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REVIEW ARTICLE

Real-world Comparisons of Direct Oral Anticoagulants for Stroke Prevention in Asian Patients with Non-valvular Atrial Fibrillation: a Systematic Review and Meta-analysis

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Abstract

Background Whether four direct oral anticoagulants (DOACs) are superior to warfarin among Asians with non-valvular atrial fibrillation (NVAF) remains unclear in the real-world setting.

Methods We searched PubMed and Medline + Journals@Ovid + EMBASE from September 17, 2009 to May 4, 2019 to perform a systematic review and meta-analysis of all observational real-world studies comparing four DOACs with warfarin specifically focused on Asian patients with NVAF.

Results From the original 212 results retrieved, 18 studies were included in the meta-analysis. Overall, DOACs were associated with lower risks of thromboembolism (hazard ratio; [95% confidence interval], 0.70; [0.63–0.78]), acute myocardial infarction (0.67; [0.57–0.79]), all-cause mortality (0.62; [0.56–0.69]), major bleeding (0.59; [0.50–0.69]), intracranial hemorrhage (0.50; [0.40–0.62]), gastrointestinal bleeding (0.66; [0.46–0.95]), and any bleeding (0.82; [0.73–0.92]) than warfarin. There was statistic heterogeneity between DOACs for the risks of thromboembolism (P interaction = 0.03) and acute myocardial infarction (P interaction = 0.007) when compared to warfarin. However, all DOACs showed lower risks of thromboembolism and acute myocardial infarction than warfarin when pooling studies that compared individual DOAC with warfarin. With regard to the other outcomes when compared to warfarin, there was no statistical heterogeneity between DOACs. In addition, the effectiveness and safety of four DOACs versus warfarin persisted in the subgroups of either standard-dose or low-dose DOACs.

Conclusions The meta-analysis shows that the DOACs had greater effectiveness and safety compared to warfarin in real-world practice for stroke prevention, among Asian patients with NVAF.

Keywords Atrial fibrillation · Direct thrombin inhibitor · Factor Xa inhibitor · Ischemic stroke · Hemorrhage · Mortality · Warfarin

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Introduction

Oral anticoagulants such as vitamin-K antagonists (e.g., warfarin) or direct oral anticoagulants (DOACs) (e.g., apixaban, dabigatran, edoxaban, and rivaroxaban) are indicated for stroke prevention in patients with atrial fibrillation (AF) when ≥ 1 more risk factors for stroke are present [1]. Previous pivotal randomized clinical trials (RCTs) have demonstrated that DOACs showed a comparable or better efficacy compared to warfarin, and were safer than warfarin, with a significant risk reduction of major bleeding and intracranial hemorrhage (ICH) in patients with non-valvular AF (NVAF) [2]. Of note, Asians may get more benefit from DOACs than non-Asians, possibly because the risk of major bleeding in Asians taking warfarin is generally higher than in non-Asians even though more Asian patients had international normalized ratio (INR) < 2.0 and less had INR > 3.0 [3, 4]. A meta-analysis of the ethnicity-specific analyses of four pivotal DOACs trials, including > 8000 Asian patients taking DOACs, suggested that standard-dose DOACs were more effective and safer in Asians than in non-Asians, whereas low-dose DOACs performed similarly in Asians and non-Asians [5].

Although the RCTs and their meta-analysis are the gold standard to evaluate the efficacy and safety of a specific treatment/drug in a specific disease, they are restricted by specific inclusion/exclusion criteria and thus only represent a highly selected and controlled scenario. The phase IV or real-world evidence provided the additional evidence in a broad spectrum of patients, beyond the highly selected and controlled population enrolled in the RCTs [6]. Recent real-world studies have reported the effectiveness and safety of DOACs among Asians with NVAF [7–11]. However, different studies in the real-world setting may show diverse results due to the different analytic methodology, enrollment criteria, and data sources. Of particular note, a high prevalence of low-dose DOAC prescription has been observed in Asian real-world practice [7–11]. Therefore, the objective of the present study was to perform a systemic review of the available real-world evidence from several large-scale phase 4 studies regarding the effectiveness and safety of the four DOACs versus warfarin, specifically focused on Asian patients with NVAF.

Methods

Search Strategy, Inclusion Criteria, and Study Outcomes

We followed the PRSIMA (preferred reporting items for systemic reviews and meta-analyses) and MOOSE (Meta-analyses of Observational Studies in Epidemiology) guidelines when performing the meta-analyses [12, 13]. Two independent reviewers (YH Chan and HF Lee) conducted a comprehensive search of PubMed, Medline, and EMBASE between the first available date and May 4, 2019. The search items were "apixaban OR dabigatran OR rivaroxaban OR edoxaban" AND "atrial fibrillation" AND "warfarin" AND "Asians OR Asian OR Asia OR Japan OR Korea OR Taiwan OR China OR Malaysia OR Thailand OR Hong Kong OR Singapore OR Philippines OR India OR Indonesia OR Pakistan OR Bangladesh" AND "database OR claim OR claims OR observational OR real-world OR registry OR retrospective". The electronic search was performed for peer-reviewed journals. We also checked the references of related abstracts to find potentially eligible studies which may have not been included in the literature yield.

