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Non-vitamin K antagonist oral anticoagulants in Asian patients with atrial fibrillation: evidences from the real-world data

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Abstract

The role of non-vitamin K antagonist oral anticoagulants (NOACs) in stroke prevention remains unclear in Asian patients with atrial fibrillation (AF). Therefore, we performed a meta-analysis to compare the efficacy and safety outcomes of NOACs in Asian patients with AF from the real-world settings. The PubMed and Embase databases were systematically searched to identify eligible observational studies until June 2019. The odds ratios (OR) and 95% confidence intervals (CIs) were calculated and then pooled by a random-effects model. A total of 18 observational studies were included. Compared with warfarin, dabigatran (OR, 0.56, 95% CI 0.43–0.73), rivaroxaban (OR, 0.54, 95% CI 0.44–0.67), apixaban (OR, 0.41, 95% CI 0.35–0.48), and edoxaban (OR, 0.19, 95% CI 0.14– 0.25) reduced the risk of major bleeding, while dabigatran (OR, 0.78, 95% CI 0.71–0.85), rivaroxaban (OR, 0.74, 95% CI 0.68–0.82), and edoxaban (OR, 0.29, 95% CI 0.22–0.39) were associated with reduced risks of stroke or systemic embolism. In addition, dabigatran versus apixaban was associated with increased risks of ischemic stroke and gastrointestinal bleeding, while rivaroxaban versus apixaban was associated with elevated risks of stroke or systemic embolism, ischemic stroke, intracranial hemorrhage, and gastrointestinal bleeding. In Asian patients with AF, NOACs are non-inferior to warfarin for stroke prevention, and apixaban may be a better choice compared with dabigatran or rivaroxaban.

Keywords Atrial fibrillation · Anticoagulants · Warfarin · Asian · Stroke prevention

Introduction

Atrial fibrillation (AF) is the most common arrhythmias and increases the risk of thromboembolic events [1]. The use of oral anticoagulant therapy remains the mainstay to prevent the AF-related stroke. The application of non-vitamin K antagonist oral anticoagulants (NOACs, including dabigatran, rivaroxaban, apixaban, and edoxaban) has generally increased due to their advantages over warfarin in terms of the reduced frequent monitoring of anticoagulant activity, and fewer drug-drug or drug-food interactions. Prior pivotal randomized clinical trials (RCTs) [2–5] and meta-analyses [6–8] have consistently showed that NOACs have relative efficacy and safety alternatives to warfarin in worldwide patients with AF. In addition, comparisons of the efficacy and safety between NOAC and NOAC have indicated that apixaban has the most favorable safety profiles [9].

With the rapid population ageing, AF patients in Asia suffer higher risks of stroke and intracranial bleeding than patients in other regions. As such, oral anticoagulation therapy for AF is particularly important in Asia. Two prior meta-analyses including the sub-analyses of NOAC trials suggest that the use of NOACs (standard dose in particular) is non-inferior to warfarin use in Asian patients with AF [10, 11]. However, the results of RCTs may be not necessarily consistent with those of real-world studies. More recently, several observational studies in Asia have compared the safety and efficacy of NOACs versus warfarin. In addition, the efficacy and safety profiles between NOAC and NOAC remain unclear, leaving physicians with difficulties in decision-making regarding the choice of NOACs. Therefore, we performed a meta-analysis to compare the efficacy and safety outcomes of NOACs in Asian patients with AF from the real-world settings.

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Methods

We preformed this systematic review and meta-analysis according to the guidance from the Cochrane Handbook for Systematic Reviews, [12] and reported the results of this meta-analysis based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations [13].

Literature search

We systematically searched the electronic databases of PubMed and Embase to identify eligible observational studies from inception to June 2019. The search terms were applied as follows: *atrial fibrillation* OR *atrial flutter* AND *non-vitamin K antagonists* OR *direct oral anticoagulants* OR *new oral anticoagulants* OR *novel oral anticoagulants* OR *dabigatran* OR *rivaroxaban* OR *apixaban* OR *edoxaban* AND *vitamin-K antagonists* OR *warfarin*. We also searched the reference lists of included studies, or related reviews, editorials, and letters for additional reports. No linguistic restriction was applied in this study.

Study eligibility criteria

Observational studies were included according to the following criteria: (1) study population: Asian patients with non-valvular AF receiving at least one NOAC compared with warfarin, or compared with other NOACs; (2) interventions: any NOAC (dabigatran, rivaroxaban, apixaban, or edoxaban) and warfarin; (3) outcomes: studies reported at least one of the efficacy (stroke or systemic embolism [SSE], ischemic stroke, all-cause death) or safety (major bleeding, intracranial hemorrhage [ICH], and gastrointestinal [GI] bleeding) outcomes; and (4) effect estimates: odds ratios (ORs) and 95% confidence intervals (CIs).

We excluded studies according to the following criteria: (1) AF patients with certain interventions (e.g., cardioversion, coronary interventions, catheter ablation, or left-atrial appendage closure); (2) AF patients with certain diseases such as coronary artery disease, liver disease, diabetes, or cancer; (3) several forms of publications such as reviews, case reports, editorials, letters, or abstracts; (4) studies that reported the results by combining different NOACs; (5) if studies used the same data source, we selected the study with the longest study period.

