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CLINICAL AND POPULATION SCIENCES

Comparative Effectiveness and Safety of Non-Vitamin K Antagonist Oral Anticoagulants in Atrial Fibrillation Patients

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BACKGROUND AND PURPOSE: Several observational studies have compared the effect of the non-vitamin K antagonist oral anticoagulants to each other in patients with atrial fibrillation. However, confounding by indication is a major problem when comparing non-vitamin K antagonist oral anticoagulant treatments in some of these studies. This meta-analysis was conducted to compare the effectiveness and safety between non-vitamin K antagonist oral anticoagulant and non-vitamin K antagonist oral anticoagulant by only including the propensity score matching studies.

METHODS: We systematically searched the PubMed and Ovid databases until May 2020 to identify relevant observational studies. Hazard ratios (HRs) and 95% CIs of the reported outcomes were collected and then pooled by a random-effects model complemented with an inverse variance heterogeneity or quality effects model.

RESULTS: A total of 17 retrospective cohort studies were included in this meta-analysis. Compared with dabigatran use, the use of rivaroxaban was significantly associated with increased risks of stroke or systemic embolism (HR, 1.16 [95% CI, 1.05–1.29]) and major bleeding (HR, 1.32 [95% CI, 1.24–1.41]), whereas the use of apixaban was associated with a reduced risk of major bleeding (HR, 0.78 [95% CI, 0.67–0.90]) but not stroke or systemic embolism (HR, 0.84 [95% CI, 0.56–1.28]). Compared with rivaroxaban use, the use of apixaban was associated with a decreased risk of major bleeding (HR, 0.63 [95% CI, 0.54–0.73]) but not stroke or systemic embolism (HR, 0.83 [95% CI, 0.67–1.04]). Reanalyses with the inverse variance heterogeneity or quality effects model produced similar results as the random-effects model.

CONCLUSIONS: Current observational comparisons with propensity score matching methods suggest that apixaban might be a better choice compared with dabigatran or rivaroxaban for stroke prevention in atrial fibrillation patients.

Key Words: anticoagulants ■ apixaban ■ atrial fibrillation ■ propensity score ■ safety

Atrial fibrillation (AF) is the most common arrhythmia, and patients with AF are 5-fold more likely to experience a stroke or systemic thromboembolism compared with those without AF.¹ Oral anticoagulants including the non-vitamin K antagonist oral anticoagulants (NOACs; ie, factor Xa inhibitors [rivaroxaban,

edoxaban, and apixaban] and direct thrombin inhibitor [dabigatran]) and warfarin are effective in preventing AF-related stroke. Current guidelines recommend treatment with NOACs as the standard of care in AF given their improved effectiveness and safety effects over warfarin and advantages regarding the ease of use.^{2–4}

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Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
HR	hazard ratio
IPTW	inverse probability of treatment weighting
NOAC	non-vitamin K antagonist oral anticoagulant
RCT	randomized clinical trial
SSE	stroke or systemic embolism

There are still no direct head-to-head randomized clinical trials (RCTs) for comparing effectiveness and safety between the different NOAC drugs. In recent years, several observational studies have directly compared the effectiveness and safety between the NOACs versus one another among AF patients, suggesting that apixaban may be a better choice compared with dabigatran or rivaroxaban in terms of the lower major bleeding risks.^{5–9}

Confounding by indication is a major problem when comparing interventions in real-world studies. Also, some of these studies used conventional multivariable regression models alone to address confounding, but NOAC treatments were not prescribed at random in studies that analyzed results using multivariable regression. Hence, the extraction of adjusted effect estimates is not enough, and there could be bias due to selective prescribing influencing the findings. In contrast, propensity score-based analytical methods could balance patient characteristics and enable a direct comparison of outcomes across the different treatment groups and thereby more closely emulate the properties of an RCT.¹⁰

Such real-world evidence in clinical practice could provide a significant platform for the comparative effectiveness and safety of NOACs and aid physicians in decision-making regarding the choice among NOACs. More recently, several studies with improved analytic methodologies have been published providing data on the outcomes of NOAC versus NOAC in real-world settings.^{11–16} This meta-analysis was conducted to compare the effectiveness and safety between NOAC and NOAC by only including propensity score-based studies.

METHODS

This meta-analysis was conducted according to the guidance from the Cochrane Handbook for Systematic Reviews. The results of this study were presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses directions. We did not obtain ethical approval because only the published studies were included. The data that support the findings of this meta-analysis would be available from the corresponding authors on a reasonable request.

