

Real-world oral anticoagulants for Asian patients with non-valvular atrial fibrillation

A PRISMA-compliant article

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Abstract

Background and Purpose: This study aimed to evaluate the comparative efficacy and safety of 4 non-vitamin K antagonist oral anticoagulants (NOACs) and warfarin in Asians with non-valvular atrial fibrillation in real-world practice through a network meta-analysis of observational studies.

Methods: We searched multiple comprehensive databases (PubMed, Embase, and Cochrane library) for studies published until August 2020. Hazard ratios and 95% confidence intervals were used for the pooled estimates. Efficacy outcomes included ischemic stroke (IS), stroke/systemic embolism (SSE), myocardial infarction (MI), and all-cause mortality, and safety outcomes included major bleeding, gastrointestinal (GI) bleeding, and intracerebral hemorrhage (ICH). The *P* score was calculated for ranking probabilities. Subgroup analyses were separately performed in accordance with the dosage range of NOACs ("standard-" and "low-dose").

Results: A total of 11, 6, and 8 studies were allocated to the total population, standard-dose group, and low-dose group, respectively. In the total study population, edoxaban ranked the best in terms of IS and ICH prevention and apixaban ranked the best for SSE, major bleeding, and GI bleeding. In the standard-dose regimen, apixaban ranked the best in terms of IS and SSE prevention. For major bleeding, GI bleeding, and ICH, edoxaban ranked the best. In the low-dose regimen, edoxaban ranked the best for IS, SSE, GI bleeding, and ICH prevention. For major bleeding prevention, apixaban ranked best.

Conclusions: All 4 NOACs had different efficacy and safety outcomes according to their type and dosage. Apixaban and edoxaban might be relatively better and more well-balanced treatment for Asian patients with non-valvular atrial fibrillation.

Abbreviations: AF = atrial fibrillation, CI = confidence interval, GI = gastrointestinal, ICH = intracerebral hemorrhage, IS = ischemic stroke, NMA = network meta-analysis, NOAC = non-vitamin K antagonist, NVAf = non-valvular atrial fibrillation, PSM = propensity score matching, RCT = randomized clinical trial, SSE = stroke/systemic embolism.

Keywords: network meta-analysis, nonvalvular atrial fibrillation, oral anticoagulants, outcome

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1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and its prevalence is rising continuously with an aging population.^[1] AF is considered an important risk factor for ischemic stroke (IS), congestive heart failure, and all-cause mortality.^[2,3] Although the prevalence and lifetime risk of AF in Asian populations is lower than that in Western populations, the burden in Asian populations may actually be higher due to the rapid increase of the elderly population in most Asian countries and a higher annual risk and burden of stroke, although both populations share similar risk factor profiles.^[1,4,5] In fact, Asians have a tendency to have higher CHADS₂ or CHA₂DS₂-VASc scores than the Caucasian population.^[6,7] This may be explained by the higher proportion of Asian patients with a previous stroke/transient ischemic attack, which is an important predictor^[8] for future stroke. Of note, Asian populations also have a higher risk of hemorrhagic stroke and major bleeding with anticoagulants than non-Asians.^[1] Moreover, good quality of long-term warfarin therapy has not been able to be adequately sustained to prevent recurrent stroke in Asians.^[9] Thus, non-vitamin K antagonist oral anticoagulants (NOACs) have become the standard oral anticoagulants in Asian patients with AF.^[10] Although the effect and safety of NOACs over warfarin seem to be relatively superior in Asians than in non-Asians,^[1,6,10] the bleeding rates with NOACs are also higher in Asian than in non-Asian patients. Therefore, it is critical to investigate which of the 4 NOACs have the best efficacy and safety profiles and to determine the proper dosage for Asian populations in the era of NOACs.

Information gathered from real-world clinical practice is needed to better understand the implementation and impact of specific interventions because data from randomized clinical trials (RCTs) are not always applicable to real-life settings. Although previous pair-wise and network meta-analyses (NMAs)^[11–15] have compared the efficacy and safety outcomes of NOACs and warfarin in Asian patients, there has been strong evidence which of them was decided to be better treatment. Specifically, novel data on edoxaban have not been corroborated, observational and clinical trial datasets have been coalesced, and separate analyses according to dose regimens have not been included in pooled results. Additionally, 3 nationwide claims studies recently have reported real-world direct comparisons in terms of the efficacy and safety of the 4 NOACs versus warfarin in the Japanese,^[16] Korean,^[17] and Taiwanese^[18] populations. Although recent study compared the efficacy and safety of 4 NOACs, including 5 RCTs and 12 observational studies,^[13] it seems at a higher risk of heterogeneity in terms of study design and enrolled population because that study performed pooled analysis of RCTs and non-RCTs from real-world data.

Therefore, we conducted an updated systematic review and NMA to evaluate the comparative efficacy and safety of all 4 NOACs versus warfarin according to dose regimens.

2. Methods

2.1. Data sources and search strategy

We searched multiple comprehensive databases (Pubmed, Embase, and Cochrane library) for studies that compared the effects of NOACs in terms of IS and thromboembolism prevention in Asian populations with non-valvular AF (NVAF). This search was conducted for studies published from the inception of the databases until August 2020 using the following

keywords and their derivatives: “atrial fibrillation,” “warfarin,” “NOAC,” “dabigatran,” “rivaroxaban,” “apixaban,” “edoxaban,” “real-world”, “claim,” and “observational study.” No language limitations were used. The search strategy, which was comprised of keywords and Medical Subject Heading terms, were primarily developed in a PubMed search and then applied to the other searches (Supplemental Digital Content Table I, <http://links.lww.com/MD/G348>). Manual searches were also conducted from the reference lists of the included studies and relevant review articles to find potentially eligible studies. We followed the Preferred Reporting Item for Systematic Reviews and Meta-analysis (PRISMA) extension statement for reporting of systematic reviews incorporating NMA.^[19] As the nature of meta-analysis of published studies, no ethical approval was warranted.

2.2. Study selection, data extraction, and quality assessment

Studies were included if they met the following criteria: observational cohort studies in Asian populations with NVAF that compared the efficacy and safety of oral anticoagulants, which included warfarin and any of the following 4 NOACs: dabigatran, rivaroxaban, apixaban, or edoxaban; reported at least one of the following clinical outcomes: IS, stroke/systemic embolism (SSE), major bleeding, gastrointestinal (GI) bleeding, intracerebral hemorrhage (ICH), myocardial infarction (MI), or all-cause mortality; and the application of the Cox proportional hazard model with or without propensity score matching (PSM), propensity score adjustment or inverse probability of treatment weighting (IPTW). Studies were excluded if enrolled patients had valvular AF, or non-Asian populations were included. The selection of individual studies was independently determined by 2 investigators (JJM and KSM). Data extraction and quality assessments of the included studies were also performed by the same 2 investigators. Any disagreement during study selection, data extraction, or quality assessment was resolved by consensus.

Eligible studies were evaluated for possible overlap according to geographic location, chronological period, sample size, outcome, and type of statistical analysis. For the studies from the same databases with overlapping patients, we opted for the study with the longest follow-up period, the larger sample size, or a recent update.

