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META-ANALYSIS

Dabigatran, rivaroxaban, and apixaban are superior to warfarin in Asian patients with non-valvular atrial fibrillation: An updated meta-analysis

Wei-Jia Li, Paraschos Archontakis-Barakakis, Leonidas Palaiodimos, Dimitrios Kalaitzoglou, Lazaros Tzelves, Apostolos Manolopoulos, Yu-Chiang Wang, Stefanos Giannopoulos, Robert Faillace, Damianos G Kokkinidis

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Abstract

BACKGROUND

Most of the randomized clinical trials that led to the wide use of non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with atrial fibrillation (AF) originated from western countries.

AIM

To systematically review and quantitatively synthesize the real-world data regarding the efficacy and safety of dabigatran, rivaroxaban, and apixaban compared to warfarin for stroke prevention in Asian patients with non-valvular AF.

METHODS

Medline, Cochrane, and ClinicalTrial.gov databases were reviewed. A random-effect model meta-analysis was used and I-square was utilized to assess the heterogeneity. The primary outcome was ischemic stroke. The secondary outcomes were all-cause mortality, major bleeding, intracranial hemorrhage, and

The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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gastrointestinal bleeding.

RESULTS

Twelve studies from East Asia or Southeast Asia and 441450 patients were included. Dabigatran, rivaroxaban, and apixaban were associated with a significant reduction in the incidence of ischemic stroke [hazard ratio (HR) = 0.78, 95% confidence interval (CI): 0.65-0.94; HR = 0.79, 95%CI: 0.74-0.85, HR = 0.70, 95%CI: 0.62-0.78; respectively], all-cause mortality (HR = 0.68, 95%CI: 0.56-0.83; HR = 0.66, 95%CI: 0.52-0.84; HR = 0.66, 95%CI: 0.49-0.90; respectively), and major bleeding (HR = 0.61, 95%CI: 0.54-0.69; HR = 0.70, 95%CI: 0.54-0.90; HR = 0.58, 95%CI: 0.43-0.78; respectively) compared to warfarin.

CONCLUSION

Dabigatran, rivaroxaban, and apixaban appear to be superior to warfarin in both efficacy and safety in Asians with non-valvular AF.

Key Words: Novel oral anticoagulant; Direct oral anticoagulant; Atrial fibrillation; Asian population; Dabigatran; Rivaroxaban; Apixaban; Warfarin

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Core Tip: Dabigatran, rivaroxaban, apixaban have better efficacy (reduction in ischemic stroke and all-cause mortality) and are safer (reduction in major bleeding) than warfarin. Dabigatran is associated with a lower rate of intracranial hemorrhage than warfarin, while rivaroxaban and apixaban appear to have a trend towards reduced intracranial hemorrhage, without statistical significance. Dabigatran, rivaroxaban, and apixaban are associated with a lower rate of gastrointestinal bleeding.

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INTRODUCTION

Stroke is the second leading cause of death and a major cause of disability globally[1,2]. It was estimated that more than 5.5 million people died secondary to stroke in 2016[3]. One third of all ischemic strokes are attributed to atrial fibrillation (AF), which leads to cardioembolism of large cerebral arteries[4]. As a consequence, AF-related strokes are more likely to be fatal or debilitating[4]. AF is the most common sustained cardiac arrhythmia with an estimated global prevalence of 2.8% and an estimated life time risk of about 25%[5]. The presence of AF is associated with a fivefold increase in stroke risk[6]. AF and stroke are independently associated with dementia onset in this population[7]. Therefore, anticoagulation therapy has been the mainstay of primary and secondary stroke prevention in patients with diagnosed AF for decades[8,9]. Warfarin was the standard of care until 2009, when dabigatran, a non-vitamin K oral anticoagulant (NOAC) was found to be non-inferior to warfarin with regards to stroke prevention in patients with AF[10]. Since then, three other NOACs have been approved, namely rivaroxaban, apixaban, and edoxaban, all of which have shown substantial clinical benefits in randomized clinical trials[10-13]. The relative ease of prescribing and adhering to NOAC therapy has resulted in a more widespread use of NOACs as opposed to warfarin[14]. However, most of the randomized clinical trials, which led to this substantial change in clinical practice, originated from western countries with underrepresentation of Asian population; yet a number of real-world studies have assessed the use of NOACs in Asians with AF. With this study we aimed to systematically review and quantitatively analyze the existing observational studies regarding the efficacy and safety of dabigatran, rivaroxaban, and apixaban compared

to warfarin for stroke prevention in Asians with non-valvular AF.

MATERIALS AND METHODS

The study was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[15]. The study protocol was submitted for registration at the International Prospective Register for Systematic Reviews.

Literature search and study eligibility

Medline, Cochrane Library, and ClinicalTial.gov were systematically searched from their inception to April 27, 2020. Two independent investigators (Li WJ and Archontakis-Barakakis P) independently searched for eligible studies. In cases where there was a disagreement regarding the eligibility of a study, a third investigator (Kokkinidis DG) was involved in order consensus to be reached.

