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Direct comparison of non-vitamin K antagonist oral anticoagulant versus warfarin for stroke prevention in non-valvular atrial fibrillation: a systematic review and meta-analysis of real-world evidences

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Abstract

Background: To overcome the several drawbacks of warfarin, non-vitamin K antagonist oral anticoagulants (NOACs) were developed. Even though randomized controlled trials (RCTs) provided high-quality evidence, the real-world evidence is still needed. This systematic review and meta-analysis proposed to measure the safety and efficacy profile between warfarin and NOACs in non-valvular atrial fibrillation (NVAF) patients in preventing stroke.

Results: We collected articles about the real-world studies comparing warfarin and NOACs for NVAF patients recorded in electronic scientific databases such as Embase, ProQuest, PubMed, and Cochrane. The pooled hazard ratio (HR) and 95% confidence interval (CI) were estimated using the generic inverse variance method. A total of 34 real-world studies, including 2287288 NVAF patients, were involved in this study. NOACs effectively reduced the stroke risk than warfarin (HR 0.77; 95% CI 0.69 to 0.87; $p < 0.01$). Moreover, NOACs effectively lowered all-cause mortality risk (HR 0.71; 95% CI 0.63 to 0.81; $p < 0.01$). From the safety aspect, compared to warfarin, NOACs significantly reduced major bleeding risk (HR 0.68; 95% CI 0.54 to 0.86; $p < 0.01$) and intracranial bleeding risk (HR 0.54; 95% CI 0.42 to 0.70; $p < 0.01$). However, NOACs administration failed to decrease gastrointestinal bleeding risk (HR 0.78; 95% CI 0.58 to 1.06; $p = 0.12$).

Conclusions: In NVAF patients, NOACs were found to be more effective than warfarin at reducing stroke risk. NOACSs also lowered the risk of all-cause mortality, cerebral hemorrhage, and severe bleeding in NVAF patients compared to warfarin.

Keywords: Non-vitamin K oral anticoagulant, Warfarin, Non-valvular atrial fibrillation, Meta-analysis, Real-world study

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Background

Atrial fibrillation (AF) puts the patients at high risk for stroke or other systemic thromboembolic events [1, 2]. Current guidelines from several cardiovascular societies recommend oral anticoagulant treatment for long-term stroke prevention strategy in AF patients [3–6]. Warfarin, a vitamin K antagonist (VKA), is an anticoagulant widely used worldwide. It effectively reduces stroke risk and mortality in AF patients [7]. However, warfarin has several drawbacks, such as the narrow therapeutic window, the requirement for stably achieved international normalized ratio (INR), the need for routine INR monitoring, the drug to food interaction, the drug to drug interaction, and drug dose adjustment [8]. A prior study revealed that an INR value below 2.0 was related to the increased risk of stroke, while an INR value above 3.0 was related to the increased bleeding risk [9]. It can be a serious problem in patients with old age, noncompliance with medication, and various comorbidities.

The non-vitamin K antagonist oral anticoagulants (NOACs), including apixaban, dabigatran, edoxaban, and rivaroxaban, were developed to overcome several drawbacks of warfarin. In the non-valvular atrial fibrillation (NVAF) population, several randomized controlled trials (RCTs) revealed that NOACs were associated with better or at least non-inferior than warfarin for systemic embolism and/or stroke prevention [10–13]. From the safety point of view, edoxaban, apixaban, and low-dose dabigatran were related to lower bleeding rates [11–13]. However, rivaroxaban and high-dose dabigatran were correlated with similar rates of bleeding [10, 11]. Even though RCTs provide good evidence, they are limited by the strict inclusion and exclusion criteria. The real-world data offer additional evidence in an extensive spectrum of the study population outside the strictly selected and controlled population involved in the RCTs [14]. Therefore, we conducted a systematic review and meta-analysis to measure the efficacy and safety profile between warfarin and NOACs in preventing stroke in NVAF patients.

Methods

Design

A systematic review and meta-analysis study was completed in January 2021 based on the guidance from preferred reporting items for systematic review and meta-analysis (PRISMA) [15]. We collected articles about the real-world studies comparing NOACs and warfarin in NVAF patients recorded in online databases such as Embase, ProQuest, PubMed, and Cochrane. Studies that satisfy the eligibility criteria were involved in the quality assessment of the study. The essential information was extracted only from high-quality studies. The exposure variable was anticoagulants treatment. We divided the patients into "NOACs group" and "warfarin group." We also performed the "head to head" comparison between each NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban) and warfarin. The stroke risk was our primary outcome. The secondary outcomes included the risk of: (1) all-cause mortality; (2) major bleeding; (3) intracranial bleeding; and (4) gastrointestinal bleeding. The pooled hazard ratio (HR) and 95% confidence interval (CI) were applied in determining the overall effect.

Search strategy

Until December 2020, articles comparing the safety and efficacy of NOACs and warfarin in NVAF were collected from electronic scientific databases such as Embase, ProQuest, PubMed, and Cochrane. We used the following keywords: "non-vitamin K antagonist oral anticoagulant" or "new oral anticoagulant" or "novel oral anticoagulant' or "NOAC," AND "direct oral anticoagulant" or "DOAC," AND "vitamin K antagonist" or "VKA," AND "warfarin," AND "dabigatran," AND "apixaban," AND "edoxaban," AND "rivaroxaban," AND "non-valvular atrial fibrillation" or "non-valvular AF" or "NVAF," AND "stroke," AND "cerebrovascular accident" or "CVA," AND "death" or "all-cause death," AND "mortality" or "all-cause mortality," AND "major bleeding" or "major hemorrhage," AND "intracranial bleeding" or "intracranial hemorrhage," AND "gastrointestinal bleeding" or "gastrointestinal hemorrhage" or "GI bleeding" or "GI hemorrhage." We also collected all relevant articles through the list of references from all accessed articles or Google Scholar. We did not apply the language restriction during the initial data searching process.

Eligibility criteria

We involved all articles which met the inclusion criteria, including: (1) cohort or real-world studies compared warfarin and NOACs in NVAF patients; (2) studies with the purpose to investigate the efficacy and/or safety profile of NOACs and warfarin in NVAF patients for stroke prevention; (3) intervention group was NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban); (4) control group was warfarin; (5) availability of data about stroke, all-cause mortality, major bleeding, intracranial bleeding, or gastrointestinal bleeding; and (6) effect estimates were in HR and 95% CI. We excluded articles with one or more theses following criteria: (1) duplications; (2) not published in English; (3) involved patients with venous thromboembolism (VTE); (4) did not specify the name of the drug; (5) did not use warfarin as VKA; and (6) outcomes of interest were not reported. Two investigators reviewed all included articles. Discussion between both investigators or consultation with the third investigator was done to resolve the disagreement.

Study quality assessment

We used the Newcastle-Ottawa scale (NOS) to evaluate the quality of the studies. It has three domains with a maximum score of 9. According to the NOS, a good quality cohort study was defined as a study with 3 to 4 stars in the selection domain, 1 to 2 stars in the comparability domain, and 2 to 3 stars in the outcome domain [16]. Two investigators performed the study quality assessment. Discrepancies between both investigators during study quality assessment were resolved by consultation or discussion with the third investigator. We only included high-quality real-world studies in this systematic review and meta-analysis.

Data extraction

Important information about (1) name of the first author; (2) date of publication; (3) enrolment period; (4) country; (5) data source; (6) type of anticoagulants; (7) number of participants; (8) CHA2DS2-VASc score; (9) HAS-BLED score; (10) follow up period duration; (11) primary statistical model; and (12) adjusted HR and 95% CI of stroke, all-cause mortality, major bleeding, intracranial bleeding, and gastrointestinal bleeding were extracted from each study. Four investigators conducted the data extraction process.

Statistical analysis

The meta-analysis was conducted using a combination of two software, Review Manager Version 5.3 (RevMan, Cochrane, Copenhagen, Denmark) and Comprehensive Meta-Analysis version 3.0 (CMA, New Jersey, USA). We conducted the meta-analysis based on the direction from the existing guideline [17]. We collected adjusted HR, 95% CI, and the number of participants in each group. Log HR was calculated using each study's logarithms, while the standard error (SE) was obtained from the CI given by each study. We applied Begg's test and Egger's test for publication bias identification. The p value of < 0.05 for Begg's test or Egger's test represented the presence of publication bias [18–20]. The Q test was applied in identifying the heterogeneity among the involved studies. In the presence of heterogeneity (p value of heterogeneity < 0.1), we used the random-effect analysis model. On the contrary, in the absence of heterogeneity (p value of heterogeneity ≥ 0.1), we used the fixed-effect analysis model [21, 22]. The pooled HR and 95% CI were determined using the generic inverse variance method [23]. Statistically significant was considered if the p value of < 0.05. Three investigators conducted the statistical analysis process.

Results

Study selection and baseline characteristics

In the beginning, we had collected 2303 potentially eligible articles from electronic scientific databases. After duplicate removal, we had 794 articles. A total of 701 articles were excluded because of unrelated to our study. We performed full-text assessment in 93 studies, then a total of 59 studies were excluded due to (1) not published in English ($n = 9$); (2) involved patients with VTE ($n = 19$); (3) did not specify the name of the drug ($n = 18$); (4) did not use warfarin as VKA ($n = 6$); and (5) outcomes of interest were not reported ($n = 7$). Finally, 34 studies were involved in this study [24–57]. The study selection flowchart is presented in Fig. 1. In this study, we only involved high-quality studies assessed by NOS (Supplementary Table 1).

A total of 2287288 NVAF patients receiving apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin from 34 real-world studies were involved in our meta-analysis. We involved studies that had been done in various countries in America, Asia, and Europe [24–57]. The mean CHA2DS2-VASc score ranged from 2 to 4.7 [24–30, 33, 36, 39–55, 57] while the HAS-BLED score ranged from 1.27 to 3.9 [24–26, 28–30, 33, 39, 40, 42, 46, 47, 49–55]. The primary statistical method included propensity score matching [25, 27, 31–35, 39, 41, 44, 47, 49, 50, 53, 55–57], propensity score weighting [24, 26, 28–30, 37, 38, 42, 43, 45, 46, 51, 52], and Cox proportional hazard model [36, 40, 48, 54]. The follow-up period duration was long enough [24–57]. Table 1 represents the baseline characteristics of the all included studies.

Heterogeneity and publication bias

Heterogeneity was represented by a p value of heterogeneity of < 0.1. It was found in almost all analyses, except for the risk of: (1) stroke between edoxaban and warfarin; (2) all-cause mortality between NOACs and warfarin; and (3) intracranial bleeding between rivaroxaban and warfarin. Therefore, in almost all analyses, the random-effect analysis model was used. The p value of Begg's test and Egger's test for all analyses were > 0.05, so, no publication bias was found in this study. The assessment of heterogeneity and publication is summarized in Table 2.

Primary outcome

Stroke

Our primary outcome was the stroke risk reduction. Our result revealed that NOACs significantly reduced stroke risk in NVAF patients (HR 0.77; 95% CI 0.69 to 0.87; $p < 0.01$) compared to warfarin (Fig. 2). The subgroup analysis for the specific agent also revealed the consistent results. Apixaban (HR 0.73; 95% CI 0.64 to 0.84; $p < 0.01$), dabigatran (HR 0.87; 95% CI 0.81 to 0.94; $p < 0.01$), edoxaban (HR 0.67; 95% CI 0.60 to 0.76; $p < 0.01$), and rivaroxaban (HR 0.81; 95% CI 0.73 to 0.90; $p < 0.01$) significantly reduced stroke risk (Fig. 3).

Fig. 1 Flow diagram summarizing the selection process of included studies. *RCT* = randomized controlled trial, *VKA* = vitamin K antagonist *VTE* = venous thromboembolism
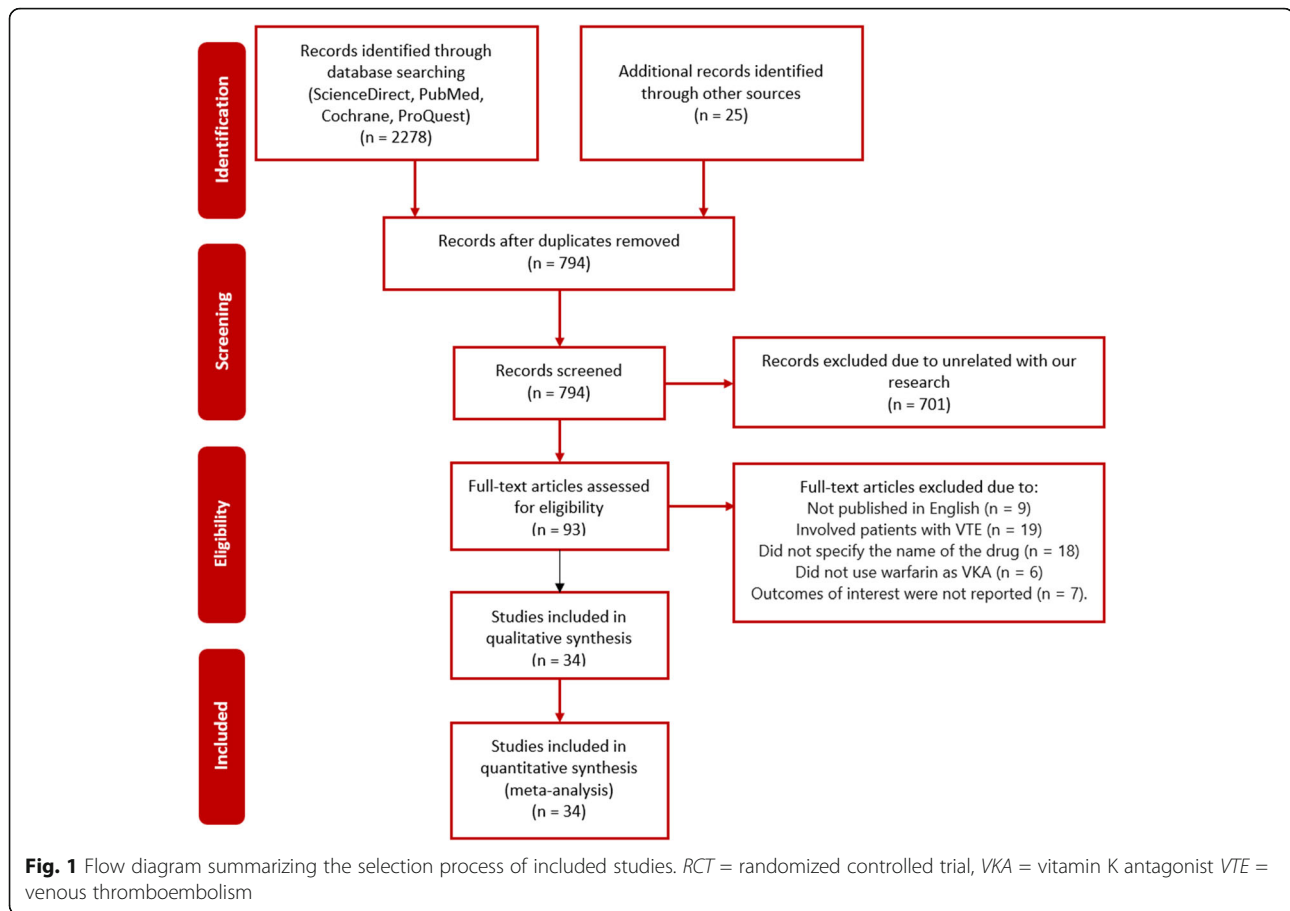
Secondary outcomes

All-cause mortality

NOACs administration successfully reduced all-cause mortality risk than warfarin (HR 0.71; 95% CI 0.63 to 0.81; $p < 0.01$) (Fig. 2). From the subgroup analysis, we found that apixaban (HR 0.69; 95% CI 0.49 to 0.98; $p = 0.04$), dabigatran (HR 0.67; 95% CI 0.57 to 0.80; $p < 0.01$), and edoxaban (HR 0.52; 95% CI 0.31 to 0.85; $p = 0.01$) were also related to lower all-cause mortality risk than warfarin (Fig. 4). However, the all-cause mortality risk between rivaroxaban and warfarin was not different significantly (HR 0.91; 95% CI 0.70 to 1.18; $p = 0.47$) (Fig. 4).