Study selection and data extraction

All studies retrieved from the literature search were screened by two reviewers (Z.B.X and Y.Z) independently. Any disagreement or uncertainty was resolved by consensus or discussion with a third author (W.G.Z). We evaluated the potentially available studies according to titles, abstracts, and full-texts, sequentially. For each included study, we extracted information about study characteristics, patient demographics, anticoagulants, follow-up time, and outcomes.

Quality assessment

The Newcastle-Ottawa Scale (NOS) item were used to evaluate the study quality of observational studies. The NOS tool involved 3 domains with a total of 9 points: the selection of cohorts (0–4 points), the comparability of cohorts (0–2 points), and the assessment of the outcome (0–3 points) [14]. In this study, an NOS score of ≥ 6 points indicated a moderate-to-high quality, and an NOS score of < 6 points indicated a low quality [15].

Statistical analysis

In this study, we assessed the efficacy and safety of any NOAC (dabigatran, rivaroxaban, apixaban, or edoxaban) versus warfarin, and compared the efficacy and safety between NOAC and NOAC. The statistical analyses were performed using the Review Manager (RevMan) version 5.3 software (The Cochrane Collaboration 2014, Nordic Cochrane Centre Copenhagen, Denmark).

We collected the sample size and number of events in each group, and calculated the ORs and 95% CIs. If the number of events was unavailable, the expected number of events was calculated using the event rates: event number = (total patient number)×(event rate [per 100 patient years])×(follow-up time [years]) [16]. The Cochrane Q test and I^2 index were used to measure the statistical heterogeneity, where $P < 0.1$ and $I^2 > 50\%$ indicated a substantial heterogeneity, respectively. Given the heterogeneity inherent across the included studies, we should draw a relatively conservative conclusion based on the results of a random-effects model. According to the Cochrane handbook, the publication bias was assessed by using the funnel plots of the reported effect estimates. When we assessed the efficacy and safety of NOACs versus warfarin, the following sensitivity analyses were performed: (1) applying a fixed-effects model to re-perform the analysis; (2) only including the studies that did not use the method of propensity score matching; (3) only including studies with the NOS score of ≤ 7 points; (4) only including studies with the follow-up time of < 1 year; and (5) deleting the study with the largest statistical weight in the pooled analysis.

Results

Study selection

As shown in Supplemental Figure 1, the literature search retrieved 8,003 records from the PubMed and Embase databases. After the title and abstract screenings, the 65 remaining

studies underwent full-text assessment. Thereinto, 47 studies did not meet with the pre-defined inclusion criteria (Supplemental Table 1): (1) clinical trials (n = 17); (2) study participants had a significant overlap (n = 12); (3) AF patients with certain comorbid diseases (n = 9); and (4) studies presented the results by combining different NOACs (n = 9). Finally, a total of 18 observational studies [17–34] were included in this meta-analysis.

The main characteristics of the included studies are shown in Supplemental Table 2. Eleven studies applied the method of propensity score matching to balance patient characteristics between study groups. All the included studies had a moderate-to-high quality with an NOS score of > 6 points.

Efficacy and safety between NOACs and warfarin

Dabigatran versus warfarin As shown in Table 1 and Fig. 1, compared with warfarin use, the use of dabigatran was associated with lower risks of SSE (OR = 0.78, 95% CI 0.71–0.85), IS (OR = 0.34, 95% CI 0.17–0.67), all-cause death (OR = 0.51, 95% CI 0.27–0.96), major bleeding (OR = 0.56, 95% CI 0.43–0.73), ICH (OR = 0.33, 95% CI 0.22–0.48), and GI bleeding (OR = 0.60, 95% CI 0.38–0.93).

Rivaroxaban versus warfarin As presented in Table 1 and Fig. 2, compared with warfarin, rivaroxaban significantly reduced the risks of SSE (OR = 0.74, 95% CI 0.68–0.82), IS (*OR* = 0.53, 95% CI 0.31–0.91), all-cause death (OR = 0.41, 95% CI 0.26–0.66), major bleeding (OR = 0.54, 95% CI 0.44–0.67), ICH (OR = 0.35, 95% CI 0.19–0.67) and GI bleeding (OR = 0.59, 95% CI 0.46–0.77).

Apixaban versus warfarin In comparison with warfarin, apixaban was associated with decreased risks of all-cause death (OR = 0.27, 95% CI 0.09–0.82), major bleeding (OR = 0.41, 95% CI 0.35–0.48), ICH (OR = 0.29, 95% CI 0.23–0.38) and GI bleeding (OR = 0.20, 95% CI 0.14–0.28), but showed marginally significant reductions in SSE (OR=0.70, 95%CI 0.49-1.01) and IS (OR=0.41, 95%CI 0.16-1.02) (Table 1 and Figure 3).

Edoxaban versus warfarin As shown in Table 1 and Supplemental Figure 2, edoxaban versus warfarin showed significant reductions in SSE (OR = 0.29, 95% CI 0.22–0.39) [19], IS (OR = 0.29, 95% CI 0.23–0.36) [19, 22], all-cause death (OR = 0.26, 95% CI 0.20–0.34) [22], major bleeding (OR = 0.19, 95% CI 0.14–0.25) [19, 22], ICH (OR = 0.14, 95% CI 0.09–0.23) [19, 22] and GI bleeding (OR = 0.17, 95% CI 0.07–0.43) [19, 22].