The search algorithm was ("novel oral anticoagulants" OR "direct oral anticoagulants" OR "non-vitamin K antagonist oral anticoagulants" OR NOAC OR DOAC OR dabigatran OR rivaroxaban OR apixaban OR warfarin OR coumadin OR "vitamin K antagonist") AND (atrial fibrillation OR AF OR AFIB) AND (real-world OR "real world" OR observational OR cohort OR post-approval). The reference list of pertinent reviews and observational studies was also manually searched for further potentially eligible studies. Duplicate publications were removed at the end of the literature search.

The pre-specified inclusion criteria were: (1) Retrospective or prospective observational studies; (2) Studies where the majority or all study participants were of Asian race; (3) Studies comparing warfarin to one of the NOACs; and (4) Studies examining at least one of the following outcomes: Thromboembolic stroke, intracranial hemorrhage, any bleeding, major bleeding, gastrointestinal bleeding. We excluded randomized control trials and studies that presented comparisons between different NOACs. Studies on valvular AF (*i.e.*, diagnosis of mitral stenosis or mitral valve replacement or repair) were also excluded.

Data extraction and outcomes

Data extraction was performed based on a pre-defined data extraction form by two independent investigators (Li WJ and Kokkinidis DG) blinded to each other. Disagreements were resolved following discussion and final decision was reached by consensus and as needed with the addition of a third reviewer (Archontakis-Barakakis P). The primary outcome was ischemic stroke (as defined by the individual studies) occurring during study follow up period. The secondary outcomes were all-cause mortality, major bleeding (as defined by the included studies), intracranial hemorrhage, and gastrointestinal bleeding.

Risk of bias assessment

Two independent reviewers (Palaiodimos L and Tzelves L) assessed the risk of bias of the included studies with the Risk of Bias in Non-Randomized Studies - of Interventions tool[16]. Studies were assessed as having low, moderate, serious or critical risk of bias for the following domains: Confounding measurement and account, selection of participants, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and results reporting.

Statistical analysis

When potentially duplicated populations were encountered, studies were not analyzed together under the same comparison and outcome. The larger one of the two studies was the one that was prioritized. Hazard ratios (HRs) with the corresponding 95% confidence interval (CI) were used for evaluation of outcomes. A random effects model was used to account for heterogeneity among studies. Heterogeneity was assessed with the Higgins I-square (I^2) statistic. $I^2 > 75\%$ indicated significant heterogeneity. Forest plots were used to graphically display the effect size in each study and the pooled estimates. Funnel plots and the Egger's test were used for assessment of publication bias. A P value < 0.05 was considered significant. R 3.4 version (RStudio software, RStudio, Inc.) was used as statistical software.

RESULTS

Our literature search has yielded 127 potentially relevant records after duplicates were removed. After excluding studies for multiple reasons (Figure 1), twelve studies were included in our analysis. All of the studies were conducted in countries or regions located in East Asia or Southeast Asia with the majority of their study participants being Asians. Most of the studies were products of large databases/registries (9 out of 12). In ClinicalTrials.gov database, we only found DARING-AF trial (comparison of efficacy and safety among dabigatran, rivaroxaban, and apixaban in non-valvular AF) which attempted to evaluate the efficacy and safety of NOACs in Asian patients but no results were posted. The baseline study characteristics are presented in Table 1. The patient characteristics are presented in Table 2. The risk of bias assessment is presented in Figure 2.

Dabigatran vs warfarin

Dabigatran was associated with a significant reduction in the incidence of ischemic stroke (HR = 0.78, 95%CI: 0.65-0.94, Figure 3), all-cause mortality (HR = 0.68, 95%CI: 0.56-0.83, Figure 3), major bleeding (HR = 0.61, 95%CI: 0.54-0.69, Figure 3), intracranial hemorrhage (HR = 0.51, 95%CI: 0.42-0.62, Figure 3), and gastrointestinal bleeding (HR = 0.65, 95%CI: 0.46-0.94, Figure 3), compared to warfarin.

Rivaroxaban vs warfarin

Rivaroxaban was associated with a statistically significant lower rate of ischemic stroke (HR = 0.79, 95%CI: 0.74-0.85, Figure 4), all-cause mortality (HR = 0.66, 95%CI: 0.52-0.84, Figure 4), major bleeding (HR = 0.70, 95%CI: 0.54-0.90, Figure 4), and gastrointestinal bleeding (HR = 0.79, 95%CI: 0.69-0.90, Figure 4), compared with the warfarin group. Although there was a tendency towards reduction in the rate of intracranial hemorrhage (HR = 0.76, 95%CI: 0.52-1.11, Figure 4) in rivaroxaban group, the result was not statistically significant.

Apixaban vs warfarin

Apixaban was associated with a lower rate of ischemic stroke (HR = 0.70, 95%CI: 0.62-0.78, Figure 5), all-cause mortality (HR = 0.66, 95%CI: 0.49-0.90, Figure 5), major bleeding (HR = 0.58, 95%CI: 0.43-0.78, Figure 5), and gastrointestinal bleeding (HR = 0.39, 95%CI: 0.17-0.89, Figure 5). However, there was no difference in the intracranial hemorrhage, although a clear trend was noticed (HR = 0.64, 95%CI: 0.40-1.02, Figure 5) towards apixaban superiority.