Major bleeding

NOACs effectively reduced major bleeding risk (HR 0.68; 95% CI 0.54 to 0.86; $p < 0.01$) than warfarin (Fig. 2). The subgroup analysis also revealed the consistent results. Apixaban (HR 0.57; 95% CI 0.53 to 0.63; $p < 0.01$), dabigatran (HR 0.75; 95% CI 0.67 to 0.83; $p < 0.01$), edoxaban (HR 0.55; 95% CI 0.45 to 0.66; $p < 0.01$), and rivaroxaban (HR 0.90; 95% CI 0.82 to 0.98; $p = 0.01$)

was associated with major bleeding risk reduction (Fig. 5).

Intracranial bleeding

NOACs administration was correlated with the lower risk for intracranial bleeding (HR 0.54; 95% CI 0.42 to 0.70; $p < 0.01$) than warfarin (Fig. 2). The similar results were also found in the agent-specific level. Apixaban (HR 0.57; 95% CI 0.48 to 0.68; $p < 0.01$), dabigatran (HR 0.44; 95% CI 0.38 to 0.52; $p < 0.01$), edoxaban (HR 0.44; 95% CI 0.26 to 0.76; $p < 0.01$), and rivaroxaban (HR 0.69; 95% CI 0.64 to 0.74; $p < 0.01$) effectively reduced major bleeding risk (Fig. 6).

Gastrointestinal bleeding

The analysis results for gastrointestinal bleeding were different from major bleeding and intracranial bleeding. Overall, NOACs did not significantly reduce the gastrointestinal bleeding risk (HR 0.78; 95% CI 0.58 to 1.06; p = 0.12) (Figure 2). The subgroup analysis demonstrated conflicting results. Compared with warfarin, apixaban (HR 0.58; 95% CI 0.51 to 0.67; $p < 0.01$) and edoxaban

Table 1 Baseline characteristics of the studies

Study	Country	Enrolment period	Data source	Drugs	Participants	CHA2DS2VASc	HASBLED	Follow-up	Primary statistical method	NOS
Adeboyeje G, 2017 [24]	USA	November 2009 to January 2016	HealthCore Integrated Research Environment	A/D/R/W	44057	3.3 (mean)	2.1 (mean)	139–285 days (median)	PSW	7
Amin A, 2017 [25]	USA	January 2012 to December 2014	Center of Medicare and Medicaid Services	A/D/R/W	180020	4.4–4.7 (mean)	3.1–3.3 (mean)	196.1–203.8 days (median)	PSM	7
Bang OY, 2020 [26]	South Korea	January 2015 and November 2016	Korean Health Insurance Review and Assessment Service Database	A/D/R/W	48389	4.4–4.52 (mean)	3.5–3.54 (mean)	105–175 days (median)	PSW	8
Cha MJ, 2017 [27]	South Korea	January 2014 to December 2015	Korean National Health Insurance Service Database	A/D/R/W	34833	3.51–3.6 (mean)	NA	1.2 years (mean)	PSM	8
Chan YH, 2018 [28]	Taiwan	June 2012 to December 2016	Taiwan National Health Insurance Research Database	A/D/R/W	73074	3.26–3.89 (mean)	2.64–2.97 (mean)	0.76–1.47 years (mean)	PSW	7
Chan YH, 2019 [29]	Taiwan	June 2012 to December 2017	Taiwan National Health Insurance Research Database	A/D/E/R/W	89683	3.6 (mean)	2.6–2.7 (mean)	16 months	PSW	8
Cho MS, 2019 [30]	Korea	July 2015 to December 2016	Korean National Health Insurance Service Database	A/D/R/W	56504	3.5–3.7 (mean)	2.5–2.6 (mean)	15 months (median)	PSW	8
Coleman CI, 2017 [31]	USA	January 2012 to June 2015	Truven MarketScan	A/D/R/W	9684	5 (median)	3–4 (median)	0.5–0.6 years (mean)	PSM	8
Costa OS, 2020 [32]	USA	November 2010 to 30 September 2018	Optum Research Database	R/W	71226	3 (median)	2 (median)	2 years (median)	PSM	8
Deitelzweig S, 2017 [33]	USA	January 2013 to September 2015	Humana Research Database	A/D/R/W	32488	4.3–4.6 (mean)	2.9–3.1 (mean)	6.4–7.1 months (mean)	PSM	7
Graham DJ, 2015 [34]	USA	October 2010 to December 2012	Medicare	D/W	134414	NA	NA	180 days	PSM	8
Graham DJ, 2019 [35]	USA	October 2010 to September 2015	Medicare	A/D/R/W	448586	NA	NA	300 days	PSM	8
Halvorsen S, 2017 [36]	Norway	January 2013 to June 2015	Norwegian Patient Registry Norwegian Prescription Database	A/D/R/W	32675	2.46–3.09 (mean)	NA	143–212 days (median)	Cox proportional hazard model	7
Hernandez I, 2015 [37]	USA	October 2010 to October 2011	Medicare	D/W	9404	NA	NA	177 days (mean)	PSW	8
Hsu CC, 2018 [38]	Taiwan	January 1999 to December 2015	Taiwan National Health Insurance Research Database	D/R/W	1211	NA	NA	1.7 years (median)	PSW	7
Huybrechts KF, 2020 [39]	USA	October 2010 to September 2015	IBM MarketScan Medicare Optum Research Database	A/D/R/W	169112	3.01–3.05 (mean)	2.25–2.26 (mean)	1 year	PSM	8

Table 1 Baseline characteristics of the studies *(Continued)*

Study	Country	Enrolment period	Data source	Drugs	Participants	CHA2DS2VASc	HASBLED	Follow-up	Primary statistical method	NOS
Kjerpeseth LJ, 2019 [40]	Norway	July 2013 to December 2015	Norwegian Prescription Database Norwegian Patient Registry Norwegian Cause of Death Registry National Registry	A/D/R/W	30820	2.9–3.5 (mean)	2.2–2.6 (mean)	365 days	Cox proportional hazard model	7
Kohsaka S, 2020 [41]	Japan	March 2011 to July 2018	Japanese Administrative Claims	A/D/E/R/W	73989	3.8 (mean)	NA	2 years	PSM	8
Larsen TB, 2016 [42]	Denmark	August 2011 to October 2015	Danish National Prescription Registry Danish National Patient Register Danish Civil Registration System	A/D/R/W	61678	2.7 (mean)	2.2 (mean)	1.9 years (mean)	PSW	8
Lauffenburger JC, 2015 [43]	USA	October 2010 to December 2012	Truven Health MarketScan Medicare	D/W	64935	2.3–2.9 (mean)	NA	358 days (mean)	PSW	8
Lee SR, 2018 [44]	South Korea	January 2014 to December 2016	National Health Insurance Service Database	E/W	16244	3.22–3.25 (mean)	NA	0.3 to 0.9 years (median)	PSM	9
Lee SR, 2019 (1) [45]	South Korea	January 2014 to December 2016	National Health Insurance Service Database	A/D/E/R/W	24974	3 (mean)	NA	1.2 years (median)	PSW	9
Lee SR, 2019 (2) [46]	South Korea	January 2015 to December 2017	National Health Insurance Service Database	A/D/E/R/W	116804	3.54–3.6 (mean)	2.69–2.71 (mean)	1 year	PSW	9
Li X, 2017 [47]	USA	January 2012 to September 2015	Truven MarketScan IMS PharMetrics Plus Database Optum Clinformatics Data Mart Humana Research Database	A/W	76940	3.2 (mean)	2.6 (mean)	179.2–199.9 days (mean)	PSM	8
Lip YH, 2016 (1) [48]	USA	January 2013 to December 2013	Truven MarketScan Medicare	A/D/R/W	29338	2.58–3.22 (mean)	NA	90.37–127.55 days (median)	Cox proportional hazard model	7
Lip YH, 2016 (2) [49]	USA	January 2012 to December 2014	Truven MarketScan Medicare	A/D/R/W	45361	2.6–3 (mean)	2–2.2 (mean)	148.1–178.1 days (median)	PSM	7
Maura G, 2015 [50]	France	July 2011 to November 2012	French National Health Insurance Information System French Hospital Discharge Database	D/R/W	32807	2.4–3.6 (mean)	2–2.4 (mean)	80–87 days (median)	PSM	9
Mitsuntisuk P, 2020 [51]	Thailand	January 2012 to April 2018	9 Hospitals in Thailand	A/D/R/W	2055	3.25–3.86 (mean)	1.27–1.65 (mean)	1.9–2.82 years (mean)	PSW	8
Nielsen PB, 2017 [52]	Denmark	August 2011 to February 2016	Danish National Prescription Registry Danish Civil Registration System Danish National Patient Register	A/D/R/W	55644	3.3 (mean)	2.4 (mean)	2.5 years	PSW	8
Rutherford OCW, 2020	Norway	January 2013 to December	The Norwegian Patient Registry	A/D/R/W	65563	2.93–3.23 (mean)	2.25–2.43 (mean)	12 months	PSM	8

Table 1 Baseline characteristics of the studies *(Continued)*

Study	Country	Enrolment period	Data source	Drugs	Participants	CHA2DS2VASc	HASBLED	Follow-up	Primary statistical method	NOS
[53]		2017	The Norwegian Prescription Database							
Staerk L, 2017 [54]	Denmark	August 2011 to December 2015	Danish National Prescription Registry Danish Civil Registration System Danish National Patient Register	A/D/R/W	43299	2–2.2 (mean)	2.7–3.11 (mean)	204–386 days (median)	Cox proportional hazard model	7
Villines TC, 2015 [55]	USA	October 2009 to July 2013	Department of Defense Database	D/W	25586	3.4 (mean)	3.9 (mean)	217.2–297.3 days (mean)	PSM	7
Yao X, 2016 [56]	UA	October 2010 to June 2015	OptumLabs Data Warehouse	A/D/R/W	76354	3–4 (median)	2 (median)	6 months	PSM	7
Yu HT, 2018 [57]	Korea	January 2016 to December 2016	National Health Insurance Service	E/W	9537	4.2 (mean)	NA	5 months (median)	PSM	8

A = apixaban, *CHA2DS2-VASc* = congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, *D* = dabigatran, *E* = edoxaban, *HASBLED* = Hypertension, Abnormal renal or liver function, Stroke, Bleeding history, Labile international normalized ratio (INR), age ≥ 65 years, and antiplatelet Drug or alcohol use, *NA* = not available, *NOS* = Newcastle-Ottawa Scale, *PSM* = propensity score matching, *PSW* = propensity score weighting, *R* = rivaroxaban, *W* = warfarin

(HR 0.62; 95% CI 0.44 to 0.87; $p < 0.01$) were related with the gastrointestinal bleeding risk reduction (Fig. 7). However, the administration of dabigatran (HR 0.99; 95% CI 0.87 to 1.12; $p = 0.88$) and rivaroxaban (HR 1.00; 95% CI 0.86 to 1.17; $p = 0.97$) failed to reduce gastrointestinal bleeding risk (Fig. 7). All outcomes are summarized in Table 2.

Discussion

Our systematic review and meta-analysis study, including more than 2.2 million NVAF patients, assessed the safety and efficacy profile of warfarin and NOACs for stroke prevention in the real-world population. We analyzed the results of the real-world studies regarding anticoagulant treatment for NVAF in several countries across America, Asia, and Europe. Our study sample is smaller than the study conducted by Wang et al., which included more than 2.3 million patients [58]. However, Wang et al. only assessed the bleeding risk generally. They did not analyze the specific outcome for safety and efficacy profiles [58]. In this study, we tried to analyze the efficacy (stroke risk and all-cause mortality risk) and safety (intracranial bleeding risk, gastrointestinal bleeding risk, and major bleeding risk) profiles specifically.

The efficacy endpoint of our study included stroke risk (primary outcome) and all-cause mortality risk. In our study, NOACs effectively reduced stroke risk compared to warfarin. Our finding was similar to previous meta-analysis studies [59, 60]. In subgroup analysis, apixaban, dabigatran, and rivaroxaban also showed significant

stroke risk reduction. These results supported the findings of the prior meta-analysis study [61]. However, our study provided new real-world evidence about the benefit of edoxaban for stroke risk reduction compared to warfarin. Our study also revealed that NOACs effectively reduced all-cause mortality compared to warfarin. This result was not different from the previous meta-analysis studies of RCTs [60, 62]. Our analysis on apixaban, dabigatran, and edoxaban showed the benefit of all-cause mortality risk reduction. Our results were similar to the results of previous studies [61, 63]. However, we failed to provide evidence of the advantage of rivaroxaban to reduce all-cause mortality risk.