We systematically searched the electronic PubMed and Ovid databases until May 2020 to identify all studies comparing the

effect of one NOAC (dabigatran, rivaroxaban, apixaban, and edoxaban) against another in patients with AF (Table I in the [Data Supplement](#)). Observational studies applied the propensity score-based methods (eg, propensity score matching or inverse probability of treatment weighting [IPTW]) to balance patient characteristics between the two treatment groups. The primary effectiveness outcome was stroke or systemic embolism (SSE), whereas the primary safety outcome was major bleeding. Our secondary effectiveness outcomes included ischemic stroke and all-cause death, whereas the secondary safety outcomes were intracranial bleeding and gastrointestinal bleeding (Table II in the [Data Supplement](#)). Data abstraction and quality assessment were performed by 2 reviewers independently. The Newcastle-Ottawa Scale was used to evaluate the study quality. Hazard ratios (HRs) and 95% CIs of the reported outcomes were collected and then pooled by a random-effects model complemented with an inverse variance heterogeneity or quality effects model.

All the analyses were performed using the Review Manager, version 5.3, software (the Cochrane Collaboration 2014, Nordic Cochrane Centre Copenhagen, Denmark), the Stata software (version 15.0; Stata Corp LP, College Station, TX), and MetaXL (version 5.3). Full details of the literature search strategy, inclusion and exclusion criteria, data abstraction, quality assessment, and statistical analysis were presented in the [Data Supplement](#).

RESULTS

Study Selection

The flowchart of the literature retrieval of this meta-analysis is shown in Figure I in the [Data Supplement](#). A total of 7220 studies from the electronic databases and the reference lists of published reviews were identified after we removed duplicated publications. In the process of the title and abstract screenings, 7189 studies were excluded that did not meet the predefined inclusion criteria. And subsequently, 31 remaining studies were assessed by the full-text screenings, and 14 studies were excluded because (1) 7 studies did not apply the propensity score-based methods and (2) 7 studies used the same data sources (Table III in the [Data Supplement](#)). Finally, a total of 17 retrospective cohort studies^{11,12,14,16–29} were included in this meta-analysis.

Characteristics of the Included Studies

As presented in Table IV in the [Data Supplement](#), 65% of the included studies were derived from nationwide or health insurance claims databases in the United States (n=11), whereas the rest came from Denmark (n=2), China (n=1), Korea (n=1), France (n=1), and Norway (n=1). We noted that some studies in the United States applied the same data sources, but the different comparisons of NOACs or the different outcomes across these studies were included for our analysis. For example, Graham et al and Amin et al extracted the studied populations from the Medicare database, but they reported different end points of analysis (ischemic stroke, all-cause death,

intracranial bleeding, and gastrointestinal bleeding in the study of Graham et al, whereas SSE and major bleeding in the study of Amin et al).

A total of 14 studies^{11,12,14,17,19–23,25–29} used propensity score matching, and 3 studies^{16,18,24} used IPTW to achieve a balanced distribution of confounders between the study groups, respectively. The propensity score-matched variables of included studies are shown in Table V in the [Data Supplement](#). We found that only one study by Lee et al¹⁸ provided the data on edoxaban compared with other NOACs, and thus, the studied comparisons of rivaroxaban versus dabigatran, apixaban versus dabigatran, and apixaban versus rivaroxaban were adopted for our current meta-analysis.

Patient characteristics between NOAC versus NOAC are shown in Table 1. There were no systematic

differences in the baseline patient characteristics including age, the proportion of women, total scores of stroke or bleeding risk predictive models, comorbid diseases, and medications. For the quality assessment, a total of 4, 12, and 1 studies had a Newcastle-Ottawa Scale score of 8, 7, and 6 points, respectively (Table VI in the [Data Supplement](#)). Therefore, all the included studies showed a moderate to high quality and were acceptable.

Comparative Effectiveness and Safety

Crude event rates of the effectiveness and safety outcomes of NOACs (dabigatran, rivaroxaban, and apixaban) to each other are presented in Table VII in the [Data Supplement](#), whereas the pooled HRs of the studied outcomes between NOAC versus NOAC are summarized in Table 2.

Table 1. Baseline Characteristics of the Propensity Score-Matched Patients With Atrial Fibrillation