We included observation studies comparing ≥ 1 DOACs versus warfarin. In all comparisons, warfarin was used as the reference. For study in which some of the included studies have used the same database, only the study with the longest follow-up period was used unless the study periods did not overlap between studies or unless the study reported another outcome. The assessed outcomes included thromboembolism (ischemic stroke/stroke or systemic embolism), acute myocardial infarction (AMI), all-cause mortality, ICH, gastrointestinal bleeding (GIB), major bleeding, and any bleeding.

Statistical Analysis

All statistical analyses were performed by using the Review Manager 5.3 (The Cochrane Collaboration 2014, The Nordic Cochrane Center, Copenhagen, Denmark). The logarithmic hazard ratio (HR) of the matched or adjusted effect estimates and the corresponding errors were pooled based on the random effect analysis. The degree of heterogeneity between studies was evaluated by using the I^2 index. Values of < 25%, 25–50%, and ≥ 50% were defined as low, moderate, and high degree of heterogeneity, respectively [14]. We used the funnel plot of the reported effect estimates to assess the risk of publication bias. Sensitivity analyses were performed in standard-dose and low-dose DOAC subgroups, respectively. For all comparison in the present study, $P < 0.05$ was taken as statistically significant.

Results

The literature search yields 212 results, of which 18 were finally included in the study. Apixaban was assessed in four studies [7, 9, 11, 15], dabigatran in 15 [7, 10, 11, 15–25], rivaroxaban in nine [7, 10, 11, 15, 17, 22, 23, 26, 27], and edoxaban in two studies [11, 28] (Fig. 1). Table 1 summarized the baseline characteristics. The majority of patient cohorts were contributed from seven studies, with one nationwide study using the Taiwan National Health Insurance Database with 23 million enrollees, [11] other three nationwide studies using the Korea

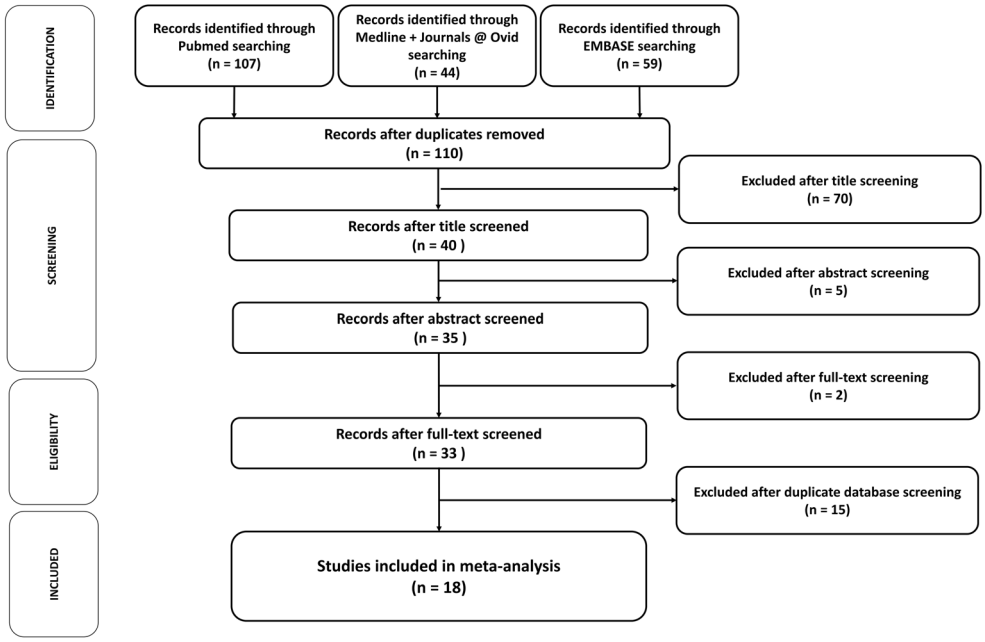

Fig. 1 Flow-chart of enrolled studies selection process

National Health Insurance Database with 50 million enrollees [7, 15, 28]. Another three studies using a large and local health care database with 13 million enrollees in Japan [9, 10, 25]. The patient numbers of the other studies were less than 3000 patients.

Risk of Bias Evaluation

Among the 18 included studies, nine used a propensity score matching method [9, 10, 15, 19, 20, 24, 25, 27, 28], two used propensity score weighting methods [7, 11], and six used multivariable logistic regression [16–18, 21–23] to balance confounding factors between DOACs and warfarin. Rivaroxaban and warfarin were already randomized at baseline in one study [26] (Table 1). A bias evaluation is summarized in Supplemental Table I. Overall, most studies reported a low risk of bias, while five studies had a risk of selection bias [10, 11, 20, 23, 25], and three studies had a risk of performance bias [10, 17, 18]. The funnel plot visually shows the possibility of bias or small-study effects (Supplemental Fig. I).