Our study revealed that NOACs were correlated with a lower risk of intracranial bleeding and major bleeding than warfarin. Our findings supported the previous evidence from the meta-analysis of RCTs comparing NOACs and warfarin [62]. In subgroup analysis, apixaban, dabigatran, edoxaban, and rivaroxaban also showed similar results for major bleeding and intracranial bleeding. Our findings on the meta-analysis of apixaban, dabigatran, edoxaban, and rivaroxaban were consistent with the prior meta-analysis studies [61, 63, 64]. In our study, the gastrointestinal bleeding risk between NOACs and warfarin was not significantly different. Our result was different from the previous meta-analysis studies. A meta-analysis of RCTs from Ruff et al. demonstrated that NOACs were related to greater gastrointestinal bleeding risk [62]. However, in the meta-analysis of real-world studies from Chan et al., NOACs significantly

Table 2 Summary of the outcomes of interest

Outcomes	NOACs (n)	Warfarin (n)	Model	HR	95% CI		p value of heterogeneity	p value of Begg's test	p value of Egger's test	p
					Lower limit	Upper limit				
Stroke										
Apixaban	256909	474732	Random	0.73	0.64	0.84	< 0.01	0.77	0.77	< 0.01
Dabigatran	345545	365144	Random	0.87	0.81	0.94	< 0.01	0.70	0.78	< 0.01
Edoxaban	46035	78185	Fixed	0.67	0.60	0.76	0.84	1.00	0.46	< 0.01
Rivaroxaban	336406	486587	Random	0.81	0.73	0.90	< 0.01	0.19	0.41	< 0.01
All NOACs	984895	1604648	Random	0.77	0.69	0.87	< 0.01	0.73	0.85	< 0.01
All-cause mortality										
Apixaban	95097	309813	Random	0.69	0.49	0.98	< 0.01	1.00	0.60	0.04
Dabigatran	216235	390118	Random	0.67	0.57	0.80	< 0.01	0.35	0.06	< 0.01
Edoxaban	16210	16785	Random	0.52	0.31	0.85	0.02	1.00	0.53	0.01
Rivaroxaban	128600	310114	Random	0.91	0.70	1.18	< 0.01	0.76	0.89	0.47
All NOACs	456142	1026830	Fixed	0.71	0.63	0.81	0.14	0.31	0.08	< 0.01
Major bleeding										
Apixaban	234818	314596	Random	0.57	0.53	0.63	< 0.01	0.42	0.20	< 0.01
Dabigatran	292539	382810	Random	0.75	0.67	0.83	< 0.01	0.27	0.15	< 0.01
Edoxaban	48875	81025	Random	0.55	0.45	0.66	0.09	0.71	0.27	< 0.01
Rivaroxaban	337030	377026	Random	0.90	0.82	0.98	< 0.01	0.38	0.06	0.01
All NOACs	913262	1155457	Random	0.68	0.54	0.86	< 0.01	0.73	0.63	< 0.01
Intracranial bleeding										
Apixaban	251901	442439	Random	0.57	0.48	0.68	< 0.01	0.71	0.06	< 0.01
Dabigatran	323015	488790	Random	0.44	0.38	0.52	< 0.01	1.00	0.14	< 0.01
Edoxaban	48875	81025	Random	0.44	0.26	0.76	< 0.01	1.00	0.06	< 0.01
Rivaroxaban	326289	439920	Fixed	0.69	0.64	0.74	0.14	0.08	0.07	< 0.01
All NOACs	950080	1452174	Random	0.54	0.42	0.70	< 0.01	0.73	0.26	< 0.01
Gastrointestinal bleeding										
Apixaban	242813	401123	Random	0.58	0.51	0.67	< 0.01	0.43	0.07	< 0.01
Dabigatran	326750	490358	Random	0.99	0.87	1.12	< 0.01	0.08	0.06	0.88
Edoxaban	48875	81025	Random	0.62	0.44	0.87	< 0.01	1.00	0.09	< 0.01
Rivaroxaban	312311	396000	Random	1.00	0.86	1.17	< 0.01	0.58	0.06	0.97
All NOACs	930749	1368506	Random	0.78	0.58	1.06	< 0.01	0.73	0.75	0.12

CI = confidence interval, *HR* = hazard ratio, *NOACs* = non-vitamin K antagonist oral anticoagulants

decreased gastrointestinal bleeding risk [63]. Our study revealed that apixaban and edoxaban effectively reduced gastrointestinal bleeding risk. However, our study also revealed that the bleeding risks between dabigatran and rivaroxaban were not different significantly. Our results on apixaban and edoxaban supported the results of previous real-world meta-analysis studies [61, 63]. The previous meta-analysis studies on dabigatran and rivaroxaban showed conflicting results. A meta-analysis study from Chan et al. [63] showed that dabigatran and rivaroxaban did not significantly reduce the gastrointestinal bleeding risk, while a meta-analysis study from Xue

et al. showed that dabigatran and rivaroxaban reduced gastrointestinal bleeding risk [61]. Those two previous meta-analyses included only the real-world data from Asian countries [61, 63]. However, our study provided real-world evidence beyond the Asian population.

Our study demonstrated that NOACS, including apixaban, dabigatran, edoxaban, and rivaroxaban, consistently revealed a significant decrease in the risk of stroke, all-cause mortality, major bleeding, and intracranial bleeding in the real-world setting. The situation in the real-world setting was quite different than in the RCTs. In RCTs, the mean time in the therapeutic range (TTR)

A. Stroke

Study or Subgroup	log[Hazard Ratio]	SE	NOAC Total	Warfarin Total	Weight	Hazard Ratio IV, Random, 95% CI
Apixaban	-0.31471074	0.06937212	256909	474732	22.4%	0.73 [0.64, 0.84]
Dabigatran	-0.13926207	0.03797152	345545	565144	28.5%	0.87 [0.81, 0.94]
Edoxaban	-0.40047757	0.06459198	46035	78185	23.4%	0.67 [0.59, 0.76]
Rivaroxaban	-0.21072103	0.05340665	336406	486587	25.6%	0.81 [0.73, 0.90]
Total (95% CI)			984895	1604648	100.0%	0.77 [0.69, 0.87]

Heterogeneity: Tau² = 0.01; Chi² = 14.21, df = 3 (P = 0.003); I² = 79%
Test for overall effect: Z = 4.33 (P < 0.0001)

B. All-cause mortality

Study or Subgroup	log[Hazard Ratio]	SE	NOAC Total	Warfarin Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Apixaban	-0.37106368	0.17682651	95097	309813	13.5%	0.69 [0.49, 0.98]
Dabigatran	-0.40047757	0.0864749	216235	390118	56.4%	0.67 [0.57, 0.79]
Edoxaban	-0.65392647	0.25731699	16210	16785	6.4%	0.52 [0.31, 0.86]
Rivaroxaban	-0.09431068	0.13321402	128600	310114	23.8%	0.91 [0.70, 1.18]
Total (95% CI)			456142	1026830	100.0%	0.71 [0.63, 0.81]

Heterogeneity: Chi² = 5.41, df = 3 (P = 0.14); I² = 45%
Test for overall effect: Z = 5.23 (P < 0.00001)

C. Major bleeding

Study or Subgroup	log[Hazard Ratio]	SE	NOAC Total	Warfarin Total	Weight	Hazard Ratio IV, Random, 95% CI
Apixaban	-0.55341066	0.04440942	234818	314596	25.8%	0.57 [0.53, 0.63]
Dabigatran	-0.28740844	0.05394523	292539	382810	25.4%	0.75 [0.67, 0.83]
Edoxaban	-0.60659316	0.09450914	48875	81025	23.0%	0.55 [0.45, 0.66]
Rivaroxaban	-0.10870598	0.04315205	337030	377026	25.8%	0.90 [0.82, 0.98]
Total (95% CI)			913262	1155457	100.0%	0.68 [0.54, 0.86]

Heterogeneity: Tau² = 0.06; Chi² = 60.72, df = 3 (P < 0.00001); I² = 95%
Test for overall effect: Z = 3.16 (P = 0.002)

D. Intracranial bleeding

Study or Subgroup	log[Hazard Ratio]	SE	NOAC Total	Warfarin Total	Weight	Hazard Ratio IV, Random, 95% CI
Apixaban	-0.56655575	0.08872941	251901	442439	27.6%	0.57 [0.48, 0.68]
Dabigatran	-0.81390084	0.07935657	323015	488790	28.3%	0.44 [0.38, 0.52]
Edoxaban	-0.81175298	0.27577034	48875	81025	13.2%	0.44 [0.26, 0.76]
Rivaroxaban	-0.3734864	0.03430669	326289	439920	30.9%	0.69 [0.64, 0.74]
Total (95% CI)			950080	1452174	100.0%	0.54 [0.42, 0.70]

Heterogeneity: Tau² = 0.05; Chi² = 29.32, df = 3 (P < 0.00001); I² = 90%
Test for overall effect: Z = 4.65 (P < 0.00001)

E. Gastrointestinal bleeding

Study or Subgroup	log[Hazard Ratio]	SE	NOAC Total	Warfarin Total	Weight	Hazard Ratio IV, Random, 95% CI
Apixaban	-0.53707982	0.0699878	242813	401123	26.5%	0.58 [0.51, 0.67]
Dabigatran	-0.00932581	0.06402778	326750	490358	26.7%	0.99 [0.87, 1.12]
Edoxaban	-0.47780749	0.17496194	48875	81025	20.7%	0.62 [0.44, 0.87]
Rivaroxaban	0.00291066	0.07778928	312311	396000	26.2%	1.00 [0.86, 1.17]
Total (95% CI)			930749	1368506	100.0%	0.78 [0.58, 1.06]

Heterogeneity: Tau² = 0.09; Chi² = 41.38, df = 3 (P < 0.00001); I² = 93%
Test for overall effect: Z = 1.56 (P = 0.12)

Fig. 2 Comparison of NOACs versus warfarin for **A** stroke, **B** all-cause mortality, **C** major bleeding, **D** intracranial bleeding, and **E** gastrointestinal bleeding. CI = confidence interval; NOACs = non-vitamin K antagonist oral anticoagulants

of INR 2.0 to 3.0 ranged from 55 to 64% [10–12]. However, in most of the real-world studies, the TTR could not be recorded [24–50, 52–55, 57]. Real-world studies usually have a role in providing complementary sources of knowledge, and their results are fruitful to validate the findings from RCTs. Our study also revealed that NOACs failed to minimize the risk of gastrointestinal bleeding. The possible explanations were the unavailability of the data about: (1) patients' age; (2) the underlying gastrointestinal disease; and (3) the administration of

A. Apixaban

Study or Subgroup	log[Hazard Ratio]	SE	Apixaban Total	Warfarin Total	Weight	Hazard Ratio IV, Random, 95% CI
Amin A, 2017	-0.86750057	0.15537634	20803	20803	5.8%	0.42 [0.31, 0.57]
Cha MJ, 2017	-0.39600995	0.29533357	2189	23222	3.3%	0.67 [0.38, 1.20]
Chan YH, 2019	-0.34249031	0.15373578	9952	19761	5.9%	0.71 [0.53, 0.96]
Coleman CI, 2017	-0.23572233	0.39199102	1257	1257	2.3%	0.79 [0.37, 1.70]
Deitelzweig S, 2017	-0.40047757	0.16070915	7107	7107	5.7%	0.67 [0.49, 0.92]
Graham DJ, 2019	-0.34249031	0.08278112	72921	183003	7.4%	0.71 [0.60, 0.84]
Huybrechts KF, 2020	-0.26136476	0.12775114	19588	19588	6.4%	0.77 [0.60, 0.99]
Kjerpeseth LJ, 2019	0.04879016	0.15613084	10550	6435	5.8%	1.05 [0.77, 1.43]
Kohsaka S, 2020	-0.46203546	0.09451962	22752	19059	7.1%	0.63 [0.52, 0.76]
Larsen TB, 2016	0.10436002	0.08271572	6349	35436	7.4%	1.11 [0.94, 1.31]
Lee SR, 2019 (1)	-0.7985077	0.16219855	3395	9884	5.7%	0.45 [0.33, 0.62]
Lee SR, 2019 (2)	-0.37833644	0.06575468	22177	25420	7.6%	0.68 [0.60, 0.78]
Li X, 2017	-0.40047757	0.06719956	38470	38470	7.6%	0.67 [0.59, 0.76]
Mitsuntisuk P, 2020	-0.73396918	0.20330577	405	605	4.8%	0.48 [0.32, 0.71]
Nielsen PB, 2017	0.17395331	0.11481574	4400	38893	6.7%	1.19 [0.95, 1.49]
Staerk L, 2017	-0.02020271	0.14374482	6899	18094	6.1%	0.98 [0.74, 1.30]
Yao X, 2016	-0.18632958	0.22692266	7695	7695	4.4%	0.83 [0.53, 1.29]
Total (95% CI)			**256909**	**474732**	**100.0%**	**0.73 [0.64, 0.84]**

Heterogeneity: Tau² = 0.06; Chi² = 84.85, df = 16 (P < 0.00001); I² = 81%
Test for overall effect: Z = 4.52 (P < 0.00001)

0.1 0.2 0.5 1 2 5 10
Favours [Apixaban] Favours [Warfarin]

B. Dabigatran

Study or Subgroup	log[Hazard Ratio]	SE	Dabigatran Total	Warfarin Total	Weight	Hazard Ratio IV, Random, 95% CI
Amin A, 2017	0.21511138	0.14626442	16731	16731	4.5%	1.24 [0.93, 1.65]
Cha MJ, 2017	0.03343478	0.1750537	3741	23222	3.5%	1.03 [0.73, 1.46]
Chan YH, 2019	-0.19845094	0.14158343	22371	19761	4.7%	0.82 [0.62, 1.08]
Coleman CI, 2017	-0.51082562	0.38571693	981	981	0.9%	0.60 [0.28, 1.28]
Graham DJ, 2015	-0.22314355	0.09175056	67207	67207	7.3%	0.80 [0.67, 0.96]
Graham DJ, 2019	-0.22314355	0.07357257	86293	183003	8.6%	0.80 [0.69, 0.92]
Huybrechts KF, 2020	-0.13926207	0.09273153	29448	29448	7.2%	0.87 [0.73, 1.04]
Kjerpeseth LJ, 2019	-0.07257069	0.18072134	5984	6435	3.3%	0.93 [0.65, 1.33]
Kohsaka S, 2020	-0.10536052	0.118651	8003	19059	5.7%	0.90 [0.71, 1.14]
Larsen TB, 2016	0.21511138	0.14198517	12701	35436	4.6%	1.24 [0.94, 1.64]
Lauffenburger JC, 2015	-0.09431068	0.05880814	21070	43865	9.7%	0.91 [0.81, 1.02]
Lee SR, 2019 (1)	-0.597837	0.12431226	4241	9884	5.4%	0.55 [0.43, 0.70]
Lee SR, 2019 (2)	-0.21072103	0.0662953	17745	25420	9.1%	0.81 [0.71, 0.92]
Mitsuntisuk P, 2020	-0.34249031	0.25316538	441	605	2.0%	0.71 [0.43, 1.17]
Nielsen PB, 2017	-0.08338161	0.07499914	8875	38893	8.5%	0.92 [0.79, 1.07]
Staerk L, 2017	-0.11653382	0.10578811	12613	18094	6.4%	0.89 [0.72, 1.10]
Villines TC, 2015	-0.17435339	0.15312869	12793	12793	4.2%	0.84 [0.62, 1.13]
Yao X, 2016	0.05826891	0.14958928	14307	14307	4.3%	1.06 [0.79, 1.42]
Total (95% CI)			**345545**	**565144**	**100.0%**	**0.87 [0.81, 0.94]**