Sensitivity analysis As shown in Supplemental Table 3, all the sensitivity analyses produced similar results to the main analyses, suggesting that compared with warfarin, all NOACs had lower or similar rates of thromboembolic and bleeding events.

Table 1 Efficacy and safety of NOACs versus warfarin for stroke prevention in Asian patients with AF

Outcomes	Dabigatran versus warfarin			Rivaroxaban versus warfarin			Apixaban versus warfarin			Edoxaban versus warfarin		
	Dabigatran (events/total)	Warfarin (events/total)	Pooled OR (95% CI)	Rivaroxaban (events/total)	Warfarin (events/total)	Pooled OR (95% CI)	Apixaban (events/total)	Warfarin (events/total)	Pooled OR (95% CI)	Edoxaban (events/total)	Warfarin (events/total)	Pooled OR (95% CI)
SSE	965/28731	1338/30891	0.78 (0.71–0.85)	1008/35242	1033/26418	0.74 (0.68–0.82)	316/35140	1112/47147	0.70 (0.49–1.01)	53/4577	759/19761	0.29 (0.22–0.39)
IS	696/28660	1879/50709	0.34 (0.17–0.67)	963/40866	1534/48914	0.53 (0.31–0.91)	218/12427	1355/47147	0.41 (0.16–1.02)	86/9178	1025/31944	0.29 (0.23–0.36)
All cause death	1666/25382	4597/48921	0.51 (0.27–0.96)	2220/35751	4606/49054	0.41 (0.26–0.66)	352/8644	4573/48122	0.27 (0.09–0.82)	68/4601	658/12183	0.26 (0.20–0.34)
Major bleeding	692/35207	1415/40955	0.56 (0.43–0.73)	863/43041	1575/41072	0.54 (0.44–0.67)	221/22638	1104/37458	0.41 (0.35–0.48)	56/9178	1044/31944	0.19 (0.14–0.25)
ICH	261/35912	1100/59084	0.33 (0.22–0.48)	302/41772	919/50603	0.35 (0.19–0.67)	64/12855	871/48708	0.29 (0.23–0.38)	19/9178	463/31944	0.14 (0.09–0.23)
GI bleeding	377/31355	553/32410	0.60 (0.38–0.93)	354/34481	454/24857	0.59 (0.46–0.77)	37/10238	432/23925	0.20 (0.14–0.28)	29/9178	559/31944	0.17 (0.07–0.43)

AF, atrial fibrillation; *NOACs*, non-vitamin K antagonist oral anticoagulants; *SSE*, stroke or systemic embolism; *IS*, ischemic stroke; *ICH*, intracranial hemorrhage; *GI*, gastrointestinal; *OR*, odds ratio; *CI*, confidence interval

