Systematic Review and Meta-Analysis

Medicine®

OPEN

The role of non-vitamin K antagonist oral anticoagulants in Asian patients with atrial fibrillation

A PRISMA-compliant article

Xuyang Liu, MS[a,*], Manxiang Huang, MS[a], Caisheng Ye, MS[a], Junquan Zeng, MS[b], Changai Zeng, MS[c], Jianyong Ma, MD[d]

Abstract

Background: Given the huge burden of atrial fibrillation (AF) and AF-related stroke in Asia, stroke prevention represents an urgent issue in this region. We herein performed a network meta-analysis to examine the role of non-vitamin K antagonist oral anticoagulants (NOACs) in Asian patients with AF.

Methods: A systematic search of the publications was conducted in PubMed and Embase databases for eligible studies until July 2019. The odds ratios (ORs) and 95% confidence intervals (CIs) were regarded as the effect estimates. The surface under the cumulative ranking area (SUCRA) for the ranking probabilities was calculated.

Results: A total of 17 studies were included. For comparisons of NOACs vs warfarin, dabigatran (OR = 0.77, 95% CI 0.68–0.86), rivaroxaban (OR = 0.72, 95% CI 0.65–0.81), apixaban (OR = 0.56, 95% CI 0.49–0.65), but not edoxaban reduced the risk of stroke or systemic embolism, wheres dabigatran (OR = 0.56, 95% CI 0.41–0.76), rivaroxaban (OR = 0.66, 95% CI 0.50–0.86), apixaban (OR = 0.49, 95% CI 0.36–0.66), and edoxaban (OR = 0.34, 95% CI 0.24–0.49) decreased the risk of major bleeding. In reducing the risk of stroke or systemic embolism, apixaban and rivaroxaban ranked the best and second best (SUCRA 0.2% and 31.4%, respectively), followed by dabigatran (50.2%), edoxaban (75.2%), and warfarin (93.0%). In reducing the risk of major bleeding, edoxaban, and apixaban ranked the best and second best (1.5% and 30.8%, respectively), followed by dabigatran (48.4%), rivaroxaban (69.2%), and warfarin (100%).

Conclusion: NOACs were at least as effective as warfarin, but more safer in Asians with AF. Apixaban was superior to other NOACs for reducing stroke or systemic embolism, while edoxaban showed a better safety profile than other NOACs.

Abbreviations: AF = atrial fibrillation, CI = confidence interval, ENGAGE AF-TIMI 48 = Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48, GI = gastrointestinal, ICH = intracranial hemorrhage, IS = ischemic stroke, MI = myocardial infarction, NOACs = non-vitamin K antagonist oral anticoagulants, OR = odds ratio, PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses, RCTs = randomized clinical trials, SSE = stroke or systemic embolism, SUCRA = surface under the cumulative ranking area, TTR = time in therapeutic range.

Keywords: anticoagulants, Asia, atrial fibrillation, stroke prevention, warfarin

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia. Oral anticoagulation treatment is the cornerstone in the stroke prevention for AF.[1,2] Based on the previous data of randomized clinical trials (RCTs), non-vitamin K antagonist oral anticoagulants (NOACs; i.e., dabigatran, rivaroxaban, apixaban, edoxaban) are non-inferior in reducing the risks of stroke and bleeding compared with warfarin.[3–6] In recent years, NOACs have changed the landscape of anticoagulation in AF because of

Editor: Simone Gulletta.

XL and CZ are joint senior authors.

All authors declare that they have no potential conflicts of interest that might be relevant to the contents of this review.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Cardiology, [b] Department of internal medicine, [c] Department of stomatology, Jinggangshan University, Ji'an, Jiangxi, China, [d] Department of Pharmacology and Systems Physiology, University of Cincinnati College of Medicine, Cincinnati, OH.

[*] Correspondence: Xuyang Liu, Department of Cardiology, Jinggangshan University, Ji'an 343009, Jiangxi , China (e-mail: lxy0136@163.com).

How to cite this article: Liu X, Huang M, Ye C, Zeng J, Zeng C, Ma J. The role of non-vitamin K antagonist oral anticoagulants in Asian patients with atrial fibrillation: a PRISMA-compliant article. Medicine 2020;99:27(e21025).

Received: 11 March 2020 / Received in final form: 23 May 2020 / Accepted: 2 June 2020

http://dx.doi.org/10.1097/MD.0000000000021025

their superior efficacy and safety profiles compared with warfarin. However, only small percentage of Asian subjects were included in these RCTs. Whether the use of NOACs is effective and safe in Asians is still exploratory.

There are some distinctiveness of anticoagulation between Asians and non-Asians.[7,8] First, the baseline risks of thromboembolism and bleeding are higher in Asians than non-Asians.[9] As such, more Asian patients would have been deemed ineligible for anticoagulation. Second, given the variations of genetic polymorphisms for warfarin metabolism in Asians, Asians are more sensitive to warfarin and more prone to excessive bleeding.[10,11] Third, Asian patients tend to have a reduced creatinine clearance, lower body weight, lesser use of gastric antacid drugs, and greater use of antiplatelet medications.[7] These differences may affect the role of anticoagulation in AF patients. Therefore, stroke prevention in AF represent an urgent issue of public health in Asia. Two prior meta-analyses have suggested that NOACs (standard dose in particular) are non-inferior to warfarin in Asian patients.[12,13] However, the efficacy and safety profiles amongst NOACs remain unclear, leaving physicians with difficulties in decision-making regarding the choice of NOACs. In addition, the results of real-world data are sometimes quite different from those of the RCTs. More recently, several observational studies comparing the effect of NOACs vs warfarin in Asian patients have been reported. Therefore, we conducted a network meta-analysis to examine the efficacy and safety of NOACs in Asians with AF.

2. Methods

This meta-analysis was performed according to the Cochrane Collaboration guideline[14] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for network meta-analysis.[15] This was a meta-analysis of published studies, and no ethical approval was warranted.