DISCUSSION

This study was a systematic review and meta-analysis of observational studies comparing the efficacy and safety of NOACs to warfarin in Asians with non-valvular AF. To the best of our knowledge, this is the first real-world data meta-analysis on this topic that is focused on Asian patient population. Our findings can be summarized as following: (1) Dabigatran, rivaroxaban, and apixaban were associated with significantly lower incidence of ischemic stroke and all-cause mortality compared to warfarin; (2) NOACs were associated with significantly fewer major bleeding events and gastrointestinal bleeding events compared to warfarin; and (3) Dabigatran was associated with significantly fewer intracranial bleeding events compared to warfarin; no significant difference in intracranial bleeding between the other two studied NOACs and warfarin was found, but a trend favoring rivaroxaban and apixaban was noted.

Dabigatran is a direct thrombin inhibitor that prevents the conversion of fibrinogen to fibrin and has been used for stroke and systemic embolism prevention in non-valvular AF since 2010[8]. The landmark trial that led to the approval and wide use of dabigatran, the randomized evaluation of long-term anticoagulation therapy (RE-LY) study, demonstrated that patients in the dabigatran arm (dose 150 mg twice daily) had significantly lower risk for stroke or systemic embolism [relative risk (RR) = 0.66, 95%CI: 0.53-0.82] and intracranial bleeding (RR = 0.40, 95%CI: 0.27-0.60) compared to warfarin arm in the two-year follow-up[10]; these findings are consistent with the results of our meta-analysis. The RE-LY trial did not show a significant difference between dabigatran and warfarin in terms of all-cause mortality and major bleeding but revealed higher gastrointestinal bleeding event rates in the dabigatran arm[10]. Real-world studies, which mainly included non-Asians, have confirmed that dabigatran has

Table 1 Baseline characteristics of included studies

Ref.	Design	Setting/data source	Country/region	Study period	Major eligibility criteria	Major exclusion criteria	OAC comparison groups	Outcomes of interest
Chan *et al*[25], 2016	Database, retrospective cohort study	National Health Insurance Research Database	Taiwan	June 1, 2012 to December 31, 2013	NVAF patients, age ≥ 30 years old	PE or DVT, joint replacement or valvular surgery within 6 mo before AF was diagnosed, ESRD, switcher from dabigatran to warfarin	Dabigatran *vs* warfarin	Ischemic stroke, intracranial hemorrhage, major GI bleeding, all-cause mortality
Yap *et al*[26], 2016	Single-center, retrospective cohort study	Malaysia's National Heart Institute	Malaysia	January, 2009 to December, 2013	NVAF patients	Not mentioned	Dabigatran *vs* warfarin	Ischemic CVA, major bleeding
Cha *et al*[27], 2017	Database, retrospective cohort study	Korean National Health Insurance Service database	Korea	January, 2014 to December, 2015	NVAF patients with CHA2DS2-VASc score ≥ 2 taking anticoagulants for primary prevention of stroke/systemic embolism	Thromboembolic event/TIA or ICH, patients received joint replacement, medications change between warfarin and NOACs	Dabigatran *vs* warfarin, rivaroxaban *vs* warfarin, apixaban *vs* warfarin	Ischemic stroke, intracranial hemorrhage, or all-cause mortality
Kohsaka *et al*[28], 2017	Database, retrospective cohort study	275 acute care hospitals across Japan	Japan	March 1, 2011 to March 31, 2016	NVAF patients 18 yr or older without use of any OAC within 180 d before the index date	Valvular AF, post-operative AF, mechanical-valvular AF, rheumatic AF	Dabigatran *vs* warfarin, rivaroxaban *vs* warfarin, apixaban *vs* warfarin	Major bleeding
Chan *et al*[29], 2018	Database, retrospective cohort study	National HealthInsurance Research Database	Taiwan	June 1, 2012 to December 31, 2016	NVAF patients ≥ 30 years old	More than 1 NOAC use during treatment course, diagnosis of valvular AF, VTE or joint replacement therapy, ESRD requiring renal replacement therapy within 6 mo before the index date	Dabigatran *vs* warfarin, rivaroxaban *vs* warfarin, apixaban *vs* warfarin	All-cause mortality, intracranial hemorrhage, GI bleeding, major bleeding
Huang *et al*[30], 2018	Database, retrospective cohort study	National Health Insurance Research Database	Taiwan	June 1, 2012 to December 31, 2015	NVAF patients ≥ 20 years old, at least 1 inpatient or 2 separate outpatient diagnoses of AF	Prosthetic heart valve or MV disease during the study period, pregnant, cancer, or chronic dialysis within 12 months prior to index date	Rivaroxaban *vs* warfarin	Ischemic stroke, intracranial hemorrhage, GI bleeding
Okumura *et al*[31], 2018	Multi-center, prospective cohort study	63 institutions in the Tokyo area	Japan	September 1, 2013 to December 31, 2015	NVAF patients, age ≥ 20 years old, treatment with any anticoagulant drug for stroke prophylaxis	Not mentioned	Dabigatran *vs* warfarin, rivaroxaban *vs* warfarin, apixaban *vs* warfarin	Intracranial hemorrhage, major bleeding, all-cause mortality
Koretsune *et al*[32], 2018	Database, retrospective cohort study	Hospital Information systems and administration database by Medical Data Vision	Japan	March 14, 2011 to June 30, 2016	NVAF patients, age ≥ 18, new user of either dabigatran or warfarin	Dialysis, kidney transplant, atrial flutter, valvular AF, mechanical valve replacement, rheumatic AF or MV prolapse/regurgitation or stenosis; or DVT or PE < 6 months before the AF diagnosis	Dabigatran *vs* warfarin	Major bleeding, intracranial hemorrhage, GI bleeding
Chan *et al*[33], 2019	Database, retrospective cohort study	National Health Insurance Research Database	Taiwan	June 1, 2012 to December 31, 2017	NVAF patients	More than one NOAC use, ESRD, DVT, PE, joint replacement therapy up to 6 mo prior to the index date.	Dabigatran *vs* warfarin, rivaroxaban *vs* warfarin, apixaban *vs* warfarin	Ischemic stroke, intracranial hemorrhage, major bleeding, major GI bleeding