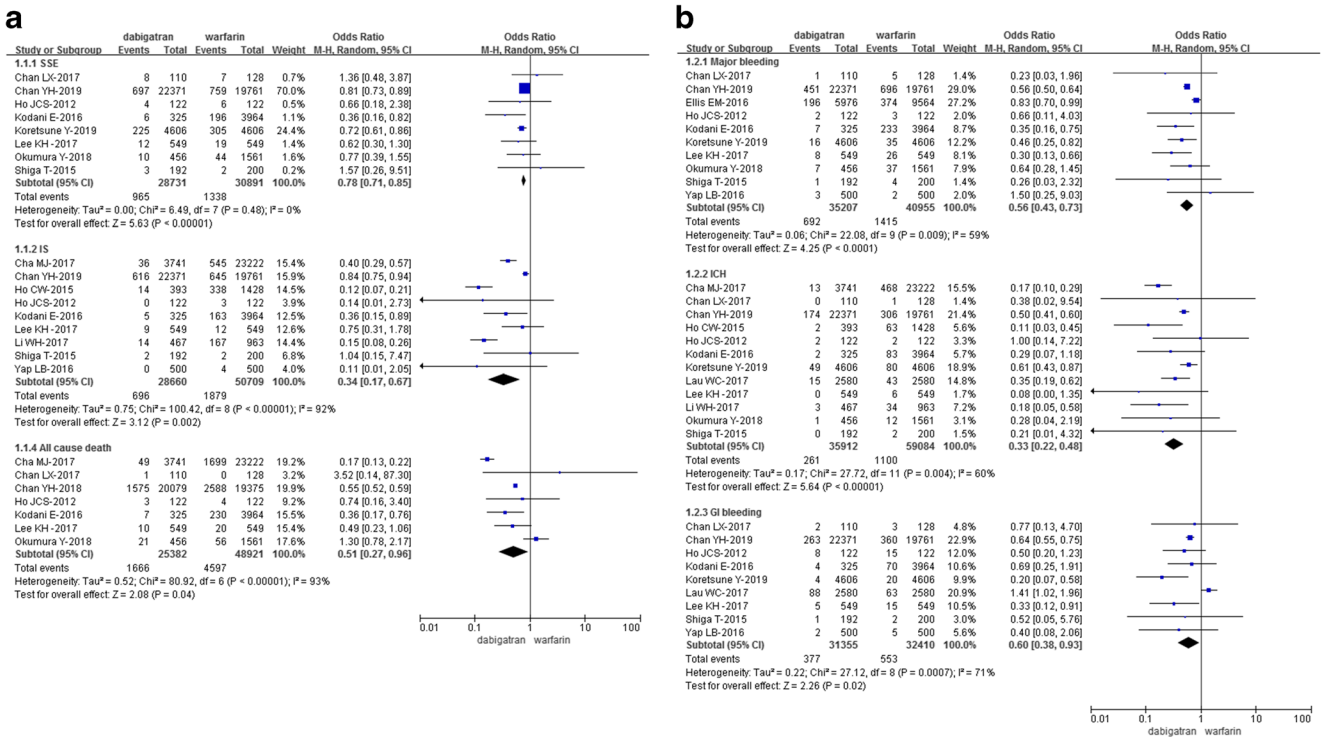

Fig. 1 Forest plot for comparing the efficacy (**a**) and safety (**b**) outcomes of dabigatran with warfarin in Asian patients with AF. AF, atrial fibrillation; SSE, stroke or systemic embolism; IS, ischemic stroke; ICH, intracranial hemorrhage; GI, gastrointestinal; CI, confidence interval

Efficacy and safety between NOAC and NOAC

Dabigatran versus rivaroxaban As shown in Table 2 and Supplemental Figure 3, there were no differences between dabigatran and rivaroxaban for the efficacy and safety outcomes including SSE (OR = 1.08, 95% CI 0.98–1.19), IS (OR = 1.04, 95% CI 0.94–1.15), all-cause death (OR = 0.99, 95% CI 0.62–1.57), major bleeding (OR = 1.11, 95% CI 0.68–1.79), ICH (OR = 0.96, 95% CI 0.80–1.15) and GI bleeding (OR = 1.15, 95% CI 0.95–1.41).

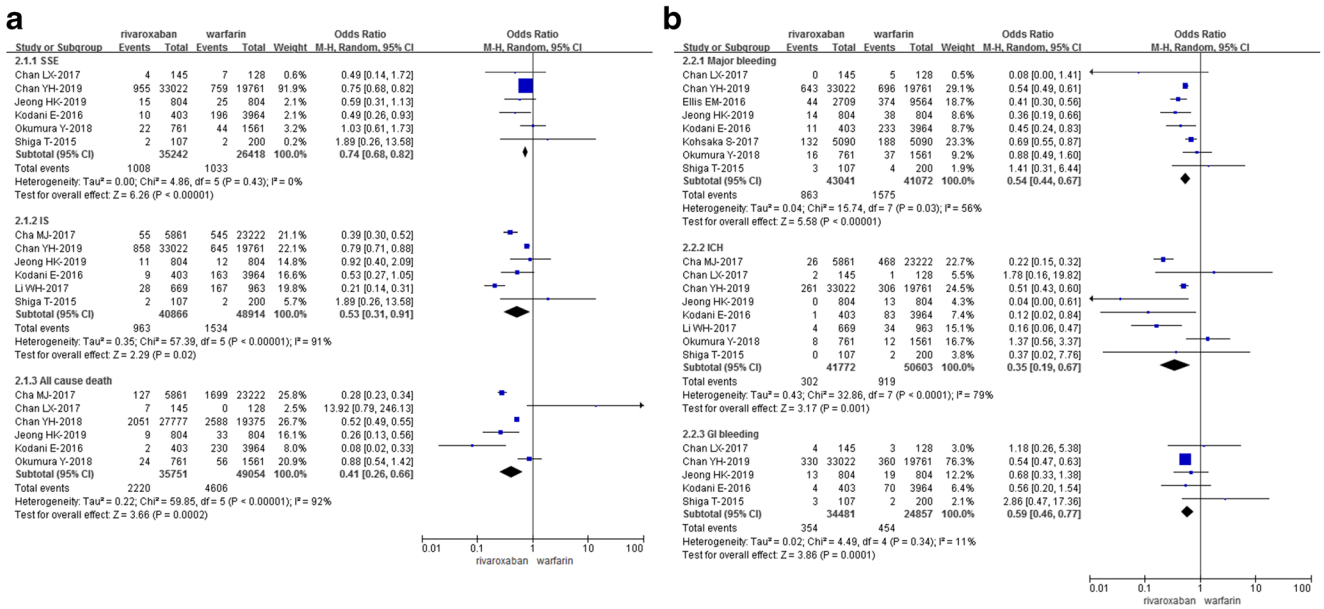

Fig. 2 Forest plot for comparing the efficacy (**a**) and safety (**b**) outcomes of rivaroxaban with warfarin in Asian patients with AF. AF, atrial fibrillation; SSE, stroke or systemic embolism; IS, ischemic stroke; ICH, intracranial hemorrhage; GI, gastrointestinal; CI, confidence interval