The publication year, study country, study period, data source, statistical method, number of patients in each treatment arm, type or dosage of the NOACs (ie, total-, standard-, or low-dose), CHA₂DS₂-VASc score, (adjusted) hazard ratios, and 95% confidence intervals (CIs), if possible, for the outcomes of interest were extracted using a pre-determined format. The primary outcomes of efficacy and safety were IS and major bleeding, respectively. The secondary efficacy outcome was SSE, MI, and all-cause mortality, and the secondary safety outcomes were GI bleeding and ICH. Due to variations in the definition and characterization of major bleeding, each original study's definition was used accordingly.

Quality assessments were conducted using the Risk of Bias Assessment Tool for Non-Randomized Studies.^[20]

2.3. Statistical analyses

The NMA was performed based on a frequentist method with random-effects model to compare the relative effects of the 4

NOACs versus warfarin. Outcomes were compared through both direct and indirect or mixed evidence using the hazard ratios and 95% CIs. *P* scores were then created to rank these interventions. For each outcome, the interventions with higher *P* scores were considered more desirable compared to the others.^[21] The hierarchy of the treatments was determined using the *P* score, where a larger *P* score value represented a better rank. Clustered ranking plots using the *P* score were created to summarize 2 different outcomes simultaneously.

The inconsistency of the NMA was assessed in 2 ways: global inconsistency and local inconsistency. Global inconsistency was assessed using the design-by-treatment interaction model to calculate inconsistency in the network as a whole.^[22] Local inconsistency was assessed only when available using a loop-specific approach to calculate the difference between direct and indirect evidence in each closed loop.^[23]

For conventional pair-wise meta-analyses as direct evidence, we measured the pooled effects using the generic inverse variance method with a random-effects model. If at least 2 studies were present, a conventional meta-analysis was performed, that is, each NOAC was compared with the other NOACs or with warfarin. We used Cochrane *Q* and *I*² statistics to estimate the extent of heterogeneity. *I*² percentages of 25%, 50%, and 75% were indicative of low, moderate, and high heterogeneities, respectively.

Subgroup analyses regarding the available clinical outcomes were separately performed according to the dose range of the 4 NOACs (“standard-” and “low-dose”). The total dose included all patient groups regardless of dosage. It was not possible to confirm whether the dosage used was a regular or a reduced dose; therefore, the categories standard-dose and low-dose were used. Because the categorization of standard- and low-dose rivaroxaban was unequal in several studies, rivaroxaban was classified according to the dose criteria defined and applied in each study. Additionally, body weight and serum creatinine data were not available; therefore, label adherence could not be assessed in this study.

We used a comparison-adjusted funnel plot to assess network-wide publication bias. A 2-sided *P* value < .05 was considered statistically significant. An NMA for mixed comparisons was conducted using R version 3.6 software (<http://www.r-project.org>), and a pair-wise meta-analysis for direct comparison was performed using the Comprehensive Meta-Analysis version 3.0 and Review Manager (RevMan) version 5.3.

3. Results

3.1. Study characteristics

Eleven studies were ultimately included in the present analysis (Fig. 1). They were performed in South Korea, Japan, China (Hong Kong), Taiwan, and Malaysia. All those included a warfarin treatment group as a comparison, and 3 studies compared all 4 NOAC treatments to warfarin.^[16–18] One study compared dabigatran and rivaroxaban^[24], and one study compared the efficacy and safety of dabigatran, rivaroxaban, and apixaban.^[25] Of the total 359,107 patients included in this present meta-analysis, 86,687 and 272,420 patients were classified into the warfarin and 4 NOAC treatment groups (dabigatran, n=61,033; apixaban, n=66,967; rivaroxaban, n=108,024; edoxaban, n=36,396), respectively. Low-dose dabigatran, rivaroxaban, apixaban, and edoxaban were administered to 78%, 67%, 57%, and 65% of the patients, respectively. The baseline characteristics of the included studies are listed in Table 1. There were 9 studies^[16–18,24–29] with dabigatran, 6 studies^[16–18,24,25,30] with rivaroxaban, 4 studies^[16–18,25] with apixaban, and 4 studies^[16–18,31] with edoxaban. Five studies^[16–18,25,31] originated from health claims data, and 6 studies^[24,26–30] from single-center registry data. As the primary statistical method, 7 studies^[16–18,25,27,30,31] utilized the Cox proportional hazard model after PSM and 4^[24,26,28,29] utilized a multivariate Cox regression model. In the subgroup analysis according to the NOAC dosage, 6 studies^[16–18,25,30,31] were allocated to

Table 1
Baseline characteristics of the included studies.

	Region	Study period	Data source	Primary statistical method	Total-dose treatments (% of low dose)				Warfarin	CHA ₂ DS ₂ - VASc	Age
					Dabigatran	Rivaroxaban	Apixaban	Edoxaban			
Chan et al, 2019 ^[16]	Taiwan	June 2012 to Dec. 2017	NHI Database	PSM	22,371 (86%)	33,022 (94%)	9952 (64%)	4577 (64%)	19,761	3.6	74.7
Lee et al, 2019 ^[17]	Korea	January 2015 to December 2017	Korean NHI	PSM	17,745 (67%)	35,965 (58%)	22,177 (50%)	15,496 (59%)	25,420	3.56	71.0
Ho et al, 2012 ^[26]	Hong Kong	January 2020 to November 2011	Single-center cohort	Multivariable cox regression	122 (95%)	NA	NA	NA	122	2.4*	70.1
Jeong et al, 2019 ^[30]	Korea	January 2014 to December 2016	Single-center cohort	PSM	NA	804 (51%)	NA	NA	804	3.4	70.9
Naganuma et al, 2016 ^[27]	Japan	March 2011 to December 2013	Single-center cohort	PSM	181 (73%)	NA	NA	NA	181	3.05	69.0
Kohsaka et al, 2020 ^[16]	Japan	March 2011 to July 2018	Health claims data	PSM (s-IPTW)	6925 (76.2%)	16,564 (47.2%)	22,336 (57.3%)	12,262 (75.4%)	15,902	3.8	76
Chan et al, 2016 ^[28]	Hong Kong	2010 to 2013	Single-center cohort	Multivariable cox regression	129 (100%)	NA	NA	NA	442	4.8	84.8
Li et al, 2016 ^[24]	Hong Kong	January 2008 to December 2014	Single-center cohort	Multivariable cox regression	467 (97%)	669 (41%)	NA	NA	963	3.7	73.1
Yap et al, 2016 ^[29]	Malaysia	January 2009 to December 2013	Single-center cohort	Multivariable cox regression	500 (41%)	NA	NA	NA	500	3.05	66.1
Cho et al, 2019 ^[25]	Korea	July 2015 to December 2016	Korean NHI	PSM	12,593 (75%)	21,000 (59%)	12,502 (63%)	NA	10,409	3.58	73.2
Lee et al, 2018 ^[31]	Korea	January 2014 to December 2016	Korean NHI	PSM	NA	NA	NA	4061 (56%)	12,183	3.24	70.6

NHI = National Health Insurance, PSM = propensity score matching, s-IPTW = inverse probability of treatment weighting with stabilized weights, NA = not available.
* Implies CHADS₂ score.