Comparison between DOACs and Warfarin: Overall Effect

For the effectiveness outcomes, overall DOACs were associated with lower risks of thromboembolism (hazard ratio [HR], 0.70; 95% confidential interval [CI], 0.63–0.78), AMI (HR, 0.67; 95% CI, 0.57–0.79), and all-cause mortality (HR, 0.62; 95% CI, 0.56–0.69) than warfarin. For the safety outcomes, overall DOACs were associated with lower risks of major bleeding (HR, 0.59; 95% CI, 0.50–0.69), ICH (HR, 0.50; 95% CI, 0.40–0.62), GIB (HR, 0.66; 95% CI, 0.46–0.95), and any bleeding (HR, 0.82; 95% CI, 0.73–0.92) than warfarin (Fig. 2). There was statistic heterogeneity between DOACs for the risks of thromboembolism (P interaction = 0.03) and AMI (P interaction = 0.007). However, the lower risks of thromboembolism or AMI compared to warfarin were consistent among all DOACs. There was no statistic heterogeneity between DOACs for the risks of mortality and all safety outcomes (all P interaction > 0.05).

Comparisons between Specific DOAC and Warfarin

For the effectiveness outcomes, all four DOACs were associated with a lower risk of thromboembolism, AMI, and mortality than warfarin in Asian patients with NVAF (Figs. 3, 4, 5 and 6). For the safety outcome, dabigatran (HR, 0.45; 95% CI, 0.34–0.59; $I^2 = 33\%$, $N = 10$), rivaroxaban (HR, 0.65; 95% CI, 0.46–0.91; $I^2 = 41\%$, $N = 4$), and edoxaban (HR, 0.41; 95% CI, 0.27–0.61; $I^2 = 0\%$, $N = 3$) were associated with a lower risk of ICH than warfarin; only edoxaban (HR, 0.47; 95% CI, 0.33–0.65; $I^2 = 26\%$, $N = 3$) was associated with a lower risk of GIB than warfarin; apixaban (HR, 0.55; 95% CI, 0.39–0.78; $I^2 = 80\%$, $N = 3$), dabigatran (HR, 0.65; 95% CI, 0.51–0.81; $I^2 = 52\%$, $N = 9$), rivaroxaban (HR, 0.69; 95% CI, 0.49–0.96; $I^2 = 79\%$, $N = 5$), and edoxaban (HR, 0.48; 95% CI, 0.36–0.63; $I^2 = 31\%$, $N = 3$) were all associated with a lower risk of major bleeding than warfarin; apixaban (HR, 0.78; 95% CI, 0.73–0.83; $I^2 = 0\%$, $N = 2$) and dabigatran (HR, 0.76; 95% CI, 0.61–0.95; $I^2 = 72\%$, $N = 6$) were associated with a lower risk of any bleeding than warfarin in Asian patients with NVAF (Figs. 3, 4, 5 and 6).

Table 1 The summary of enrolled studies in the present meta-analysis

Author, year	Region	Enrolled period	Data source	Primary statistical method	Cohort size					Age	CHA_2DS_2-VASc	Estimated follow-up period
					Apixaban LD (2.5 mg), %	Dabigatran LD (110 mg), %	Rivaroxaban LD (15/10 mg), %	Edoxaban LD (30 mg), %	Warfarin			
Cha et al. 2017 [15]	Korea	January 2014 to December 2015	Korea National Health Insurance Database	PSM	2189 42%	3741 63%	5681 50%	NR NR	23,222	69	3.6	1.2 years
Chan et al. 2016 [18]	Hong Kong	2010 to 2013	Single-center retrospective cohort registry	Multivariate cox regression	NR NR	129 100%	NR NR	NR NR	442	85	4.8	2.6 years
Chan et al. 2018 [22]	Singapore	June 2011 to December 2013	Single-center retrospective cohort registry	Multivariate cox regression	NR NR	110 NR	145 NR	NR NR	128	70–72	1.6–2.0	NR
Chan et al. 2019 [11]	Taiwan	June 2012 to December 2017	Taiwan National Health Insurance Database	PSW	9952 64%	22,371 89%	33,022 94%	4577 64%	19,761	71–76	3.3–3.9	0.5–1.0 years
Cho et al. 2019 [7]	Korea	July 2015 to December 2016	Korea National Health Insurance Database	PSW	12,502 63%	12,593 75%	21,000 59%	NR NR	10,499	71–74	3.5–3.7	1.3 years
Ho et al. 2012 [16]	Hong Kong	January 2010 to November 2011	Single-center retrospective cohort registry	Multivariate cox regression	NR NR	122 90%	NR NR	NR NR	122	64–68	2.3–2.5 ($CHADS_2$)	0.9 years
Jeong et al. 2019 [27]	Korea	January 2014 to December 2016	Single-center retrospective cohort registry	PSM	NR NR	NR NR	804 51%	NR NR	804	70–71	3.3–3.4	1 years
Kohsaka et al. 2017 [10]	Japan	March 2011 to June 2016	Hospital information systems and administration database provided by Medical Data Vision	PSM	5977 57%	5090 78%	6726 100%	NR NR	14,037	72–78	2.9–3.6	1 years
Kohsaka et al. 2018 [9]	Japan	March 2011 to June 2016	Hospital information systems and administration database provided by Medical Data Vision	PSM	11,972 58%	NR NR	NR NR	NR NR	11,972	77–78	3.4–3.5	1 years
Koretsune et al. 2018 [25]	Japan	March 2011 to June 2016	Hospital information systems and administration database provided by Medical Data Vision	PSM	NR NR	4606 78%	NR NR	NR NR	4606	72–78	3.2–3.9	0.5–0.6 years