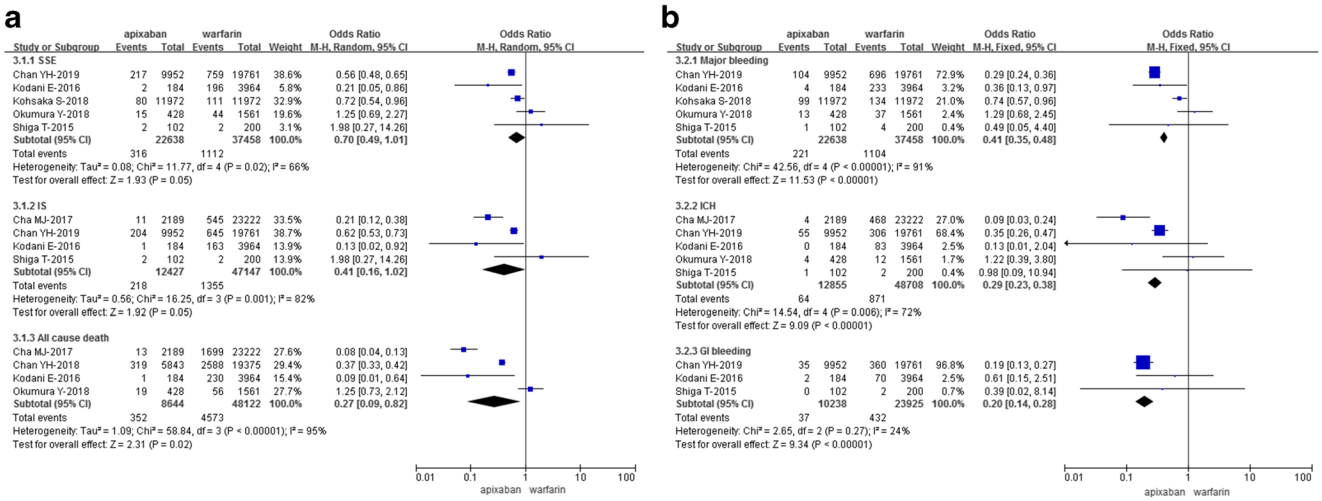

Fig. 3 Forest plot for comparing the efficacy (**a**) and safety (**b**) outcomes of apixaban with warfarin in Asian patients with AF. AF, atrial fibrillation; SSE, stroke or systemic embolism; IS, ischemic stroke; ICH, intracranial hemorrhage; GI, gastrointestinal; CI, confidence interval

Dabigatran versus apixaban In comparison with apixaban, dabigatran was significantly associated with increased risks of IS (OR = 1.38, 95% CI 1.18–1.61), all-cause death (OR = 1.51, 95% CI 1.17–1.95), and GI bleeding (OR = 3.20, 95% CI 2.27–4.51), but had no statistical differences in SSE (OR = 1.16, 95% CI 0.71–1.87), major bleeding (OR = 1.02, 95% CI 0.43–2.44), and ICH (OR = 1.30, 95% CI 0.77–2.21) (Table 2 and Supplemental Figure 4).

Rivaroxaban versus apixaban Rivaroxaban had significantly elevated risks of SSE (OR = 1.31, 95% CI 1.13–1.51), IS (OR = 1.31, 95% CI 1.13–1.52), ICH (OR = 1.45, 95% CI 1.11–1.90), and GI bleeding (OR = 2.75, 95% CI 1.89–3.99), but showed similar rates of all-cause death (OR = 1.48, 95% CI 0.76–2.88) and major bleeding (OR = 1.34, 95% CI 0.72–2.52) as for apixaban (Table 2 and Supplemental Figure 5).

Of note, no syntheses conducted for outcomes regarding edoxaban versus other NOACs due to the insufficient studies.

Publication bias

As shown in Supplemental Figures 6–11, there were no obvious publication biases inspected by the funnel plots.

Discussion

In the real-world Asian patients with AF, our present meta-analysis first showed that (1) compared with warfarin, all NOACs reduced the risks of bleeding events and all-cause death, whereas dabigatran, rivaroxaban, and edoxaban were associated with decreased risks of SSE and IS; and (2) apixaban versus dabigatran was associated with decreased risks of IS and GI bleeding; and apixaban versus rivaroxaban was associated with reduced risks of SSE, IS, ICH, and GI bleeding. The real-world evidences from Asian patients with AF suggested that NOACs were non-inferior to warfarin, and apixaban might be a better option available compared with dabigatran or rivaroxaban.

Previously, Wang and colleagues [11] performed a meta-analysis by including Asian patients with AF from the NOAC trials for dabigatran (Randomized Evaluation of Long-Term Anticoagulation Therapy; RE-LY), rivaroxaban (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; ROCKET AF), rivaroxaban (Japanese-Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; J-ROCKET AF), apixaban (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ARISTOTLE), and edoxaban (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48-ENGAGE AF; TIMI 48). In their analyses, compared with warfarin, standard-dose NOACs are associated with lower risks of both efficacy (SSE and all-cause death) and safety (major bleeding and ICH) outcomes, whereas low-dose NOACs have a favorable safety profile with reductions in major bleeding and ICH. Subsequently, 2017 consensus on stroke prevention in Asians with AF recommends standard-dose NOACs as the first choice [35]. Of note, a limitation in the study of Wang et al. [11] was that the results were driven by combining different NOACs. In addition, whether NOACs in real-world daily practice would show the efficacy and safety differences from participants in the NOAC trials remains unclear. Our current real-world data support the findings of Wang et al. [11] and strengthen the validity of NOACs in Asia. The different types of NOACs were analyzed separately in our study, suggesting that dabigatran, rivaroxaban, and edoxaban