Jeong *et al*[34], 2019	Single-center, retrospective cohort study	Chonnam National University Hospital	Korea	January, 2014 to December, 2016	NVAF patients, CHA2DS2-VASc > 2	Valvular AF, or any OAC class change	Rivaroxaban *vs* warfarin	Ischemic stroke, major bleeding, GI bleeding, intracranial bleeding, all-cause mortality
Lee *et al*[35], 2019	Database, retrospective cohort study	Korean Health Insurance Review Database	Korea	January, 2015 to December, 2017	NVAF patients naïve to OAC treatment	Not mentioned	Dabigatran *vs* warfarin, rivaroxaban *vs* warfarin, apixaban *vs* warfarin	Ischemic stroke, intracranial hemorrhage, GI bleeding, major bleeding
Cho *et al*[36], 2019	Database, retrospective cohort study	Korean National Health Insurance Service	Korea	July 1, 2015 to December 31, 2016	NVAF patients with new prescription of anticoagulants, age ≥ 18	Less than 30 d of anticoagulants use, two or more types of anticoagulants user, CHA2DS2-VASc score < 2, prior PE or DVT, underwent joint replacement surgery, dialysis patients	Dabigatran *vs* warfarin, rivaroxaban *vs* warfarin, apixaban *vs* warfarin	All-cause mortality, major bleeding

NVAF: Nonvalvular atrial fibrillation; OAC: Oral anticoagulant; DVT: Deep venous thrombosis; PE: Pulmonary embolism; MV: Mitral valve; ESRD: End stage renal disease; GI: Gastrointestinal.

an overall better efficacy and safety profile compared to warfarin, however superiority of dabigatran in each of the individual outcomes was not consistent across studies[17-19]. In contrast, our findings demonstrated that dabigatran was associated with 32% lower all-cause mortality, 39% lower risk for major bleeding, and 35% lower risk for gastrointestinal bleeding compared to warfarin. This meta-analysis focused on Asian population reveals consistent superiority of dabigatran compared to warfarin for all important outcomes.

Rivaroxaban acts by inhibiting activated factor Xa (FXa), a key molecule in the coagulation cascade[8]. Rivaroxaban once daily oral direct FXa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in AF (ROCKET AF) trial was published in 2011 paving the way for approval of rivaroxaban for stroke prevention in patients with non-valvular AF[11]. The rivaroxaban group was associated with significantly fewer stroke events compared to warfarin group (HR = 0.79, 95%CI: 0.66-0.96) which is in agreement with the findings of our meta-analysis but failed to demonstrate significant result in intention-to-treat population. No difference in major bleeding events between rivaroxaban and warfarin groups was demonstrated in ROCKET-AF (HR = 1.04, 95%CI: 0.90-1.20)[11]. However, an increased risk of decrease in hemoglobin more than or equal to 2 g/dL in rivaroxaban group was seen. This is different from our study that found that Asian patients on rivaroxaban had 30% lower risk for major bleeding events occurrence compared to patients receiving warfarin. The findings from a large real-world study from Canada and the United States revealed no significant difference for stroke and bleeding outcomes between the rivaroxaban and warfarin groups[20]. A propensity score matching analysis from Denmark demonstrated that patients on rivaroxaban had lower stroke rates but similar bleeding rates to patients on warfarin[21]. Observational data from Coleman *et al*[22] showed that rivaroxaban reduced stroke rates in patients with non-valvular AF compared to warfarin without any significant difference in bleeding rates. While

