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Non–Vitamin K Antagonist Oral Anticoagulants Versus Warfarin in Asians With Atrial Fibrillation

Meta-Analysis of Randomized Trials and Real-World Studies

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Background and Purpose—Several randomized trials and real-world studies have reported the efficacy and safety of non–vitamin K antagonist oral anticoagulants (NOACs) in Asian patients with atrial fibrillation; and therefore, this meta-analysis was aimed to compare the effects of NOACs with warfarin for atrial fibrillation stroke prevention in Asians.

Methods—The PubMed and Embase databases were searched from January 2009 to February 2019 for studies on comparisons of NOACs versus warfarin in Asians. Risk ratios (RRs) with 95% CIs were pooled using a random-effects model.

Results—Five NOAC trials and 21 observational cohorts were included. For the NOAC trials, compared with warfarin, NOACs was associated with reduced risks of stroke or systemic embolism (RR, 0.73; 95% CI, 0.59–0.90), all-cause death (RR, 0.83; 95% CI, 0.73–0.95), major bleeding (RR, 0.59; 95% CI, 0.48–0.72), and intracranial bleeding (RR, 0.36; 95% CI, 0.26–0.49). For the real-world data, compared with warfarin, NOACs was associated with decreased rates of stroke or systemic embolism (RR, 0.75; 95% CI, 0.68–0.82), ischemic stroke (RR, 0.70; 95% CI, 0.59–0.83), myocardial infarction (RR, 0.74; 95% CI, 0.58–0.93), all-cause death (RR, 0.67; 95% CI, 0.59–0.77), major bleeding (RR, 0.63; 95% CI, 0.55–0.73), intracranial bleeding (RR, 0.50; 95% CI, 0.43–0.59), and gastrointestinal bleeding (RR, 0.65; 95% CI, 0.51–0.84). The results did not change in the subgroup analyses based on the type and dose of NOACs.

Conclusions—Based on published NOAC trials and real-world studies, the use of NOACs is noninferior to warfarin in Asians with atrial fibrillation irrespective of the NOAC type and dose. **(*Stroke*. 2019;50:2819-2828. DOI: 10.1161/STROKEAHA.119.026054.)**

Key Words: anticoagulants ■ atrial fibrillation ■ embolism ■ myocardial infarction ■ warfarin

Atrial fibrillation (AF), one of the most common arrhythmias, affects millions of people worldwide; and AF-related thromboembolic events are the leading cause of neurological disability and mortality.[1,2] Appropriate thromboprophylaxis is an urgent need for stroke prevention in AF.[3,4] Although vitamin K antagonists, such as warfarin, have proven effective for stroke prevention,[5] their shortcomings (eg, marked inter and intraindividual variations in medication dosage, narrow therapeutic window, frequent monitoring of anticoagulant activity, and interactions with other drugs) would limit their use in clinical practice.[6,7] More recently, 4 phase III randomized clinical trials (RCTs) have demonstrated that non–vitamin K antagonist oral anticoagulants (NOACs) are at least as effective as vitamin K antagonists and even have a better safety profile in the worldwide AF patients.[8–11]

Wang et al[12] have demonstrated that standard-dose NOACs are more effective and safer in Asians than that in non-Asians, whereas low-dose NOACs versus warfarin have similar efficacy and safety outcomes between Asian and non-Asian race. For this study, 5 subanalyses of NOAC-related trials[13–17] were analyzed for rivaroxaban (ROCKET AF [Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation]),[13] apixaban (ARISTOTLE [Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation]),[14] dabigatran (RE-LY [Randomized Evaluation of Long-Term Anticoagulation Therapy]),[15] edoxaban (ENGAGE AF-TIMI 48 [Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48]),[16] and rivaroxaban (J-ROCKET AF [Japanese-Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation]).[17] Another meta-analysis found that standard-dose versus low-dose NOACs show a reduced rate of ischemic stroke without an excess of bleeding risks.[18] And subsequently, 2017 consensus of the Asia Pacific

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Heart Rhythm Society on stroke prevention in AF recommends that standard-dose NOACs should be considered as the first choice in Asians.[19] Nevertheless, in the study of Wang et al,[12] the ENGAGE AF-TIMI 48 trial[16] compared the safety and efficacy of edoxaban versus warfarin in East Asians with non-East Asians. However, the East Asian group did not include the Japanese population, whereas patients from all other countries, including South Asia, were regarded as the non-East Asian group.[16] Given the fact that the effect of edoxaban versus warfarin for patients with Asian race is still unclear, Chao et al[20] reperformed the subanalysis of the ENGAGE AF-TIMI 48 trial. Therefore, the first section of this meta-analysis was aimed to update the available information of NOACs versus warfarin in Asians with AF.

