by excluding each individual study. The meta-analysis incidence of bleeding was as follows:

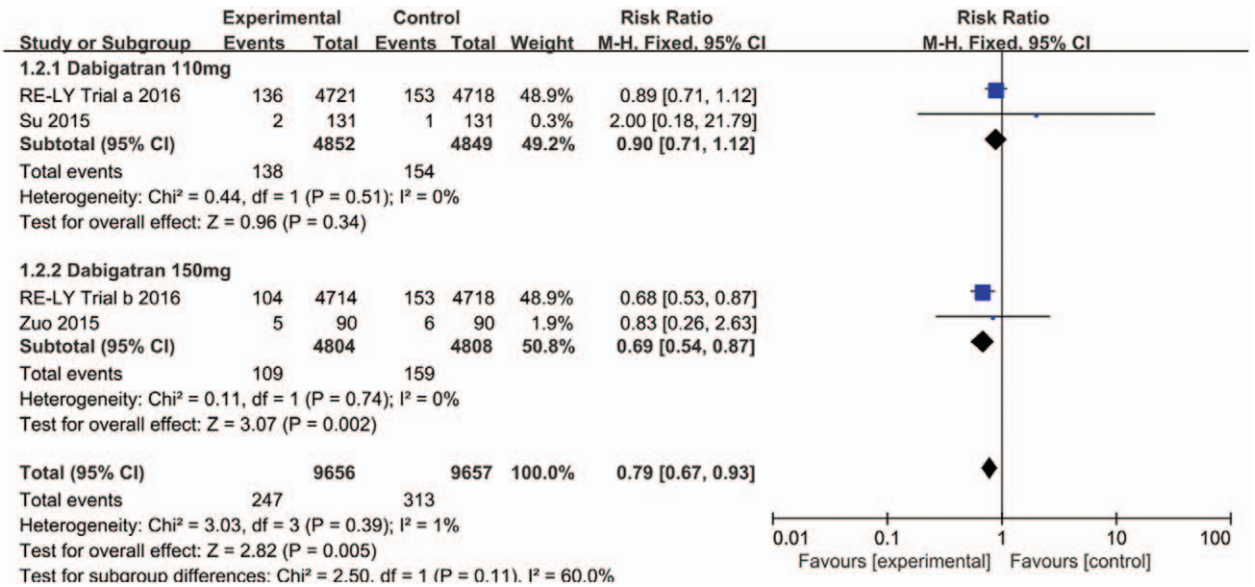

Figure 2. Forest plot of healed ulcers.stroke.

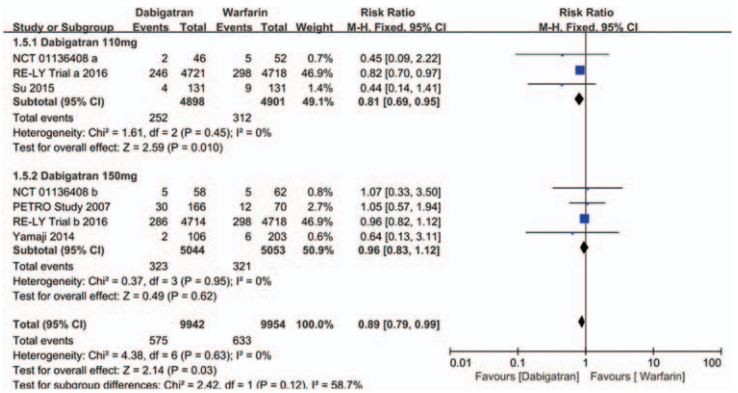

Figure 3. Forest plot of bleeding.

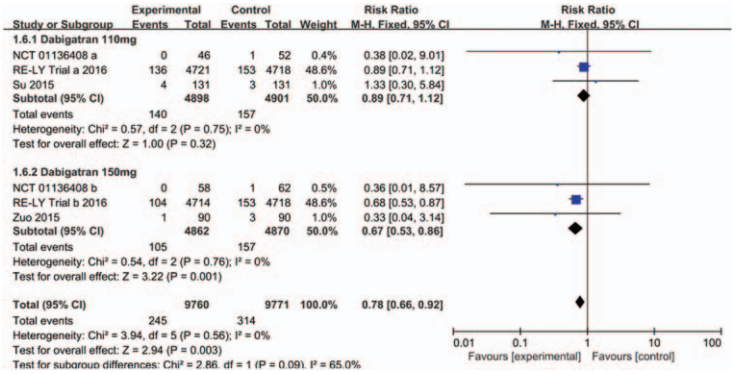

Figure 4. Forest plot of embolic events.

RR, 2.22; 95% CI, 0.87–5.62; $P = .32$; and $I^2 = 81\%$. Exclusion of the RE-LY a 2016 or RE-LY b 2016 study resulted in significantly different results, as shown in Figure 5, but a similar meta-analysis outcome was obtained which demonstrated that our conclusion was stable and this heterogeneity was not affected by the combined results. No publication bias was obtained in the Begg Test on the study endpoints, as shown in Table 2.