Table 2 Patient characteristics of included studies

Ref.	Patient Number (Api)	Patient Number (Riv)	Patient Number (Dab)	Patient Number (War)	Age (Api)	Age (Riv)	Age (Dab)	Age (War)	HAS-BLED (Api)	HAS-BLED (Riv)	HAS-BLED (Dab)	HAS-BLED (War)	CHA2DS2-VASc (Api)	CHA2DS2-VASc (Riv)	CHA2DS2-VASc (Dab)	CHA2DS2-VASc (War)
Chan *et al*[25], 2016	N/A	N/A	9940	9913	N/A	N/A	75 ± 10	76 ± 10	N/A	N/A	2.57 ± 1.01	2.58 ± 1.06	N/A	N/A	4.13 ± 1.59	4.16 ± 1.75
Yap *et al*[26], 2016	N/A	N/A	500	500	N/A	N/A	65.3 ± 11.3	66.8 ± 11.3	N/A	N/A	1.57 ± 0.96	1.67 ± 0.94	N/A	N/A	2.69 ± 1.54	3.40 ± 1.54
Cha *et al*[27], 2017	2189	5681	3741	23222	70.3 ± 10.0	70.5 ± 9.9	69.3 ± 10.0	68.82 ± 11.1	N/A	N/A	N/A	N/A	3.57 ± 1.29	3.60 ± 1.32	3.51 ± 1.28	3.57 ± 1.31
Kohsaka *et al*[28], 2017	5977	5090	6726	6726 (War-Dab matched); 5090 (War-Riv matched); 5977 (War-Api matched)	77.4 ± 10.0	75.8 ± 10.0	73.1 ± 9.9	73.3 ± 10.5 (War-Dab matched); 76.2 ± 10.5 (War-Riv matched); 77.7 ± 10.0 (War-Api matched)	N/A	N/A	N/A	N/A	3.5 ± 1.6	3.3 ± 1.6	3.0 ± 1.6	3.0 ± 1.6 (War-Dab matched); 3.4 ± 1.6 (War-Riv matched); 3.5 ± 1.5 (War-Api matched)
Chan *et al*[29], 2018	5843	27777	20079	19375	76 ± 10	76 ± 10	76 ± 10	76 ± 10	2.96 ± 1.12	2.96 ± 0.51	2.96 ± 0.59	2.97 ± 0.61	3.89 ± 1.56	3.89 ± 0.71	3.88 ± 0.82	3.89 ± 0.88
Huang *et al*[30], 2018	N/A	9637	N/A	9637	N/A	75.2 ± 10.24	N/A	74.98 ± 10.6	N/A	2.21 ± 1.46	N/A	2.33 ± 1.49	N/A	4.02 ± 1.92	N/A	4.11 ± 2
Okumura *et al*[31], 2018	428	761	456	1561	73.2 ± 10.1	71.5 ± 9.1	70.9 ± 9.5	72.2 ± 9.3	1.42 ± 0.81	1.32 ± 0.77	1.07 ± 0.71	1.61 ± 0.88	3.12 ± 1.47	2.87 ± 1.45	2.83 ± 1.46	3.08 ± 1.51
Koretsune *et al*[32], 2018	N/A	N/A	4606	4606	N/A	N/A	74 ± 10	73 ± 11	N/A	N/A	2.1 ± 1.0	2.1 ± 1.1	N/A	N/A	3.3 ± 1.7	3.3 ± 1.7
Chan *et al*[33], 2019	9952	33022	22371	19761	76 ± 10.5	75.3 ± 10.6	74.2 ± 10.4	70.6 ± 13.4	2.9 ± 1.1	2.9 ± 1.1	2.8 ± 1.1	2.6 ± 1.3	3.9 ± 1.6	3.8 ± 1.6	3.7 ± 1.5	3.2 ± 1.8
Jeong *et al*[34], 2019	N/A	804	N/A	804	N/A	71.4 ± 10.5	N/A	70.4 ± 10.2	N/A	N/A	N/A	N/A	N/A	3.3 ± 1.8	N/A	3.4 ± 1.8
Lee *et al*[35], 2019	22177	35965	17745	25420	72.7 ± 10.2	72.0 ± 9.9	70.8 ± 9.9	67.3 ± 12.6	2.75 ± 1.04	2.77 ± 1.02	2.67 ± 1.01	2.58 ± 1.14	3.76 ± 1.41	3.63 ± 1.40	3.55 ± 1.37	3.18 ± 1.61
Cho *et al*[36], 2019	12502	21000	12593	10409	74.3 ± 8.9	73.8 ± 8.8	72.9 ± 8.9	70.8 ± 11	2.5 ± 0.9	2.5 ± 0.9	2.5 ± 0.9	2.6 ± 1.0	3.7 ± 1.2	3.6 ± 1.2	3.5 ± 1.2	3.5 ± 1.2

HAS-BLED: Hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; War: Warfarin; Dab: Dabigatran; Riv: Rivaroxaban; Api: Apixaban; N/A: Not applicable.

another study from the United States showed higher risk of gastrointestinal bleeding in the rivaroxaban group[23], our study yielded favorable result pointing toward reduction of gastrointestinal bleeding of rivaroxaban in Asian patients. In summary,