Table 1 (continued)

Author, year	Region	Enrolled period	Data source	Primary statistical method	Cohort size					Age	CHA_2DS_2-VASc	Estimated follow-up period
					Apixaban LD (2.5 mg), %	Dabigatran LD (110 mg), %	Rivaroxaban LD (15/10 mg), %	Edoxaban LD (30 mg), %	Warfarin			
Lau et al. 2016 [24]	Hong Kong	January 2010 to December 2013	Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority	PSM	NA NA	1261 NA	NR NR	NR NR	1261	NR	NR	NR
Lau et al. 2017 [19]	Hong Kong	January 2010 to December 2014	CDARS of the Hong Kong Hospital Authority	PSM	NR NR	2580 75%	NR NR	NR NR	2580	74	3.3	1.2 years
Lee et al. 2017 [20]	Korea	January 2012 to December 2013	Single-center retrospective cohort registry	PSM	NR NR	549 67%	NR NR	NR NR	549	72	3.3	1 years
Li et al. 2016 [17]	Hong Kong	January 2008 to December 2014	Observational study from a hospital-based AF registry	Multivariate cox regression	NR NR	467 97%	669 41%	NR NR	963	73	3.7	1.8 years
Mao et al. 2014 [26]	China	July 2009 to December 2010	Single-center prospective cohort registry	Randomization at baseline	NR NR	NR NR	176 NR	NR NR	177	75	3.4 ($CHADS_2$)	1 years
Naganuma et al. 2016 [21]	Japan	March 2011 to December 2013	Single-center retrospective cohort registry	Multivariate cox regression	NR NR	181 69%	NR NR	NR NR	181	69	3.0–3.1	1.3 years
Wee et al. 2017 [23]	Singapore	July 2012 and September 2015	Multiple-center retrospective cohort registry	Multivariate cox regression	8 NR	27 NR	121 NR	NR NR	224	68–70	3–4	0.4 years
Yu et al. 2018 [28]	Korea	January 2009 to December 2013	Korea National Health Insurance Database	PSM	NR NR	NR NR	NR NR	5856 58%	5856	68–73	4.2–4.9	0.4 years

CHA_2DS_2-VASc = congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, female; LD = low dose; NR = not reported; PSM = propensity score matching; PSW = propensity score weighting

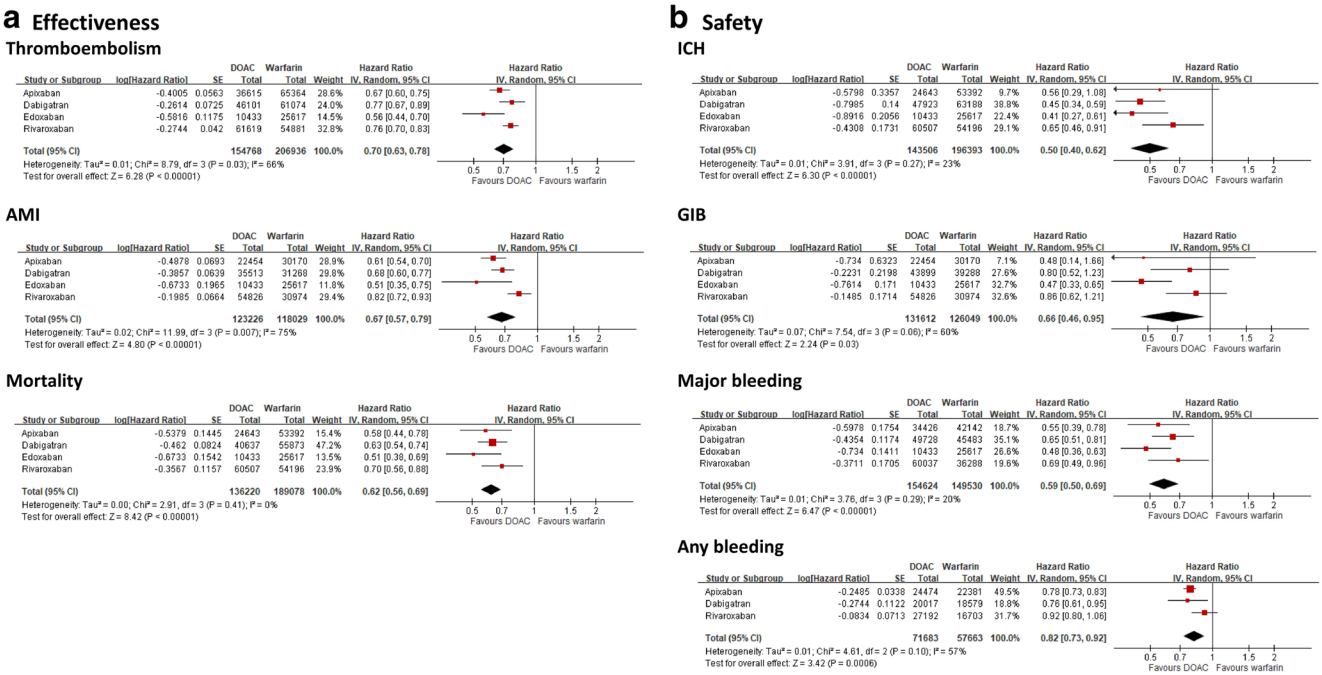

Fig. 2 Direct oral anti-coagulant (DOACs) vs. warfarin for effectiveness outcomes: thromboembolism (ischemic stroke/stroke or systemic embolism), acute myocardial infarction (AMI), mortality, and safety outcomes: intracranial hemorrhage (ICH), gastrointestinal bleeding (GIB), major bleeding, and any bleeding in Asian patients with NVAF. Abbreviations: AMI = acute myocardial infarction; CI = confidence interval; DOAC = direct oral anti-coagulant; ICH = intracranial hemorrhage; GIB = gastrointestinal bleeding; NVAF = nonvalvular atrial fibrillation