2.1. Data searches

A systematic search of the literatures was conducted in the PubMed and Embase databases for eligible studies published between January 2009 and July 2019, because the first paper about the use of dabigatran in AF was published in 2009.[6] The search terms restricted to the title/abstract were included: *(atrial fibrillation* OR *atrial flutter)* AND (*non-vitaminK antagonist oral anticoagulants* OR *direct oral anticoagulants* OR *dabigatran* OR *rivaroxaban* OR *apixaban* OR *edoxaban)* AND (*vitamin-K antagonists* OR *warfarin)*. No language restriction was applied in the search.

2.2. Study eligibility criteria

We included the studies according the inclusion criteria:

1. Study population: Asian patients with non-valvular AF receiving at least 1 NOAC compared to other NOACs and/or warfarin.
2. Outcomes: studies reported at least one of the following efficacy and safety outcomes: stroke or systemic embolism (SSE), ischemic stroke (IS), myocardial infarction (MI), all-cause death, major bleeding, intracranial hemorrhage (ICH), and gastrointestinal (GI) bleeding.
3. Study design: RCTs and observational cohorts.

For the observational studies, the method of propensity score matching was applied to balance patient characteristics between study groups. We excluded the studies according to the exclusion criteria:

1. AF patients undergoing cardioversion, ablation, or left-atrial appendage closure.
2. AF patients with certain diseases such as acute coronary syndrome, liver disease, or cancer.
3. Studies did not report the results of different NOACs separately.

2.3. Data extraction

We extracted the following information: study characteristics, patient demographics, drugs and dosages, follow-up duration, and outcomes used in this study. In each treatment group, number of events, event rates, and sample size were collected for the reported outcomes of interest.

2.4. Risk of bias assessment

For RCTs, the methodological quality was evaluated according to the Cochrane risk of bias assessment tool.[16] For observational studies, the Newcastle-Ottawa Scale (NOS) item were used to evaluate the study quality.[17] An NOS score of <6 points indicated a low quality.[18]

2.5. Statistical analysis

The statistical analyses were performed using the Stata software (version 15.0, Stata Corp LP, College Station, TX) with the network package. Treatment effects were expressed as the odds ratios (ORs) with 95% confidence intervals (CIs). The network plots obtained from the Stata software were used to ensure that studies were connected by interventions. A random-effects model was utilized to calculate the evidence inconsistency, which was displayed by inconsistency factor plots.[19,20] The relative rankings for all treatments were presented as probabilities. The surface under the cumulative ranking area (SUCRA) for the ranking probabilities was calculated. The larger the SUCRA value, the higher the probability of outcomes. The subgroup analysis based on the study design (RCTs and observational studies) was performed. Possible presence of publication bias was checked via observing the symmetry characteristics in the funnel plots.

3. Results

3.1. Study selection

The selection process is illustrated in Supplemental Fig. 1, http://links.lww.com/MD/E488, a total of 8696 citations (2999 through PubMed, and 5697 through Embase) were retrieved. After screening the titles and/or abstracts, 75 articles were selected for full-text review. According to the pre-defined inclusion criteria, 5 RCTs (dabigatran,[21] rivaroxaban,[22,23] apixaban,[24] edoxaban[9]) and 12 observational studies were included in the final analysis (Supplemental Table 1, http://links.lww.com/MD/E491).

The baseline characteristics of the included studies are shown in Tables 1–2. All of the 5 RCTs had a low risk of bias (Supplemental Table 2, http://links.lww.com/MD/E492), whereas all of the 12

Table 1

Baseline characteristics of the included phase III clinical trials.

	RE-LY (Hori M-2013)	ROCKET-AF (Wong KS-2014)	ARISTOTLE (Goto S-2014)	ENGAGE AF-TIMI 48 (Chao T-2019)	J-ROCKET AF (Hori M-2012)
Basal characteristics					
Sample size, n	2782	932	1993	2909	1278
Age, y	68.0	69.7	69.0	68.7	71.1
Female, %	36.2	38.2	35.0	32.6	19.4
Weight, kg	66.3	66.9	67.0	66.4	–
CrCl, mL/min	65.3	65.1	–	63.1	–
$CHADS_2$	2.2	3.2	2.1	2.8	3.3
$CHADS_2 \geq 2$, %	69.8	100.0	60.7	–	100.0
CHA_2DS_2-VASc	–	4.4	3.3	4.1	–
HAS-BLED	–	2.9	1.7	2.7	–
Comorbidities					
Age≥75 y, %	27.4	34.4	24.4	34.0	39.0
Hypertension	71.2	80.0	82.3	83.9	79.5
Diabetes mellitus	25.1	37.0	25.2	34.1	38.0
Heart failure	36.3	38.7	26.2	50.6	40.8
Prior MI	9.3	5.5	5.9	6.0	7.7
Previous stroke/TIA	24.2	65.0	28.8	40.1	63.6
Aspirin, %	47.1	38.2	31.9	32.5	36.4
CrCl≤50 mL/min, %	26.6	24.5	23.1	32.2	22.2
Prior VKA, %	36.5	49.1	–	49.4	90.0
TTR of warfarin users,%	56.5	47.1	60.0	64.1	62.9
INR targets for VKAs	2.0–3.0 (2.0–2.6 for Japanese patients aged ≥70 y)	2.0–3.0	2.0–3.0	2.0–3.0	2.0–3.0 (1.6- 2.6 for patients aged ≥70 y)
Asian countries involved	China mainland, Hong Kong, India, Japan, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand	China mainland, Hong Kong, South Korea, Taiwan	China mainland, Hong Kong, Japan, Malaysia, Philippines, Singapore, South Korea, Taiwan	China, India, Japan, Korea, Philippines, Taiwan, Thailand	Japan
NOACs involved	Dabigatran 110 mg or 150 mg twice daily	Rivaroxaban 20 mg once daily (15 mg for patients with CrCl of 30–49 ml/min)	Apixaban 5 mg twice daily (2.5 mg for patients with ≥2 of the following criteria: age ≥80 yrs, weight ≤60 kg, or a serum creatinine ≥1.5 mg/dl)	Edoxaban 30 mg or 60 mg once daily (15 mg or 30 mg, respectively for patients with CrCl of 30–50 ml/min, weight ≤60 kg, or in those requiring concomitant use of verapamil, quinidine, or dronedarone)	Rivaroxaban 15 mg once daily (10 mg for patients with CrCl of 30–49 ml/min)