Heterogeneity: Tau² = 0.01; Chi² = 34.92, df = 17 (P = 0.006); I² = 51%
Test for overall effect: Z = 3.48 (P = 0.0005)

0.1 0.2 0.5 1 2 5 10
Favours [Dabigatran] Favours [Warfarin]

C. Edoxaban

Study or Subgroup	log[Hazard Ratio]	SE	Edoxaban Total	Warfarin Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Chan YH, 2019	-0.34249031	0.17682651	4577	19761	11.0%	0.71 [0.50, 1.00]
Kohsaka S, 2020	-0.30110509	0.11644958	12592	19059	25.4%	0.74 [0.59, 0.93]
Lee SR, 2018	-0.36672528	0.1728672	12183	4061	11.5%	0.69 [0.49, 0.97]
Lee SR, 2019 (1)	-0.40047757	0.30714156	1187	9884	3.6%	0.67 [0.37, 1.22]
Lee SR, 2019 (2)	-0.46362402	0.08418693	15496	25420	48.5%	0.63 [0.53, 0.74]
Total (95% CI)			**46035**	**78185**	**100.0%**	**0.67 [0.60, 0.76]**

Heterogeneity: Chi² = 1.43, df = 4 (P = 0.84); I² = 0%
Test for overall effect: Z = 6.75 (P < 0.00001)

0.1 0.2 0.5 1 2 5 10
Favours [Edoxaban] Favours [Warfarin]

D. Rivaroxaban

Study or Subgroup	log[Hazard Ratio]	SE	Rivaroxaban Total	Warfarin Total	Weight	Hazard Ratio IV, Random, 95% CI
Amin A, 2017	-0.35667494	0.08706873	52476	52476	8.4%	0.70 [0.59, 0.83]
Cha MJ, 2017	0.03633193	0.14520478	5681	23222	6.0%	1.04 [0.78, 1.38]
Chan YH, 2019	-0.27443685	0.14593872	33022	19761	6.0%	0.76 [0.57, 1.01]
Coleman CI, 2017	-0.73396918	0.25565572	2604	2604	3.1%	0.48 [0.29, 0.79]
Graham DJ, 2019	-0.32850407	0.07033442	106369	183003	9.2%	0.72 [0.63, 0.83]
Huybrechts KF, 2020	-0.12783337	0.08926063	35520	35520	8.3%	0.88 [0.74, 1.05]
Kjerpeseth LJ, 2019	0.19885086	0.15617076	7851	6435	5.6%	1.22 [0.90, 1.66]
Kohsaka S, 2020	-0.30110509	0.10301626	17481	19059	7.7%	0.74 [0.60, 0.91]
Larsen TB, 2016	-0.15082289	0.09380907	7192	35436	8.1%	0.86 [0.72, 1.03]
Lee SR, 2019 (1)	-0.71334989	0.11411236	6297	9884	7.3%	0.49 [0.39, 0.61]
Lee SR, 2019 (2)	-0.23319389	0.05219179	35965	25420	9.9%	0.79 [0.71, 0.88]
Mitsuntisuk P, 2020	0.24686008	0.31478988	604	605	2.3%	1.28 [0.69, 2.37]
Nielsen PB, 2017	-0.07257069	0.13600012	3476	38893	6.4%	0.93 [0.71, 1.21]
Staerk L, 2017	-0.11653382	0.14654118	5693	18094	6.0%	0.89 [0.67, 1.19]
Yao X, 2016	0.00995033	0.15183105	16175	16175	5.8%	1.01 [0.75, 1.36]
Total (95% CI)			**336406**	**486587**	**100.0%**	**0.81 [0.73, 0.90]**

Heterogeneity: Tau² = 0.03; Chi² = 46.06, df = 14 (P < 0.0001); I² = 70%
Test for overall effect: Z = 4.00 (P < 0.0001)

0.1 0.2 0.5 1 2 5 10
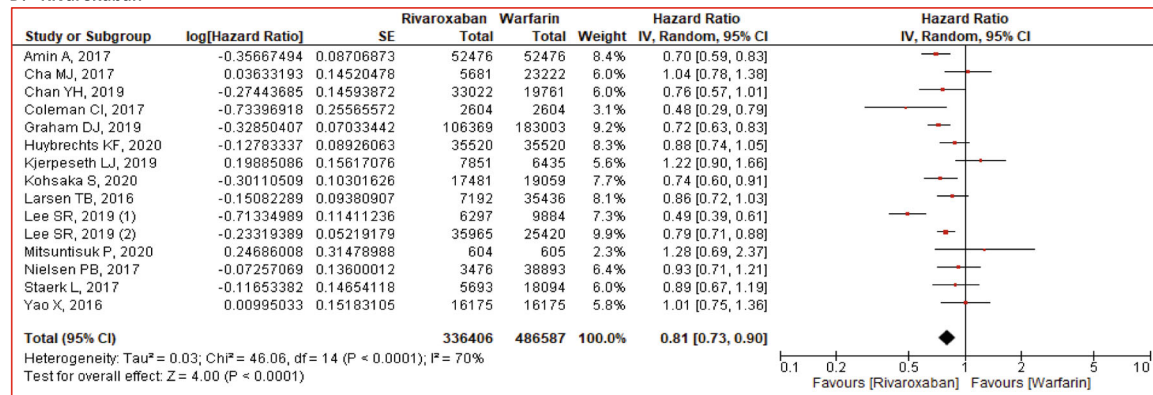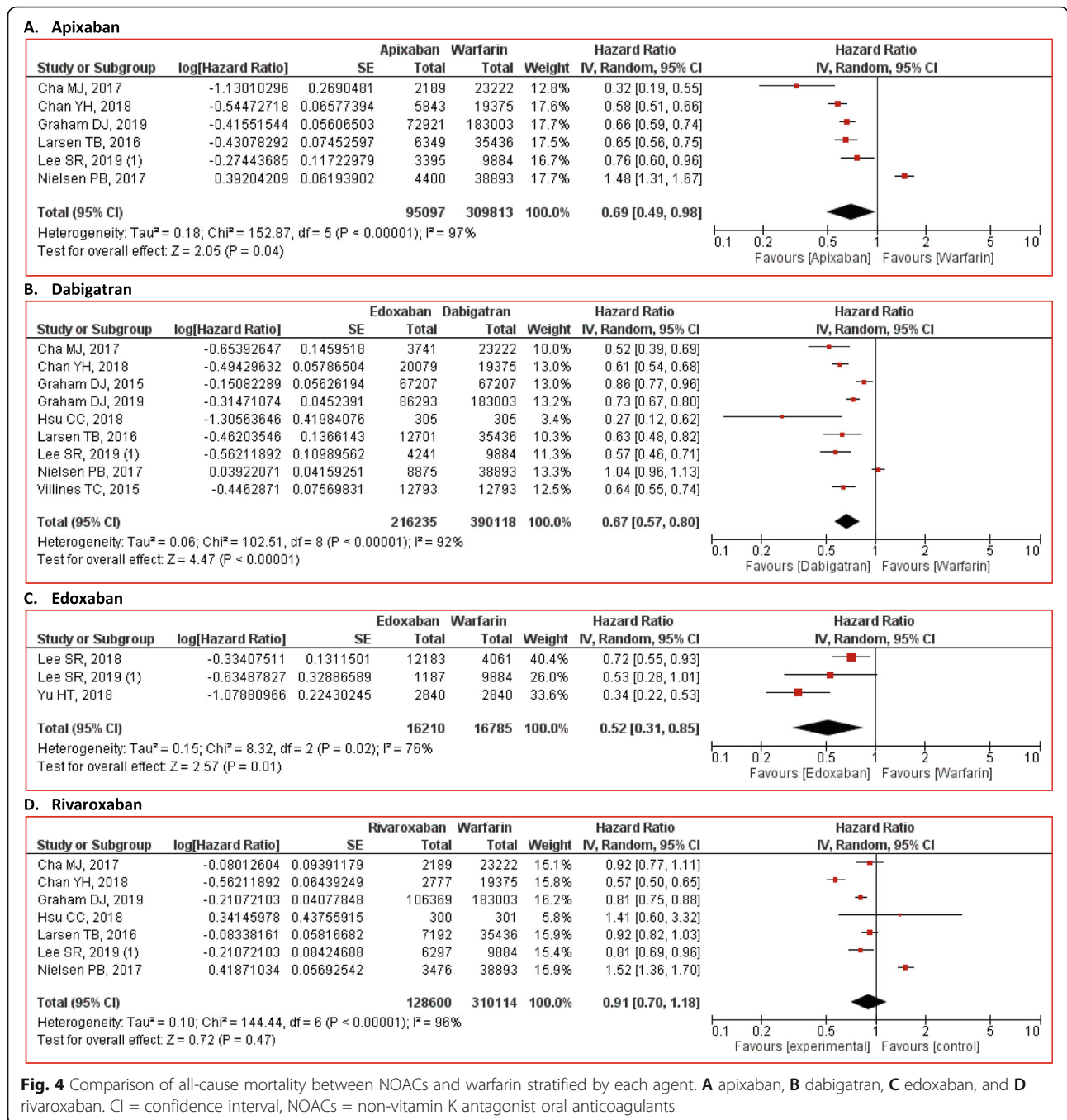Favours [Rivaroxaban] Favours [Warfarin]

Fig. 3 Comparison of stroke between NOACs and warfarin stratified by each agent. **A** Apixaban, **B** dabigatran, **C** edoxaban, and **D** rivaroxaban. CI = confidence interval, NOACs = non-vitamin K antagonist oral anticoagulants

A. Apixaban

Study or Subgroup	log[Hazard Ratio]	SE	Apixaban Total	Warfarin Total	Weight	Hazard Ratio IV, Random, 95% CI
Cha MJ, 2017	-1.13010296	0.2690481	2189	23222	12.8%	0.32 [0.19, 0.55]
Chan YH, 2018	-0.54472718	0.06577394	5843	19375	17.6%	0.58 [0.51, 0.66]
Graham DJ, 2019	-0.41551544	0.05606503	72921	183003	17.7%	0.66 [0.59, 0.74]
Larsen TB, 2016	-0.43078292	0.07452597	6349	35436	17.5%	0.65 [0.56, 0.75]
Lee SR, 2019 (1)	-0.27443685	0.11722979	3395	9884	16.7%	0.76 [0.60, 0.96]
Nielsen PB, 2017	0.39204209	0.06193902	4400	38893	17.7%	1.48 [1.31, 1.67]
Total (95% CI)			**95097**	**309813**	**100.0%**	**0.69 [0.49, 0.98]**

Heterogeneity: Tau² = 0.18; Chi² = 152.87, df = 5 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.05 (P = 0.04)

Favours [Apixaban]   Favours [Warfarin]

B. Dabigatran

Study or Subgroup	log[Hazard Ratio]	SE	Edoxaban Total	Dabigatran Total	Weight	Hazard Ratio IV, Random, 95% CI
Cha MJ, 2017	-0.65392647	0.1459518	3741	23222	10.0%	0.52 [0.39, 0.69]
Chan YH, 2018	-0.49429632	0.05786504	20079	19375	13.0%	0.61 [0.54, 0.68]
Graham DJ, 2015	-0.15082289	0.05626194	67207	67207	13.0%	0.86 [0.77, 0.96]
Graham DJ, 2019	-0.31471074	0.0452391	86293	183003	13.2%	0.73 [0.67, 0.80]
Hsu CC, 2018	-1.30563646	0.41984076	305	305	3.4%	0.27 [0.12, 0.62]
Larsen TB, 2016	-0.46203546	0.1366143	12701	35436	10.3%	0.63 [0.48, 0.82]
Lee SR, 2019 (1)	-0.56211892	0.10989562	4241	9884	11.3%	0.57 [0.46, 0.71]
Nielsen PB, 2017	0.03922071	0.04159251	8875	38893	13.3%	1.04 [0.96, 1.13]
Villines TC, 2015	-0.4462871	0.07569831	12793	12793	12.5%	0.64 [0.55, 0.74]
Total (95% CI)			**216235**	**390118**	**100.0%**	**0.67 [0.57, 0.80]**

Heterogeneity: Tau² = 0.06; Chi² = 102.51, df = 8 (P < 0.00001); I² = 92%
Test for overall effect: Z = 4.47 (P < 0.00001)

Favours [Dabigatran]   Favours [Warfarin]

C. Edoxaban

Study or Subgroup	log[Hazard Ratio]	SE	Edoxaban Total	Warfarin Total	Weight	Hazard Ratio IV, Random, 95% CI
Lee SR, 2018	-0.33407511	0.1311501	12183	4061	40.4%	0.72 [0.55, 0.93]
Lee SR, 2019 (1)	-0.63487827	0.32886589	1187	9884	26.0%	0.53 [0.28, 1.01]
Yu HT, 2018	-1.07880966	0.22430245	2840	2840	33.6%	0.34 [0.22, 0.53]
Total (95% CI)			**16210**	**16785**	**100.0%**	**0.52 [0.31, 0.85]**

Heterogeneity: Tau² = 0.15; Chi² = 8.32, df = 2 (P = 0.02); I² = 76%
Test for overall effect: Z = 2.57 (P = 0.01)

Favours [Edoxaban]   Favours [Warfarin]

D. Rivaroxaban

Study or Subgroup	log[Hazard Ratio]	SE	Rivaroxaban Total	Warfarin Total	Weight	Hazard Ratio IV, Random, 95% CI
Cha MJ, 2017	-0.08012604	0.09391179	2189	23222	15.1%	0.92 [0.77, 1.11]
Chan YH, 2018	-0.56211892	0.06439249	2777	19375	15.8%	0.57 [0.50, 0.65]
Graham DJ, 2019	-0.21072103	0.04077848	106369	183003	16.2%	0.81 [0.75, 0.88]
Hsu CC, 2018	0.34145978	0.43755915	300	301	5.8%	1.41 [0.60, 3.32]
Larsen TB, 2016	-0.08338161	0.05816682	7192	35436	15.9%	0.92 [0.82, 1.03]
Lee SR, 2019 (1)	-0.21072103	0.08424688	6297	9884	15.4%	0.81 [0.69, 0.96]
Nielsen PB, 2017	0.41871034	0.05692542	3476	38893	15.9%	1.52 [1.36, 1.70]
Total (95% CI)			**128600**	**310114**	**100.0%**	**0.91 [0.70, 1.18]**