Nevertheless, populations from RCTs are generally selected with strict eligibility criteria under careful protocol-based follow-up. As such, data from RCTs are not always valid for real-world AF patients. Prior meta-analyses of real-world studies have compared the efficacy and safety outcomes between NOAC and warfarin users in the worldwide population,[21–25] but the relationship in Asian real-world patients with AF is still unknown. The incidence of AF and AF-associated complications are substantially higher in Asians than non-Asians because Asia is a region with the largest population and has the rapidly aging population. Of particular note, Asian patients with AF have higher risks of stroke and bleeding (in particular intracranial bleeding) than non-Asians. Furthermore, there are important differences in baseline characteristics between Asian and non-Asian patients. For example, compared with non-Asians, Asian patients generally have a younger age, lower body weight, and lower prevalence of cardiovascular comorbidities, but show a higher risk of prior cerebrovascular events. In addition, since Asians are the major factor attributable to stroke and intracranial bleeding in anticoagulated patients, more Asian patients would have been deemed ineligible for treatment because of higher stroke and bleeding risks. As such, stroke prevention in AF represents an urgent issue of public health in Asia. However, whether the use of NOACs is effective and safe in Asians is still exploratory. In recent years, several observational studies have investigated the effect of NOACs versus warfarin in Asian patients with AF, but their results remain controversial. Therefore, the second section of this meta-analysis was to compare the efficacy and safety of NOACs versus warfarin for stroke prevention in the real-world Asians with AF.

Methods

The results of this meta-analysis were presented based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[26] There was no need to provide the ethical approval because we performed this study by including the studies that have already been published. The data that support the findings of this meta-analysis are available from the corresponding author on reasonable request.

The PubMed and Embase databases were systematically searched with no linguistic restrictions from January 1, 2009 to February 9, 2019 for all studies that comparing the efficacy and safety of any NOAC (dabigatran, rivaroxaban, edoxaban, or apixaban) with warfarin in Asian patients with AF (Table I in the online-only Data Supplement). Data for this meta-analysis were retrieved from RCTs, subanalyses of RCTs, or observational cohorts that had Asian patients enrolled. Data abstraction and quality assessment were performed by 2 reviewers (Z. Xue and H. Zhang) independently. To assess the efficacy and safety of NOACs versus warfarin in Asian patients with AF, we included the following clinical outcomes: (1) thromboembolic events, including stroke or systemic embolism (SSE), ischemic stroke, and myocardial infarction; (2) major bleeding, intracranial bleeding, and gastrointestinal bleeding; and (3) all-cause death. The methodological quality of RCTs was evaluated for the bias risk according to the Cochrane risk of bias assessment tool, whereas the Newcastle-Ottawa Scale tool was applied to evaluate the study quality for the observational studies.

All of the statistical analyses were performed by using the Review Manager 5.3 software (the Nordic Cochrane Center, Rigshospitalet, Denmark) and Stata software (version 12.0, Stata Corp LP, College Station, TX). Full details of the literature search strategy, inclusion and exclusion criteria, data abstraction, quality assessment, and statistical analysis were presented in the online-only Data Supplement.

Results

Study Selection

The process of literature retrieval and screening is presented in Figure I in the online-only Data Supplement. A total of 7565 studies were initially retrieved through the electronic searches. No additional studies were added after we searched the reference lists of previous reviews.[21–25,27,28] A total of 1213 studies were excluded based on the duplicated publications. In the screenings of titles and abstracts, 2267 studies were excluded because they only included non-Asians, or were certain publication types, or evaluated AF patients complicating other diseases or interventions. Subsequently, the 65 remaining articles were reviewed in more detail. As shown in Table II in the online-only Data Supplement, 39 studies were excluded because (1) studies not reporting the matched or adjusted risk ratios (RRs) and its corresponding 95% CIs (n=6); (2) studies not using warfarin as a reference (n=13); (3) the efficacy and safety outcomes did not meet with the pre-established criterion (n=8); and (4) participants had a substantial overlap (n=12). Finally, a total of 26 studies (5 subanalyses of RCTs[13–15,17,20] and 21 observational cohorts) were included.

The baseline characteristics of 26 included studies are shown in Table III in the online-only Data Supplement. For the quality assessment, all of the 5 NOAC trials had a low risk of bias (Table IV in the online-only Data Supplement), whereas all of the 21 observational studies had a moderate-to-high quality with a Newcastle-Ottawa Scale score of ≥6 points (Table V in the online-only Data Supplement).

Efficacy and Safety of NOACs Versus Warfarin Based on RCTs

Efficacy

As shown in Table 1 and Figure II in the online-only Data Supplement, compared with warfarin use, the use of NOACs was significantly associated with decreased risks of SSE (RR, 0.73; 95% CI, 0.59–0.90) in Asians, but not in non-Asians (RR, 0.90; 95% CI, 0.80–1.03; $P_{interaction}$=0.09). Similar risks of ischemic stroke and myocardial infarction were observed in both Asian and non-Asian groups (both $P_{interaction}$>0.05). Compared with warfarin, NOACs significantly reduced the rate of all-cause death both in Asian (RR, 0.83; 95% CI, 0.73–0.95) and non-Asian (RR, 0.91; 95% CI, 0.87–0.95) patients ($P_{interaction}$=0.22).