CHA_2DS_2-VASc = Congestive heart failure/left ventricular ejection fraction ≤40%, Hypertension, age 75 years of age and older, Diabetes mellitus, Stroke/transient ischemic attack/thromboembolism history, Vascular disease, Age 65 to 74 years, Sex (female), $CHADS_2$ = Congestive heart failure, Hypertension, 75 years of age and older, Diabetes mellitus, Stroke/transient ischemic attack history, CrCl = creatinine clearance, HAS-BLED = Hypertension, Abnormal liver/renal function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly, INR = international normalized ratio, MI = myocardial infarction, NOAC = non-vitamin K antagonist oral anticoagulant, TIA = transient ischemic attack, TTR = time within therapeutic range, VKA = vitamin K antagonist.

observational studies had a moderate-to-high quality (Table 2). Supplemental Table 3, http://links.lww.com/MD/E493 shows event rates of the efficacy and safety outcomes in the groups of NOACs or warfarin.

3.2. Efficacy and safety between NOACs vs warfarin

3.2.1. Dabigatran vs Warfarin. In comparison with warfarin use, the use of dabigatran reduced the risks of SEE (OR = 0.77, 95% CI 0.68–0.86), major bleeding (OR = 0.56, 95% CI 0.41–0.76), and ICH (OR = 0.44 95% CI 0.33–0.60). The outcomes of IS, MI, all cause death and GI bleeding were not different between the 2 groups (Fig. 1).

3.2.2. Rivaroxaban vs Warfarin. Rivaroxaban was associated with lower risks of SEE (OR = 0.72, 95% CI 0.65–0.81), major bleeding (OR = 0.66, 95% CI 0.50–0.86), ICH (OR = 0.53, 95% CI 0.37–0.75) than warfarin. The risks of IS, MI, all cause death, and GI bleeding were comparable between the 2 groups (Fig. 1).

3.2.3. Apixaban vs Warfarin. Compared with warfarin, apixaban reduced the risks of SEE by 46% (OR = 0.56, 95% CI 0.49–0.65), all cause death by 65% (OR = 0.35, 95% CI 0.16–0.76), major bleeding by 51% (OR = 0.49, 95% CI 0.36–0.66), ICH by 55% (OR = 0.45, 95% CI 0.31–0.64), and GI bleeding by 61% (OR = 0.39, 95% CI 0.20–0.76). No noticeable differences were found in IS and MI between apixaban and warfarin (Fig. 1).

3.2.4. Edoxaban vs Warfarin. Compared with warfarin users, edoxaban users had lower risks of IS (OR = 0.54, 95% CI 0.37–0.77), MI (OR = 0.48, 95% CI 0.24–0.96), major bleeding (OR = 0.34, 95% CI 0.24–0.49), ICH (OR = 0.24, 95% CI 0.16–0.36), and GI bleeding (OR = 0.38, 95% CI 0.19–0.76). There were no differences in SEE and all cause death between them (Fig. 1).

3.2.5. Subgroup analysis. We performed the subgroup analysis defined by study design. As shown in Supplemental Tables 4, http://links.lww.com/MD/E494 to 5, http://links.lww.com/MD/E495, the pooled data from RCTs and observational studies were generally consistent with the main analyses.

3.3. Efficacy and safety between NOAC and NOAC

3.3.1. Rivaroxaban vs edoxaban. Rivaroxaban users had higher risks of major bleeding (OR = 1.92, 95% CI 1.29–2.85) and ICH (OR = 2.20, 95% CI 1.41–3.45) than edoxaban users. There were no differences in efficacy outcomes of interest and GI bleeding between them (Fig. 2).

3.3.2. Dabigatran vs edoxaban. Dabigatran was associated with increased risks of IS (OR = 1.68, 95% CI 1.11–2.55), major bleeding (OR = 1.63, 95% CI 1.09–2.45), and ICH (OR = 1.84, 95% CI 1.19–2.84) compared with edoxaban. Similar rates of SSE, MI, all cause death, and GI bleeding were observed between these 2 groups (Fig. 2).

Table 2

Baseline characteristics of the included observational studies.