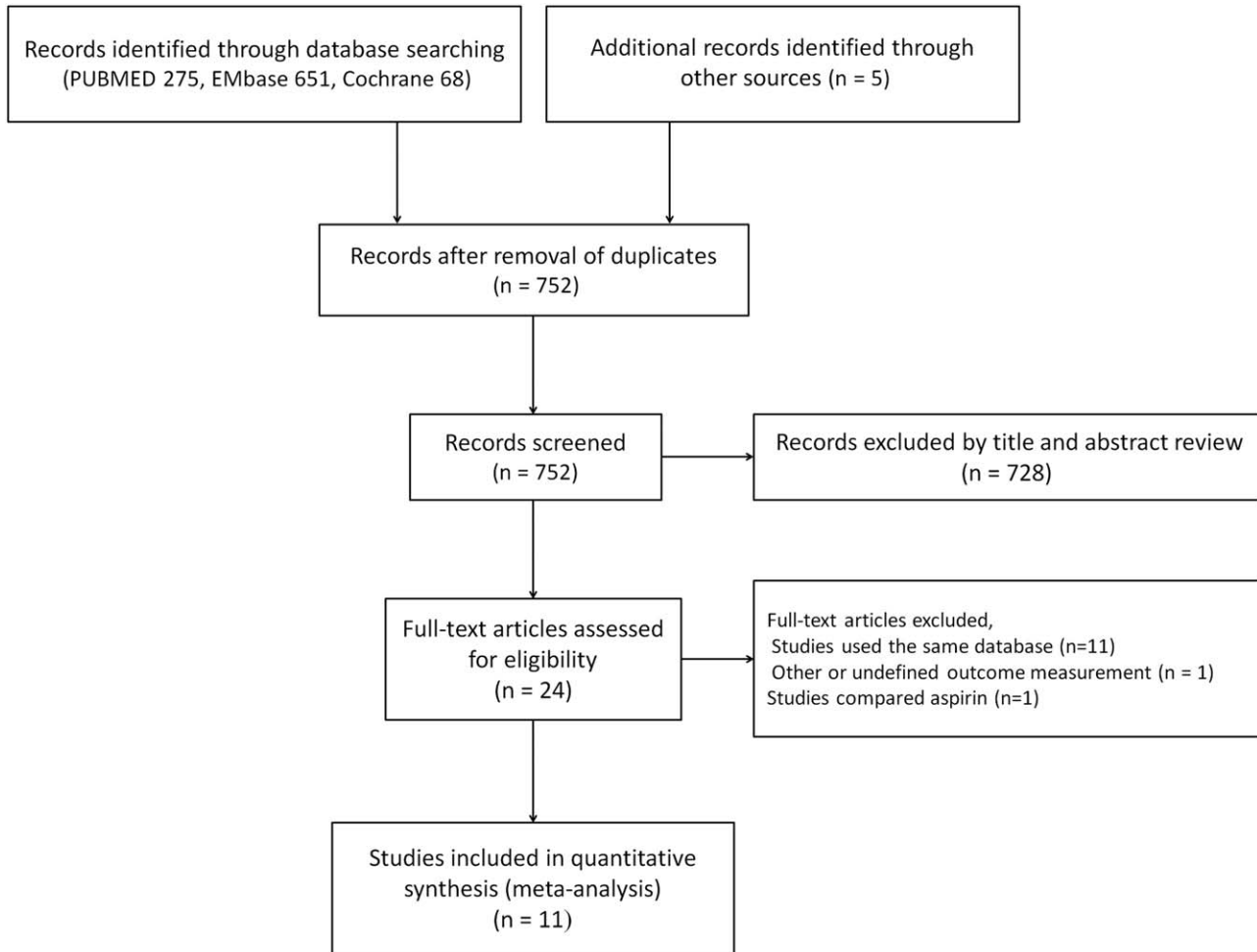


Figure 1. PRISMA chart.

standard-dose regimens, and 8 studies^[16–18,24,25,28,30,31] to low-dose regimens.

3.2. Risk of bias assessment

For the majority of the studies included in our review, there was low risk of bias in the 6 domains (Supplemental Digital Content Figure 1, <http://links.lww.com/MD/G348>). For 2 studies^[26,27]; however, incomplete outcome data were associated with a high risk of bias. In 4 studies^[26–29], the risk of bias was unclear for the selective outcome reporting and/or incomplete outcome data items because there was insufficient information to determine the level of risk.

3.3. Comparisons between total-dose NOACs and Warfarin

Network plots under each outcome are shown in Supplemental Digital Content Figure 2, <http://links.lww.com/MD/G348>. Of the 11 studies, 7^[16–18,24,28–30] included 1 direct comparison between the 5 different treatments concerning IS. There were 5 studies^[16,18,25,27,30] with no direct comparisons in terms of SSE, 7 studies^[16–18,26,27,29,30] with 2^[17,18] direct comparisons concerning major bleeding, 6^[16–18,26,29,30] studies with 2^[17,18]

direct comparisons concerning GI bleeding, 6^[16–18,26,28,30] studies with 1^[17] direct comparison concerning ICH, 2^[18,30] studies with no direct comparison concerning MI, and 3^[25,30,31] studies with no direct comparison concerning all-cause mortality.

3.4. Ischemic stroke

All 4 NOACs significantly reduced the risk of IS in mixed comparisons with warfarin (Fig. 2A). Apixaban was associated with a lower risk compared with dabigatran and rivaroxaban (Table 2). Edoxaban also had a lower risk than rivaroxaban. Dabigatran had a higher risk than edoxaban. Comparisons between the other NOACs were insignificant. In direct comparisons to warfarin, all NOACs except dabigatran had a statistically lower risk of IS with low heterogeneity (Table 2). However, because IS was not directly compared between the 4 NOACs in the included studies, these data could not be assessed.