Safety

As shown in Table 1 and Figure III in the online-only Data Supplement, compared with warfarin use, the use of NOACs was significantly associated with reduced risks of major

Table 1. Summary of NOACs Versus Warfarin in Patients With AF Using Randomized Clinical Trials

	All NOACs		Dose of NOACs	
	Asians	Non-Asians	Standard Dose	Low Dose
SSE				
No. of studies	5	4	2	2
RRs and 95% CIs	0.73 (0.59–0.90)	0.90 (0.80–1.03)	0.59 (0.36–0.96)	0.93 (0.71–1.21)
$P_{interaction}$	0.09		0.11	
Ischemic stroke				
No. of studies	4	3	3	2
RRs and 95% CIs	0.86 (0.60–1.22)	1.08 (0.91–1.28)	0.74 (0.54–1.02)	1.26 (0.84–1.88)
$P_{interaction}$	0.25		0.04	
All-cause death				
No. of studies	5	4	2	2
RRs and 95% CIs	0.83 (0.73–0.95)	0.91 (0.87–0.95)	0.76 (0.62–0.94)	0.86 (0.68–1.09)
$P_{interaction}$	0.22		0.45	
MI				
No. of studies	5	4	2	2
RRs and 95% CIs	0.94 (0.66–1.36)	1.08 (0.92–1.26)	0.93 (0.51–1.69)	0.80 (0.43–1.49)
$P_{interaction}$	0.52		0.73	
Major bleeding				
No. of studies	5	4	2	2
RRs and 95% CIs	0.59 (0.48–0.72)	0.80 (0.64–0.99)	0.68 (0.51–0.91)	0.46 (0.30–0.70)
$P_{interaction}$	0.04		0.14	
Intracranial bleeding				
No. of studies	5		2	2
RRs and 95% CIs	0.36 (0.26–0.49)	0.44 (0.34–0.56)	0.35 (0.13–0.98)	0.31 (0.16–0.60)
$P_{interaction}$	0.33		0.84	
Gastrointestinal bleeding				
No. of studies	3	2	2	2
RRs and 95% CIs	0.85 (0.64–1.13)	1.11 (0.76–1.63)	0.31 (0.16–0.60)	0.82 (0.54–1.26)
$P_{interaction}$	0.27		0.70	

AF indicates atrial fibrillation; MI, myocardial infarction; NOACs, non–vitamin K antagonist oral anticoagulants; RR, risk ratio; and SSE, stroke or systemic embolism.

bleeding (Asian: RR, 0.59; 95% CI, 0.48–0.72; non-Asian: RR, 0.80; 95% CI, 0.64–0.99) and intracranial bleeding (Asian: RR, 0.36; 95% CI, 0.26–0.49; non-Asian: RR, 0.44; 95% CI, 0.34–0.56) in both Asian and non-Asian groups. The decrease in major bleeding was more prominent in Asians than that in non-Asians ($P_{interaction}$=0.04). In addition, we found a similar risk of gastrointestinal bleeding in both Asian (RR, 0.85; 95% CI, 0.64–1.13) and non-Asian (RR, 1.1; 95% CI, 0.76–1.63) patients ($P_{interaction}$=0.27).

Subgroup Analysis

The subgroup analysis was performed based on the dose of NOACs (standard dose versus low dose). As shown in Table 1, compared with warfarin users, standard-dose NOAC users had lower risks of SSE, all-cause death, major bleeding, intracranial bleeding, and gastrointestinal bleeding, whereas low-dose NOAC users showed reduced risks of major bleeding and intracranial bleeding but had comparable risks of efficacy outcomes.

Efficacy and Safety of NOACs Versus Warfarin Based on Observational Studies

Efficacy

As presented in Table 2, compared with warfarin use, the use of NOACs was significantly associated with decreased rates of SSE (RR, 0.75; 95% CI, 0.68–0.82; Figure 1), ischemic stroke (RR, 0.70; 95% CI, 0.59–0.83; Figure IV in the online-only Data Supplement), myocardial infarction (RR, 0.74; 95% CI, 0.58–0.93; Figure V in the online-only Data Supplement), and all-cause death (RR, 0.67; 95% CI, 0.59–0.77; Figure 2).

Table 2. Summary of NOACs Versus Warfarin in Patients With AF Using Observational Studies

Items	SSE			All-Cause Death			Major Bleeding			Intracranial Bleeding			Gastrointestinal Bleeding		
	No. of Studies	RRs and 95% CIs	I^2 Statistic	No. of Studies	RRs and 95% CIs	I^2 statistic	No. of studies	RRs and 95% CIs	I^2 statistic	No. of studies	RRs and 95% CIs	I^2 Statistic	No. of Studies	RRs and 95% CIs	I^2 Statistic
All NOACs	16	0.75 (0.68–0.82)	43%	11	0.67 (0.59–0.77)	83%	14	0.63 (0.55–0.73)	65%	6	0.50 (0.43–0.59)	11%	7	0.65 (0.51–0.84)	64%
Type of NOACs															
Dabigatran	8	0.73 (0.64–0.84)	32%	6	0.51 (0.43–0.62)	58%	9	0.63 (0.53–0.76)	39%	5	0.51 (0.43–0.62)	0%	5	0.69 (0.54–0.87)	55%
Rivaroxaban	4	0.81 (0.69–0.94)	43%	3	0.59 (0.49–0.70)	91%	3	0.74 (0.52–1.04)	87%	2	0.55 (0.42–0.72)	0%	…	…	…
Apixaban	4	0.64 (0.58–0.72)	0%	3	0.58 (0.45–0.76)	84%	4	0.58 (0.46–0.72)	69%	2	0.43 (0.29–0.62)	0%	…	…	…
Dosage of NOACs															
Standard dose	6	0.73 (0.57–0.92)	66%	6	0.47 (0.33–0.66)	89%	5	0.65 (0.57–0.75)	6%	4	0.37 (0.27–0.52)	0%	3	0.54 (0.32–0.90)	45%
Low dose	7	0.72 (0.64–0.81)	49%	7	0.68 (0.60–0.77)	73%	6	0.53 (0.40–0.70)	82%	4	0.52 (0.44–0.61)	0%	3	0.76 (0.54–1.06)	73%
Age, y															
<65	3	0.67 (0.46–0.96)	0%	3	0.49 (0.30–0.82)	28%	2	0.49 (0.22–1.07)	0%	3	0.48 (0.27–0.86)	0%	2	0.58 (0.16–2.16)	0%
≥65	9	0.63 (0.50–0.79)	58%	8	0.60 (0.51–0.71)	58%	6	0.51 (0.34–0.75)	64%	10	0.46 (0.38–0.56)	0%	8	0.92 (0.73–1.16)	17%
<75	6	0.68 (0.59–0.78)	0%	6	0.59 (0.44–0.78)	45%	5	0.50 (0.34–0.74)	45%	5	0.42 (0.27–0.63)	0%	4	0.42 (0.21–0.87)	0%
≥75	8	0.63 (0.46–0.86)	75%	6	0.60 (0.51–0.71)	57%	4	0.60 (0.38–0.96)	66%	8	0.49 (0.37–0.65)	19%	6	0.99 (0.80–1.23)	0%
Follow-up time															
<1 y	5	0.70 (0.50–0.96)	68%	4	0.70 (0.49–1.01)	65%	4	0.55 (0.46–0.66)	0%	3	0.49 (0.36–0.65)	0%	2	0.80 (0.55–1.16)	23%
≥1 y	7	0.73 (0.67–0.81)	21%	6	0.63 (0.53–0.74)	66%	9	0.68 (0.56–0.84)	67%	4	0.50 (0.39–0.63)	41%	5	0.60 (0.44–0.83)	70%