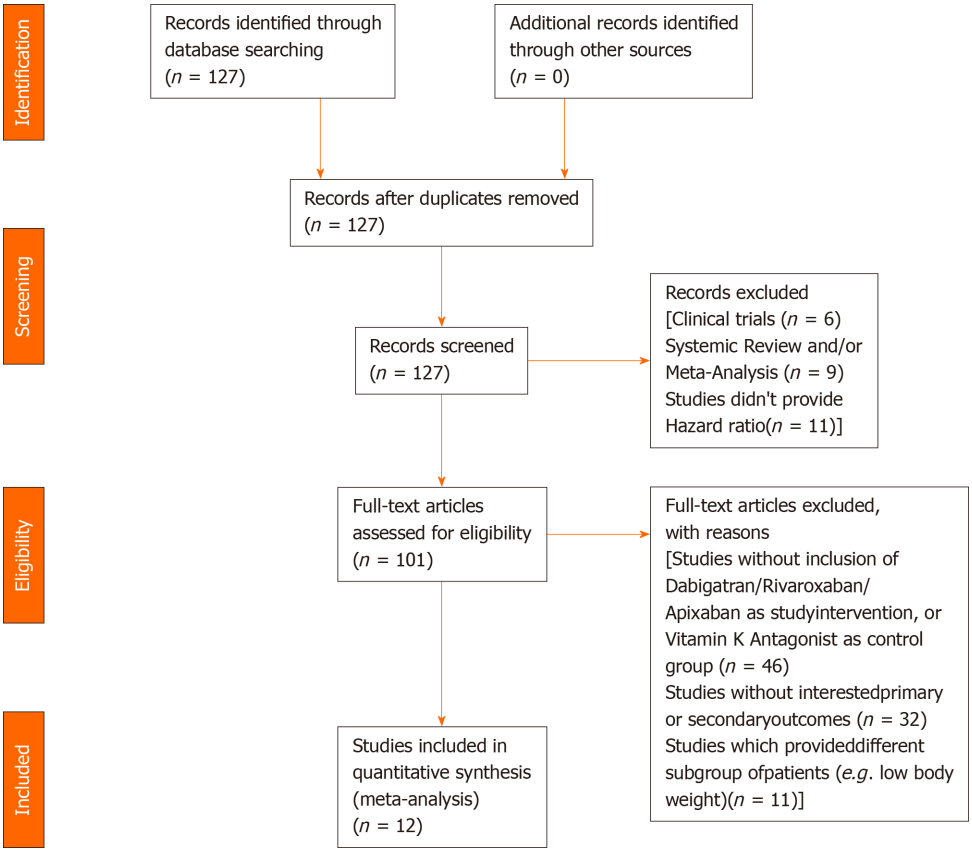

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

our meta-analysis showed that Asian patients with non-valvular AF on rivaroxaban had less stroke and bleeding rates compared to those on warfarin.

Apixaban is another FXa inhibitor approved for stroke prevention in patients with non-valvular AF[8]. The publication of the results of the apixaban for reduction in stroke and other thromboembolic events in AF (ARISTOTLE) trial was the milestone after which apixaban became one of the most widely prescribed oral anticoagulants[12]. In ARISTOTLE trial, patients with non-valvular AF were randomized in the apixaban and warfarin groups. The apixaban group had significantly lower stroke and major bleeding events rates, and lower mortality compared to warfarin group. Large real-world studies mainly in non-Asians confirmed the randomized trial data[18,24]. With this meta-analysis, we demonstrate that apixaban is more efficacious and safer than warfarin in our Asian population, as well.

The main strengths of our study are its strict methodology, robust analysis, and the relatively large number of included studies and overall patient sample. Our study has a number of limitations, mainly associated with the observational nature of the included studies. The patient populations of the individual studies were heterogeneous despite the fact that the vast majority was of Asian race. We were unable to adjust for baseline comorbidities because we did not have access to patient level data. For some of the outcomes, the number of eligible studies was limited which decreases the certainty in our findings.

CONCLUSION

In conclusion, the present systematic review and meta-analysis revealed that dabigatran, rivaroxaban, and apixaban, appear to be superior to warfarin in terms of efficacy (stroke prevention, all-cause mortality) and safety outcomes (bleeding events) in Asians with non-valvular AF.

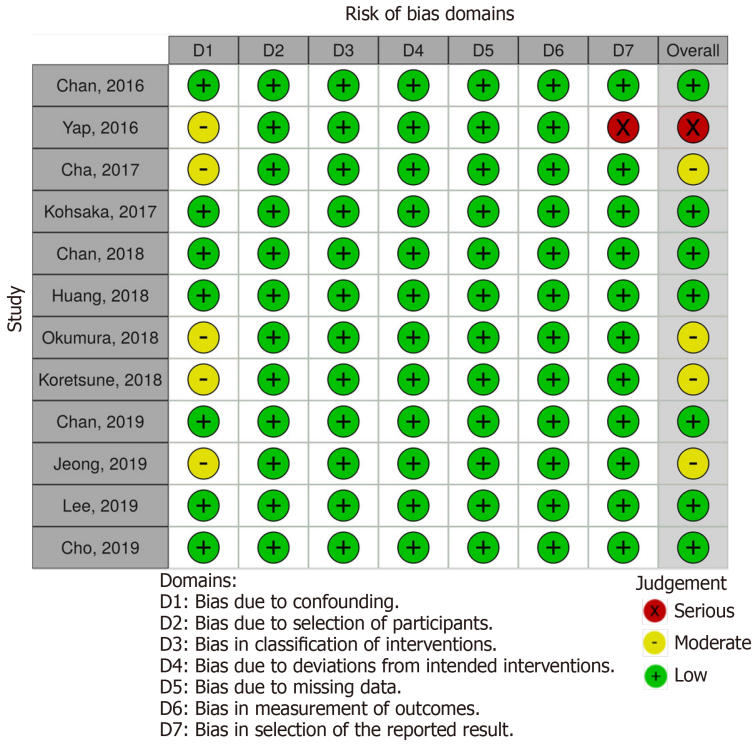

Figure 2 Risk of bias assessment of included studies using risk of bias in non-randomized studies-of interventions tool.