Standard-dose and Low-dose DOACs

Only six studies reported outcomes of patients taking standard or low-dose DOACs, respectively [7, 10, 11, 20, 27, 28]. There were 64%, 89%, 94%, and 64% of patients taking low-dose apixaban (2.5 mg twice daily), dabigatran (110 mg twice daily), rivaroxaban (15 or 10 mg once daily), and edoxaban (30 mg once daily) in Taiwan [11]. There were 63%, 75%, and 59% of patients taking low-dose apixaban (2.5 mg twice daily), dabigatran (110 mg twice daily), and rivaroxaban (15 mg once daily) in Korea [7, 28]. In Japan, only low-dose rivaroxaban 15 mg/10 mg once daily was approved for stroke prevention in NVAF patients, and patients taking rivaroxaban in Japan was classified as the low-dose subgroup [10].

Both standard-dose (5 mg twice daily; $n = 8254$) and low-dose (2.5 mg twice daily; $n = 14{,}200$) apixaban were associated with lower risks of thromboembolism, major bleeding, and mortality than warfarin ($n = 30{,}170$) (Supplemental Fig. II). Both standard-dose (150 mg twice daily; $n = 5871$) and

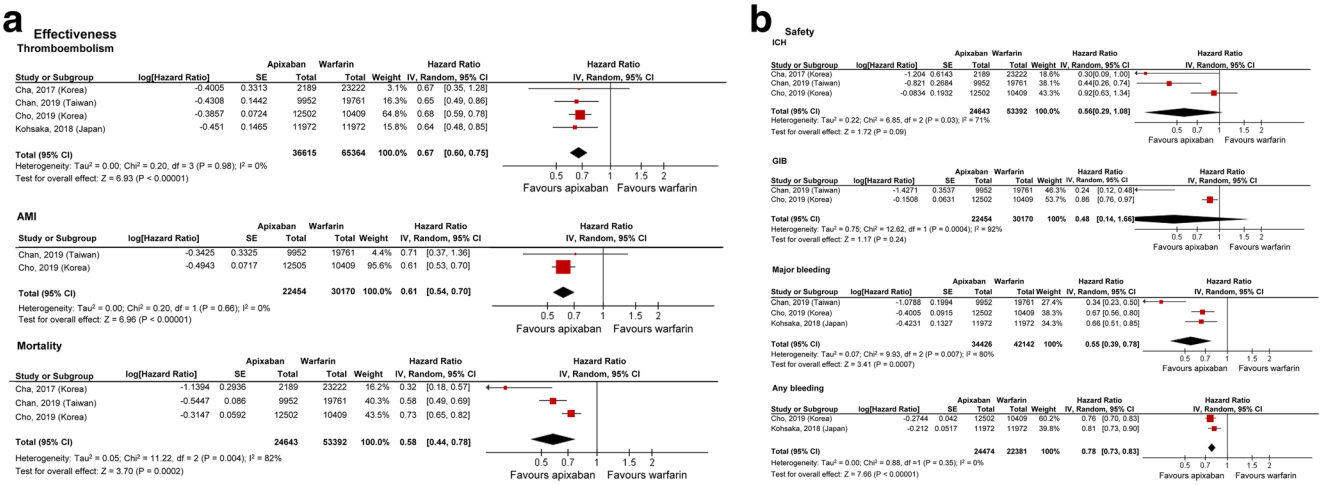

Fig. 3 Apixaban vs. warfarin for effectiveness (**a**) and safety outcomes (**b**) in Asian patients with NVAF. Abbreviations as in Fig. 2