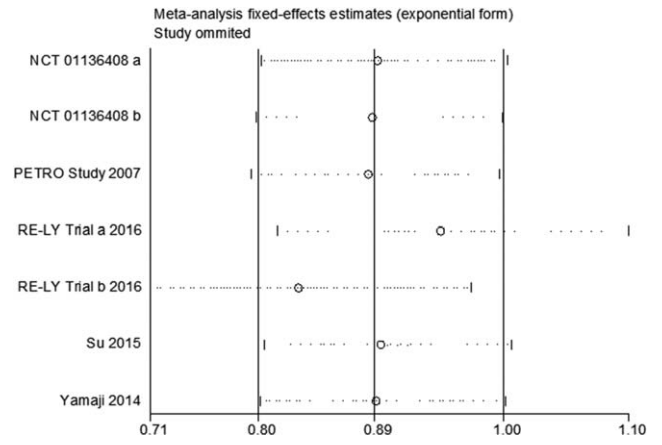

Figure 5. Sensitivity analysis of bleeding.

4. Discussion

This meta-analysis included 20086 patients who undered non-valvular atrial fibrillation randomized to dabigatran or warfarin in 6 RCTs. Based on this meta-analysis, we found that there is no significant difference between 110 mg dabigatran and warfarin on the rate of stroke and embolic events. However, the 110 mg dabigatran associated lower incidence of bleeding compared with warfarin. When compared with 150 mg dabigatran, warfarin associated with lower incidence of stroke and embolic events but similar in the incidence of bleeding.

The incidence of atrial fibrillation increased year by year, and the prevalence rate of atrial fibrillation in Chinese population was 0.77% in which the prevalence rate of non-valvular atrial was 65.2%.[11] There was a study reported that the rate of ischemic stroke approximate 5%~5%, and the incidence of stroke in elderly patients with up to 5. 5% that 6 times of the atrial fibrillation, thus preventing the prevention of ischemic stroke is

Table 2

Begg test of each endpoint.

Endpoints	*P* value
Incidence of stroke	1.000
Incidence of bleeding	.548
Incidence of embolic events	.707

particularly important.[12] In recent years, many new anticoagulants have been developed which can maintain the excellent anticoagulant effect and control the bleeding complications in the minimum.

A huge multicenter cross-sectional study[13] reported 3 kinds of new oral anticoagulants that dabigatran was the most frequently used NOAC, followed by rivaroxaban and apixaban. NOACs were preferred over warfarin for embolic complications in patients with NVAF in this study and the dose of NOACs maybe influence the clinical incidence of bleeding and embolic events. A relative study[14] showed that compared with warfarin, 150 mg of dabigatran group could reduce the risk of stroke in patients who undered atrial fibrillation and that dabigatran 110 mg showed similar efficacy. There are many reviews compare the direct oral anticoagulants compared to warfarin used in patients with atrial fibrillation. Dabigatran versus warfarin is a part of these reviews that in the study of Sharma et al[15] reported the higher risk of major bleeding than vitamin k antagonists was observed with dabigatran 150 mg but not with the 110 mg dose. In another review,[16] dabigatran demonstrated a minimal benefit for stroke and associated with decreased risk of bleeding compared with warfarin.

This is the first meta-analysis that focuses on dabigatran versus warfarin used in patients who undered non-valvular atrial fibrillation that never been done in other studies. Compare with previous reviews, we included newest clinical trials about dabigatran and warfarin, also, subgroup analysis was conducted according to the dose of dabigatran to obtain more precise results. The subgroup outcomes are similar to the multicenter cross-sectional study that the 110 mg dabigatran associated lower incidence of bleeding compare with warfarin. When compared with 150 mg dabigatran, warfarin associated with lower incidence of stroke and embolic events but similar in the incidence of bleeding. Additional, sensitivity and publication bias analysis were conducted to demonstrate the stability and low heterogeneity of our meta-analysis.

There are some limitations to our study although the meta-analysis included all of the clinical data available and met the inclusion criteria. First, the limited number of clinical trials and sample sizes restricted the power of our analysis. Second, the differences in patient clinical endpoint management, such as the definition of bleeding and embolic events are different in each clinical trial. Third, we can not get the patient level data to conduct further subgroup analysis. Finally, more RCTs associated with dabigatran versus warfarin are needed to further explore the efficacy and safety profile of dabigatran in clinical practice. Detailed subgroup analysis can be conducted when enough clinical trials published by professors in the future.

5. Conclusion

No significant difference was obtained between 110 mg dagigatran and warfarin on the incidence of stroke and embolic events. However, the 110 mg dabigatran associated lower incidence of bleeding compared with warfarin. When compared with 150 mg dabigatran, warfarin associated with lower incidence of stroke and embolic events but similar in the incidence of bleeding.

Author contributions

HMC, YBY, and JL carried out the studies, participated in collecting data, and drafted the manuscript. GHF and RYF performed the statistical analysis and participated in its design. GHF, RYF, and FG helped to draft the manuscript. All authors read and approved the final manuscript.

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