AF indicates atrial fibrillation; NOACs, non–vitamin K antagonist oral anticoagulants; RR, risk ratio; and SSE, stroke or systemic embolism.

Safety

As shown in Table 2, compared with the use of warfarin, the use of NOACs was significantly associated with reduced risks of major bleeding (RR, 0.63; 95% CI, 0.55–0.73; Figure 3), intracranial bleeding (RR, 0.50; 95% CI, 0.43–0.59; Figure 4), and gastrointestinal bleeding (RR, 0.65; 95% CI, 0.51–0.84; Figure VI in the online-only Data Supplement).

Sensitivity and Subgroup Analysis

After exclusion of one study at a time, the corresponding results did not change substantially. As shown in Table 2, the subgroup analyses were performed based on the NOAC type (dabigatran, rivaroxaban, edoxaban, and apixaban), NOAC dose (standard dose versus low dose), age (<65 versus ≥65 years or <75 versus ≥75 years), and follow-up time (<1 versus ≥1 year). Compared with warfarin, dabigatran, rivaroxaban, and apixaban had lower or similar rates of thromboembolic and bleeding events. Compared with warfarin users, standard-dose NOAC users had lower risks of SSE, all-cause death, major bleeding, intracranial bleeding, and gastrointestinal bleeding, whereas low-dose NOAC users showed reduced risks of SSE, all-cause death, major bleeding, and intracranial bleeding, but had a comparable risk of gastrointestinal bleeding. In other subgroup analyses based on age, design of study, and follow-up time, NOACs were at least as effective and safe as warfarin for stroke prevention.

Publication Bias

For the meta-analysis of the reported efficacy and safety outcomes, there was seemingly no potential publication bias by inspecting the funnel plots (Figures VII and VIII in the online-only Data Supplement). Consistently, the results from the Egger and Begg tests indicated no publication bias (all $P>0.1$; Figure IX in the online-only Data Supplement).

Discussion

Based on published NOAC trials, the use of NOACs versus warfarin was associated with decreased risks of efficacy (SSE and all-cause death) and safety (major bleeding and intracranial bleeding) outcomes. In addition, compared with warfarin users, standard-dose NOAC users had reduced risks of both efficacy (SSE and all-cause death) and safety (major bleeding, intracranial bleeding, and gastrointestinal bleeding) outcomes, whereas low-dose NOAC users showed decreased rates of safety (major bleeding and intracranial bleeding) outcomes and comparable risks of efficacy outcomes (SSE and all-cause death). Therefore, NOACs (standard dose in particular) might be preferentially indicated in