References	Location	Study design	Study period	Data source	Age (y)	$CHADS_2$ score	CHA_2DS_2-VASc score	HAS-BLED score	Oral anticoagulants*	Dose of NOAC therapy	TTR (%) of warfarin users	Follow-up period (y)	Outcomes used in this meta-analysis	NOS items
Koretsune Y-2019	Japan	Retrospective cohort	14 March 2011 to 30 June 2016	Medical Data Vision Database	73.5	2.1	3.3	2.1	DA, Warfarin	78% of patients (110 mg BID or less); 21% (150 mg BID)	NA	0.49–0.58	SSE, Major bleeding, ICH, GI bleeding	7
Lee SR-2019	Korea	Retrospective cohort	January 2015 to December 2017	National Health Insurance Service	71.0	2.1	3.6	2.7	DA, RIV, API, EDO, Warfarin	41% of patients received regular dose NOACs	NA	0.79	IS, Major bleeding, ICH, GI bleeding	8
Jeong HK-2019	Korea	Retrospective cohort	January 2014 to December 2016	Chonnam National University Hospital	70.9	NA	3.4	NA	RIV, Warfarin	51.5% of patients (15 mg QD); 48.5% (20 mg QD)	NA	1.0	SSE, IS, MI, All cause death, Major bleeding, ICH, GI bleeding	7
Chan YH-2019	China, Taiwan	Retrospective cohort	1 June 2012 to 31 December 2017	National Health Insurance Research Database	74.7	NA	3.6	2.6	DA, RIV, API, EDO, Warfarin	64%, 64%, 94%, and 89% of patients received EDO (30/15 mg QD), API (2.5 mg BID), RIV (15/10 mg QD), and DA (110 mg BID), respectively	NA†	NA	SSE, IS, MI, Major bleeding, ICH, GI bleeding	8
Kohsaka S-2018	Japan	Retrospective cohort	1 March 2011 to 30 June 2017	Medical Data Vision Database	77.7	2.2	3.4	NA	API, Warfarin	60.6% of patients (2.5 mg BID); 39.4% (5 mg BID)	NA	NA	SSE, Major bleeding	7
Lee SR-2018	Korea	Retrospective cohort	January 2014 to December 2016	National Health Insurance Service	70.5	1.7	3.2	NA	EDO, Warfarin	56% of patients (30 mg QD); 44% (60 mg QD)	NA	Median 0.3	All cause death	8
Chan YH-2018	China, Taiwan	Retrospective cohort	1 June 2012 to 31 December 2016	National Health Insurance Research Database	76.0	NA	3.9	3.0	DA, RIV, API, Warfarin	62%, 94%, and 88% of patients received API (2.5 mg BID), RIV (15/10 mg QD), and DA (110 mg BID), respectively	NA	0.76–1.55	All cause death	8
Cha MJ-2017	Korea	Retrospective cohort	January 2014 to December 2015	National Health Insurance Service database	69.3	NA	3.6	NA	DA, RIV, API, Warfarin	42.2%, 50.2%, and 62.6% of patients received API (2.5 mg BID), RIV (15/10 mg QD), and DA (110 mg BID), respectively	NA	1.2	All cause death	8
Kohsaka S-2017	Japan	Retrospective cohort	1 March 2011 to 31 March 2016	Medical Data Vision database	76.0	2.2	3.4	NA	RIV, Warfarin	100% of patients (15/10 mg QD)	NA	1.0	Major bleeding	8
Lee KH -2017	Korea	Retrospective cohort	January 2012 to December 2013	Chonnam National University Hospital	Median 72.0	NA	3.3	NA	DA, Warfarin	65.1% of patients (110 mg BID); 34.9% (150 mg BID)	NA	1.0	SSE, IS, MI, All cause death, Major bleeding, ICH, GI bleeding	8
Naganuma 2017	Japan	Retrospective cohort	March 2011 to December 2013	Tokyo Women's Medical University Hospital	69.0	2.0	3.1	1.5	DA, Warfarin	72.9% of patients (110 or 75 mg BID); 27.1% (150 mg BID)	60.0	1.3	SSE, Major bleeding	7
Lau WC-2017	China, Hong Kong	Prospective cohort	1 January 2010 and 31 December 2014	Clinical Data Analysis and Reporting System	73.9	2.1	3.3	NA	DA, Warfarin	84% of patients (110 mg BID or less)	NA‡	NA	ICH, GI bleeding	8

API = apixaban, CHA_2DS_2-VASc = Congestive heart failure/left ventricular ejection fraction ≤40%, Hypertension, age 75 years of age and older, Diabetes mellitus, Stroke/transient ischemic attack/thromboembolism history, Vascular disease, Age 65–74 years, Sex (female), $CHADS_2$ = Congestive heart failure, Hypertension, 75 years of age and older, Diabetes mellitus, Stroke/transient ischemic attack history, DA = dabigatran, EDO = edoxaban, GI = gastrointestinal, HAS-BLED = Hypertension, Abnormal liver/renal function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly, ICH = intracranial hemorrhage, IS = ischemic stroke, MI = myocardial infarction, NA = not available, NOS = Newcastle-Ottawa Scale, RIV = rivaroxaban, SSE = stroke or systemic embolism, TTR = time within therapeutic range.

* presented the anticoagulants that were used in this meta-analysis.

† Although the mean TTR was not reported, NOACs vs those patients taking warfarin with a high level of TTR were compared.

‡ The mean INR (international normalized ratio) of warfarin users was 1.8.

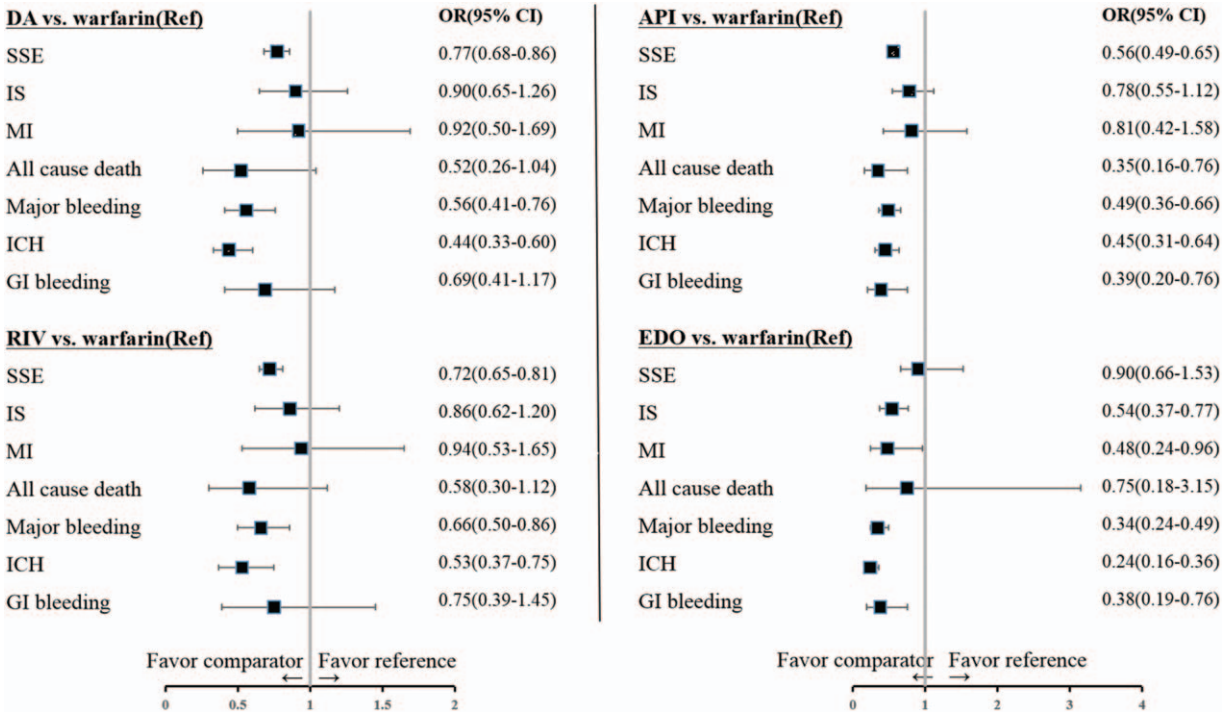


Figure 1. Efficacy and safety outcomes of NOACs with warfarin in Asian patients with AF. AF = atrial fibrillation, CIs = confidence intervals, GI = gastrointestinal, ICH = intracranial hemorrhage, IS = ischemic stroke, NOACs = non-vitamin K antagonist oral anticoagulants, ORs = odds ratios, SSE = stroke or systemic embolism.