Heterogeneity: Tau² = 0.10; Chi² = 144.44, df = 6 (P < 0.00001); I² = 96%
Test for overall effect: Z = 0.72 (P = 0.47)

Favours [experimental]   Favours [control]

Fig. 4 Comparison of all-cause mortality between NOACs and warfarin stratified by each agent. **A** apixaban, **B** dabigatran, **C** edoxaban, and **D** rivaroxaban. CI = confidence interval, NOACs = non-vitamin K antagonist oral anticoagulants
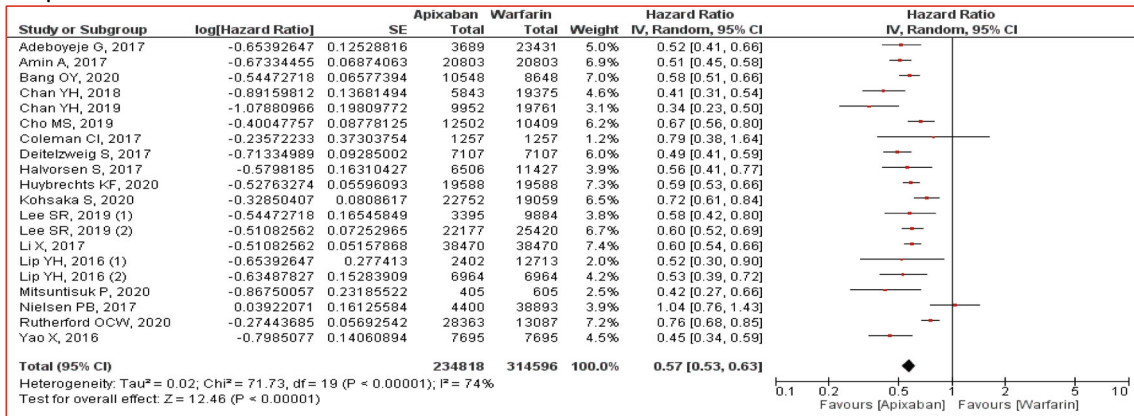
gastroprotective agents. Moreover, the mean HAS-BLED score among the included studies also varied. That could be the essential confounding factor.

In daily clinical practice, NOACs offer more benefit than warfarin due to: (1) rapid onset of action; (2) fixed dosing; (3) few drug to drug interactions; (4) few drug to food interactions; (5) no routine laboratory monitoring; and (6) short blood-thinning effect. However, NOACs also have 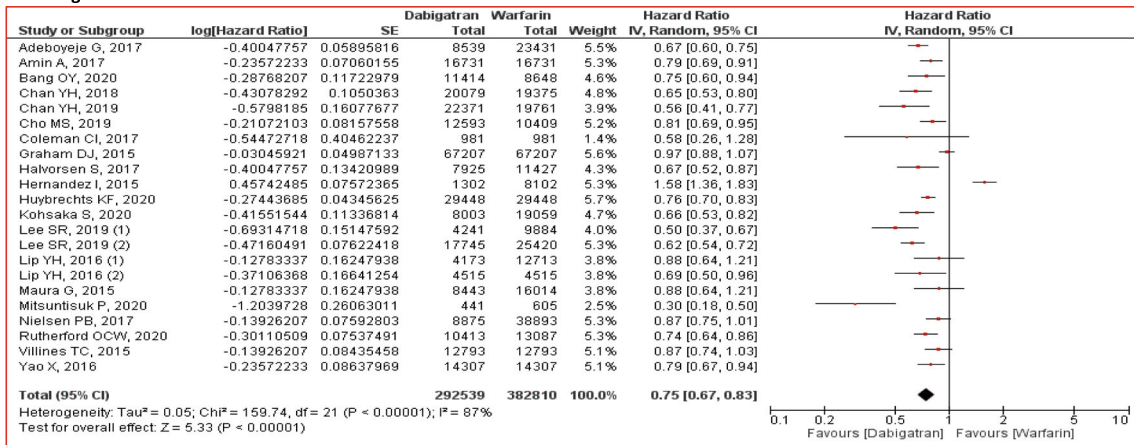several drawbacks, such as the high cost and the unavailability of reversal agents [65, 66]. According to our results, we recommend NOACs as the first choice for stroke prevention in NVAF patients.

There were several limitations of our systematic review and meta-analysis study. First, almost all involved studies did not provide data about the treatment regimen's compliance or persistence. Second, the TTR of warfarin users was not reported in almost all studies. The favorable safety and efficacy profile of NOACs might have
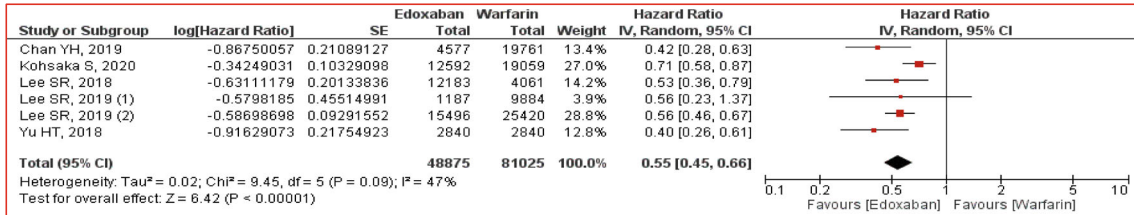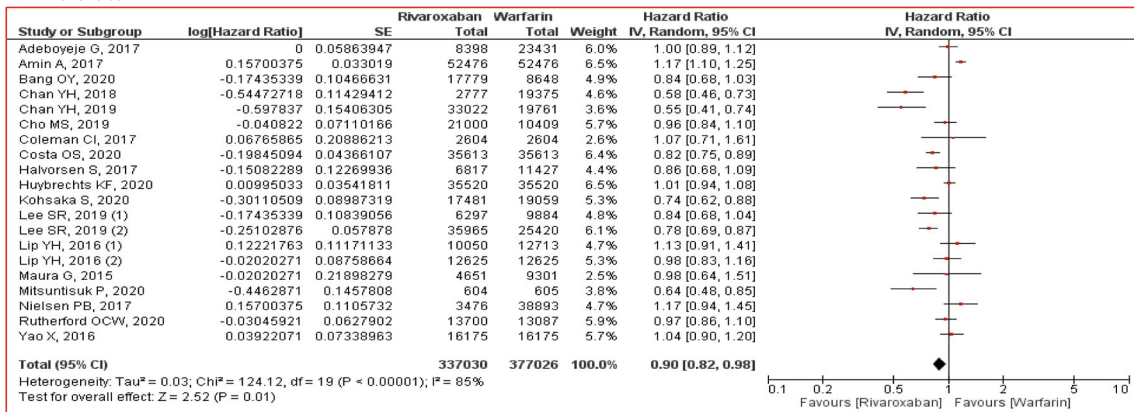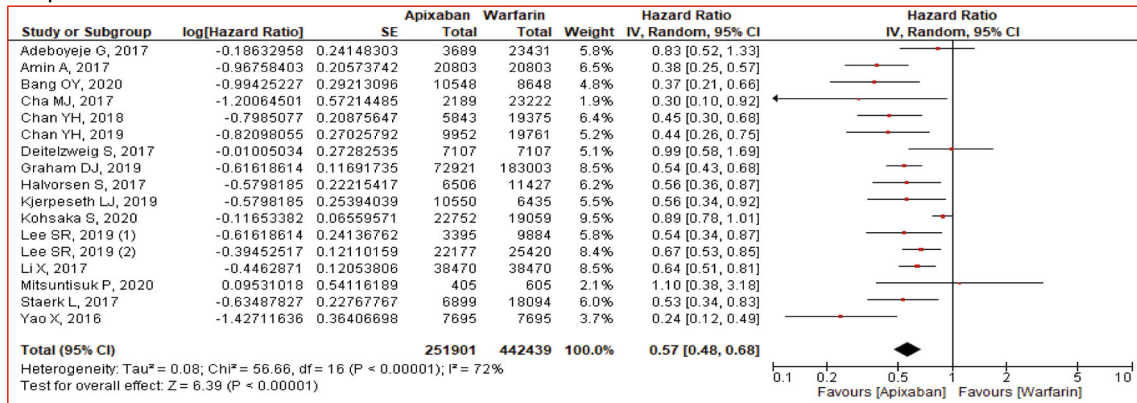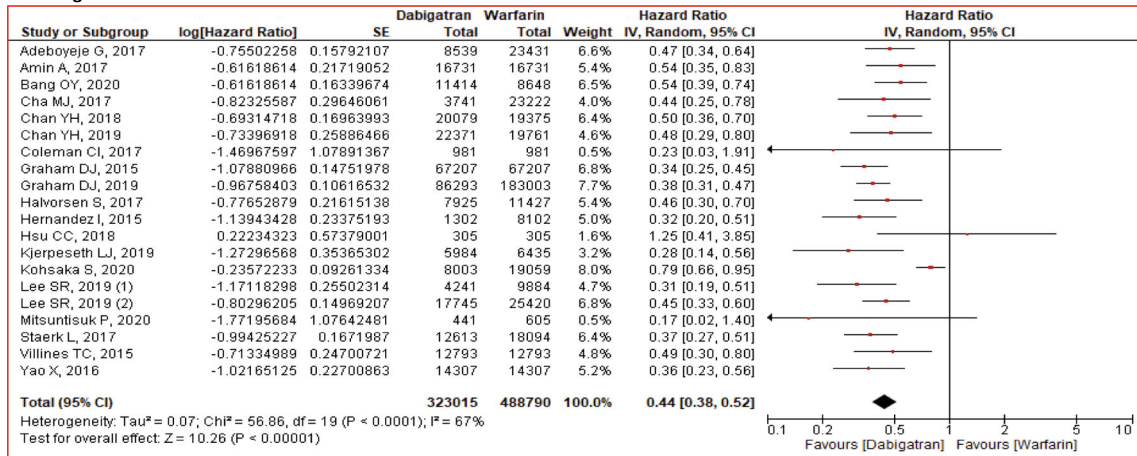
Fig. 5 Comparison of major bleeding between NOACs and warfarin stratified by each agent. **A** apixaban, **B** dabigatran, **C** edoxaban, and **D** rivaroxaban. CI = confidence interval, NOACs = non-vitamin K antagonist oral anticoagulants
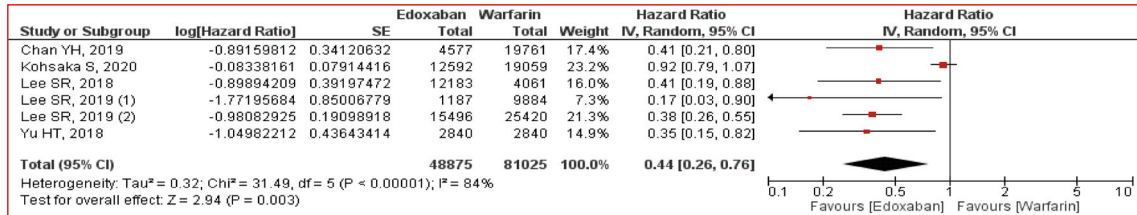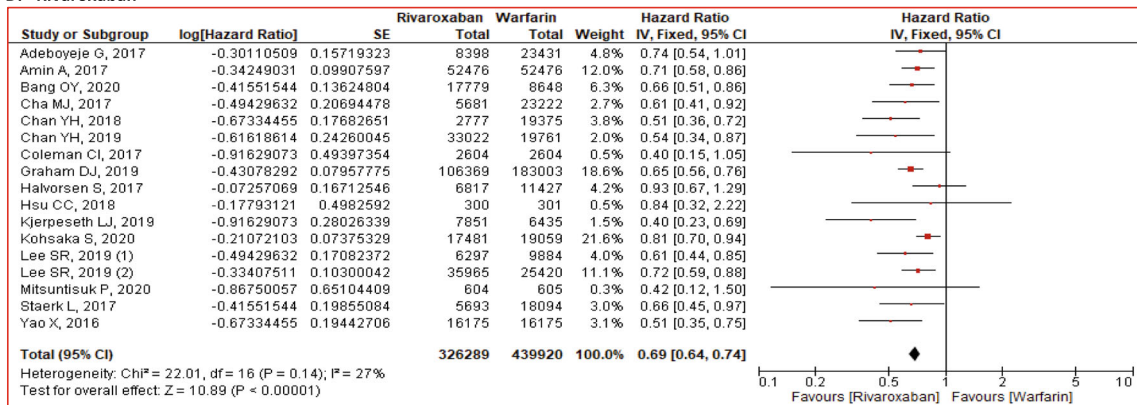
A. Apixaban

Study or Subgroup	log[Hazard Ratio]	SE	Apixaban Total	Warfarin Total	Weight	Hazard Ratio IV, Random, 95% CI
Adeboyeje G, 2017	-0.18632958	0.24148303	3689	23431	5.8%	0.83 [0.52, 1.33]
Amin A, 2017	-0.96758403	0.20573742	20803	20803	6.5%	0.38 [0.25, 0.57]
Bang OY, 2020	-0.99425227	0.29213096	10548	8648	4.8%	0.37 [0.21, 0.66]
Cha MJ, 2017	-1.20064501	0.57214485	2189	23222	1.9%	0.30 [0.10, 0.92]
Chan YH, 2018	-0.7985077	0.20875647	5843	19375	6.4%	0.45 [0.30, 0.68]
Chan YH, 2019	-0.82098055	0.27025792	9952	19761	5.2%	0.44 [0.26, 0.75]
Deitelzweig S, 2017	-0.01005034	0.27282535	7107	7107	5.1%	0.99 [0.58, 1.69]
Graham DJ, 2019	-0.61618614	0.11691735	72921	183003	8.5%	0.54 [0.43, 0.68]
Halvorsen S, 2017	-0.5798185	0.22215417	6506	11427	6.2%	0.56 [0.36, 0.87]
Kjerpeseth LJ, 2019	-0.5798185	0.25394039	10550	6435	5.5%	0.56 [0.34, 0.92]
Kohsaka S, 2020	-0.11653382	0.06559571	22752	19059	9.5%	0.89 [0.78, 1.01]
Lee SR, 2019 (1)	-0.61618614	0.24136762	3395	9884	5.8%	0.54 [0.34, 0.87]
Lee SR, 2019 (2)	-0.39452517	0.12110159	22177	25420	8.4%	0.67 [0.53, 0.85]
Li X, 2017	-0.4462871	0.12053806	38470	38470	8.5%	0.64 [0.51, 0.81]
Mitsuntisuk P, 2020	0.09531018	0.54116189	405	605	2.1%	1.10 [0.38, 3.18]
Staerk L, 2017	-0.63487827	0.22767767	6899	18094	6.0%	0.53 [0.34, 0.83]
Yao X, 2016	-1.42711636	0.36406698	7695	7695	3.7%	0.24 [0.12, 0.49]
Total (95% CI)			**251901**	**442439**	**100.0%**	**0.57 [0.48, 0.68]**