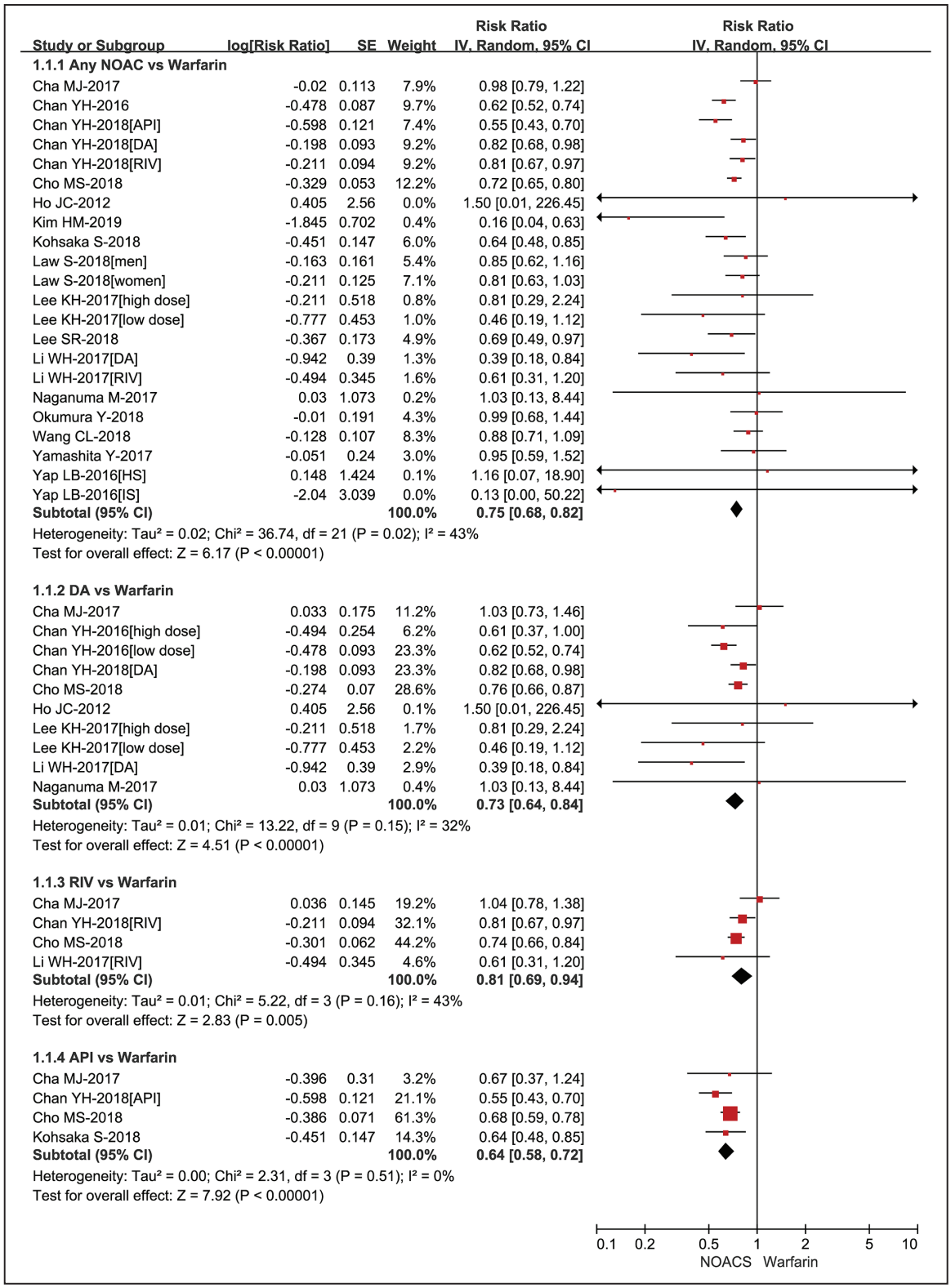

Figure 1. Forest plot for comparing the stroke or systemic embolism of non–vitamin K antagonist oral anticoagulants (NOACs) with warfarin in real-world Asian patients with atrial fibrillation. API indicates apixaban; DA, dabigatran; IV, inverse of the variance; and RIV, rivaroxaban.

Asian patients with AF rather than warfarin. These findings were generally consistent with those from recently published meta-analyses based on the subanalyses of RCTs.[12,18] Notably, our data also suggested that the use of standard-dose NOACs was related to a decrease in gastrointestinal bleeding compared with warfarin use.

Participants in the RCTs do not always represent the broad range of AF patients in real-world daily practice. Evidence from