3.3.3. Apixaban vs edoxaban. Apixaban had a lower risk of SSE (OR = 0.62, 95% CI 0.44–0.89), but higher rate of ICH (OR = 1.86, 95% CI 1.17–2.94) than edoxaban. The rates of IS, MI, all cause death, major bleeding, and GI bleeding were comparable between apixaban and edoxaban (Fig. 2).

3.3.4. Dabigatran vs rivaroxaban. All the efficacy (SSE, IS, MI, and all cause death) and safety (major bleeding, ICH, and GI bleeding) outcomes between dabigatran and rivaroxaban were comparable (Fig. 2).

3.3.5. Apixaban vs rivaroxaban. Compared with rivaroxaban users, apixaban users showed a decreased risk of SSE (OR = 0.78, 95% CI 0.66–0.91), but had similar rates of other efficacy and safety outcomes (Fig. 2).

3.3.6. Apixaban vs dabigatran. The results between apixaban and dabigatran were similar to those of apixaban vs rivaroxaban. Compared with dabigatran use, the use of apixaban only decreased the SSE (OR = 0.74, 95% CI 0.62–0.87) (Fig. 2).

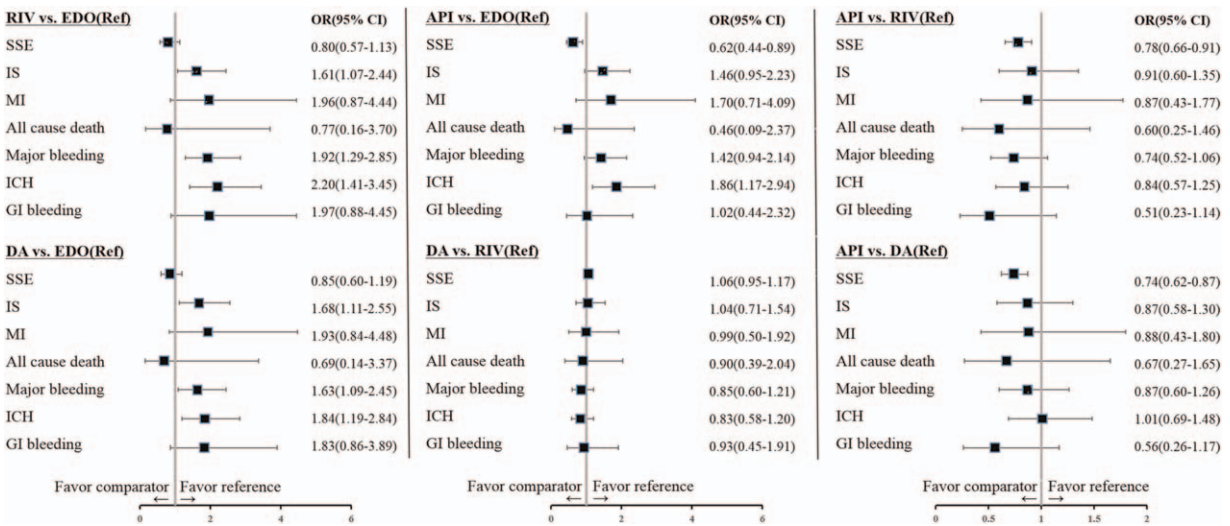


Figure 2. Efficacy and safety outcmes between NOAC vs NOAC in Asian patients with AF. AF = atrial fibrillation, CIs = confidence intervals, GI = gastrointestinal, ICH = intracranial hemorrhage, IS = ischemic stroke, NOAC = non-vitamin K antagonist oral anticoagulant, ORs = odds ratios, SSE = stroke or systemic embolism.