Heterogeneity: Tau² = 0.08; Chi² = 56.66, df = 16 (P < 0.00001); I² = 72%
Test for overall effect: Z = 6.39 (P < 0.00001)

Favours [Apixaban]   Favours [Warfarin]

B. Dabigatran

Study or Subgroup	log[Hazard Ratio]	SE	Dabigatran Total	Warfarin Total	Weight	Hazard Ratio IV, Random, 95% CI
Adeboyeje G, 2017	-0.75502258	0.15792107	8539	23431	6.6%	0.47 [0.34, 0.64]
Amin A, 2017	-0.61618614	0.21719052	16731	16731	5.4%	0.54 [0.35, 0.83]
Bang OY, 2020	-0.61618614	0.16339674	11414	8648	6.5%	0.54 [0.39, 0.74]
Cha MJ, 2017	-0.82325587	0.29646061	3741	23222	4.0%	0.44 [0.25, 0.78]
Chan YH, 2018	-0.69314718	0.16963993	20079	19375	6.4%	0.50 [0.36, 0.70]
Chan YH, 2019	-0.73396918	0.25886466	22371	19761	4.6%	0.48 [0.29, 0.80]
Coleman CI, 2017	-1.46967597	1.07891367	981	981	0.5%	0.23 [0.03, 1.91]
Graham DJ, 2015	-1.07880966	0.14751978	67207	67207	6.8%	0.34 [0.25, 0.45]
Graham DJ, 2019	-0.96758403	0.10616532	86293	183003	7.7%	0.38 [0.31, 0.47]
Halvorsen S, 2017	-0.77652879	0.21615138	7925	11427	5.4%	0.46 [0.30, 0.70]
Hernandez I, 2015	-1.13943428	0.23375193	1302	8102	5.0%	0.32 [0.20, 0.51]
Hsu CC, 2018	0.22234323	0.57379001	305	305	1.6%	1.25 [0.41, 3.85]
Kjerpeseth LJ, 2019	-1.27296568	0.35365302	5984	6435	3.2%	0.28 [0.14, 0.56]
Kohsaka S, 2020	-0.23572233	0.09261334	8003	19059	8.0%	0.79 [0.66, 0.95]
Lee SR, 2019 (1)	-1.17118298	0.25502314	4241	9884	4.7%	0.31 [0.19, 0.51]
Lee SR, 2019 (2)	-0.80296205	0.14969207	17745	25420	6.8%	0.45 [0.33, 0.60]
Mitsuntisuk P, 2020	-1.77195684	1.07642481	441	605	0.5%	0.17 [0.02, 1.40]
Staerk L, 2017	-0.99425227	0.1671987	12613	18094	6.4%	0.37 [0.27, 0.51]
Villines TC, 2015	-0.71334989	0.24700721	12793	12793	4.8%	0.49 [0.30, 0.80]
Yao X, 2016	-1.02165125	0.22700863	14307	14307	5.2%	0.36 [0.23, 0.56]
Total (95% CI)			**323015**	**488790**	**100.0%**	**0.44 [0.38, 0.52]**

Heterogeneity: Tau² = 0.07; Chi² = 56.86, df = 19 (P < 0.0001); I² = 67%
Test for overall effect: Z = 10.26 (P < 0.00001)

Favours [Dabigatran]   Favours [Warfarin]

C. Edoxaban

Study or Subgroup	log[Hazard Ratio]	SE	Edoxaban Total	Warfarin Total	Weight	Hazard Ratio IV, Random, 95% CI
Chan YH, 2019	-0.89159812	0.34120632	4577	19761	17.4%	0.41 [0.21, 0.80]
Kohsaka S, 2020	-0.08338161	0.07914416	12592	19059	23.2%	0.92 [0.79, 1.07]
Lee SR, 2018	-0.89894209	0.39197472	12183	4061	16.0%	0.41 [0.19, 0.88]
Lee SR, 2019 (1)	-1.77195684	0.85006779	1187	9884	7.3%	0.17 [0.03, 0.90]
Lee SR, 2019 (2)	-0.98082925	0.19098918	15496	25420	21.3%	0.38 [0.26, 0.55]
Yu HT, 2018	-1.04982212	0.43643414	2840	2840	14.9%	0.35 [0.15, 0.82]
Total (95% CI)			**48875**	**81025**	**100.0%**	**0.44 [0.26, 0.76]**

Heterogeneity: Tau² = 0.32; Chi² = 31.49, df = 5 (P < 0.00001); I² = 84%
Test for overall effect: Z = 2.94 (P = 0.003)

Favours [Edoxaban]   Favours [Warfarin]

D. Rivaroxaban

Study or Subgroup	log[Hazard Ratio]	SE	Rivaroxaban Total	Warfarin Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Adeboyeje G, 2017	-0.30110509	0.15719323	8398	23431	4.8%	0.74 [0.54, 1.01]
Amin A, 2017	-0.34249031	0.09907597	52476	52476	12.0%	0.71 [0.58, 0.86]
Bang OY, 2020	-0.41551544	0.13624804	17779	8648	6.3%	0.66 [0.51, 0.86]
Cha MJ, 2017	-0.49429632	0.20694478	5681	23222	2.7%	0.61 [0.41, 0.92]
Chan YH, 2018	-0.67334455	0.17682651	2777	19375	3.8%	0.51 [0.36, 0.72]
Chan YH, 2019	-0.61618614	0.24260045	33022	19761	2.0%	0.54 [0.34, 0.87]
Coleman CI, 2017	-0.91629073	0.49397354	2604	2604	0.5%	0.40 [0.15, 1.05]
Graham DJ, 2019	-0.43078292	0.07957775	106369	183003	18.6%	0.65 [0.56, 0.76]
Halvorsen S, 2017	-0.07257069	0.16712546	6817	11427	4.2%	0.93 [0.67, 1.29]
Hsu CC, 2018	-0.17793121	0.4982592	300	301	0.5%	0.84 [0.32, 2.22]
Kjerpeseth LJ, 2019	-0.91629073	0.28026339	7851	6435	1.5%	0.40 [0.23, 0.69]
Kohsaka S, 2020	-0.21072103	0.07375329	17481	19059	21.6%	0.81 [0.70, 0.94]
Lee SR, 2019 (1)	-0.49429632	0.17082372	6297	9884	4.0%	0.61 [0.44, 0.85]
Lee SR, 2019 (2)	-0.33407511	0.10300042	35965	25420	11.1%	0.72 [0.59, 0.88]
Mitsuntisuk P, 2020	-0.86750057	0.65104409	604	605	0.3%	0.42 [0.12, 1.50]
Staerk L, 2017	-0.41551544	0.19855084	5693	18094	3.0%	0.66 [0.45, 0.97]
Yao X, 2016	-0.67334455	0.19442706	16175	16175	3.1%	0.51 [0.35, 0.75]
Total (95% CI)			**326289**	**439920**	**100.0%**	**0.69 [0.64, 0.74]**

Heterogeneity: Chi² = 22.01, df = 16 (P = 0.14); I² = 27%
Test for overall effect: Z = 10.89 (P < 0.00001)

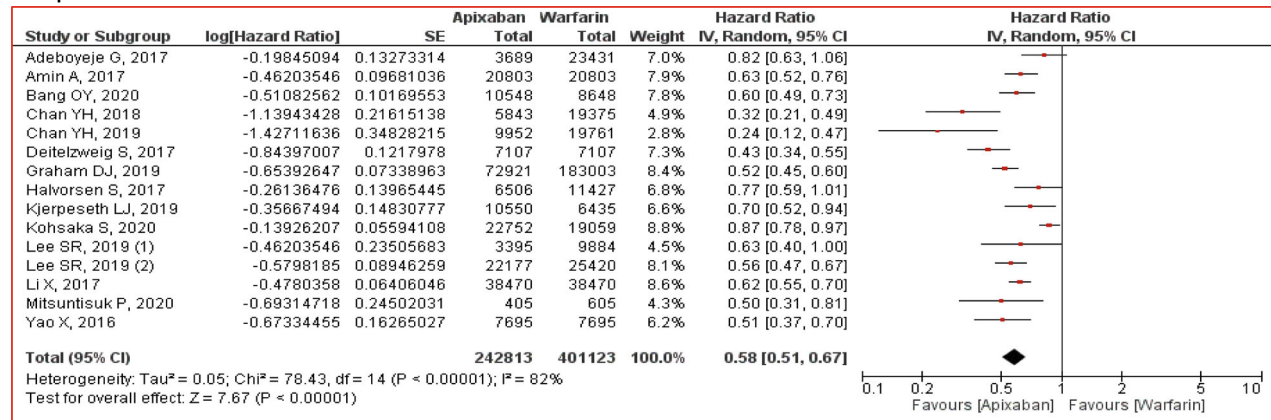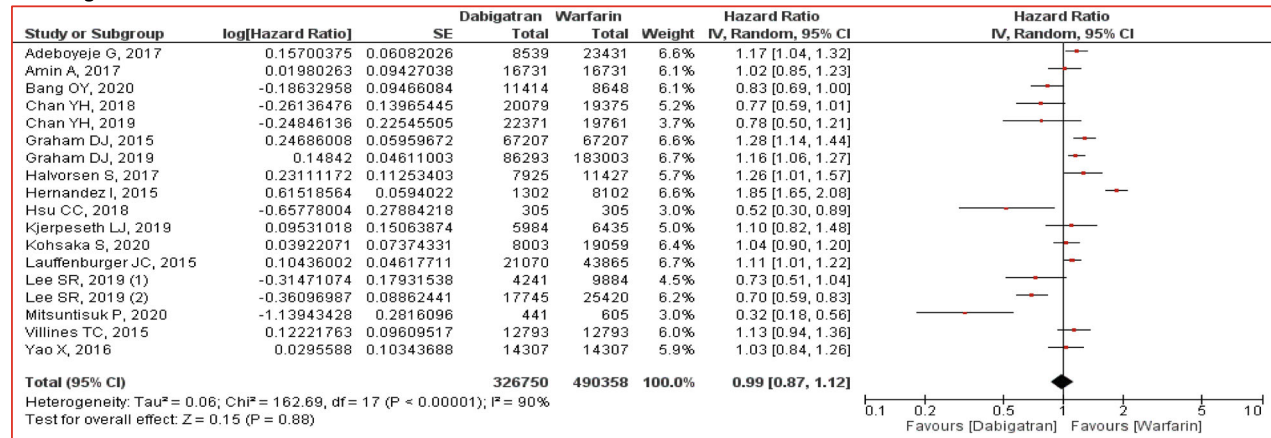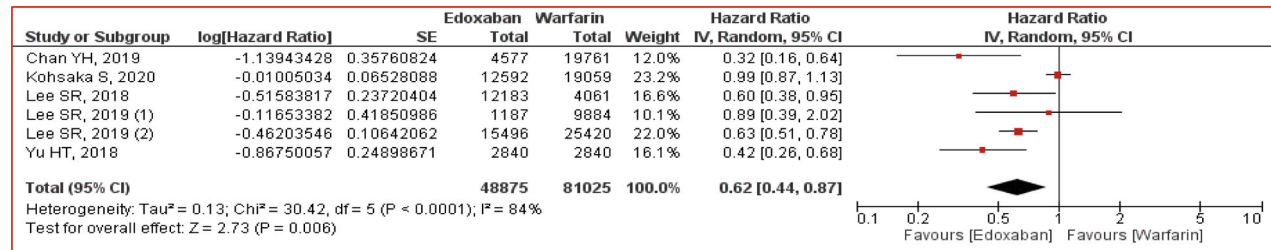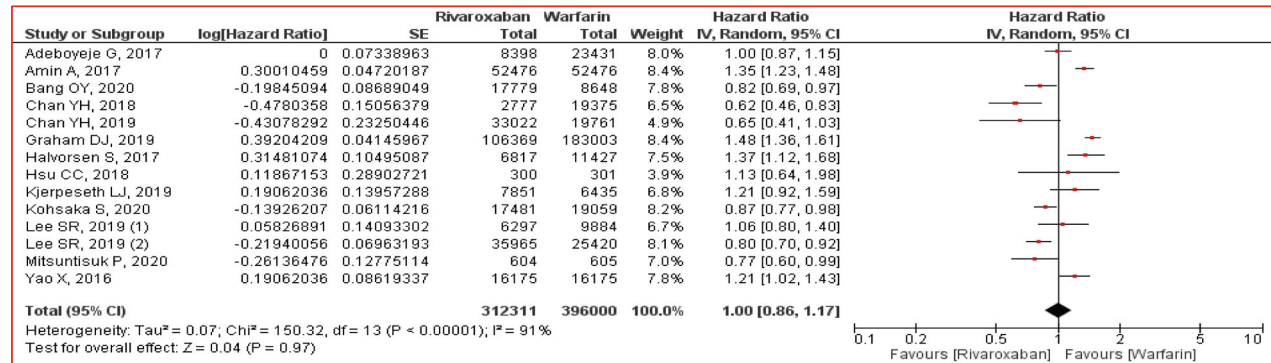Favours [Rivaroxaban]   Favours [Warfarin]

Fig. 6 Comparison of intracranial bleeding between NOACs and warfarin stratified by each agent. **A** apixaban, **B** dabigatran, **C** edoxaban, and **D** rivaroxaban. CI = confidence interval, NOACs = non-vitamin K antagonist oral anticoagulants