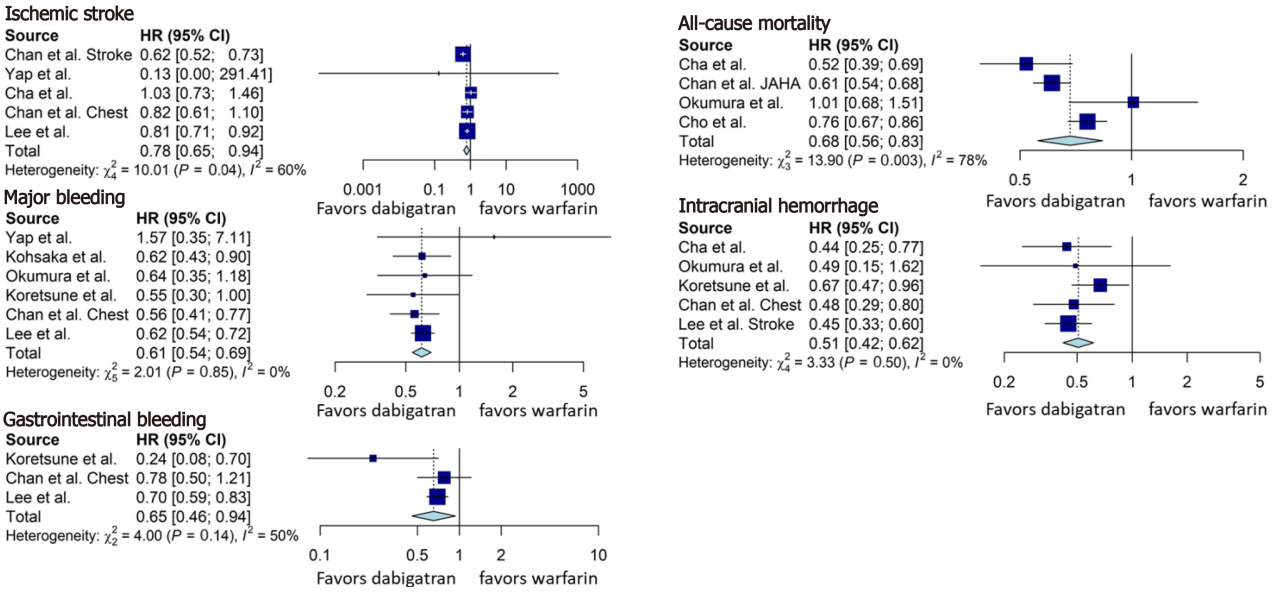

Figure 3 Forest plots comparing dabigatran with warfarin regarding hazard ratios of ischemic stroke, all-cause mortality, major bleeding, intracranial hemorrhage, and gastrointestinal bleeding. HR: Hazard ratio; CI: Confidence interval.