Table 2 Efficacy and safety between NOACs for stroke prevention in Asian patients with AF

Outcomes	Dabigatran versus rivaroxaban					Dabigatran versus apixaban					Rivaroxaban versus apixaban				
	Dabigatran		Rivaroxaban		Pooled OR (95% CI)	Dabigatran		Apixaban		Pooled OR (95% CI)	Rivaroxaban		Apixaban		Pooled OR (95% CI)
	Events	Total	Events	Total		Events	Total	Events	Total		Events	Total	Events	Total	
SSE	724	23454	993	34438	1.08 (0.98–1.19)	716	23344	236	10666	1.16 (0.71–1.87)	989	34293	236	10666	1.31 (1.13–1.51)
IS	673	27096	952	40062	1.04 (0.94–1.15)	659	26629	218	12427	1.38 (1.18–1.61)	924	39393	218	12427	1.31 (1.13–1.52)
All cause death	1653	24711	2211	34947	0.99 (0.62–1.57)	1652	24601	352	8644	1.51 (1.17–1.95)	2204	34802	352	8644	1.48 (0.76–2.88)
Major bleeding	663	29430	717	37147	1.11 (0.68–1.79)	466	23344	122	10666	1.02 (0.43–2.44)	673	34293	122	10666	1.34 (0.72–2.52)
ICH	193	27662	302	40968	0.96 (0.80–1.15)	190	27085	64	12855	1.30 (0.77–2.21)	296	40154	64	12855	1.45 (1.11–1.90)
GI bleeding	270	22998	341	33677	1.15 (0.95–1.41)	268	22888	37	10238	3.20 (2.27–4.51)	337	33532	37	10238	2.75 (1.89–3.99)

AF, atrial fibrillation; *NOACs*, non-vitamin K antagonist oral anticoagulants; *SSE*, stroke or systemic embolism; *IS*, ischemic stroke; *ICH*, intracranial hemorrhage; *GI*, gastrointestinal; *OR*, odds ratio; *CI*, confidence interval

were associated with lower risks of both efficacy and safety profiles compared with warfarin. Consistent with the sub-analysis of the ARISTOTLE trial [36], the real-world data also showed that the use of apixaban was safer than warfarin use with reductions in the bleeding risks in Asia. Of note, only two included studies [19, 22] reported the effectiveness and safety of edoxaban in real-world practice, and therefore, our data in relation to edoxaban have to be interpreted cautiously. With the rapid population ageing, data from observational studies would help overcome the under-use of anticoagulation therapy in Asia.

Among the included studies, a total of 11, 6, 3, and 2 studies reported that more than 50% of patients received reduced or low dose of dabigatran, rivaroxaban, apixaban, and edoxaban, respectively (Supplemental Table 4). In the study of Jeong et al. [18], 51.5% of patients received rivaroxaban 15 mg, but the use of both rivaroxaban 15 mg/day and 20 mg/day had similar efficacy and lower risks of major bleeding compared with warfarin use. Chan et al. [19] reported that reduced-dose NOACs (edoxaban 15–30 mg/day, apixaban 2.5 mg bid, rivaroxaban 10–15 mg/day, and dabigatran 110 mg bid) were associated with lower rates of thromboembolism and bleeding events compared with warfarin. In our meta-analysis, the subgroup analysis based on the NOAC dose could not be performed due to the limiting data.

Direct or indirect comparisons of NOACs for efficacy and safety profiles in worldwide AF patients have been reported in several studies [6, 9, 37], suggesting a better safety profile (i.e., reduced risk of major bleeding) but similar efficacy profile when comparing the use of apixaban to dabigatran or rivaroxaban. To the best of our knowledge, we first compared the efficacy and safety outcomes between NOAC and NOAC in Asian patients with AF. Our results supported apixaban as the most favorable NOAC, mainly manifesting as reduced rates of IS and GI bleeding for apixaban versus dabigatran, and lower risks of SSE, IS, ICH, and GI bleeding for apixaban versus rivaroxaban. These data might help clinicians better understand and guide the choice of anticoagulants in Asian patients with AF. However, the efficacy and safety between edoxaban with other NOACs could not be performed due to the insufficient studies. Further study with head-to-head direct comparisons would confirm the efficacy and safety differences between NOAC and NOAC. Given there are still no such RCTs currently, the real-world data with comparative assessment between NOAC and NOAC might help clinicians in decision-making for stroke prevention in Asia.

Limitations

Our meta-analysis had several limitations. First, the quality of anticoagulation activity in warfarin users and the adherence or persistence to NOACs were not considered. Second, based on

the real-world data, the residual confounders should be considered when interpreting our findings. Third, 6 included studies were from Japan, 4 studies from Korea, 5 studies from China, 1 study from Singapore, 1 study from Malaysia, and 1 study from Israel. As such, 15 of 18 studies were from Japan, Korea, and China, limiting the generalization to all Asians with AF. Finally, the numbers of studies included for quantitative syntheses of the outcomes of interest were relatively small. As such, we could not perform the subgroup analyses to explore the source of heterogeneity across the included studies.