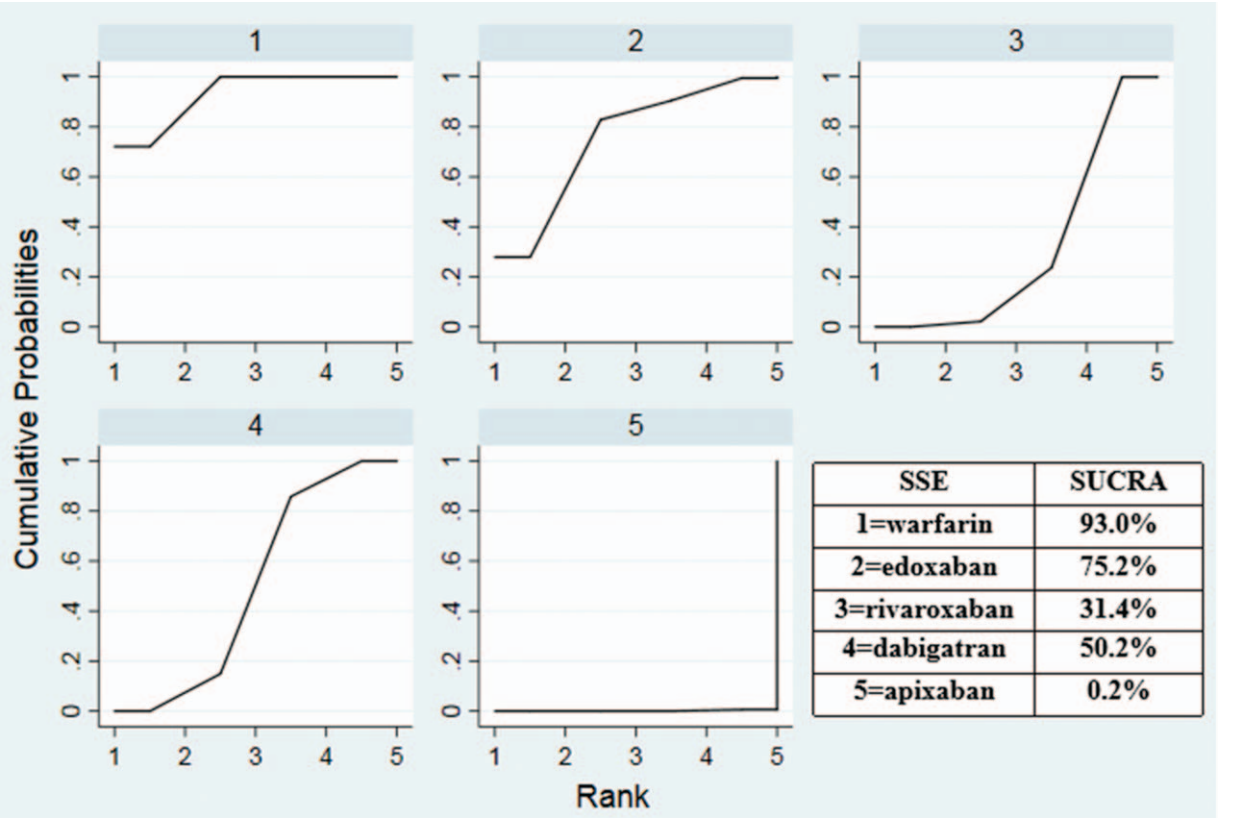


Figure 3. Rankings of SUCRA for the risk of stroke or systemic embolism amongst NOACs in Asian patients with AF. AF = atrial fibrillation, NOACs = non-vitamin K antagonist oral anticoagulants, SUCRA = surface under the cumulative ranking area.

3.3.7. Subgroup analysis. Based on RCTs, the efficacy and safety were comparable between NOACs, except that the SSE risk of dabigatran 150 mg (OR = 0.50, 95% CI 0.28–0.90) was lower than edoxaban (Supplemental Table 6, http://links.lww.com/MD/E496). Based on observational studies, the results were generally consistent with the aforementioned main analyses (Supplemental Table 7, http://links.lww.com/MD/E497).

3.4. Ranking probability

As shown in Figure 3, with regard to the prevention of SSE, apixaban and rivaroxaban ranked the best and second best (SUCRA 0.2% and 31.4%, respectively), followed by dabigatran (50.2%), edoxaban (75.2%), and warfarin (93.0%). In reducing the risk of major bleeding (Fig. 4), edoxaban and apixaban ranked the best and second best (SUCRA 1.5% and 30.8%, respectively), followed by dabigatran (48.4%), rivaroxaban (69.2%), and warfarin (100%). Consistent ranking probability among the 4 NOACs were found in ICH (Supplemental Table 8, http://links.lww.com/MD/E498)

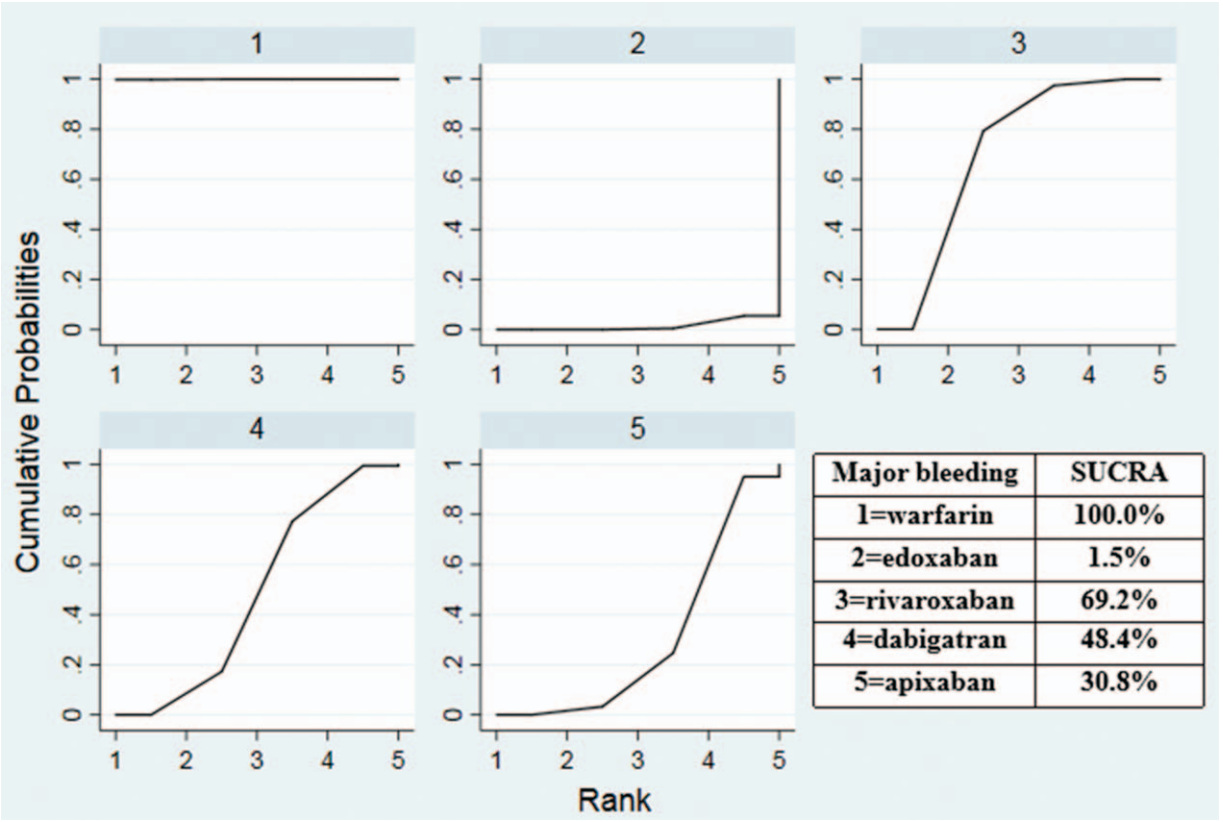
3.5. Publication Bias

As shown in Supplemental Figs. 2, http://links.lww.com/MD/E489 to 3, http://links.lww.com/MD/E490, the funnel plots of the reported efficacy and safety outcomes showed no significant publication bias.