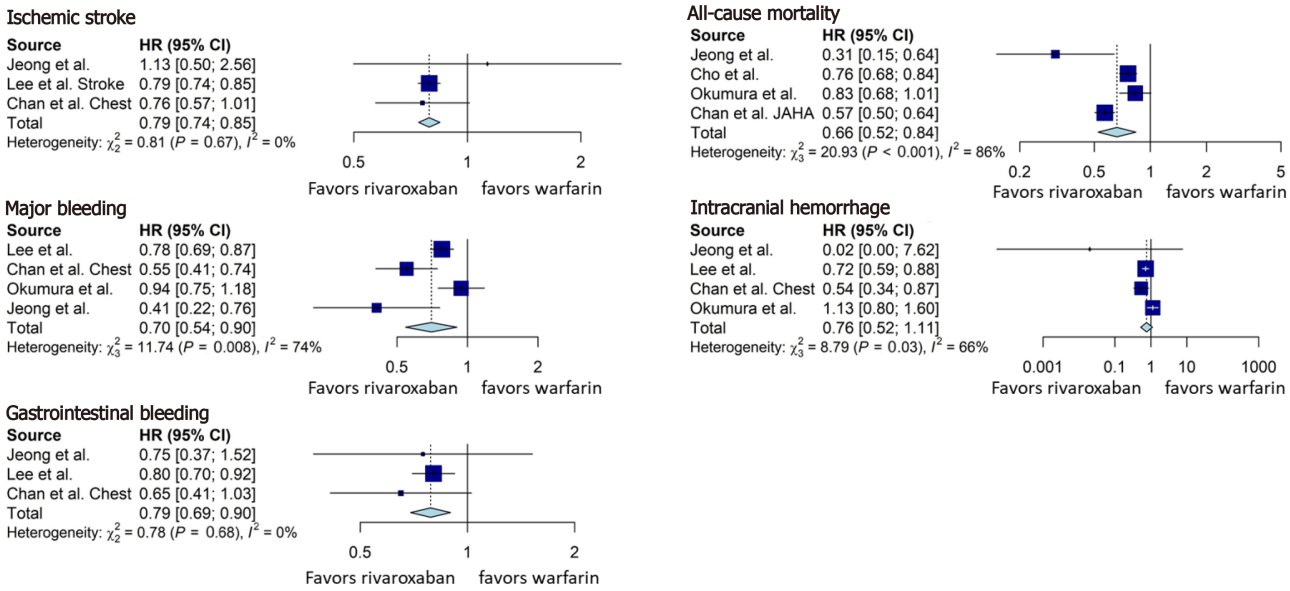

Figure 4 Forest plots comparing rivaroxaban with warfarin regarding hazard ratio of ischemic stroke, all-cause mortality, major bleeding, intracranial hemorrhage, and gastrointestinal bleeding. HR: Hazard ratio; CI: Confidence interval.

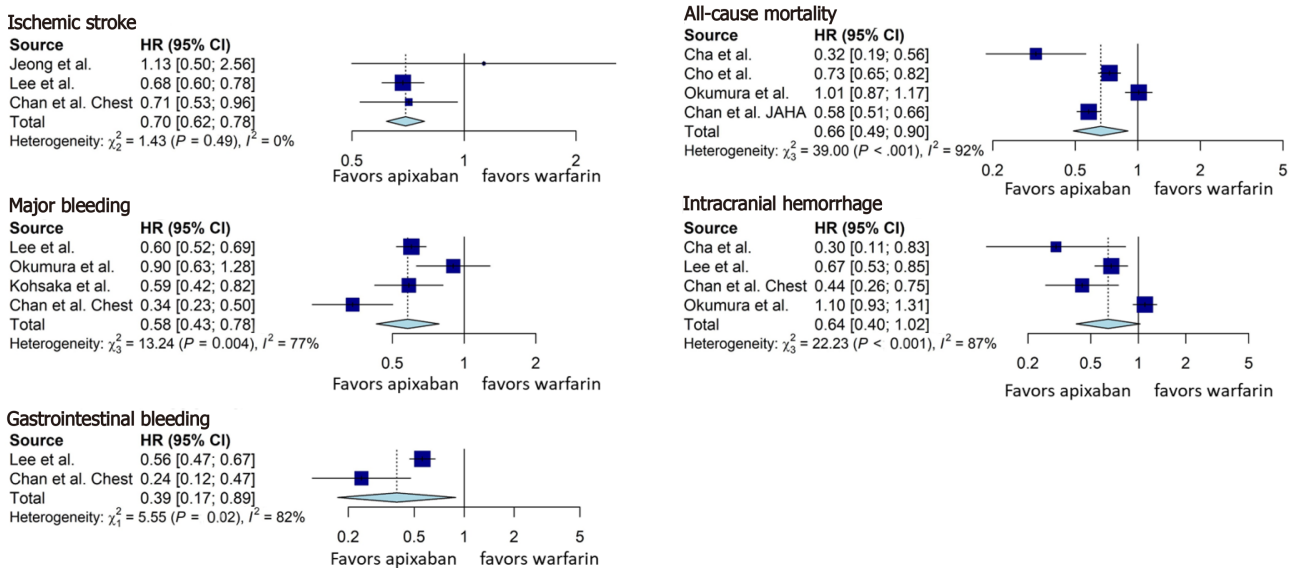

Figure 5 Forest plots comparing apixaban with warfarin regarding hazard ratio of ischemic stroke, all-cause mortality, major bleeding, intracranial hemorrhage, gastrointestinal bleeding. HR: Hazard ratio; CI: Confidence interval.

ARTICLE HIGHLIGHTS

Research background

Stroke is the second leading cause of mortality and disability worldwide with one-third of all ischemic stroke cases attributed to atrial fibrillation (AF).

Research motivation

Warfarin was the standard of care of stroke prevention in patients with nonvalvular AF but novel oral anticoagulants including dabigatran, rivaroxaban, and apixaban have demonstrated better efficacy and safety than warfarin in randomized clinical trials but they originated from Western countries where the Asian population was underrepresented.

Research objectives

We aimed to systematically review and quantitatively analyze the existing real-world observational studies regarding the efficacy and safety of dabigatran, rivaroxaban, and apixaban when they are compared with warfarin for stroke prevention in Asian patients with non-valvular AF.

Research methods

The study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Medline, Cochrane, and ClinicalTrial.gov databases were systematically searched. A random-effect model meta-analysis was used and I^2 was utilized to assess heterogeneity. Risk of bias assessment was performed for every study included.

Research results

Twelve studies were qualified for our study. Dabigatran, rivaroxaban, and apixaban were all associated with significantly reduced incidence of ischemic stroke, all-cause mortality, major bleeding, and gastrointestinal bleeding. Dabigatran was also found associated with a lower risk of intracranial hemorrhage.

Research conclusions

Dabigatran, rivaroxaban, and apixaban have better efficacy and safety profile than warfarin for stroke prevention in Asian patients with non-valvular AF.

Research perspectives

Future research which conducts a head-to-head comparison between different novel oral anticoagulants is necessary to determine the best option for Asian patients with non-valvular AF.

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