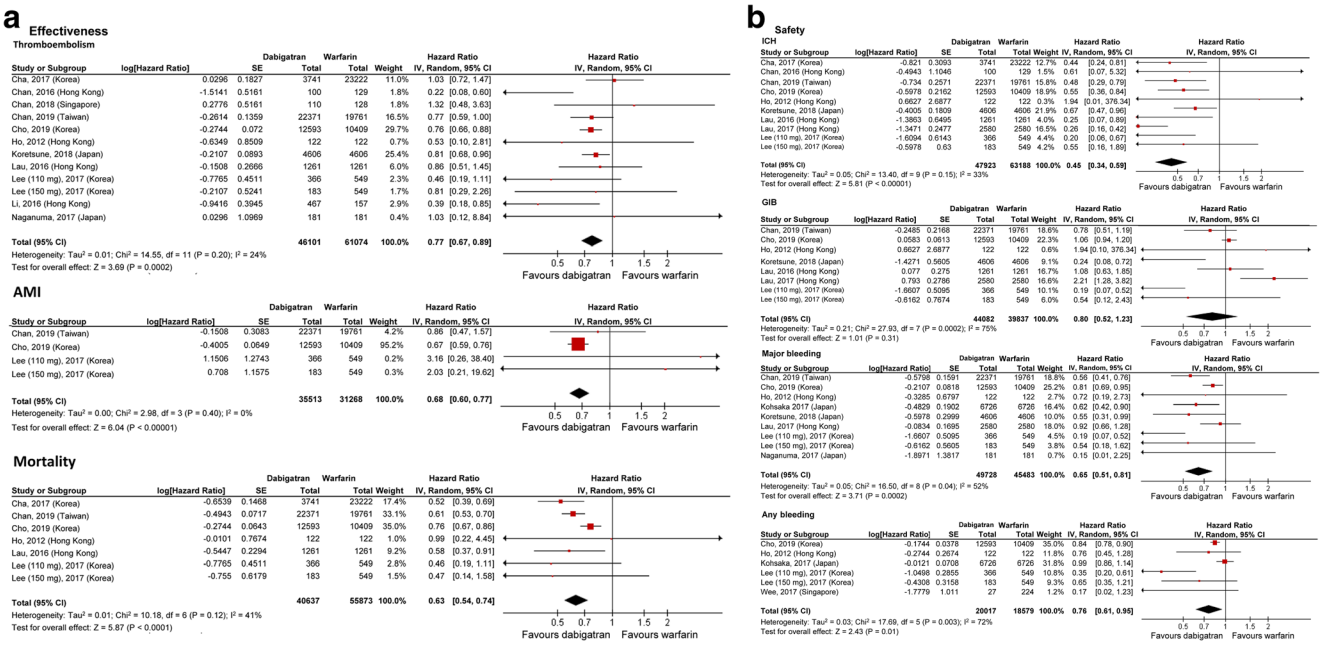

Fig. 4 Dabigatran vs. warfarin for effectiveness (**a**) and safety outcomes (**b**) in Asian patients with NVAF. Abbreviations as in Fig. 2

low-dose dabigatran (110 mg twice daily; $n = 29{,}642$) were associated with lower risks of thromboembolism and major bleeding than warfarin ($n = 30{,}719$) (Supplemental Fig. III). Both standard-dose ($n = 4493$) and low-dose edoxaban ($n = 5940$) were associated with lower risks of thromboembolism, major bleeding, and mortality than warfarin (Supplemental Fig. IV). Both standard-dose (20 mg once daily; $n = 10{,}905$) (HR, 0.77; 95% CI, 0.66–0.89; $I^2 = 0\%$, $N = 3$) and low-dose rivaroxaban (15/10 mg once daily; $n = 43{,}921$) (HR, 0.73; 95% CI, 0.64–0.83; $I^2 = 0\%$, $N = 3$) were associated with a lower risk of thromboembolism when compared with warfarin ($n = 30{,}974$) (Supplemental Fig. VA). Of note, only low-dose rivaroxaban was associated with a lower risk of major bleeding compared to warfarin (HR, 0.69; 95% CI, 0.48–0.99; $I^2 = 82\%$, $N = 4$) (Supplemental Fig. VB).

Discussion

Our study is the first meta-analysis of large phase IV clinical studies that compared four DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) with warfarin in Asian patients with regard to both effectiveness and safety outcomes. Overall, DOACs were associated with lower risks of thromboembolism, AMI, mortality, major bleeding, ICH, GIB, and any bleeding than warfarin in Asian patients with NVAF. There was statistic heterogeneity between DOACs for the risks of thromboembolism (P interaction = 0.03) and AMI (P interaction = 0.007) when compared to warfarin. However, all DOACs showed lower risks of thromboembolism and acute myocardial infarction than warfarin when pooling studies that compared individual DOAC with warfarin. There was no

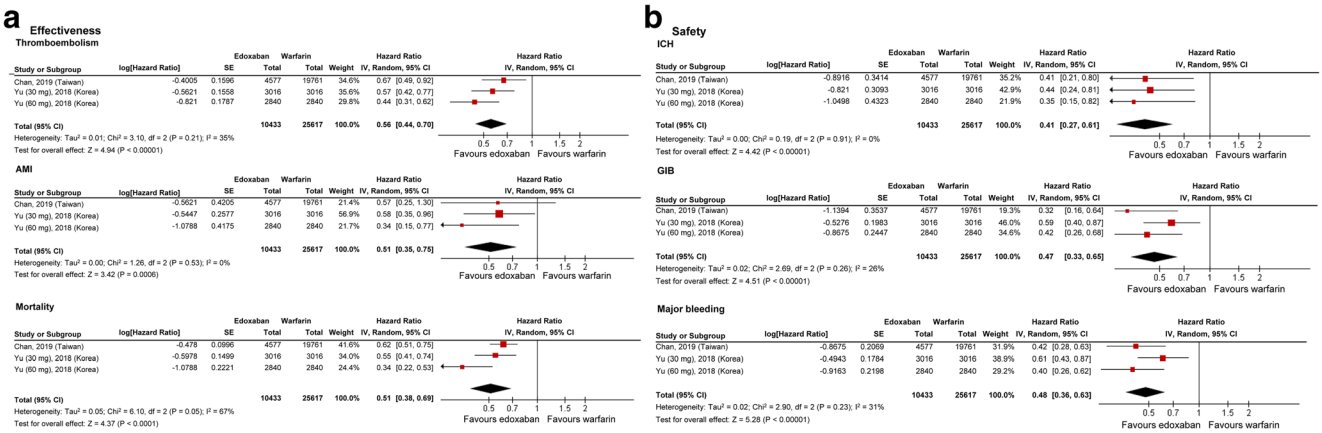

Fig. 5 Edoxaban vs. warfarin for effectiveness (**a**) and safety outcomes (**b**) in Asian patients with NVAF. Abbreviations as in Fig. 2