A. Apixaban

Study or Subgroup	log[Hazard Ratio]	SE	Apixaban Total	Warfarin Total	Weight	Hazard Ratio IV, Random, 95% CI
Adeboyeje G, 2017	-0.19845094	0.13273314	3689	23431	7.0%	0.82 [0.63, 1.06]
Amin A, 2017	-0.46203546	0.09681036	20803	20803	7.9%	0.63 [0.52, 0.76]
Bang OY, 2020	-0.51082562	0.10169553	10548	8648	7.8%	0.60 [0.49, 0.73]
Chan YH, 2018	-1.13943428	0.21615138	5843	19375	4.9%	0.32 [0.21, 0.49]
Chan YH, 2019	-1.42711636	0.34828215	9952	19761	2.8%	0.24 [0.12, 0.47]
Deitelzweig S, 2017	-0.84397007	0.1217978	7107	7107	7.3%	0.43 [0.34, 0.55]
Graham DJ, 2019	-0.65392647	0.07338963	72921	183003	8.4%	0.52 [0.45, 0.60]
Halvorsen S, 2017	-0.26136476	0.13965445	6506	11427	6.8%	0.77 [0.59, 1.01]
Kjerpeseth LJ, 2019	-0.35667494	0.14830777	10550	6435	6.6%	0.70 [0.52, 0.94]
Kohsaka S, 2020	-0.13926207	0.05594108	22752	19059	8.8%	0.87 [0.78, 0.97]
Lee SR, 2019 (1)	-0.46203546	0.23505683	3395	9884	4.5%	0.63 [0.40, 1.00]
Lee SR, 2019 (2)	-0.5798185	0.08946259	22177	25420	8.1%	0.56 [0.47, 0.67]
Li X, 2017	-0.4780358	0.06406046	38470	38470	8.6%	0.62 [0.55, 0.70]
Mitsuntisuk P, 2020	-0.69314718	0.24502031	405	605	4.3%	0.50 [0.31, 0.81]
Yao X, 2016	-0.67334455	0.16265027	7695	7695	6.2%	0.51 [0.37, 0.70]
Total (95% CI)			**242813**	**401123**	**100.0%**	**0.58 [0.51, 0.67]**

Heterogeneity: Tau² = 0.05; Chi² = 78.43, df = 14 (P < 0.00001); I² = 82%
Test for overall effect: Z = 7.67 (P < 0.00001)

B. Dabigatran

Study or Subgroup	log[Hazard Ratio]	SE	Dabigatran Total	Warfarin Total	Weight	Hazard Ratio IV, Random, 95% CI
Adeboyeje G, 2017	0.15700375	0.06082026	8539	23431	6.6%	1.17 [1.04, 1.32]
Amin A, 2017	0.01980263	0.09427038	16731	16731	6.1%	1.02 [0.85, 1.23]
Bang OY, 2020	-0.18632958	0.09466084	11414	8648	6.1%	0.83 [0.69, 1.00]
Chan YH, 2018	-0.26136476	0.13965445	20079	19375	5.2%	0.77 [0.59, 1.01]
Chan YH, 2019	-0.24846136	0.22545505	22371	19761	3.7%	0.78 [0.50, 1.21]
Graham DJ, 2015	0.24686008	0.05959672	67207	67207	6.6%	1.28 [1.14, 1.44]
Graham DJ, 2019	0.14842	0.04611003	86293	183003	6.7%	1.16 [1.06, 1.27]
Halvorsen S, 2017	0.23111172	0.11253403	7925	11427	5.7%	1.26 [1.01, 1.57]
Hernandez I, 2015	0.61518564	0.0594022	1302	8102	6.6%	1.85 [1.65, 2.08]
Hsu CC, 2018	-0.65778004	0.27884218	305	305	3.0%	0.52 [0.30, 0.89]
Kjerpeseth LJ, 2019	0.09531018	0.15063874	5984	6435	5.0%	1.10 [0.82, 1.48]
Kohsaka S, 2020	0.03922071	0.07374331	8003	19059	6.4%	1.04 [0.90, 1.20]
Lauffenburger JC, 2015	0.10436002	0.04617711	21070	43865	6.7%	1.11 [1.01, 1.22]
Lee SR, 2019 (1)	-0.31471074	0.17931538	4241	9884	4.5%	0.73 [0.51, 1.04]
Lee SR, 2019 (2)	-0.36096987	0.08862441	17745	25420	6.2%	0.70 [0.59, 0.83]
Mitsuntisuk P, 2020	-1.13943428	0.2816096	441	605	3.0%	0.32 [0.18, 0.56]
Villines TC, 2015	0.12221763	0.09609517	12793	12793	6.0%	1.13 [0.94, 1.36]
Yao X, 2016	0.0295588	0.10343688	14307	14307	5.9%	1.03 [0.84, 1.26]
Total (95% CI)			**326750**	**490358**	**100.0%**	**0.99 [0.87, 1.12]**

Heterogeneity: Tau² = 0.06; Chi² = 162.69, df = 17 (P < 0.00001); I² = 90%
Test for overall effect: Z = 0.15 (P = 0.88)

C. Edoxaban

Study or Subgroup	log[Hazard Ratio]	SE	Edoxaban Total	Warfarin Total	Weight	Hazard Ratio IV, Random, 95% CI
Chan YH, 2019	-1.13943428	0.35760824	4577	19761	12.0%	0.32 [0.16, 0.64]
Kohsaka S, 2020	-0.01005034	0.06528088	12592	19059	23.2%	0.99 [0.87, 1.13]
Lee SR, 2018	-0.51583817	0.23720404	12183	4061	16.6%	0.60 [0.38, 0.95]
Lee SR, 2019 (1)	-0.11653382	0.41850986	1187	9884	10.1%	0.89 [0.39, 2.02]
Lee SR, 2019 (2)	-0.46203546	0.10642062	15496	25420	22.0%	0.63 [0.51, 0.78]
Yu HT, 2018	-0.86750057	0.24898671	2840	2840	16.1%	0.42 [0.26, 0.68]
Total (95% CI)			**48875**	**81025**	**100.0%**	**0.62 [0.44, 0.87]**

Heterogeneity: Tau² = 0.13; Chi² = 30.42, df = 5 (P < 0.0001); I² = 84%
Test for overall effect: Z = 2.73 (P = 0.006)

D. Rivaroxaban

Study or Subgroup	log[Hazard Ratio]	SE	Rivaroxaban Total	Warfarin Total	Weight	Hazard Ratio IV, Random, 95% CI
Adeboyeje G, 2017	0	0.07338963	8398	23431	8.0%	1.00 [0.87, 1.15]
Amin A, 2017	0.30010459	0.04720187	52476	52476	8.4%	1.35 [1.23, 1.48]
Bang OY, 2020	-0.19845094	0.08689049	17779	8648	7.8%	0.82 [0.69, 0.97]
Chan YH, 2018	-0.4780358	0.15056379	2777	19375	6.5%	0.62 [0.46, 0.83]
Chan YH, 2019	-0.43078292	0.23250446	33022	19761	4.9%	0.65 [0.41, 1.03]
Graham DJ, 2019	0.39204209	0.04145967	106369	183003	8.4%	1.48 [1.36, 1.61]
Halvorsen S, 2017	0.31481074	0.10495087	6817	11427	7.5%	1.37 [1.12, 1.68]
Hsu CC, 2018	0.11867153	0.28902721	300	301	3.9%	1.13 [0.64, 1.98]
Kjerpeseth LJ, 2019	0.19062036	0.13957288	7851	6435	6.8%	1.21 [0.92, 1.59]
Kohsaka S, 2020	-0.13926207	0.06114216	17481	19059	8.2%	0.87 [0.77, 0.98]
Lee SR, 2019 (1)	0.05826891	0.14093302	6297	9884	6.7%	1.06 [0.80, 1.40]
Lee SR, 2019 (2)	-0.21940056	0.06963193	35965	25420	8.1%	0.80 [0.70, 0.92]
Mitsuntisuk P, 2020	-0.26136476	0.12775114	604	605	7.0%	0.77 [0.60, 0.99]
Yao X, 2016	0.19062036	0.08619337	16175	16175	7.8%	1.21 [1.02, 1.43]
Total (95% CI)			**312311**	**396000**	**100.0%**	**1.00 [0.86, 1.17]**

Heterogeneity: Tau² = 0.07; Chi² = 150.32, df = 13 (P < 0.00001); I² = 91%
Test for overall effect: Z = 0.04 (P = 0.97)

Fig. 7 Comparison of gastrointestinal bleeding between NOACs and warfarin stratified by each agent. **A** apixaban, **B** dabigatran, **C** edoxaban, and **D** rivaroxaban. CI = confidence interval, NOACs = non-vitamin K antagonist oral anticoagulants

been at least partly because of low TTR in warfarin users. Third, we did not conduct subgroup analysis comparing warfarin with a low or high dose of NOACs because of the limited available data. Fourth, among the involved studies, the precise inclusion or exclusion criteria and outcomes definitions varied. Last, even though we involved studies that reported the adjusted HR and 95% CI using either propensity score matching, propensity score weighting, or multi-variate Cox regression, the residual confounding factors with unmeasured variables could not be excluded from this study due to the characteristic of real-world data.

Conclusions

In conclusion, our study demonstrated that NOACs had more efficacy than warfarin in preventing stroke in NVAF patients. NOACs were also related to a lower risk of all-cause mortality, intracranial bleeding, and major bleeding than warfarin. Among NOACs, apixaban and edoxaban might have a better safety and efficacy profile compared to warfarin. A head-to-head RCT that directly compares the specific type of NOACs is needed.

Abbreviations
AF: Atrial fibrillation; CHA2DS2-VASc: Congestive heart failure, Hypertension, Age, Diabetes, previous Stroke/transient ischemic attack, VAScular disease; CI: Confidence interval; CMA: Comprehensive Meta-Analysis; CVA: Cerebrovascular accident; DOAC: Direct oral anticoagulant; GI: Gastrointestinal; HAS-BLED: Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly; HR: Hazard ratio; INR: International normalized ratio; NOAC: Non-vitamin K antagonist oral anticoagulant; NOS: Newcastle-Ottawa scale; NVAF: Non-valvular atrial fibrillation; PRISMA: Preferred reporting items for systematic review and meta-analysis; RCT: Randomized controlled trials; SE: Standard error; VKA: Vitamin K antagonist; VTE: Venous thromboembolism

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s43044-021-00194-1.

Additional file 1:. Supplementary Table 1. Newcastle-Ottawa Scale

Declarations

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References
1. Ceornodolea AD, Bal R, Severens JL (2017) Epidemiology and management of atrial fibrillation and stroke: review of data from four European countries. Stroke Res Treat 2017:1–12. https://doi.org/10.1155/2017/8593207
2. Pistoia F, Sacco S, Tiseo C, Degan D, Ornello R, Carolei A (2016) The epidemiology of atrial fibrillation and stroke. Cardiol Clin 34(2):255–268. https://doi.org/10.1016/j.ccl.2015.12.002
3. Brieger D, Amerena J, Attia J, Bajorek B, Chan KH, Connell C, Freedman B, Ferguson C, Hall T, Haqqani H, Hendriks J, Hespe C, Hung J, Kalman JM, Sanders P, Worthington J, Yan TD, Zwar N (2018) National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation 2018. Heart Lung Circ 27(10):1209–1266. https://doi.org/10.1016/j.hlc.2018.06.1043
4. Chiang C-E, Okumura K, Zhang S, Chao TF, Siu CW, Wei Lim T, Saxena A, Takahashi Y, Siong Teo W (2017) 2017 consensus of the Asia Pacific Heart Rhythm Society on stroke prevention in atrial fibrillation. J Arrhythmia 33(4):345–367. https://doi.org/10.1016/j.joa.2017.05.004
5. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW (2019) 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. J Am Coll Cardiol 74(1):104–132. https://doi.org/10.1016/j.jacc.2019.01.011
6. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, la Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, van Gelder IC, van Putte BP, Watkins CL, ESC Scientific Document Group, Kirchhof P, Kühne M, Aboyans V, Ahlsson A, Balsam P, Bauersachs J, Benussi S, Brandes A, Braunschweig F, Camm AJ, Capodanno D, Casadei B, Conen D, Crijns HJGM, Delgado V, Dobrev D, Drexel H, Eckardt L, Fitzsimons D, Folliguet T, Gale CP, Gorenek B, Haeusler KG, Heidbuchel H, Iung B, Katus HA, Kotecha D, Landmesser U, Leclercq C, Lewis BS, Mascherbauer J, Merino JL, Merkely B, Mont L, Mueller C, Nagy KV, Oldgren J, Pavlović N, Pedretti RFE, Petersen SE, Piccini JP, Popescu BA, Pürerfellner H, Richter DJ, Roffi M, Rubboli A, Scherr D, Schnabel RB, Simpson IA, Shlyakhto E, Sinner MF, Steffel J, Sousa-Uva M, Suwalski P, Svetlosak M, Touyz RM, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, la Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Neil Thomas G, Valgimigli M, van Gelder IC, Watkins CL (2021) 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J 42(5):373–498. https://doi.org/10.1093/eurheartj/ehaa612
7. Hart RG, Pearce LA, Aguilar MI (2007) Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 146(12):857–867. https://doi.org/10.7326/0003-4819-146-12-200706190-00007
8. Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, Baigent C, Huber K, Jespersen J, Kristensen S, Lip GYH, Morais J, Rasmussen L, Siegbahn A, Verheugt FWA, Weitz JI (2013) Vitamin K antagonists in heart disease: current status and perspectives (Section III): position paper of the

Waranugraha *et al. The Egyptian Heart Journal* (2021) 73:70

Page 16 of 17

ESC Working Group on Thrombosis – Task Force on Anticoagulants in Heart Disease. Thromb Haemost 110(12):1087–1107. https://doi.org/10.1160/TH13-06-0443

9. Hylek EM (1996) An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. N Engl J Med 335(8):540–546. https://doi.org/10.1056/NEJM199608223350802

10. 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, the ROCKET AF Steering Committee (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 365(10):883–891. https://doi.org/10.1056/NEJMoa1009638

11. 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 HC, Joyner CD, Wallentin L (2009) Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 361(12):1139–1151. https://doi.org/10.1056/NEJMoa0905561

12. Granger CB, Alexander JH, McMurray JJV et al (2011) Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 365(11):981–992. https://doi.org/10.1056/NEJMoa1107039

13. 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. N Engl J Med 369(22):2093–2104. https://doi.org/10.1056/NEJMoa1310907

14. Freedman B, Potpara TS, Lip GYH (2016) Stroke prevention in atrial fibrillation. Lancet 388(10046):806–817. https://doi.org/10.1016/S0140-6736(16)31257-0

15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 6(7): e1000100. https://doi.org/10.1371/journal.pmed.1000100

16. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Accessed February 22, 2021. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

17. Cleophas TJ, Zwinderman AH (2017) Modern meta-analysis: review and update of methodologies. Springer International Publishing. https://doi.org/10.1007/978-3-319-55895-0

18. Begg CB, Mazumdar M (1994) Operating Characteristics of a Rank Correlation Test for Publication Bias. Biometrics. 50(4):1088–1101. https://doi.org/10.2307/2533446

19. Egger M, Smith GD, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ. 315(7109):629–634. https://doi.org/10.1136/bmj.315.7109.629

20. Waranugraha Y, Rizal A, Setiawan D, Aziz IJ (2021) The benefit of atrioventricular junction ablation for permanent atrial fibrillation and heart failure patients receiving cardiac resynchronization therapy: an updated systematic review and meta-analysis. Indian Pacing Electrophysiol J 21(2): 101–111. https://doi.org/10.1016/j.ipej.2020.12.005

21. Fletcher J (2007) What is heterogeneity and is it important? BMJ. 334(7584): 94–96. https://doi.org/10.1136/bmj.39057.406644.68

22. Waranugraha Y, Rizal A, Setiawan D, Aziz IJ (2021) Additional complex fractionated atrial electrogram ablation does not improve the outcomes of non-paroxysmal atrial fibrillation: A systematic review and meta-analysis of randomized controlled trials. Indian Heart J 73(1):63–73. https://doi.org/10.1016/j.ihj.2020.11.004

23. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR, eds. Introduction to Meta-Analysis. Reprinted. Wiley; 2010.