3.5. Stroke/systemic embolism

All 4 NOACs significantly reduced the risk of SSE in mixed comparisons with warfarin (Fig. 2B). There was no statistical difference between the NOACs except for the marginal lower risk of SSE with apixaban compared with dabigatran (Table 2). Direct

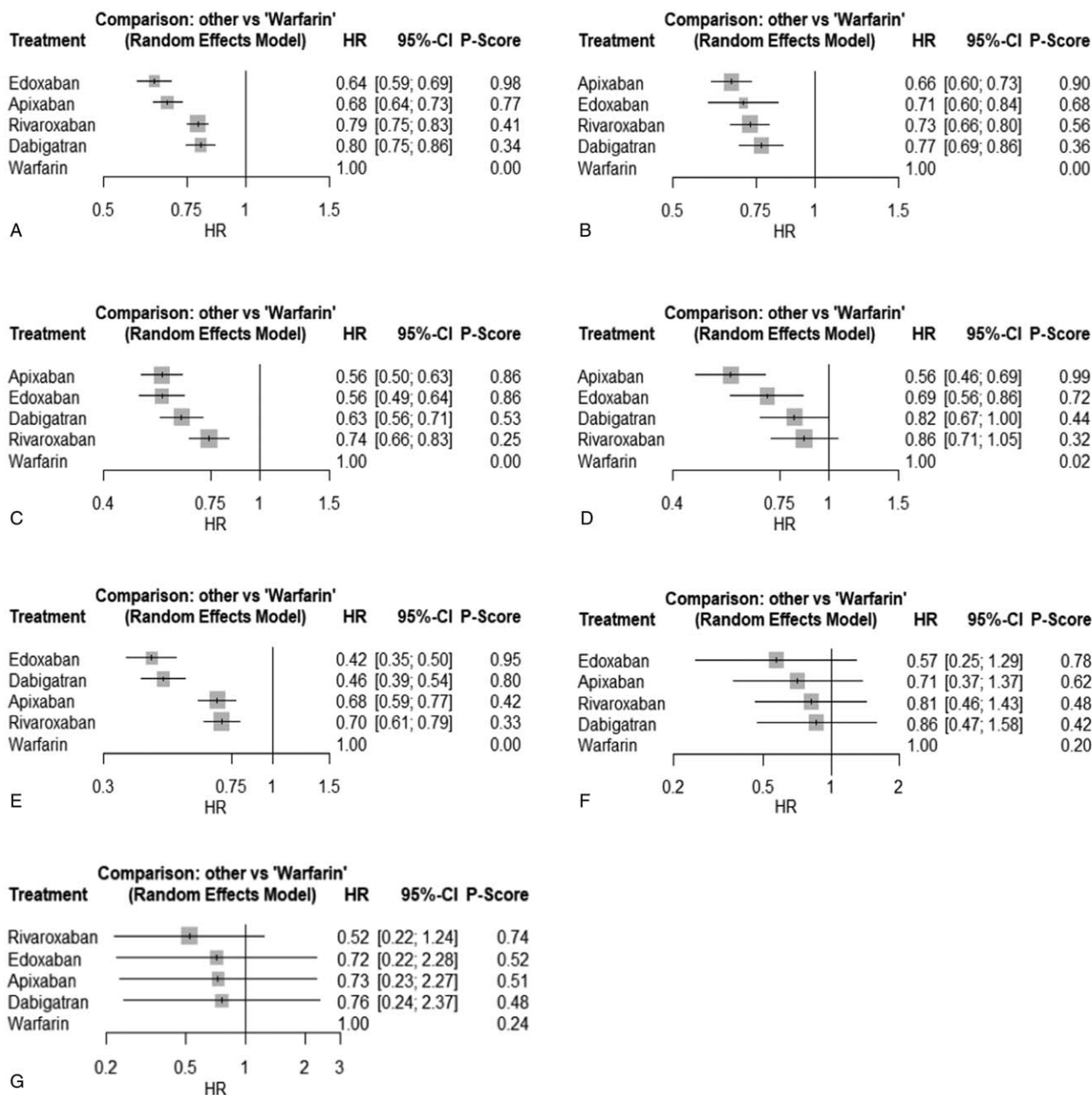


Figure 2. Forest plots of total dose NOACs and warfarin. (A) Ischemic stroke. (B) Stroke/systemic embolism, (C) Major bleeding. (D) Gastrointestinal bleeding. (E) Intracerebral hemorrhage. (F) Myocardial infarction. (G) All-cause mortality.

comparisons demonstrated that the 4 NOACs were superior to warfarin in terms of SSE (Table 2). However, there were no data concerning direct comparisons of the risk of SSE between all the NOACs; therefore, these data could not be assessed.

3.6. Major bleeding

All 4 NOACs were significantly associated with a lower risk of major bleeding compared with warfarin (Fig. 2C). Additionally, apixaban, edoxaban, and dabigatran were associated with a lower rate compared with rivaroxaban (Table 2). Comparisons between the other NOACs were insignificant. In direct comparisons to warfarin, the 4 NOACs showed similar trends

with a wide range of heterogeneity (Table 2). In addition, there was significantly less major bleeding with apixaban than with rivaroxaban.

3.7. GI bleeding

Apixaban and edoxaban significantly reduced the risk of GI bleeding compared with warfarin (Fig. 2D). Dabigatran and rivaroxaban had a marginal tendency toward lower GI bleeding compared with warfarin. Apixaban had a lower risk compared with dabigatran and rivaroxaban (Table 2). Edoxaban was comparable to the other NOACs. In direct comparisons, apixaban and rivaroxaban reduced the risk of GI bleeding compared with

Table 2
Comparisons between the 4 NOACs and warfarin according to outcomes.