Conclusions

Based on current real-world evidences, NOACs were noninferior to warfarin for AF stroke prevention in Asia. Apixaban might represent a better option compared with dabigatran or rivaroxaban.

Authors' Contributions ZB-X, Y-Z, and WG-Z performed the literature search, study selection and data extraction, quality assessment, and statistical analysis. CY-W, J-L, and X-L help check the data to ensure accuracy. ZB-X and Y-Z wrote the original draft, while WG-Z revised the draft. WG-Z edited the manuscript prior to submission to ensure the standard English grammar.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not required.

References

1. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW (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. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM (2013) Edoxaban versus warfarin in patients with atrial fibrillation. New Engl J Med. 369(22):2093–2104
3. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FWA, Zhu J, Wallentin L (2011) Apixaban versus warfarin in patients with atrial fibrillation. New Engl J Med. 365(11):981–992
4. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KAA, Califf RM (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. New Engl J Med. 365(10):883–891
5. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener H, Joyner CD, Wallentin L (2009) Dabigatran versus warfarin in patients with atrial fibrillation. New Engl J Med. 361(12):1139–1151
6. Proietti M, Romanazzi I, Romiti GF, Farcomeni A, Lip G (2018) Real-world use of apixaban for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. Stroke. 49(1):98–106
7. Ntaios G, Papavasileiou V, Makaritsis K, Vemmos K, Michel P, Lip GYH (2017) Real-world setting comparison of nonvitamin-K antagonist oral anticoagulants versus vitamin-K antagonists for stroke prevention in atrial fibrillation. Stroke. 48(9):2494–2503
8. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM (2014) Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 383(9921):955–962
9. Li G, Lip GYH, Holbrook A, Chang Y, Larsen TB, Sun X, Tang J, Mbuagbaw L, Witt DM, Crowther M, Thabane L, Levine MAH (2019) 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. 34(2):173–190
10. Wang K, Giugliano RP, Goto S, Chiu C, Lin C, Lai E, Chiang C (2016) 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. 13(12):2340–2347
11. Wang KL, Lip GY, Lin SJ, Chiang CE (2015) Non-vitamin K antagonist oral anticoagulants for stroke prevention in Asian patients with nonvalvular atrial fibrillation: meta-analysis. Stroke. 46(9):2555–2561
12. Higgins J, Green S Cochrane handbook for systematic reviews of interventions version 5.1.0[updated March 2011]. Available at: www.cochrane-handbook.org. Accessed June 23, 2019.
13. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Plos Med. 6(7):e1000097
14. Wells GA, Shea B, O Connell D, Peterson J, Welch V, Losos M, Tugwell P 2014 The Newcastle Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed June 20, 2019.
15. Zhu W, Wan R, Liu F, Hu J, Huang L, Li J, Hong K (2016) Relation of body mass index with adverse outcomes among patients with atrial fibrillation: a meta-analysis and systematic review. J Am Heart Assoc. 5(9):e4006
16. Xiong Q, Chen S, Senoo K, Proietti M, Hong K, Lip GYH (2015) The CHADS2 and CHA2DS2-VASc scores for predicting ischemic stroke among East Asian patients with atrial fibrillation: a systemic review and meta-analysis. Int J Cardiol. 195:237–242
17. Koretsune Y, Yamashita T, Yasaka M, Ono Y, Hirakawa T, Ishida K, Kuroki D, Sumida T, Urushihara H (2019) Comparative effectiveness and safety of warfarin and dabigatran in patients with nonvalvular atrial fibrillation in Japan: a claims database analysis. J Cardiol. 73(3):204–209
18. Jeong HK, Lee KH, Park HW, Yoon NS, Kim MC, Lee N, Kim JS, Ahn Y, Jeong MH, Park JC, Cho JG (2019) Real world comparison of rivaroxaban and warfarin in Korean patients with atrial fibrillation: propensity matching cohort analysis. Chonnam Med J 55(1):54
19. Chan Y, Lee H, See L, Tu H, Chao T, Yeh Y, Wu L, Kuo C, Chang S, Lip GYH (2019. Epub ahead of print]) Effectiveness and safety of four