	Rivaroxaban vs dabigatran			Apixaban vs dabigatran			Apixaban vs rivaroxaban		
	Rivaroxaban	Dabigatran	P value	Apixaban	Dabigatran	P value	Apixaban	Rivaroxaban	P value
Age, y; mean±SD	71.0±10.8	71.0±10.7	NS	72.0±10.7	71.8±10.6	NS	70.8±10.9	70.9±10.8	NS
Women, %	43.7	43.2	NS	44.4	44.4	NS	43.9	44.5	NS
CHADS ₂ (mean±SD)	1.96±1.05	1.90±1.09	NS	2.18±1.24	2.19±1.24	NS	2.30±1.30	2.57±1.25	NS
CHA ₂ DS ₂ -VASc (mean±SD)	3.28±1.71	3.23±1.77	NS	3.33±1.69	3.32±1.74	NS	3.43±1.72	3.47±1.68	NS
HAS-BLED (mean±SD)	2.42±1.18	3.67±1.20	NS	2.58±1.20	2.56±1.24	NS	2.74±1.22	2.71±1.21	NS
Comorbid conditions, %									
Hypertension	78.1	75.9	NS	81.8	81.4	NS	81.6	82.3	NS
Diabetes	29.3	28.9	NS	30.1	30.3	NS	29.9	30.2	NS
Heart failure	22.1	20.2	NS	22.5	21.0	NS	22.1	22.8	NS
Hyperlipidemia	42.6	41.4	NS	42.7	41.7	NS	42.2	42.5	NS
Ischemic heart disease	29.1	29.0	NS	28.9	29.1	NS	31.2	30.9	NS
Myocardial infarction	3.0	2.9	NS	3.0	2.8	NS	3.3	3.0	NS
Chronic kidney disease	7.8	7.6	NS	8.5	8.1	NS	8.0	8.0	NS
History of stroke or TIA	6.7	7.0	NS	6.0	6.1	NS	6.7	6.4	NS
History of bleeding	4.3	4.7	NS	5.1	4.9	NS	4.3	4.0	NS
Peripheral artery disease	16.6	15.5	NS	18.3	17.8	NS	20.0	19.7	NS
Chronic lung disease	15.4	15.4	NS	16.1	16.5	NS	16.2	16.2	NS
Medications, %									
Antiplatelet drugs	13.0	11.7	NS	20.2	19.1	NS	22.0	20.5	NS
NSAIDs	21.9	19.4	NS	20.8	18.9	NS	21.2	21.6	NS
Warfarin	NA	NA	NA	NA	NA	NA	12.5	12.5	NS
Amiodarone or dronedarone	8.4	8.2	NS	9.7	10.7	NS	9.6	10.4	NS
β-Blockers	63.6	62.8	NS	66.6	66.6	NS	67.0	66.7	NS
Statins	56.3	55.9	NS	58.4	58.5	NS	57.2	57.5	NS
ACE inhibitors or ARBs	50.8	49.4	NS	55.5	56.0	NS	46.9	49.3	NS
Calcium channel blockers	39.3	38.7	NS	41.0	41.2	NS	41.1	41.3	NS
Digoxin	11.2	11.3	NS	11.1	11.2	NS	11.1	11.3	NS
Diuretics	20.4	20.4	NS	20.0	19.9	NS	20.1	20.0	NS
Proton-pump inhibitors	29.0	28.7	NS	29.3	29.2	NS	27.9	28.3	NS
H2 blockers	NA	NA	NA	NA	NA	NS	5.3	5.3	NS

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HAS-BLED, hypertension, abnormal liver/renal function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; NA, not available; NS, nonsignificant; and TIA, transient ischemic attack.

Primary Outcomes Comparing NOAC Versus NOAC

Rivaroxaban Versus Dabigatran

As shown in Figure 1, the use of rivaroxaban compared with dabigatran was significantly associated with increased risks of SSE (1.39% versus 1.19%; HR, 1.16 [95% CI, 1.05–1.29]) and major bleeding (1.99% versus 1.60%; HR, 1.32 [95% CI, 1.24–1.41]) with no statistical heterogeneity ($I^2=0\%$).

Apixaban Versus Dabigatran

As presented in Figure 2, there was no significant difference in SSE (1.15% versus 1.39%; HR, 0.84 [95% CI, 0.56–1.28]) between the two groups, but apixaban was associated with a reduced risk of major bleeding compared with dabigatran (1.34% versus 1.94%; HR, 0.78 [95% CI, 0.67–0.90]). To examine the source of heterogeneity for SSE ($I^2=85\%$) and major bleeding ($I^2=61\%$), we found the study of Amin et al²¹ was only restricted to patients aged ≥ 65 years. As such, we excluded this study and then reperformed the meta-analysis. With this adjustment, the pooled HRs were not significantly changed, but the I^2 values of SSE and major bleeding were reduced to 2% and 55%, respectively.

Apixaban Versus Rivaroxaban

As shown in Figure 3, the outcome of SSE was comparable between apixaban versus rivaroxaban (0.98% versus 1.24%; HR, 0.83 [95% CI, 0.67–1.04]). Compared with rivaroxaban use, the use of apixaban was significantly

associated with a decreased risk of major bleeding (1.42% versus 5.07%; HR, 0.63 [95% CI, 0.54–0.73]). High heterogeneity was observed for SSE ($I^2=80\%$) and major bleeding ($I^2=83\%$). We excluded the study of Amin et al²¹ that only evaluated the safety and effectiveness of NOACs in the elderly and found that the pooled HRs were not significantly changed.