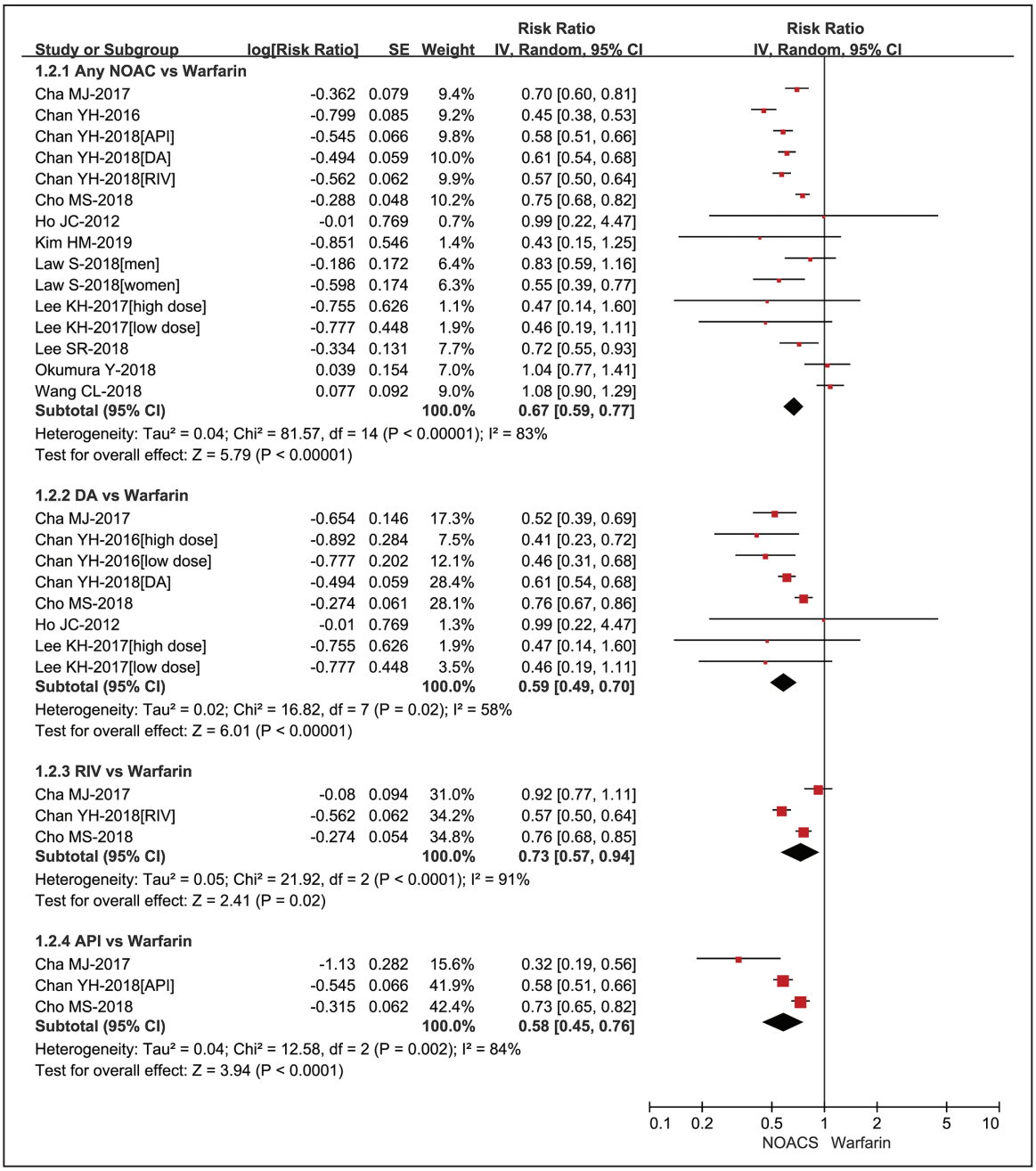

Figure 2. Forest plot for comparing the all-cause death of non–vitamin K antagonist oral anticoagulants (NOACs) with warfarin in real-world Asian patients with atrial fibrillation. API indicates apixaban; DA, dabigatran; IV, inverse of the variance; and RIV, rivaroxaban.

the real-world studies sometimes either complement or contradict the findings from the RCTs. The meta-analyses comparing the efficacy and safety outcomes of NOACs versus vitamin K antagonists for worldwide AF patients in the real-life settings have been published.[21–25] However, whether the use of NOACs is effective and safe in Asians is still exploratory. Recent observational studies have investigated the efficacy and safety of NOACs versus warfarin in Asian patients with AF. To the best of our knowledge, this was the first meta-analysis of observational studies comparing the efficacy and safety outcomes between NOACs and warfarin in Asians. Compared with warfarin use, the use of NOACs (in particular dabigatran) was associated with decreased risks of both efficacy (SSE, ischemic stroke, and all-cause death) and safety (major bleeding, intracranial bleeding, and gastrointestinal bleeding) outcomes. The statistical heterogeneity was high across the included cohorts in some comparisons; however, the corresponding results did not change in the sensitivity analysis. These real-world data were nearly consistent with the aforementioned findings of meta-analysis based on the NOAC trials. In addition, the effect of NOACs versus warfarin on myocardial infarction in real-life Asian patients was meaningful, but the plausible biological reasons for this could be not provided. Further studies would be needed to confirm if it is simply a chance effect.

Consistent with the pooled data of the NOAC trials, we found that standard-dose NOAC users had reduced risks of both efficacy and safety outcomes in real-world patients with AF. Thus,