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Ischemic stroke					
Apixaban	Ref.	0.85 (0.78–0.92)	1.07 (0.97–1.17)	0.86 (0.80–0.93)	0.68 (0.64–0.73)
Dabigatran	–	Ref.	1.26 (1.14–1.38)	1.02 (0.94–1.09)	0.80 (0.75–0.86)
Edoxaban	–	–	Ref.	0.81 (0.74–0.88)	0.64 (0.59–0.69)
Rivaroxaban	–	–	–	Ref.	0.79 (0.75–0.83)
Warfarin	0.79 (0.77–0.81)	0.75 (0.60–0.94) [†]	0.67 (0.59–0.76)	0.79 (0.77–0.81)	Ref.
Stroke/Systemic embolism					
Apixaban	Ref.	0.86 (0.75–1.00)	0.94 (0.77–1.15)	0.91 (0.80–1.05)	0.66 (0.60–0.73)
Dabigatran	–	Ref.	1.09 (0.89–1.33)	1.06 (0.92–1.22)	0.77 (0.69–0.86)
Edoxaban	–	–	Ref.	0.97 (0.80–1.18)	0.71 (0.60–0.84)
Rivaroxaban	–	–	–	Ref.	0.73 (0.66–0.80)
Warfarin	0.67 (0.60–0.73)	0.77 (0.69–0.86)	0.71 (0.60–0.84)	0.73 (0.66–0.80)	Ref.
Major bleeding					
Apixaban	Ref.	0.89 (0.78–1.03)	1.00 (0.86–1.16)	0.76 (0.66–0.87)	0.56 (0.50–0.63)
Dabigatran	0.75 (0.49–1.16) [‡]	Ref.	1.12 (0.96–1.31)	0.85 (0.74–0.98)	0.63 (0.56–0.71)
Edoxaban	1.01 (0.85–1.22)	–	Ref.	0.76 (0.65–0.88)	0.56 (0.49–0.64)
Rivaroxaban	0.75 (0.66–0.85)	–	–	Ref.	0.74 (0.66–0.83)
Warfarin	0.56 (0.42–0.75) [‡]	0.63 (0.56–0.70)	0.58 (0.45–0.74) [†]	0.68 (0.56–0.82) [†]	Ref.
GI bleeding					
Apixaban	Ref.	0.69 (0.54–0.87)	0.81 (0.63–1.03)	0.65 (0.51–0.82)	0.56 (0.46–0.69)
Dabigatran	0.53 (0.21–1.31) [‡]	Ref.	1.17 (0.91–1.51)	0.94 (0.74–1.20)	0.82 (0.67–1.00)
Edoxaban	0.83 (0.67–1.04)	–	Ref.	0.8 (0.63–1.03)	0.69 (0.56–0.86)
Rivaroxaban	0.56 (0.32–0.99) [†]	–	–	Ref.	0.86 (0.71–1.05)
Warfarin	0.56 (0.35–0.88) [‡]	0.82 (0.62–1.07) [‡]	0.65 (0.41–1.04) [‡]	0.83 (0.76–0.91)	Ref.
ICH					
Apixaban	Ref.	1.47 (1.24–1.75)	1.60 (1.32–1.95)	0.97 (0.83–1.13)	0.68 (0.59–0.77)
Dabigatran	–	Ref.	1.09 (0.88–1.34) [†]	0.66 (0.56–0.78)	0.46 (0.39–0.54)
Edoxaban	–	–	Ref.	0.61 (0.50–0.73)	0.42 (0.35–0.50)
Rivaroxaban	–	–	–	Ref.	0.70 (0.61–0.79)
Warfarin	0.65 (0.52–0.82)	0.45 (0.36–0.57)	0.50 (0.31–0.78) [†]	0.65 (0.52–0.82)	Ref.
MI					
Apixaban	Ref.	0.83 (0.34–2.01)	1.25 (0.44–3.55)	0.87 (0.37–2.07)	0.71 (0.37–1.37)
Dabigatran	–	Ref.	1.51 (0.55–4.17)	1.06 (0.46–2.42)	0.86 (0.47–1.58)
Edoxaban	–	–	Ref.	0.70 (0.26–1.89)	0.57 (0.25–1.29)
Rivaroxaban	–	–	–	Ref.	0.81 (0.46–1.43)
Warfarin	–	–	–	0.814(0.46–1.43) [†]	Ref.
All-cause Mortality					
Apixaban	Ref.	0.96 (0.19–4.79)	1.02 (0.20–5.17)	1.40 (0.33–5.83)	0.73 (0.23–2.27)
Dabigatran	–	Ref.	1.06 (0.21–5.38)	1.45 (0.35–6.06)	0.76 (0.24–2.37)
Edoxaban	–	–	Ref.	1.37 (0.32–5.82)	0.72 (0.22–2.28)
Rivaroxaban	–	–	–	Ref.	0.52 (0.22–1.24)
Warfarin	–	–	–	0.52 (0.22–1.24) [§]	Ref.

Each of the results was calculated by comparing oral anticoagulant regimens in the column with those in the row. The top half of the table depicts the results of mixed comparisons (network meta-analysis) with the column as a reference, whereas the bottom half of the table depicts the results of direct comparisons (pair-wise meta-analysis) with the row as a reference. Statistically significant HRs are presented in bold. For direct comparisons, heterogeneity is presented ([†] for low, [‡] for moderate, and [§] for high) — = no direct comparison, GI = gastrointestinal, ICH = intracerebral hemorrhage, MI = myocardial infarction, NOACs = non-vitamin K antagonists.

warfarin. Apixaban was associated with significantly less GI bleeding compared with rivaroxaban (Table 2).

3.8. Intracerebral hemorrhage

All 4 NOACs had significantly reduced risks of ICH in mixed comparisons with warfarin (Fig. 2E). However, dabigatran and edoxaban have lower risk compared to rivaroxaban. And apixaban has a higher risk of ICH compared to dabigatran and edoxaban (Table 2). The 4 NOACs were superior to warfarin in direct comparisons (Table 2). However, there were no data directly comparing the 4 NOACs.

3.9. Myocardial infarction

All 4 NOACs did not significantly reduce MI in mixed comparisons with warfarin (Fig. 2F). In direct comparison, rivaroxaban was comparable to warfarin with low heterogeneity (Table 2).

3.10. All-cause mortality

In mixed comparisons, all 4 NOACs did not significantly reduce all-cause mortality compared to warfarin (Fig. 2G). In direct comparison, there was no significant difference between rivaroxaban and warfarin with high heterogeneity (Table 2).

3.11. Clustered ranking of outcomes between the 4 NOACs and warfarin

With regard to the prevention of IS, edoxaban ranked the best and followed by apixaban (*P* scores .98 and .77, respectively) (Fig. 2A). In SSE, *P* score was highest in the apixaban followed by edoxaban (*P* scores .90 and .68, respectively) (Fig. 2B). With regard to the prevention of major bleeding, apixaban and edoxaban ranked the best and second best (*P* scores .86, and .86, respectively) (Fig. 2C). For prevention of GI bleeding, apixaban ranked the best and followed by edoxaban (*P* scores .99 and .72, respectively) (Fig. 2D). With regard to the prevention of ICH, edoxaban and dabigatran ranked the best and second best (*P* scores .95 and .80, respectively) (Fig. 2E). A total of 6 clustered ranking plots were presented using the *P* score in combination with one of the efficacy outcomes (IS or SSE) and one of safety outcomes (major bleeding, GI bleeding, or ICH) (Fig. 3). Edoxaban and apixaban were generally considered to be good balanced options in terms of efficacy and safety outcomes. Dabigatran, with the second highest *P* score, appeared to be superior in ICH prevention.

3.12. Subgroup analysis

3.12.1. Comparisons between standard-dose NOACs and warfarin. Six studies^[16–18,25,30,31] were included, and network plots for each outcome are presented in Supplemental Digital

Content Figure 3, <http://links.lww.com/MD/G348>. Compared with warfarin, all the NOACs were associated with a lower risk of IS and major bleeding (Fig. 4). Apixaban, dabigatran, and rivaroxaban had a lower risk of SSE than warfarin. The NOACs also had superior safety profiles compared with warfarin: apixaban and edoxaban in terms of GI bleeding and apixaban, dabigatran, and rivaroxaban in terms of ICH. Although not significant, edoxaban trended toward a lower risk of SSE; dabigatran and rivaroxaban toward a lower risk of GI bleeding; and rivaroxaban toward a lower risk of ICH (Supplemental Digital Content Table 2, <http://links.lww.com/MD/G348>). Compared with rivaroxaban, apixaban was associated with a lower risk of IS, SSE, major bleeding, and GI bleeding; edoxaban was associated with a lower risk of major bleeding, GI bleeding, and ICH; and dabigatran was associated with a lower risk of ICH. Apixaban was associated with significantly less GI bleeding than dabigatran. With regards to MI, all NOACs did not significantly reduce MI compared with warfarin. In direct comparisons between the 4 NOACs and warfarin (Supplemental Digital Content Table 2, <http://links.lww.com/MD/G348>), apixaban was associated with a lower risk of IS, SSE, and major bleeding. Edoxaban was associated with a lower risk of GI bleeding and ICH. Rivaroxaban was associated with a lower risk of IS and SSE. Dabigatran was associated with a lower risk of IS, SSE, major bleeding, and ICH.