Secondary Outcomes Comparing NOAC Versus NOAC

As shown in Figures II and III in the [Data Supplement](#), the use of rivaroxaban versus dabigatran was significantly associated with increased risks of all-cause death (HR, 1.24 [95% CI, 1.07–1.45]), intracranial bleeding (HR, 1.74 [95% CI, 1.54–1.97]), and gastrointestinal bleeding (HR, 1.13 [95% CI, 1.01–1.26]) but yielded no difference in ischemic stroke. Compared with dabigatran use, the use of apixaban was associated with a reduced risk of gastrointestinal bleeding (HR, 0.60 [95% CI, 0.48–0.75]) but associated with an increase in intracranial bleeding (HR, 1.31 [95% CI, 1.09–1.57]). Similar risks of ischemic stroke and all-cause death were observed between apixaban versus dabigatran (Figure IV in the [Data Supplement](#)). Apixaban versus rivaroxaban was associated with decreased risks of intracranial bleeding (HR, 0.86 [95% CI, 0.74–0.98]) and gastrointestinal bleeding (HR, 0.58 [95% CI, 0.44–0.77]) but had a comparable risk of ischemic stroke (Figure V in the [Data Supplement](#)).

Table 2. Pooled HRs of the Efficacy and Safety Outcomes Between Non-Vitamin K Antagonist Oral Anticoagulant Versus Non-Vitamin K Antagonist Oral Anticoagulant in Patients With Atrial Fibrillation

	SSE	Ischemic stroke	All-cause death	Major bleeding	Intracranial bleeding	Gastrointestinal bleeding
Rivaroxaban vs dabigatran						
No. of effect estimates	6	9	5	9	10	10
Crude event rates	1.39% vs 1.19%	0.82% vs 0.79%	1.06% vs 1.03%	1.99% vs 1.60%	0.35% vs 0.22%	1.40% vs 1.34%
HRs and 95% CIs	1.16 (1.05–1.29)	0.97 (0.90–1.04)	1.24 (1.07–1.45)	1.32 (1.24–1.41)	1.74 (1.54–1.97)	1.13 (1.01–1.26)
<i>P</i> value	0.003	0.40	0.006	<0.00001	<0.00001	0.03
I^2 statistic	0%	0%	67%	0%	0%	74%
Apixaban vs dabigatran						
No. of effect estimates	5	5	2	9	6	6
Crude event rates	1.15% vs 1.39%	0.77% vs 0.79%	0.66% vs 0.82%	1.34% vs 1.94%	0.25% vs 0.24%	0.69% vs 1.40%
HRs and 95% CIs	0.84 (0.56–1.28)	0.95 (0.82–1.09)	0.92 (0.82–1.03)	0.78 (0.67–0.90)	1.31 (1.09–1.57)	0.60 (0.48–0.75)
<i>P</i> value	0.43	0.47	0.14	0.0007	0.004	<0.00001
I^2 statistic	85%	47%	0%	61%	17%	84%
Apixaban vs rivaroxaban						
No. of effect estimates	5	4	1	9	5	5
Crude event rates	0.98% vs 1.24%	0.78% vs 0.87%	...	1.42% vs 5.07%	0.29% vs 0.39%	0.77% vs 1.19%
HRs and 95% CIs	0.83 (0.67–1.04)	0.95 (0.83–1.08)	...	0.63 (0.54–0.73)	0.86 (0.74–0.98)	0.58 (0.44–0.77)
<i>P</i> value	0.11	0.40	...	<0.00001	0.03	0.0002
I^2 statistic	80%	63%	...	83%	25%	94%

HR indicates hazard ratio; and SSE, stroke or systemic embolism.