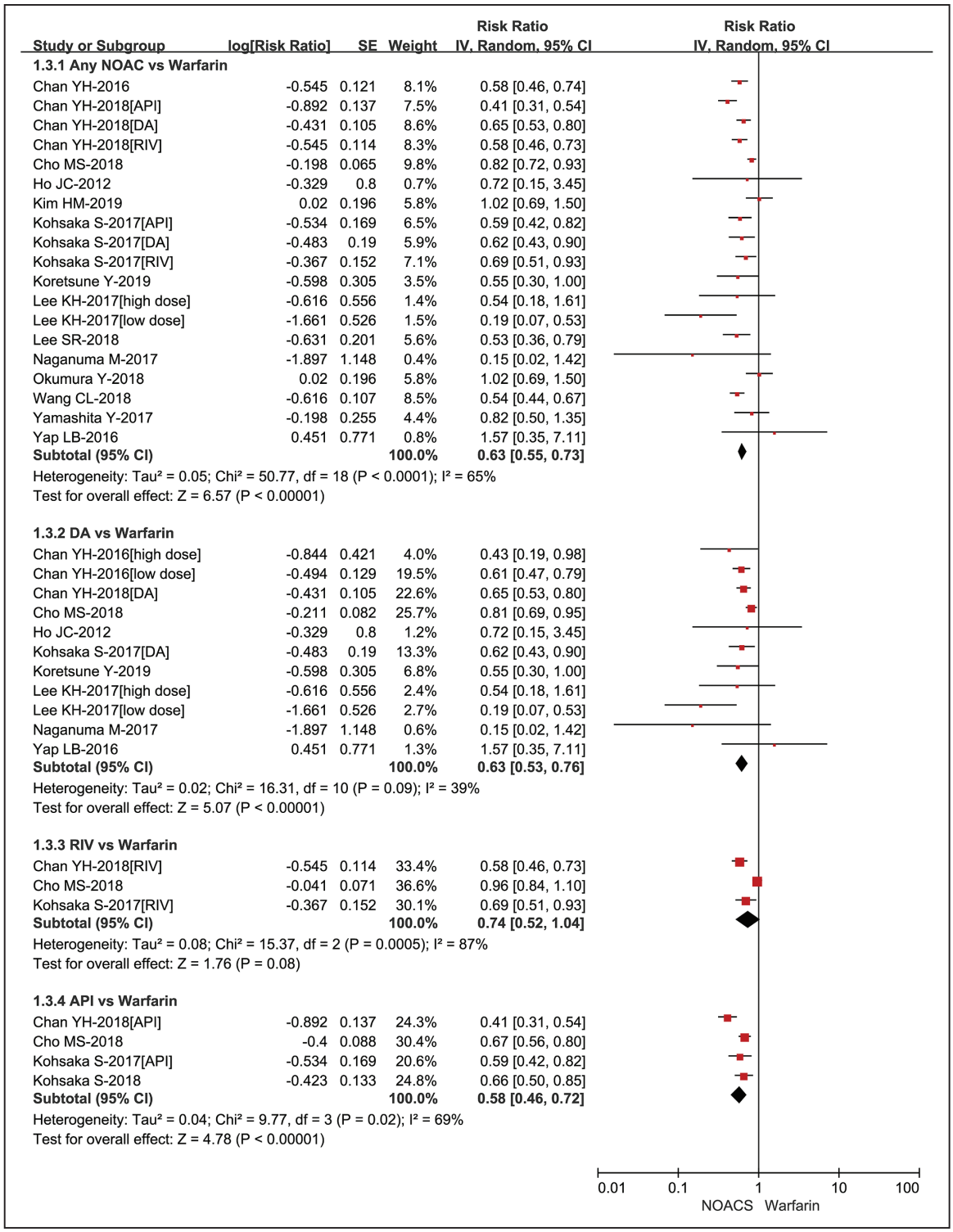

Figure 3. Forest plot for comparing the major bleeding of non–vitamin K antagonist oral anticoagulants (NOACs) with warfarin in real-world Asian patients with atrial fibrillation. API indicates apixaban; DA, dabigatran; IV, inverse of the variance; and RIV, rivaroxaban.

our findings strengthen the recommendation of standard-dose NOACs in Asians.[19] In addition, our data from the NOAC trials indicated that low-dose NOACs versus warfarin showed reduced risks of safety outcomes but comparable thromboembolic risks. By contrast, our real-world data suggested that low-dose NOACs were associated with reduced risks of both efficacy and safety outcomes of interest, indicating both standard-dose and low-dose NOACs might be appealing therapeutic options for stroke prevention in Asian patients. We speculate that the superiority of low-dose NOACs regarding the risk of thromboembolism may be due to the worse quality control of warfarin in real-world settings compared with that in the NOAC trials. Warfarin is commonly under-dosed to maintain a lower target international normalized ratio of 1.5 to 2.5 in the real-world practice in Asia,