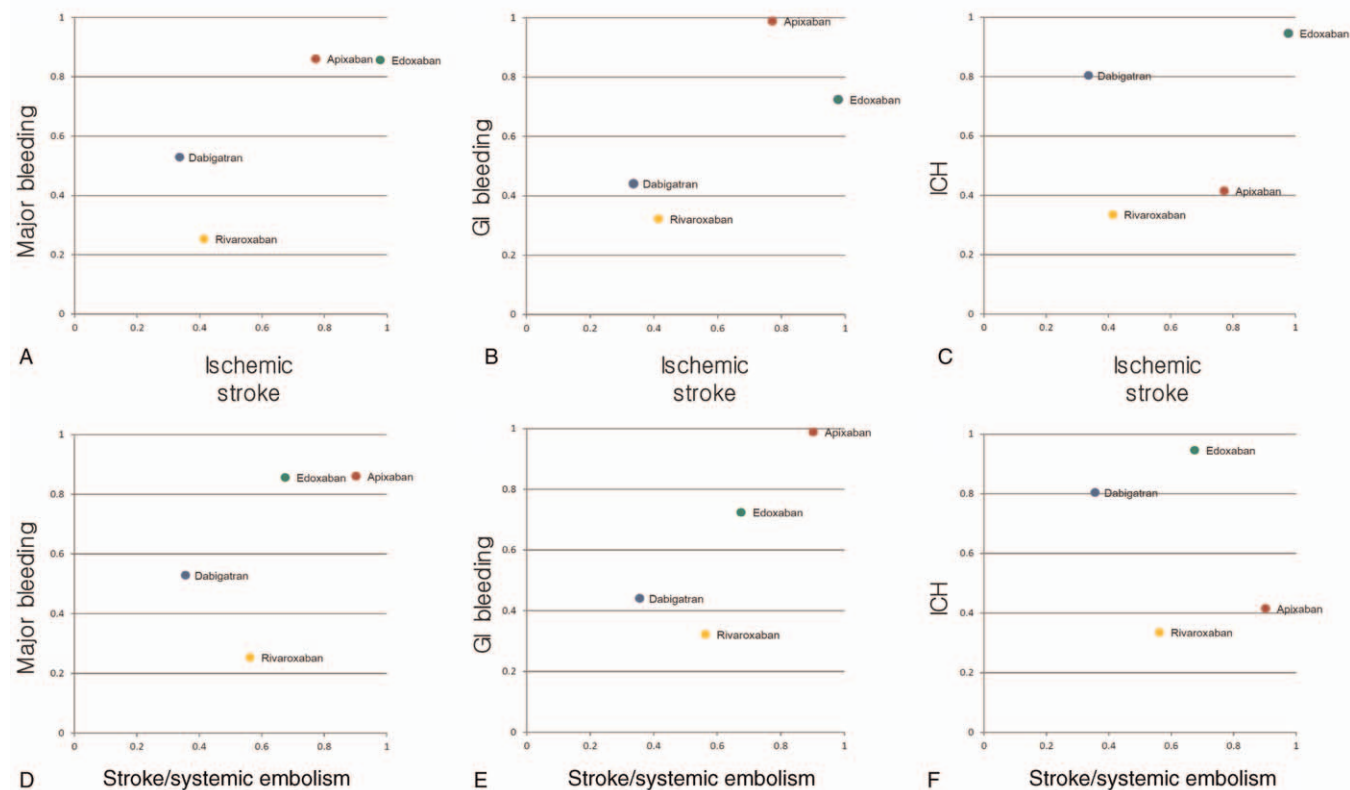


Figure 3. Clustered ranking plots. *P* score values were used to represent the probabilities of each treatment being ranked highest for each outcome. The treatments located in the upper right corner have more efficacy and safety than the other non-Vitamin K antagonist oral anticoagulants. GI = gastrointestinal, ICH = intracerebral hemorrhage.

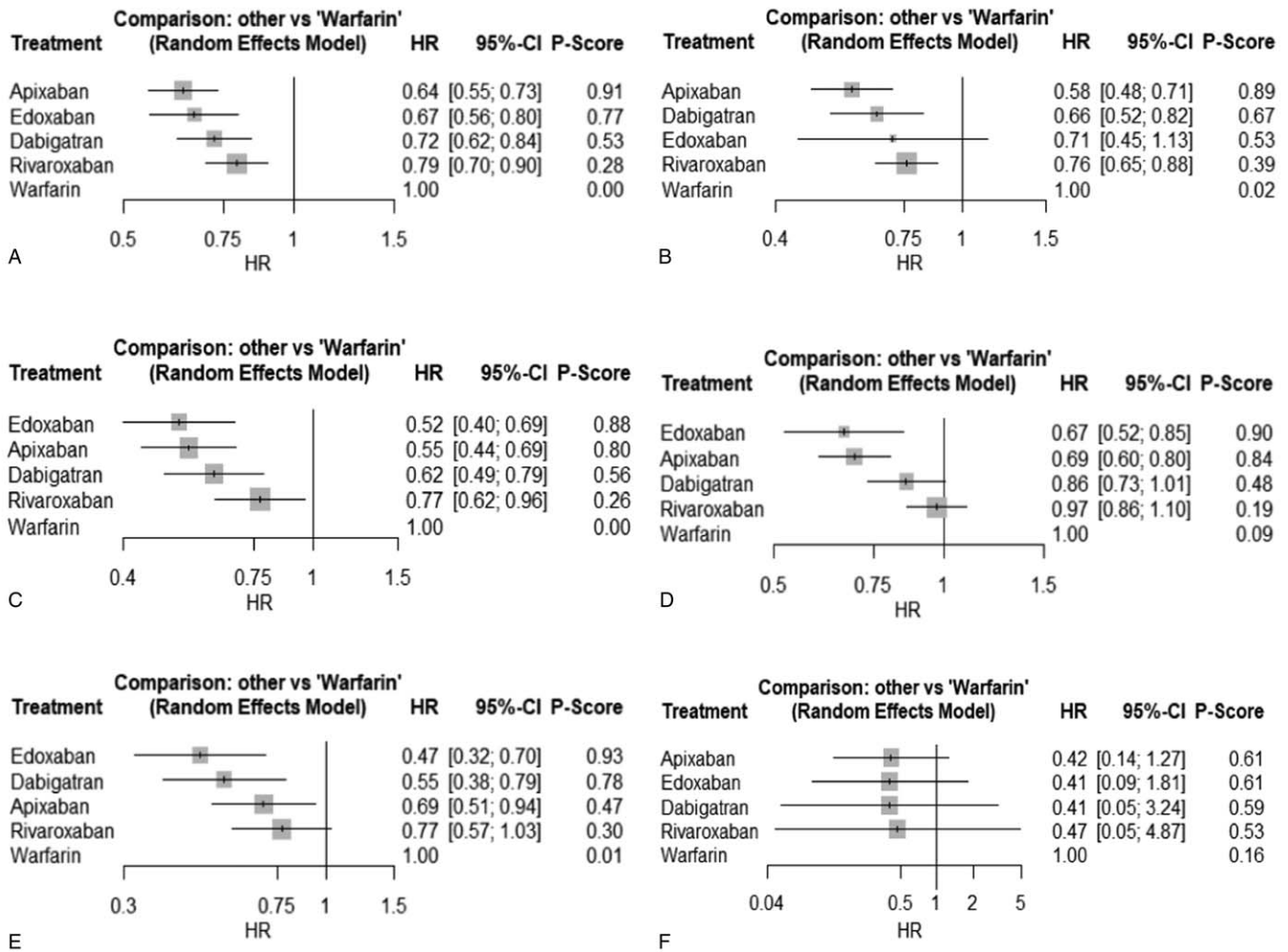


Figure 4. Forest plots of standard-dose NOACs and warfarin. (A) Ischemic stroke. (B) Stroke/systemic embolism. (C) Major bleeding. (D) Gastrointestinal bleeding. (E) Intracerebral hemorrhage. (F) Myocardial infarction.