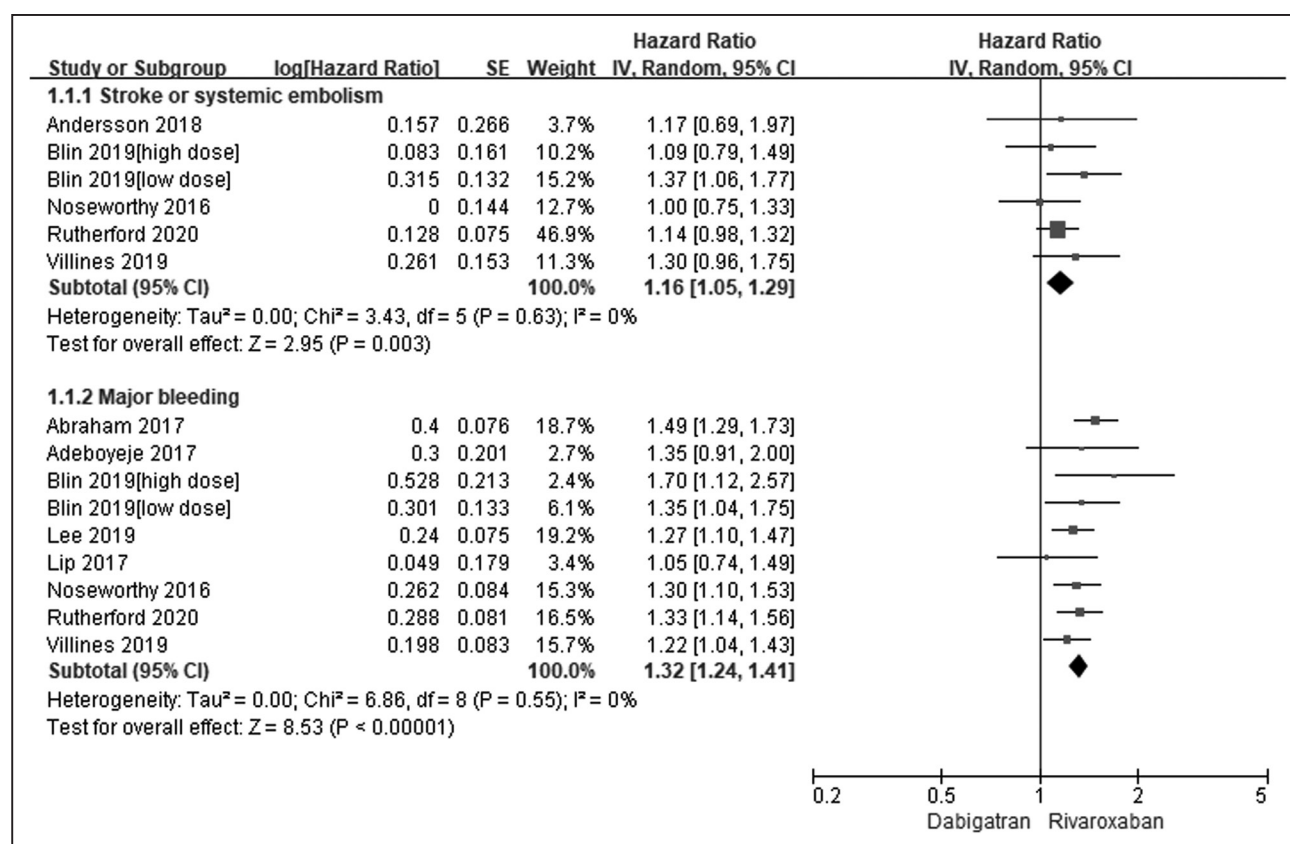


Figure 1. Comparing the primary outcomes including stroke or systemic embolism and major bleeding of rivaroxaban with dabigatran in patients with atrial fibrillation.

IV indicates inverse of the variance.

Sensitivity Analysis and Subgroup Analysis

For the primary outcomes of SSE and major bleeding, reanalyses with an inverse variance heterogeneity or quality effects model suggested similar results as the abovementioned analysis with a random-effects model (Figures VI through VIII in the [Data Supplement](#)). In the sensitivity analysis, the results were consistent with the main analysis after we excluded the studies based on the method of IPTW (Figures IX through XI in the [Data Supplement](#)) or only included the studies with a follow-up of <1 year (Figures XII through XIV in the [Data Supplement](#)). The results of the subgroup analyses are presented in Table 3. There were no significant interactions regarding primary outcomes between NOAC and NOAC stratified by age (Figures XV through XVII in the [Data Supplement](#)). Americans had fewer risks of SSE and major bleeding than non-Americans in the groups of apixaban versus dabigatran, or apixaban versus rivaroxaban, but not rivaroxaban versus dabigatran (Figures XVIII through XX in the [Data Supplement](#)).

Publication Bias

For the primary effectiveness and safety outcomes, there were seemingly no potential publication biases

by inspecting the funnel plots (Figure XXI in the [Data Supplement](#)). In addition, the Egger and Begg tests suggested no publication bias (all $P > 0.1$). For the secondary outcomes, there were no publication biases inspected by the funnel plots (Figure XXII in the [Data Supplement](#)).

DISCUSSION

In the present study, our results based on the data of observational studies with proper matching techniques and a large sample size indicated the following: (1) when compared with dabigatran use, the use of rivaroxaban was associated with increased risks of SSE and major bleeding; (2) when compared with dabigatran or rivaroxaban, apixaban was found to have a reduced risk of major bleeding but a similar risk of SSE; and (3) compared with dabigatran or apixaban, rivaroxaban was associated with increased risks of intracranial bleeding and gastrointestinal bleeding, whereas the risk of ischemic stroke was comparable among the three NOACs.