direct oral anticoagulants in Asian patients with nonvalvular atrial fibrillation. Chest. https://doi.org/10.1016/j.chest.2019.04.108
20. Okumura Y, Yokoyama K, Matsumoto N, Tachibana E, Kuronuma K, Oiwa K, Matsumoto M, Kojima T, Hanada S, Nomoto K, Arima K, Takahashi F, Kotani T, Ikeya Y, Fukushima S, Itou S, Kondo K, Chiku M, Ohno Y, Onikura M, Hirayama A (2018) Three-year clinical outcomes associated with warfarin vs. direct oral anticoagulant use among Japanese patients with atrial fibrillation — findings from the SAKURA AF Registry —. Circ J. 82(10):2500–2509
21. Chan YH, See LC, Tu HT, Yeh YH, Chang SH, Wu LS, Lee HF, Wang CL, Kuo CF, Kuo CT (2018) Efficacy and safety of apixaban, dabigatran, rivaroxaban, and warfarin in Asians with nonvalvular atrial fibrillation. J Am Heart Assoc 7(8)
22. Lee SR, Choi EK, Han KD, Jung JH, Oh S, Lip GYH (2018) Edoxaban in Asian patients with atrial fibrillation: effectiveness and safety. J Am Coll Cardiol. 72(8):838–853
23. Kohsaka S, Katada J, Saito K, Terayama Y (2018) Safety and effectiveness of apixaban in comparison to warfarin in patients with nonvalvular atrial fibrillation: a propensity-matched analysis from Japanese administrative claims data. Curr Med Res Opin. 34(9): 1627–1634
24. Li WH, Huang D, Chiang CE, Lau CP, Tse HF, Chan EW, Wong ICK, Lip GYH, Chan PH, Siu CW (2017) Efficacy and safety of dabigatran, rivaroxaban, and warfarin for stroke prevention in Chinese patients with atrial fibrillation: the Hong Kong Atrial Fibrillation Project. Clin Cardiol. 40(4):222–229
25. Cha M, Choi E, Han K, Lee S, Lim W, Oh S, Lip GYH (2017) Effectiveness and safety of non-vitamin K antagonist oral anticoagulants in Asian patients with atrial fibrillation. Stroke. 48(11):3040–3048
26. Kohsaka S, Murata T, Izumi N, Katada J, Wang F, Terayama Y (2017) Bleeding risk of apixaban, dabigatran, and low-dose rivaroxaban compared with warfarin in Japanese patients with non-valvular atrial fibrillation: a propensity matched analysis of administrative claims data. Curr Med Res Opin. 33(11):1955–1963
27. Chan LX, Wong YM, Chia P, Kek ZL (2017) A single institution's experience with using dabigatran, rivaroxaban and warfarin for prevention of thromboembolism in atrial fibrillation. Proceedings of Singapore Healthcare.;27(1):20-25.
28. Lee KH, Park HW, Lee N, Hyun DY, Won J, Oh SS, Park HJ, Kim Y, Cho JY, Kim MC, Sim DS, Yoon HJ, Yoon NS, Kim KH, Hong YJ, Kim JH, Ahn Y, Jeong MH, Park JC, Cho JG (2017) Optimal dose of dabigatran for the prevention of thromboembolism with minimal bleeding risk in Korean patients with atrial fibrillation. Ep Europace 19(suppl_4):v1–v9
29. Lau WC, Li X, Wong IC, Chan EW (2017) Bleeding-related hos-478 pital admissions and 30-day readmissions in patients with nonvalvular atrial fibrillation treated with dabigatran versus warfarin. Journal of Thrombosis and Haemostasis, 15(10), 1923-1933
30. Yap LB, Eng DTS, Sivalingam L, Rusani BI, Umadevan D, Muhammad Z, Koh KW, Aisha B, Hashim MI, Rebo R, Hussin A, Kaur S, Shanmugam R, Omar R (2016) A comparison of dabigatran with warfarin for stroke prevention in atrial fibrillation in an Asian population. Clin Appl Thromb Hemost 22(8):792–797
31. Kodani E, Atarashi H, Inoue H, Okumura K, Yamashita T, Origasa H (2016) Beneficial effect of non-vitamin K antagonist oral anticoagulants in patients with nonvalvular atrial fibrillation – results of the J-RHYTHM Registry 2. Circ J. 80(4):843–851
32. Ellis MH, Neuman T, Bitterman H, Dotan SG, Hammerman A, Battat E, Eikelboom JW, Ginsberg JS, Hirsh J (2016) Bleeding in patients with atrial fibrillation treated with dabigatran, rivaroxaban or warfarin: a retrospective population-based cohort study. Eur J Intern Med. 33:55–59
33. Shiga T, Naganuma M, Nagao T, Maruyama K, Suzuki A, Murasaki K, Hagiwara N (2015) Persistence of non-vitamin K antagonist oral anticoagulant use in Japanese patients with atrial fibrillation: a single-center observational study. J Arrhythm. 31(6):339–344
34. Ho JCS, Chang AM, Yan BP, Yu CM, Lam YY, Lee VWY (2012) Dabigatran compared with warfarin for stroke prevention with atrial fibrillation: experience in Hong Kong. Clin Cardiol. 35(12):E40–E45
35. Chiang C, Okumura K, Zhang S, Chao T, Siu C, Wei Lim T, Saxena A, Takahashi Y, Siong TW (2017) 2017 consensus of the Asia Pacific Heart Rhythm Society on stroke prevention in atrial fibrillation. J Arrhythm. 33(4):345–367
36. Goto S, Zhu J, Liu L, Oh BH, Wojdyla DM, Aylward P, Bahit MC, Gersh BJ, Hanna M, Horowitz J, Lopes RD, Wallentin L, Xavier D, Alexander JH (2014) 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. 168(3):303–309
37. Lip GY, Larsen TB, Skjoth F, Rasmussen LH (2012) Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. J Am Coll Cardiol. 60(8):738–746