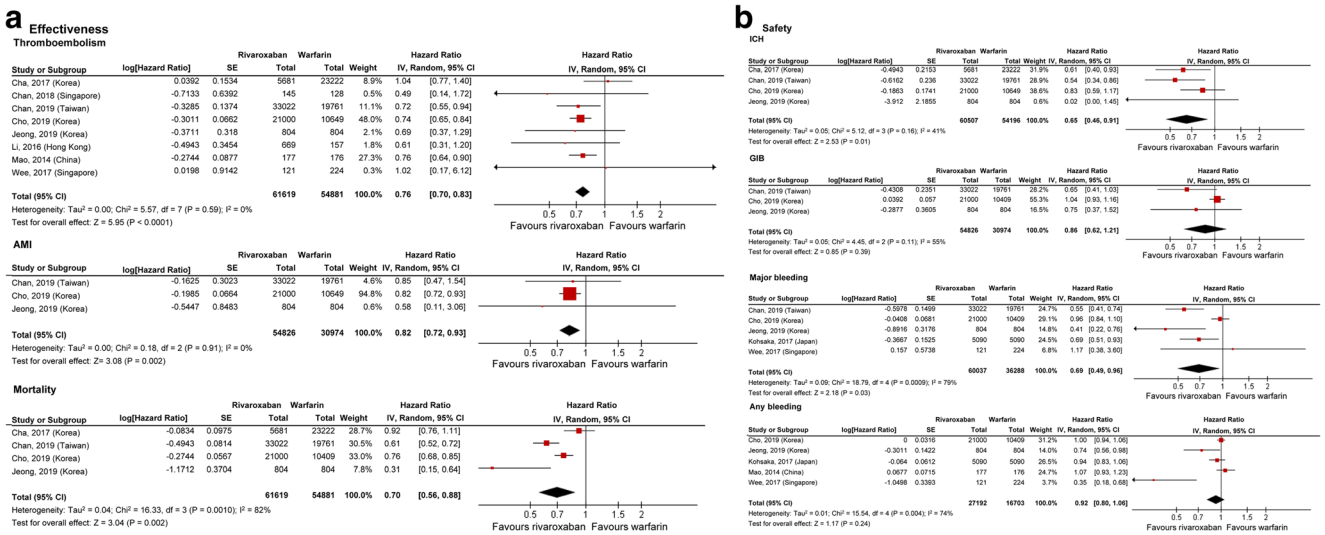

Fig. 6 Rivaroxaban vs. warfarin for effectiveness (**a**) and safety outcomes (**b**) in Asian patients with NVAF. Abbreviations as in Fig. 2

statistic heterogeneity between DOACs for the risks of the other outcomes (all *P* interaction > 0.05) when compared to warfarin. The effectiveness and safety of four DOACs versus warfarin persisted in the subgroup of either standard- or low-dose DOACs.

This present meta-analysis is the largest systematic assessment of real-world data in Asian patients with AF, and includes around 160,000 Asian patients taking DOACs and supports the finding of the post-hoc analysis of four pivotal RCTs [5], indicating that DOACs are more effective and safer than warfarin in Asians patients with NVAF. The post-hoc analysis of RCTs indicated that DOACs showed better efficacy and safety profiles in Asians than in non-Asians [5]: DOACs significantly reduced the risk of stroke/systemic embolism in Asians, and the reduction was more prominent compared to non-Asian patients. For the safety outcomes, DOACs reduced major bleeding more in Asians than in non-Asian patients. The present meta-analysis indicated that all DOACs were associated with a lower risk of AMI than warfarin, which is discordant from the result of a post-hoc analysis of RCTs showing a comparable risk of AMI for four DOACs versus warfarin in Asians with NVAF [5]. Only a few real-world studies reported the outcome of AMI for DOACs versus warfarin [7, 11, 20, 27, 28], and two studies reported that the four DOACs were associated with a significantly lower risk of AMI than warfarin in Korea [7, 28]. In the contrast, a comparable risk of AMI for four DOACs versus warfarin was observed in Taiwan's real-world practice [11]. Of note, our meta-analysis is compatible with previous studies showing that all DOACs were associated with a significant standardized absolute risk reduction of AMI compared with warfarin in a large real-life cohort setting [29]. A previous study indicated that warfarin inhibits the carboxylation Matrix Gla protein, an inhibitor of calcification, and warfarin has been associated with an increase in vascular calcification and atherosclerosis, which may support our findings of an increased risk of AMI in patients taking warfarin [29–31]. Whether the advantage of a lowering risk of AMI for DOACs versus warfarin is country-specific or not needs further evaluation. Our meta-analysis also shows that the four DOACs were associated with a lower risk of mortality than warfarin, which is partially discordant from the previous post-hoc analysis of four DOACs versus warfarin in NVAF Asians regarding the risk of all-cause mortality [5]. Our meta-analysis is based on all real-world, observational, and nonrandomized studies, which are prone to be confounded by indication even after statistical adjustment (e.g., a perceived risk may result in conscious avoidance in use of DOACs in specific patient populations). Nevertheless, the meta-analysis of four DOAC RCTs indicated that all-cause mortality was significantly lower for overall DOACs versus warfarin among the Asian subgroup (OR, 0.80; 95% CI, [0.65–0.98]; $P = 0.030$).