Current guidelines have recommended NOACs as the first choice in the management of nonvalvular AF patients.^{2,4} However, the effectiveness and safety profiles among NOACs are undefined because of the lack of head-to-head RCTs, leaving physicians with a dilemma in

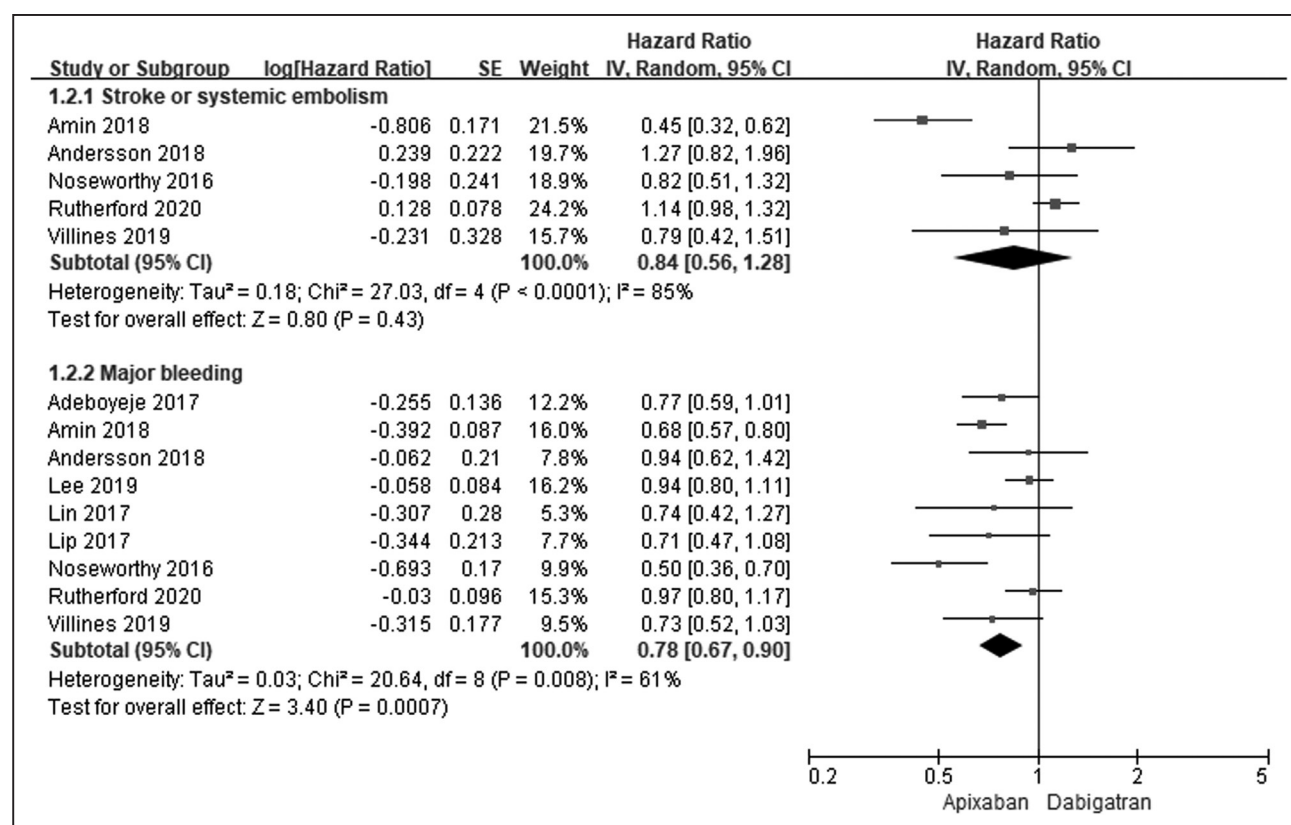


Figure 2. Comparing the primary outcomes including stroke or systemic embolism and major bleeding of apixaban with dabigatran in patients with atrial fibrillation.

IV indicates inverse of the variance.

decisions of initial therapeutic choices. In 2012, Schneeweiss et al³⁰ performed the first indirect comparisons among NOACs by including 44 535 patients with AF enrolled in phase III RCTs for dabigatran, rivaroxaban, and apixaban. The authors found no significant differences in term of effectiveness outcomes between the NOAC groups, whereas apixaban had a better safety profile than rivaroxaban or dabigatran.³⁰ In addition, meta-analyses based on the data of observational studies indirectly compared one NOAC with another via a common comparator, warfarin.^{31–33} Also, several observational studies and meta-analyses provided a significant platform for the direct comparative effectiveness and safety profiles between NOACs.^{5,6,9} These indirect and direct comparisons consistently observed broadly similar effectiveness profiles between NOAC agents but suggested that apixaban could be safer for stroke prevention compared with dabigatran or rivaroxaban.

Nevertheless, some studies only used conventional multivariable logistic or survival regression models to address the potential confounders. Pooling data of heterogeneous real-world studies without proper matching statistical techniques may influence the reliability of their findings. Indeed, confounding by indication when comparing NOAC treatments should be considered when interpreting the findings of real-world data. Propensity score

matching and IPTW are increasingly used to reduce confounding due to an imbalance in study covariates.