24. Adeboyeje G, Sylwestrzak G, Barron JJ et al (2017) Major bleeding risk during anticoagulation with warfarin, dabigatran, apixaban, or rivaroxaban in patients with nonvalvular atrial fibrillation. J Manag Care Spec Pharm 23(9):968–978. https://doi.org/10.18553/jmcp.2017.23.9.968

25. Amin A, Keshishian A, Trocio J, Dina O, le H, Rosenblatt L, Liu X, Mardekian J, Zhang Q, Baser O, Vo L (2017) Risk of stroke/systemic embolism, major bleeding and associated costs in non-valvular atrial fibrillation patients who initiated apixaban, dabigatran or rivaroxaban compared with warfarin in the United States Medicare population. Curr Med Res Opin 33(9):1595–1604. https://doi.org/10.1080/03007995.2017.1345729

26. Bang OY, On YK, Lee M-Y et al (2020) The risk of stroke/systemic embolism and major bleeding in Asian patients with non-valvular atrial fibrillation

treated with non-vitamin K oral anticoagulants compared to warfarin: Results from a real-world data analysis. Ai T, ed. PLoS One 15(11):e0242922. https://doi.org/10.1371/journal.pone.0242922

27. Cha M-J, Choi E-K, Han K-D, Lee SR, Lim WH, 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. https://doi.org/10.1161/STROKEAHA.117.018773

28. Chan Y, See L, Tu H et al (2018) Efficacy and safety of apixaban, dabigatran, rivaroxaban, and warfarin in Asians with nonvalvular atrial fibrillation. J Am Heart Assoc 7(8):e008150. https://doi.org/10.1161/JAHA.117.008150

29. Chan Y-H, Lee H-F, See L-C, Tu HT, Chao TF, Yeh YH, Wu LS, Kuo CT, Chang SH, Lip GYH (2019) Effectiveness and safety of four direct oral anticoagulants in Asian patients with nonvalvular atrial fibrillation. Chest. 156(3):529–543. https://doi.org/10.1016/j.chest.2019.04.108

30. Cho MS, Yun JE, Park JJ, Kim YJ, Lee J, Kim H, Park DW, Nam GB (2019) Outcomes after use of standard- and low-dose non–vitamin k oral anticoagulants in Asian patients with atrial fibrillation. Stroke. 50(1):110–118. https://doi.org/10.1161/STROKEAHA.118.023093

31. Coleman CI, Peacock WF, Bunz TJ, Alberts MJ (2017) Effectiveness and safety of apixaban, dabigatran, and rivaroxaban versus warfarin in patients with nonvalvular atrial fibrillation and previous stroke or transient ischemic attack. Stroke. 48(8):2142–2149. https://doi.org/10.1161/STROKEAHA.117.017474

32. Costa OS, Beyer-Westendorf J, Ashton V, Milentijevic D, Moore KT, Bunz TJ, Coleman CI (2020) Effectiveness and safety of rivaroxaban versus warfarin in obese nonvalvular atrial fibrillation patients: analysis of electronic health record data. Curr Med Res Opin 36(7):1081–1088. https://doi.org/10.1080/03007995.2020.1762554

33. Deitelzweig S, Luo X, Gupta K, Trocio J, Mardekian J, Curtice T, Lingohr-Smith M, Menges B, Lin J (2017) Comparison of effectiveness and safety of treatment with apixaban vs. other oral anticoagulants among elderly nonvalvular atrial fibrillation patients. Curr Med Res Opin 33(10):1745–1754. https://doi.org/10.1080/03007995.2017.1334638

34. Graham DJ, Reichman ME, Wernecke M, Zhang R, Southworth MR, Levenson M, Sheu TC, Mott K, Goulding MR, Houstoun M, MaCurdy TE, Worrall C, Kelman JA (2015) Cardiovascular, bleeding, and mortality risks in elderly medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. Circulation. 131(2):157–164. https://doi.org/10.1161/CIRCULATIONAHA.114.012061

35. Graham DJ, Baro E, Zhang R et al (2019) Comparative stroke, bleeding, and mortality risks in older medicare patients treated with oral anticoagulants for nonvalvular atrial fibrillation. Am J Med 132(5):596–604.e11. https://doi.org/10.1016/j.amjmed.2018.12.023

36. Halvorsen S, Ghanima W, Fride Tvete I, Hoxmark C, Falck P, Solli O, Jonasson C (2017) A nationwide registry study to compare bleeding rates in patients with atrial fibrillation being prescribed oral anticoagulants. Eur Heart J - Cardiovasc Pharmacother 3(1):28–36. https://doi.org/10.1093/ehjcvp/pvw031

37. Hernandez I, Baik SH, Piñera A, Zhang Y (2015) Risk of Bleeding With Dabigatran in Atrial Fibrillation. JAMA Intern Med 175(1):18–24. https://doi.org/10.1001/jamainternmed.2014.5398

38. Hsu C-C, Hsu P-F, Sung S-H, Tu ST, Yu BH, Huang CJ, Cheng HM (2018) Is there a preferred stroke prevention strategy for diabetic patients with non-valvular atrial fibrillation? Comparing warfarin, dabigatran and rivaroxaban. Thromb Haemost 118(01):072–081. https://doi.org/10.1160/TH17-02-0095

39. Huybrechts KF, Gopalakrishnan C, Bartels DB, Zint K, Gurusamy VK, Landon J, Schneeweiss S (2020) Safety and effectiveness of dabigatran and other direct oral anticoagulants compared with warfarin in patients with atrial fibrillation. Clin Pharmacol Ther 107(6):1405–1419. https://doi.org/10.1002/cpt.1753

40. Kjerpeseth LJ, Selmer R, Ariansen I, Karlstad Ø, Ellekjær H, Skovlund E (2019) Comparative effectiveness of warfarin, dabigatran, rivaroxaban and apixaban in non-valvular atrial fibrillation: A nationwide pharmacoepidemiological study. Garcia de Frutos P, ed. PLoS One 14(8):e0221500. https://doi.org/10.1371/journal.pone.0221500

41. Kohsaka S, Katada J, Saito K, Jenkins A, Li B, Mardekian J, Terayama Y (2020) Safety and effectiveness of non-vitamin K oral anticoagulants versus warfarin in real-world patients with non-valvular atrial fibrillation: a retrospective analysis of contemporary Japanese administrative claims data. Open Heart 7(1):e001232. https://doi.org/10.1136/openhrt-2019-001232

42. Larsen TB, Skjøth F, Nielsen PB, Kjældgaard JN, Lip GYH. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants

Waranugraha *et al. The Egyptian Heart Journal* (2021) 73:70

Page 17 of 17

and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. BMJ. Published online June 16, 2016:i3189. doi: https://doi.org/10.1136/bmj.i3189

43. Lauffenburger JC, Farley JF, Gehi AK, Rhoney DH, Brookhart MA, Fang G (2015) Effectiveness and safety of dabigatran and warfarin in real-world US patients with non-valvular atrial fibrillation: a retrospective cohort study. J Am Heart Assoc 4(4):e001798. https://doi.org/10.1161/JAHA.115.001798

44. Lee S-R, Choi E-K, Han K-D, Jung J-H, Oh S, Lip GYH (2018) Edoxaban in Asian patients with atrial fibrillation. J Am Coll Cardiol 72(8):838–853. https://doi.org/10.1016/j.jacc.2018.05.066

45. Lee S-R, Choi E-K, Han K-D, Jung JH, Cha MJ, Oh S, Lip GYH (2019) Non–vitamin K antagonist oral anticoagulants in Asian patients with supranormal renal function. Stroke. 50(6):1480–1489. https://doi.org/10.1161/STROKEAHA.118.024264

46. Lee S-R, Choi E-K, Kwon S, Han KD, Jung JH, Cha MJ, Oh S, Lip GYH (2019) Effectiveness and safety of contemporary oral anticoagulants among Asians with nonvalvular atrial fibrillation. Stroke. 50(8):2245–2249. https://doi.org/10.1161/STROKEAHA.119.025536

47. Li X, Deitelzweig S, Keshishian A, Hamilton M, Horblyuk R, Gupta K, Luo X, Mardekian J, Friend K, Nadkarni A, Pan X, Lip GYH (2017) Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in "real-world" clinical practice: A propensity-matched analysis of 76,940 patients. Thromb Haemost 117(06):1072–1082. https://doi.org/10.1160/TH17-01-0068

48. Lip GYH, Pan X, Kamble S, Kawabata H, Mardekian J, Masseria C, Bruno A, Phatak H (2016) Major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban or warfarin: a "real-world" observational study in the United States. Int J Clin Pract 70(9):752–763. https://doi.org/10.1111/ijcp.12863

49. Lip GYH, Keshishian A, Kamble S, Pan X, Mardekian J, Horblyuk R, Hamilton M (2016) Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin: A propensity score matched analysis. Thromb Haemost 116(11):975–986. https://doi.org/10.1160/TH16-05-0403

50. Maura G, Blotière P-O, Bouillon K, Billionnet C, Ricordeau P, Alla F, Zureik M (2015) Comparison of the short-term risk of bleeding and arterial thromboembolic events in nonvalvular atrial fibrillation patients newly treated with dabigatran or rivaroxaban versus vitamin K antagonists: a French Nationwide Propensity-Matched Cohort Study. Circulation. 132(13):1252–1260. https://doi.org/10.1161/CIRCULATIONAHA.115.015710

51. Mitsuntisuk P, Nathisuwan S, Junpanichjaroen A, et al. Real-world comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants vs. warfarin in a developing country. Clin Pharmacol Ther. Published online November 22, 2020:cpt.2090. doi:10.1002/cpt.2090

52. Nielsen PB, Skjøth F, Søgaard M, Kjældgaard JN, Lip GYH, Larsen TB (2017) Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. BMJ. 356:j510. https://doi.org/10.1136/bmj.j510

53. Rutherford O-CW, Jonasson C, Ghanima W, Söderdahl F, Halvorsen S (2020) Comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in atrial fibrillation: a nationwide cohort study. Eur Heart J - Cardiovasc Pharmacother 6(2):75–85. https://doi.org/10.1093/ehjcvp/pvz086

54. Staerk L, Fosbøl EL, Lip GYH, Lamberts M, Bonde AN, Torp-Pedersen C, Ozenne B, Gerds TA, Gislason GH, Olesen JB (2017) Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation: a nationwide cohort study. Eur Heart J 38:907–915. https://doi.org/10.1093/eurheartj/ehw496

55. Villines TC, Schnee J, Fraeman K, Siu K, Reynolds MW, Collins J, Schwartzman E (2015) A comparison of the safety and effectiveness of dabigatran and warfarin in non-valvular atrial fibrillation patients in a large healthcare system. Thromb Haemost 114(12):1290–1298. https://doi.org/10.1160/TH15-06-0453

56. Yao X, Abraham NS, Sangaralingham LR, Bellolio MF, McBane RD, Shah ND, Noseworthy PA (2016) Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. J Am Heart Assoc 5(6):e003725. https://doi.org/10.1161/JAHA.116.003725

57. Yu HT, Yang P-S, Kim T-H, Jang E, Kim D, Uhm JS, Kim JY, Pak HN, Lee MH, Lip GYH, Joung B (2018) Impact of renal function on outcomes with edoxaban in real-world patients with atrial fibrillation: a nationwide cohort study. Stroke. 49(10):2421–2429. https://doi.org/10.1161/STROKEAHA.118.021387

58. Wang YP, Kehar R, Iansavitchene A, Lazo-Langner A (2020) Bleeding risk in nonvalvular atrial fibrillation patients receiving direct oral anticoagulants and warfarin: a systematic review and meta-analysis of observational studies. TH Open 04(03):e145–e152. https://doi.org/10.1055/s-0040-1714918

59. Capodanno D, Capranzano P, Giacchi G, Calvi V, Tamburino C (2013) Novel oral anticoagulants versus warfarin in non-valvular atrial fibrillation: A meta-analysis of 50,578 patients. Int J Cardiol 167(4):1237–1241. https://doi.org/10.1016/j.ijcard.2012.03.148

60. Hicks T, Stewart F, Eisinga A (2016) NOACs versus warfarin for stroke prevention in patients with AF: a systematic review and meta-analysis. Open Heart 3(1):e000279. https://doi.org/10.1136/openhrt-2015-000279

61. Xue Z, Zhou Y, Wu C, Lin J, Liu X, Zhu W (2020) Non-vitamin K antagonist oral anticoagulants in Asian patients with atrial fibrillation: evidences from the real-world data. Heart Fail Rev 25(6):957–964. https://doi.org/10.1007/s10741-019-09878-y

62. 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. https://doi.org/10.1016/S0140-6736(13)62343-0

63. Chan Y-H, Lee H-F, Chao T-F, Wu CT, Chang SH, Yeh YH, See LC, Kuo CT, Chu PH, Wang CL, Lip GYH (2019) Real-world comparisons of direct oral anticoagulants for stroke prevention in asian patients with non-valvular atrial fibrillation: a systematic review and meta-analysis. Cardiovasc Drugs Ther 33(6):701–710. https://doi.org/10.1007/s10557-019-06910-z

64. Proietti M, Romanazzi I, Romiti GF, Farcomeni A, Lip GYH (2018) Real-world use of apixaban for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. Stroke. 49(1):98–106. https://doi.org/10.1161/STROKEAHA.117.018395

65. Wadhera RK, Russell CE, Piazza G (2014) Warfarin versus novel oral anticoagulants: how to choose? Circulation. 130(22):e191–e193. https://doi.org/10.1161/CIRCULATIONAHA.114.010426

66. Mekaj A, Mekaj Y, Duci S, Miftari E (2015) New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. Ther Clin Risk Manag 11:967–977. https://doi.org/10.2147/TCRM.S84210

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