Apixaban ranked highest in terms of efficacy (IS, SSE and MI), whereas edoxaban ranked highest in terms of safety. Dabigatran had the second highest *P* score for IS and ICH.

3.12.2. Comparisons between 4 low-dose NOACs and warfarin. Eight studies^[16–18,24,25,28,30,31] were included, and network plots for each outcome are presented in Supplemental Digital Figure 4, <http://links.lww.com/MD/G348>. Compared with warfarin, all 4 NOACs were associated with a lower risk of SSE. Dabigatran and rivaroxaban were associated with a lower risk of IS; apixaban with a lower risk of major bleeding; and dabigatran, edoxaban, and rivaroxaban with a lower risk of ICH (Fig. 5). In mixed comparisons between the 4 NOACs, there was no significant difference between them (Supplemental Digital Table 3, <http://links.lww.com/MD/G348>). When directly compared with warfarin, the 4 NOACs ranked higher for IS and SSE (Supplemental Digital Table 3, <http://links.lww.com/MD/G348>). However, only apixaban was associated with a lower risk of major bleeding. All the NOACs except apixaban were associated with a lower risk of ICH. No comparison between all 4 of the NOACs was found.

Edoxaban ranked highest in terms of IS, SSE, GI bleeding, and ICH prevention and the second highest in terms of major bleeding

prevention; however, IS, major bleeding, and GI bleeding prevention were all nonsignificant. For major bleeding prevention, apixaban had the highest *P* score. Dabigatran ranked second in IS and ICH prevention.

3.12.3. Assessment of heterogeneity and inconsistency in NMA. There was no significant global or local inconsistency between the direct and indirect estimates in IS and ICH. With regard to major bleeding and GI bleeding, global inconsistency was observed, whereas local inconsistency was not. Global inconsistency was not observed in SSE and MI; however, local inconsistency was not performed due to an incomplete network between the drugs. With regard to all-cause mortality, global inconsistency was observed, whereas local inconsistency was not acquired due to an incomplete network between the drugs (Supplemental Digital Content Figure 2, <http://links.lww.com/MD/G348>). For standard-dose regimens, global and local inconsistencies were not observed for any of the outcomes except SSE and MI. In SSE and MI, global inconsistency was not observed; however, local inconsistency was not acquired due to incomplete network between the drugs (Supplemental Digital Content Figure 3, <http://links.lww.com/MD/G348>). For the low-dose regimen, global inconsistency was not observed for IS, SSE,

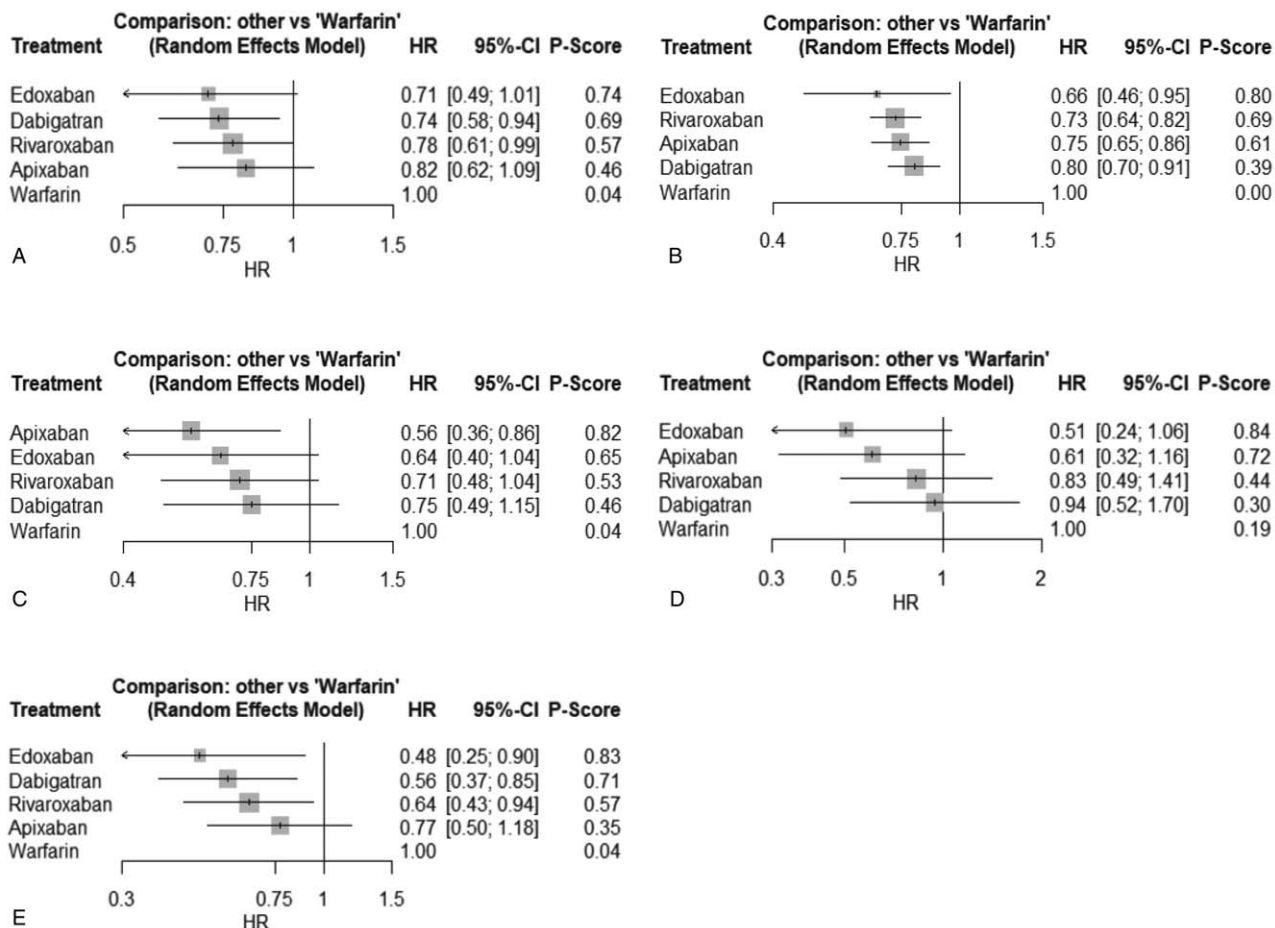


Figure 5. Forest plots of low-dose NOACs and warfarin. (A) Ischemic stroke. (B) Stroke/systemic embolism. (C) Major bleeding. (D) Gastrointestinal bleeding. (E) Intracerebral hemorrhage.

or ICH. Local inconsistencies were not observed for any outcome due to incomplete networks between the drugs (Supplemental Digital Content Figure 4, <http://links.lww.com/MD/G348>).