In our current study, all 17 included studies applied the methods of propensity score matching or IPTW to achieve a balanced patient characteristic between the NOAC groups when comparisons are made. Consistent with findings of previous meta-analyses,^{5,6} the results of our direct comparisons showed that apixaban produced less risk of major bleeding than dabigatran or rivaroxaban, providing updated evidence in support of apixaban for preventing AF-related stroke. Of note, Bonde et al¹³ performed an instrumental variable analysis of an AF cohort, suggesting that rivaroxaban was associated with a higher risk of major bleeding compared with apixaban.

In contrast to previous studies suggesting no statistically significant efficacy differences among 3 NOACs,^{5,6} our study with a large sample size has demonstrated that rivaroxaban produced a significantly higher risk of SSE than dabigatran. Although Douros et al⁶ suggested that the use of apixaban compared with dabigatran was associated with a nonsignificant increased risk of intracranial bleeding (HR, 1.27 [95% CI, 0.98–1.63]), our current data show that apixaban versus dabigatran was significantly associated with an increase in intracranial bleeding (HR, 1.31 [95% CI, 1.09–1.57]).

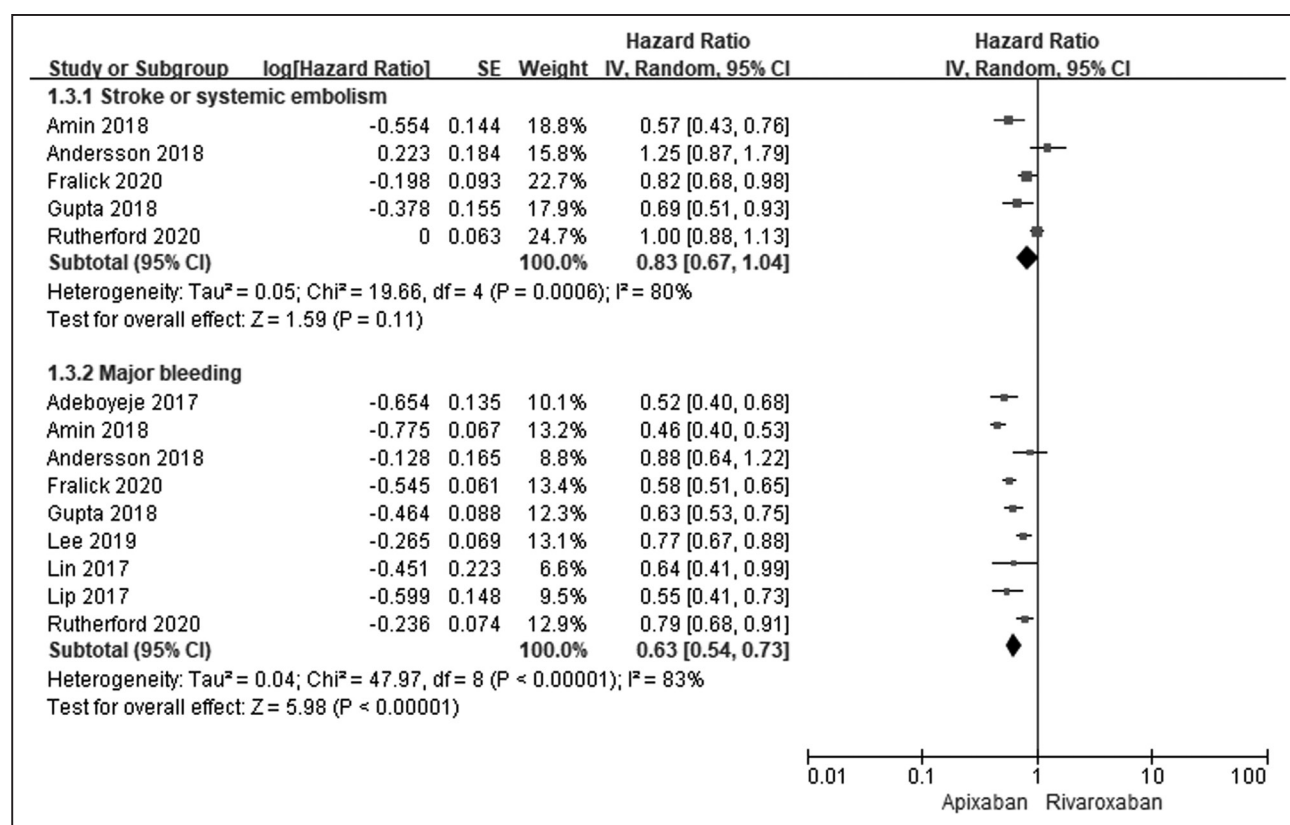


Figure 3. Comparing the primary outcomes including stroke or systemic embolism and major bleeding of apixaban with rivaroxaban in patients with atrial fibrillation.

IV indicates inverse of the variance.

