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

A PRISMA-compliant article

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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, whereas 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 (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.1–3 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.4–6 In recent years, NOACs have changed the landscape of anticoagulation in AF because of...
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. First, the baseline risks of thromboembolism and bleeding are higher in Asians than non-Asians. 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. 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. 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. 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 and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for network meta-analysis. 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. 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 (SE), 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. For observational studies, the Newcastle-Ottawa Scale (NOS) item were used to evaluate the study quality. An NOS score of <6 points indicated a low quality.

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. 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] and edoxaban[25]) 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 (Horst M-2013) | ROCKET-AF (Wong IS-2014) | ARISTOTLE (Goto S-2014) | ENGAGE AF-TIMI 48 (Chao T-2019) | J-ROCKET AF (Horst M-2012) |
|----------------|-----------------------|--------------------------|--------------------------|-------------------------------|---------------------------|
| **Basal characteristics** |
| Sample size, n | 2782                  | 932                      | 1993                     | 2909                          | 1278                       |
| Age, y          | 69.0                  | 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                          | –                          |
| DCC, mL/min     | 65.3                  | 65.1                     | –                        | 63.1                          | –                          |
| CHADS2          | 2.2                   | 3.2                      | 2.1                      | 2.8                           | 3.3                        |
| CHADS2 ≥2, %    | 69.8                  | 100.0                    | 60.7                     | –                             | 100.0                      |
| CHA2DS2-VASc    | 4.4                   | –                        | 3.3                      | 4.1                           | –                          |
| HAS-BLED        | –                     | 1.7                      | –                        | –                             | –                          |
| **Asian countries involved** |
| China mainland, Japan, Malaysia, Philippines, Singapore, South Korea, Taiwan |
| China mainland, Hong Kong, China, India, Japan, Korea, 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) |
| 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) |

CHADS2-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), 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 in 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<sub>2</sub> score | CHA<sub>2</sub>DS<sub>2</sub>-VASc score | HAS-BLED score | Oral anticoagulants<sup>∗</sup> | 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                         | 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, RV, EDO, Warfarin         | NA        | NA                           | 8          |
| Jeong HK-2019    | Korea           | Retrospective cohort  | January 2014 to December 2016 | Chonnam National University Hospital            | 70.9    | NA                       | 3.4                                      | NA               | RV, Warfarin                  | 51.5% of patients (15 mg QD); 48.5% (20 mg QD) | NA            | 1.0                               | 7          |
| Chan YH-2019     | China, Taiwan   | Retrospective cohort  | 1 June 2012 to 31 December 2016 | National Health Insurance Research Database     | 74.7    | NA                       | 3.6                                      | 2.6               | DA, RV, EDO, Warfarin         | 64%, 64%, 94%, and 88% of patients received EDO (15 mg QD); AP (2.5 mg BID); RV (15 mg QD); and DA (110 mg BID), respectively | NA<sup>†</sup> | NA                               | 8          |
| Kohsaka S-2018   | Japan           | Retrospective cohort  | 1 March 2011 to 30 June 2016  | 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                               | 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                         | 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, RV, API, Warfarin         | 62%, 94%, and 88% of patients received API (2.5 mg BID); RV (15 mg QD); and DA (110 mg BID), respectively | NA<sup>†</sup> | 0.76-1.55                         | 8          |
| Cha MJ-2017      | Korea           | Retrospective cohort  | January 2014 to December 2015 | National Health Insurance Service database      | 69.3    | NA                       | 3.6                                      | NA               | DA, RV, API, Warfarin         | 42.2%, 50.2%, and 62.6% of patients received API (2.5 mg BID); RV (15 mg QD); and DA (110 mg BID), respectively | NA<sup>†</sup> | 1.2                               | 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               | RV, Warfarin                  | 100% of patients (15/10 mg QD) | NA            | 1.0                               | 8          |
| Lee KH-2017      | Korea           | Retrospective cohort  | January 2012 to December 2013 | Chonnam National University Hospital            | 72.0    | NA                       | 3.3                                      | NA               | DA, Warfarin                  | 65.1% of patients (110 mg BID); 34.9% (150 mg BID) | NA<sup>†</sup> | 1.0                               | 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                               | 7          |
| Lau WC-2017      | China, Hong Kong| Retrospective 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<sup>†</sup> | NA                               | 8          |

API = apixaban, CHADS<sub>2</sub>-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), CHA<sub>2</sub>DS<sub>2</sub> = 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, IS = ischemic stroke, MI = myocardial infarction, NA = not available, NOACs = Novel oral anticoagulants, SSE = stroke or systemic embolism, TTR = time within therapeutic range.

<sup>∗</sup>Presented the anticoagulants that were used in this meta-analysis.

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

<sup>‡</sup>The mean INR (international normalized ratio) of warfarin users was 1.8.
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).
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-performed 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
time in therapeutic range (TTR) in the real-world studies is poorer compared with that in the RCTs. Moreover, the TTR of warfarin is low in Asians with AF. 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. And subsequently, NOACs vs warfarin were found to increase the risk of GI bleeding in non-Asians rather than Asians. 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 patients indicated that apixaban was superior to dabigatran and rivaroxaban in SSE risk of dabigatran 150mg was lower than that of edoxaban. A previous review including 4 RCTs also indicated more benefits in Asian patients treated with dabigatran 150mg. 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

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