3.12.4. Assessment of publication bias. The Begg-Mazumdar rank correlation test showed no significant publication bias in any meta-analysis (all *P* values > .05) except for major bleeding (*P* = .01) for total-dose and GI bleeding (*P* = .02) for standard-dose regimens. We could not perform a publication bias test for GI bleeding at low dose (*n* = 4), MI at total (*n* = 2) and standard doses (*n* = 2), and all-cause mortality at total dose (*n* = 3) due to the small number of included studies.

4. Discussion

In the present study, we have provided updated efficacy and safety profiles for all 4 NOACs with >350,000 Asian patients with NVAF from real-world studies. All 4 NOACs had better efficacy (IS and SSE) and safety (major bleeding, GI bleeding, and ICH) than warfarin in the total study population. Similar trends were sustained when standard- and low-dose regimens of the 4 NOACs were compared with warfarin. To the best of our knowledge, we have demonstrated for the first time that apixaban and edoxaban might be relatively better and more well-balanced

treatment options for Asian patients with NVAF, irrespective of dose regimens.

Previous NMA has reported better efficacy and/or safety with apixaban compared with dabigatran and rivaroxaban among Asians with NVAF, although these studies did not include edoxaban.^[15] Recent NMA has also reported that apixaban is superior to other NOACs in terms of reducing SSE, whereas edoxaban is safer than other NOACs.^[13] Another pair-wise meta-analysis^[11] in Asian populations and NMA^[32] based on Asian and Western populations also found that apixaban had the most favorable balance of safety and efficacy. These findings were consistent with our results, especially in terms of the comparative advantage of apixaban in the standard-dose regimen. Additionally, in the apixaban group, the higher proportion of standard dose treatment (43%) may be partial explanation of better outcomes than dabigatran or rivaroxaban.

With regard to the beneficial effect of edoxaban over warfarin, dabigatran, and rivaroxaban, there might be several explanations. In the ENGAGE AF-TIMI 48 substudy, standard-dose edoxaban had better outcomes for SSE events than the well-managed warfarin group irrespective of ethnicity, whereas the same dose of edoxaban in Asians showed a more favorable but nonsignificant trend compared with that in Westerners with respect to IS.^[33] In our study, edoxaban showed a better protective effect for IS compared with warfarin, dabigatran, and

rivaroxaban. Indeed, edoxaban was the most effective in terms of safety profiles. One possible reason is that our study only included Asians in real-world settings. Although we could not evaluate TTR in the warfarin group from this study, it is possible that warfarin control was relatively poor in these real-world populations, as has been reported in previous studies.^[1,34,35] The difference in the effects of edoxaban and warfarin could be intensified in real-world datasets. In addition, because Asian patients have lower body weight and body mass index than Western patients, there is a possibility that the preserved efficacy and better safety profile are due to lower trough concentrations and anti-Factor Xa activity even at standard doses of edoxaban. In fact, a higher proportion of standard dose edoxaban was observed in this study; 35% of patients were prescribed standard-dose edoxaban, whereas 22% and 33% of patients were prescribed standard-dose dabigatran and rivaroxaban, respectively. Moreover, a reduction in dose could preserve the efficacy of edoxaban while increasing its safety.^[36]

The significance and magnitude of low-dose NOACs on outcomes appear to be diminished compared with standard-dose regimens. In fact, only apixaban reduced major bleeding and no NOACs reduced the risk of GI bleeding. In addition, only low-dose dabigatran and rivaroxaban reduced the risk of IS, in contrast to the effect of standard-dose regimens of all the NOACs. This can be attributed to the relatively small sample size and subsequent wide range of CIs when each drug and warfarin were compared. Most importantly, this might be associated with some immeasurable confounding factors such as decisions made by physicians. Physicians often use low-dose NOAC for patients with a high risk of bleeding, and this preference is more reflected in studies using real-world data. Although reducing the dose of NOACs might be considered a way to increase safety by lowering the risk of bleeding in fragile patients, off-label underdosing of NOACs has been shown to be associated with an increased risk of thrombotic events including stroke or systemic embolism, without any safety benefit.^[37–39]

Our research has several strengths compared with previous NMAs. First, our NMA is based on the latest Korean, Taiwanese, and Japanese claims data directly evaluating the efficacy and safety of 4 NOACs versus warfarin in real-life situations with head-to-head comparisons. Second, to reduce the influence of confounding factors in real-world data, our analysis was based on studies comparing warfarin and the 4 NOACs using PSM or multivariate analyses. Third, this was the first NMA performed according to NOAC dosages: subgroup analyses were performed to compare the effect of NOACs versus warfarin according to standard- and low-dose groups.

Our study had some limitations. First, since this study is an NMA using real-world data, lack of control for unknown confounders in the derived data may exaggerate the bias for the results. Especially, results based mainly on health claims data are susceptible to several biases because of coding errors, missing data, and a lack of clinically relevant data^[40] such as quality of anticoagulation control in the warfarin group, compliance, and label adherence of NOACs. Because it is more difficult for Asian patients to maintain target international normalized ratio levels while taking warfarin than Western patients, their TTRs are often lower than those of Western patients. Thus, the effectiveness of the NOACs may have been overestimated. In addition, label adherence could not be confirmed because bodyweight and/or serum creatinine clearance was not known. Therefore, it was not possible to determine whether the appropriate dosage was used,

and the patients were therefore divided into standard- and low-dose groups. A recent observational study demonstrated that inadequate apixaban dosing was not clinically effective in terms of stroke protection, as compared with warfarin.^[40] However, low-dose dabigatran regardless of guideline-concordant use showed similar efficacy and safety compared with standard-dose dabigatran.^[41] Considering that, at low doses, only dabigatran and rivaroxaban were associated with a decreased risk of IS in our study, it can be estimated that the off-label 50% dose reduction of apixaban and edoxaban does not guarantee sufficient IS prevention. Second, because only a few studies reported direct comparisons, some mixed and direct comparison results were different, affecting the heterogeneity and inconsistency of our results. Third, there was no comparison between standard-dose and low-dose regimens due to the lack of comparative real-world data. Therefore, our results should be interpreted with caution, and additional large-scale data and analyses in the future should be performed to help to determine the optimal NOAC and dosage.

5. Conclusions

Our present updated NMA has provided new insights into the efficacy and safety of NOACs in Asian patients with NVAF. Our results suggest that, compared with other NOACs and warfarin, edoxaban, and apixaban offered a favorable balance of efficacy and safety. However, considering the limitations of real-world data, large clinical trials are needed to confirm these results.

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