4. Discussion

Based on data from either RCTs or real world studies, NOACs were at least as effective as warfarin, and had better safety profiles in Asians with AF. For the prevention of SSE, apixaban and rivaroxaban ranked the best, followed by rivaroxaban, dabigatran, edoxaban, and warfarin sequentially. Edoxaban had the best effect in reducing the bleeding risks (major bleeding and ICH), followed by apixaban, dabigatran, rivaroxaban, and warfarin sequentially. In Asian patients with AF, NOACs appeared to be preferred over warfarin, and apixaban, or edoxaban might be a relatively better choice for stroke prevention.

A prior meta-analysis by Wang et al[13] have suggested that compared with warfarin, standard-dose NOACs are associated with reduced risks of efficacy (SSE and all cause death) and safety (major bleeding and ICH) outcomes, whereas low-dose NOACs only have better safety profiles (major bleeding and ICH). In this study by Wang et al,[13] 5 RCTs for NOACs (dabigatran,[21] rivaroxaban,[22,23] apixaban,[24] edoxaban[25]) were included for the analysis. However, in the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48) trial,[25] the East Asian group did not include the Japanese patients, whereas the non-East Asian group also included patients from South Asia. And subsequently, Chao et al[9] re-preformed the sub-analysis of the ENGAGE AF-TIMI 48 trial to determine the effect of edoxaban vs warfarin for stroke prevention in Asians with AF. Currently, we updated the available information of NOACs vs warfarin by including the study of Chao et al.[9] The results were generally consistent with the findings of Wang et al.[13] Our results for safety outcomes based on observational studies were in-keeping with RCTs. NOACs were at least as effective as warfarin, while demonstrating superiority in some aspects. The anticoagulation quality of warfarin as reflected by



Major bleeding	SUCRA
1=warfarin	100.0%
2=edoxaban	1.5%
3=rivaroxaban	69.2%
4=dabigatran	48.4%
5=apixaban	30.8%

Figure 4. Rankings of SUCRA for the risk of major bleeding amongst NOACs in Asian patients with AF. AF = atrial fibrillation, NOACs = non-vitamin K antagonist oral anticoagulants, SUCRA = surface under the cumulative ranking area.

time in therapeutic range (TTR) in the real-world studies is poorer compared with that in the RCTs.[26] Moreover, the TTR of warfarin is low in Asians with AF.[27,28] The poor anticoagulation quality of warfarin in the real-world studies might explain that NOACs have greater benefits than warfarin in Asians with AF. With regard to GI bleeding, a prior meta-analysis of RCTs showed that NOACs increased this risk compared with warfarin.[29] And subsequently, NOACs vs warfarin were found to increase the risk of GI bleeding in non-Asians rather than Asians.[13] In our current study, edoxaban and apixaban were associated with a lower risk of GI bleeding compared with warfarin.

In our analysis based on the real-world data, apixaban had a lower risk of SEE compared with other NOACs, and edoxaban was associated with a lower rate of IS in comparison with dabigatran or rivaroxaban. Similar efficacy was observed between dabigatran and rivaroxaban. For the safety aspects, the better profiles in major bleeding and ICH was found in edoxaban users. Prior analyses in the global AF patents indicated that apixaban was superior to dabigatran and rivaroxaban,[30–33] consistent with our findings only from Asians. No data regarding edoxaban were reported in the previous meta-analyses.[30–33] Instead, our current study demonstrated that edoxaban users showed greater safety profiles (major bleeding and ICH) than users with other NOACs.

Real-world studies usually act as a complementary source of knowledge, and their results are beneficial to validate the RCT findings.[34] Considering the efficacy and safety between NOAC and NOAC, the subgroup analysis based on study design was performed in our present study. Based on the data from RCTs, there were no significant differences regarding the efficacy and safety outcomes between NOAC and NOAC, except that the SSE risk of dabigatran 150 mg was lower than that of edoxaban. A previous review including 4 RCTs also indicated more benefits in Asian patients treated with dabigatran 150 mg.[35] Based on the real-world researches, edoxaban and apixaban showed lower risks of thromboembolic or bleeding events compared to dabigatran and rivaroxaban. Evidence from the real-world studies appeared to contradict findings from the hallmark trials.

4.1. Limitations

Several limitations might influence the validity of this meta-analysis. First, most studies enrolled did not report the anticoagulation quality in Asians such as the adherence or persistence to NOACs and the TTR of warfarin users. Second, a large proportion of Asian patients taken a reduced dose of NOACs. However, we did not perform the subgroup analysis based on the NOAC dose due to the limiting data. Third, since only 4 studies on the effectiveness and safety of edoxaban were included, caution was warranted when interpreting the corresponding results. Finally, our study employed the RCT and real-world data to conduct indirect comparisons for efficacy and safety between NOACs using the common comparator arm (warfarin). Nevertheless, the utility and credibility of their results were limited given the differences in the population, study design, outcome, and TTR of warfarin users across the included studies.

5. Conclusions

NOACs were at least as effective as warfarin, but more safer than warfarin in Asian patients with AF. Apixaban was superior to other NOACs for reducing SSE, while edoxaban showed a better safety profile than other NOACs. Further head-to-head RCTs for the direct comparisons between NOAC and NOAC could confirm our findings.

Author contributions

Data curation: Junquan Zeng, Caisheng Ye.
Formal analysis: Manxiang Huang.
Investigation: Jianyong Ma.
Methodology: Junquan Zeng, Manxiang Huang.
Software: Junquan Zeng, Manxiang Huang.
Supervision: Xuyang Liu, Changai Zeng.
Validation: Junquan Zeng, Xuyang Liu.
Writing – original draft: Xuyang Liu.
Writing – review & editing: Jianyong Ma, Xuyang Liu.