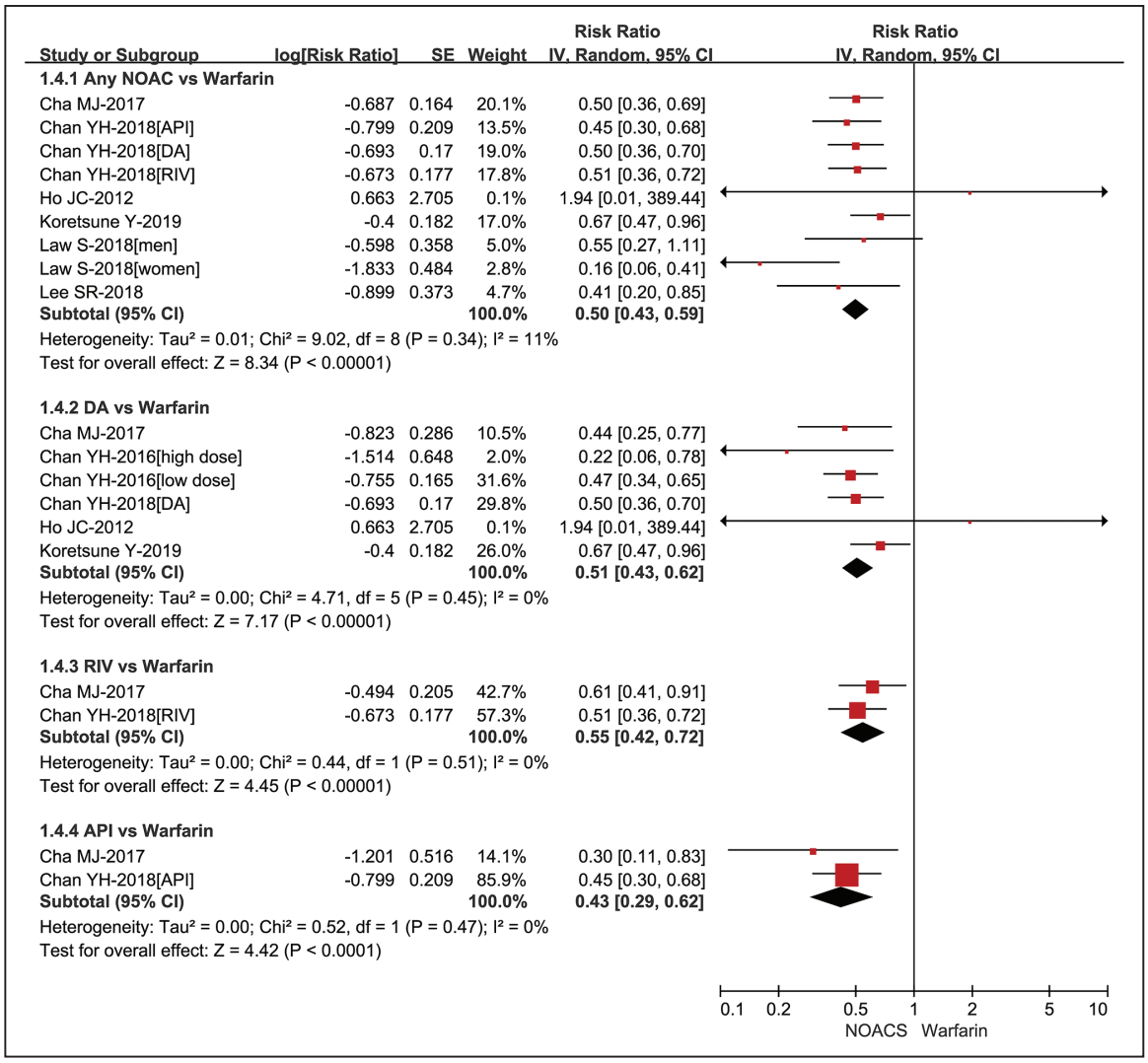

Figure 4. Forest plot for comparing the intracranial bleeding of non–vitamin K antagonist oral anticoagulants (NOACs) with warfarin in real-world Asian patients with atrial fibrillation. API indicates apixaban; DA, dabigatran; IV, inverse of the variance; and RIV, rivaroxaban.

which may reduce the antithrombotic effects. Clinical outcomes would be better in warfarin users with time within therapeutic range ≥60% than in those with time within therapeutic range <60%. Further studies could take time within therapeutic range of warfarin users into consideration to confirm if the advantage of low-dose NOACs over warfarin existed. And before that, NOACs (standard dose in particular) might be preferentially indicated in Asian patients with AF rather than warfarin.

Although our main results included data from >1 NOAC (mostly from dabigatran), the subgroup analysis based on the NOAC type suggested that dabigatran, rivaroxaban, and apixaban had better efficacy and safety profiles than warfarin in Asians with AF. Data on the efficacy and safety profiles of edoxaban in real-world settings are scarce. To date, Lee et al[29] have separately reported the effect of edoxaban versus warfarin in Asians, suggesting that the use of edoxaban has lower risks of thromboembolic and bleeding events. In the subgroups of age ≥65 or ≥75 years, NOACs versus warfarin was associated with reduced risks of both efficacy and safety outcomes of interest, suggesting that the advantage for NOACs over warfarin may persist in the elderly patients.

Asia has the rapidly aging population; and the estimated population with AF and AF-associated stroke will be 72 million and 2.9 million in 2050, respectively.[30] As such, oral anticoagulation therapy is mandatory for AF patients with a high risk of stroke in Asia. In the subanalyses of these NOAC trials, racial differences in baseline characteristics (eg, age, body weight, comorbidities), and rates of clinical outcomes between Asian and non-Asian patients have been reported.[13–16] Of particular note, Asian patients with AF have higher incidences of stroke and bleeding (in particular intracranial bleeding) than non-Asians.[13,14,16,31] Therefore, more evidence should be explored to determine whether the use of NOACs is as effective and safe in Asians as that in non-Asians. Here, our meta-analysis suggested that compared with warfarin, (1) for the NOAC trials, standard-dose NOACs had reduced risks of both thromboembolic and bleeding events, whereas low-dose NOACs showed decreased rates of bleeding events and comparable thromboembolic risks; and (2) for the real-world data, both standard-dose and low-dose NOACs had reduced risks of efficacy and safety outcomes. Therefore, our findings would strengthen the current recommendation of standard-dose NOACs in Asians.[19] However, our real-world data indicated that low-dose

NOACs might also be an appealing therapeutic option for stroke prevention in Asian patients, but further studies should take more information into consideration before any recommendation could be made. Finally, although current publications supported that the use of NOACs was at least noninferior to warfarin in Asians irrespective of the NOAC type, further studies should focus on this issue and confirm the finding in relation to edoxaban. Our meta-analysis on NOAC data from observational studies in the Asians added important information and might help to overcome the under-use of oral anticoagulation therapy in Asian countries.

Limitations

Several limitations should be acknowledged in this meta-analysis. First, the population across the included studies was heterogeneous, which might result in uncontrolled confounding. Second, although the matched or multivariate-adjusted RRs were included, residual confounders might exist due to the nature of real-world data. Second, most of the included observational cohorts were retrospective, and furthermore, high-quality prospective studies could be included to confirm the corresponding results. Third, we did not perform the subgroup analysis based on time within therapeutic range of warfarin users because of the limited data. Finally, the number of included studies in some subgroups was small, limiting the validity of the corresponding findings.

Conclusions

Based on published NOAC trials and real-world studies, the use of NOACs is noninferior to warfarin in Asian patients with AF irrespective of the NOAC type. Both standard-dose and low-dose NOACs may be effective and safe for stroke prevention in Asians.

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Disclosures

None.

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