Our analyses are in contrast with previous meta-analyses of real-world data comparing different DOACs versus warfarin regarding the risk of thromboembolism, major bleeding, and mortality which were mainly focused on non-Asians [32]. This indicated that apixaban was associated with a comparable risk of thromboembolism, and a lower risk of major bleeding and mortality than warfarin; dabigatran with a comparable risk of thromboembolism, major bleeding, and a lower risk of mortality than warfarin; rivaroxaban with a comparable risk of thromboembolism, major bleeding, and mortality when compared with warfarin. In contrast, our meta-analyses specifically focused on Asians indicated that four DOACs were all associated with lower risks of thromboembolism and major bleeding than warfarin. Our analysis also indicates that edoxaban showed consistent effectiveness and safety profiles both using a large nationwide registry in Taiwan and Korea. Previous studies have reported that the time in therapeutic range of INR target of 2.0–3.0 was usually less than 50%

among Asian patients with NVAF [3, 4, 33, 34]. The mean time in therapeutic range may be even lower in Asian daily practice than in the RCTs. Hence, the clinical advantages of DOACs versus warfarin may be even more pronounced in the Asian patients than in non-Asians.

By and large, the effectiveness and safety results were consistent with the main results when analyzed within standard-dose and low-dose DOAC subgroups. Our studies showed that both standard and low-dose apixaban, dabigatran, and edoxaban were all associated with lower risks of thromboembolism and major bleeding than warfarin. Our present meta-analysis is generally consistent with the post-hoc analysis of ROCKET AF trial regarding the risk of major bleeding (HR, 0.63; 95% CI, 0.37–1.09] and any bleeding (HR, 1.01; 95% CI, 0.79–1.30) among Asian population [5]. In all countries outside Japan, rivaroxaban 20/15 mg daily was the label dosage approved for stroke prevention in NVAF patients [35]. In Japan, a low-dose rivaroxaban 15/10 mg once daily is the label recommended dosage approved for stroke prevention among patients with NVAF [36]. Of note, Taiwan is the only country with either the ROCKET AF (20/15 mg once daily) or the J-ROCKET AF dosage criteria (15/10 mg once daily) approved for stroke prevention in AF population around the world, and 95% of patients taking rivaroxaban 15/10 mg once daily for stroke prevention in Taiwan [11]. Our analysis shows that rivaroxaban 15/10 mg daily showed a significantly lower risk of major bleeding than the warfarin both in Taiwan (HR, 0.54; 95% CI, 0.40–0.73) and Japan (HR, 0.69; 95% CI, 0.51–0.93) (Supplemental Fig. V), which is in contrast to the rivaroxaban 20/15 mg daily showing a comparable risk of major bleeding to the warfarin in Korea (HR, 0.96; 95% CI, 0.84–1.10) (Fig. 6). In Taiwan, rivaroxaban (where 95% of patients took 15/10 mg once daily) retained its effectiveness over warfarin as well as the rivaroxaban 20/15 mg once daily over warfarin in Korea and in China [7, 11].

Limitations

The present study had several limitations. First, a high prevalence of low-dose DOAC prescriptions was observed in the present Asian-specific meta-analysis. The lack of important information including body weights and renal function data makes it difficult to determine whether patients taking low-dose DOACs were actually taking an adjusted dose or "off-label" low dose in the large main cohorts from Korea, Japan, and Taiwan. Second, most studies in the meta-analysis did not report the quality of oral anticoagulant treatment (time in therapeutic range for patients taking warfarin) nor the persistence or adherence to DOACs treatment. It is possible that the favorable effectiveness of DOACs on thromboembolism and mortality in this Asian-specific meta-analysis were at least partly due to low time in therapeutic range for those patients taking warfarin. Third, although we adopted the studies reporting adjusted HRs by using either multi-variate Cox regression, propensity score weighting, or matching with several variables, residual confounding with unmeasured variables and selective prescribing behavior could not be excluded in the present meta-analysis due to the nature of real-world data. Nevertheless, the meta-analysis reflects the real-world practice of anticoagulation therapy among Asians with NVAF. Lastly, the exact inclusion criteria and definitions of outcomes varied among the included studies. In addition, all of studies included in the meta-analysis were performed at East Asia, which may not represent the whole Asia.

Conclusions

The Asian-specific meta-analysis shows that DOACs were associated with better effectiveness and safety than warfarin in patients with NVAF. Both standard-dose and low-dose DOACs performed equally well, with regard to effectiveness and safety in Asian patients with NVAF.

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Compliance with Ethical Standards

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