References

[1] January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. Circulation 2019;R665.
[2] Zhou Y, Ma J, Zhu W. Efficacy and safety of direct oral anticoagulants versus warfarin in patients with atrial fibrillation across BMI categories: a systematic review and meta-analysis. Am J Cardiovasc Drug 2020; 20:51–60.
[3] Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. New Engl J Med 2013;369:2093–104.
[4] Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. New Engl J Med 2011;365: 981–92.
[5] Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. New Engl J Med 2011;365:883–91.
[6] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. New Engl J Med 2009;361:1139–51.
[7] Li Y, Lee S, Choi E, et al. Stroke prevention in atrial fibrillation: focus on asian patients. Korean Circ J 2018;48:665.
[8] Gallagher C, Sanders P, Wong CX. Anticoagulation for atrial fibrillation in cirrhosis of the liver: are low-dose non-vitamin K oral anticoagulants a reasonable alternative to warfarin? J Am Heart Assoc 2019;8:e12102.
[9] Chao T, Chen S, Ruff CT, et al. Clinical outcomes, edoxaban concentration, and anti-factor Xa activity of Asian patients with atrial fibrillation compared with non-Asians in the ENGAGE AF-TIMI 48 trial. Eur Heart J 2019;40:1518–27.
[10] Gaikwad T, Ghosh K, Shetty S. VKORC1 and CYP2C9 genotype distribution in Asian countries. Thromb Res 2014;134:537–44.
[11] Mega JL, Walker JR, Ruff CT, et al. Genetics and the clinical response to warfarin and edoxaban: findings from the randomised, double-blind ENGAGE AF-TIMI 48 trial. LANCET 2015;385:2280–7.
[12] Wang K, Giugliano RP, Goto S, et al. Standard dose versus low dose non–vitamin K antagonist oral anticoagulants in Asian patients with atrial fibrillation: a meta-analysis of contemporary randomized controlled trials. Heart Rhythm 2016;13:2340–7.
[13] Wang KL, Lip GY, Lin SJ, et al. Non-vitamin K antagonist oral anticoagulants for stroke prevention in Asian patients with nonvalvular atrial fibrillation: meta-analysis. Stroke 2015;46:2555–61.
[14] Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0[updated March 2011]. XXXX;Available at: www.cochrane-handbook.org. Accessed July 25, 2019
[15] Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777–84.
[16] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[17] Zhu W, Wan R, Liu F, et al. Relation of body mass index with adverse outcomes among patients with atrial fibrillation: a meta-analysis and systematic review. J Am Heart Assoc 2016;5:e4006.
[18] Liao X, Fu Y, Ma J, et al. Non-vitamin K antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and peripheral artery disease: a systematic review and meta-analysis. Cardiovasc Drug Ther 2020;34:391–9.
[19] Chaimani A, Higgins JP, Mavridis D, et al. Graphical tools for network meta-analysis in STATA. PLoS One 2013;8:e76654.
[20] Higgins JP, Jackson D, Barrett JK, et al. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Methods 2012;3:98–110.
[21] Hori M, Connolly SJ, Zhu J, et al. Dabigatran versus warfarin: effects on ischemic and hemorrhagic strokes and bleeding in Asians and non-Asians with atrial fibrillation. Stroke 2013;44:1891–6.
[22] Wong KS, Hu DY, Oomman A, et al. Rivaroxaban for stroke prevention in East Asian patients from the ROCKET AF trial. Stroke 2014;45:1739–47.
[23] Hori M, Matsumoto M, Tanahashi N, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation - the J-ROCKET AF study -. Circ J 2012;76:2104–11.
[24] Goto S, Zhu J, Liu L, et al. Efficacy and safety of apixaban compared with warfarin for stroke prevention in patients with atrial fibrillation from East Asia: a subanalysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. Am Heart J 2014;168:303–9.
[25] Yamashita T, Koretsune Y, Yang Y, et al. Edoxaban vs. warfarin in East Asian patients with atrial fibrillation- an ENGAGE AF-TIMI 48 subanalysis. Circ J 2016;80:860–9.
[26] Chan Y, Lee H, See L, et al. Effectiveness and safety of four direct oral anticoagulants in Asian patients with nonvalvular atrial fibrillation. Chest 2019;156:529–43.
[27] Oh S, Goto S, Accetta G, et al. Vitamin K antagonist control in patients with atrial fibrillation in Asia compared with other regions of the world: Real-world data from the GARFIELD-AF registry. Int J Cardiol 2016;223:543–7.
[28] Chiang C, Okumura K, Zhang S, et al. 2017 consensus of the Asia Pacific Heart Rhythm Society on stroke prevention in atrial fibrillation. J Arrhythmia 2017;33:345–67.
[29] Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955–62.
[30] López-López JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ 2017;j5058.
[31] Proietti M, Romanazzi I, Romiti GF, et al. Real-world use of apixaban for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. Stroke 2018;49:98–106.
[32] Cohen AT, Hill NR, Luo X, et al. A systematic review of network meta-analyses among patients with nonvalvular atrial fibrillation: a comparison of efficacy and safety following treatment with direct oral anticoagulants. Int J Cardiol 2018;269:174–81.
[33] Li G, Lip GYH, Holbrook A, et al. Direct comparative effectiveness and safety between non-vitamin K antagonist oral anticoagulants for stroke prevention in nonvalvular atrial fibrillation: a systematic review and meta-analysis of observational studies. Eur J Epidemiol 2019;34:173–90.
[34] Fawzy AM, Yang WY, Lip GY. Safety of direct oral anticoagulants in real-world clinical practice: translating the trials to everyday clinical management. Expert Opin Drug Saf 2019;18:187–209.
[35] Lip GY, Wang KL, Chiang CE. Non-vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention in Asian patients with atrial fibrillation: time for a reappraisal. Int J Cardiol 2015;180:246–54.