Because there are no head-to-head comparisons between NOACs, there is no direct evidence to inform physicians and patients on the choices among NOACs in relation to effectiveness and safety. Our current meta-analysis utilizing the real-world data was designed to directly compare the effectiveness and safety profiles of 3 individual NOAC drugs in patients with AF. Our results strengthen the validity of apixaban superior to dabigatran or rivaroxaban for stroke prevention in AF. Real-world studies using propensity score-based matching methods to balance patient characteristics could to some degree reduce confounding due to imbalance in study covariates. However, the propensity score-based matching methods in previous observational studies still could not control for all the unknown or unmeasurable confounders, which could have underestimated stroke and bleeding risks between NOACs.

Populations in the RCTs are generally selected with strict inclusion/exclusion criteria, and whether the results of RCTs could be applied to patients in routine care is unclear. Real-world studies usually act as a complementary source of knowledge, and their results are beneficial to validate the RCT findings. If RCTs and real-world studies point toward similar findings, they will provide robustness evidence supporting the validity of apixaban in clinical settings. Until head-to-head RCTs that reflect

routine use of NOACs are available, our direct comparisons based on real-world studies could help clinicians in decision-making for the choice of NOACs among patients with AF.

Strengths and Limitations

To our best knowledge, this was the first meta-analysis using propensity score-based matching techniques to balance patient characteristics before a direct comparison between NOACs. Another strength of this study was that the results of analyses with the inverse variance heterogeneity or quality effects models were essentially identical to those of primary analysis with the random-effects model.

Nevertheless, we should acknowledge several limitations of this meta-analysis. First, associations rather than causality could be evaluated due to the nature of retrospective cohorts included for analysis. Second, despite proper adjustments and matching in the included studies, potential unmeasured residual confounders (eg, race, patient adherence, persistence, and duration of NOAC treatments) will still exist at both individual trial and meta-analysis levels, which might have accounted for the heterogeneity identified for some reported outcomes. Third, except for death, no

Table 3. Subgroup Analysis of the Primary Outcomes Between Non-Vitamin K Antagonist Oral Anticoagulant Versus Non-Vitamin K Antagonist Oral Anticoagulant in Patients With Atrial Fibrillation

	Rivaroxaban vs dabigatran			Apixaban vs dabigatran			Apixaban vs rivaroxaban		
	No. of effect estimates	HRs and 95% CIs	<i>P</i> _{interaction}	No. of effect estimates	HRs and 95% CIs	<i>P</i> _{interaction}	No. of effect estimates	HRs and 95% CIs	<i>P</i> _{interaction}
SSE									
Overall	6	1.16 (1.05–1.29)		5	0.84 (0.56–1.28)		5	0.83 (0.67–1.04)	
Age, y									
≤70	3	1.06 (0.87–1.28)		2	1.03 (0.67–1.58)		2	0.98 (0.65–1.48)	
>70	3	1.06 (0.87–1.28)	1.00	3	0.74 (0.38–1.47)	0.43	3	0.75 (0.51–1.08)	0.33
Location									
Americans	2	1.13 (0.88–1.46)		3	0.63 (0.41–0.99)		3	0.70 (0.56–0.87)	
Non-Americans	4	1.17 (1.05–1.32)	0.81	2	1.15 (1.00–1.33)	0.01	2	1.05 (0.88–1.25)	0.005
Major bleeding									
Overall	9	1.32 (1.24–1.41)		9	0.78 (0.67–0.90)		9	0.63 (0.54–0.73)	
Age, y									
≤70	5	1.37 (1.22–1.54)		5	0.71 (0.57–0.88)		5	0.61 (0.52–0.71)	
>70	4	1.28 (1.18–1.40)	0.35	4	0.83 (0.68–1.01)	0.29	4	0.65 (0.50–0.84)	0.12
Location									
Americans	5	1.40 (1.28–1.53)		6	0.68 (0.61–0.76)		6	0.55 (0.49–0.62)	
Non-Americans	4	1.33 (1.20–1.46)	0.42	3	0.95 (0.85–1.07)	<0.0001	3	0.79 (0.71–0.86)	<0.00001

HR indicates hazard ratio; and SSE, stroke or systemic embolism.

other cardiovascular events (eg, myocardial infarction and hospitalization) were included in the quantitative syntheses of efficacy outcomes because the corresponding number of included studies were small. Fourth, comparative effectiveness and safety of edoxaban versus other NOACs could not be assessed due to the insufficient studies. Finally, the dosage of NOACs was not considered in the subgroup analysis due to the limiting data. Finally, we could not perform a subgroup analysis based on race/ethnic diversity due to the limited data reported in the included studies.

Conclusions

Current observational comparisons with propensity score-based matching methods suggest that apixaban might be a better choice compared with dabigatran or rivaroxaban for stroke prevention in patients with AF.

ARTICLE INFORMATION

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Disclosures

Dr Lip is a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseen, and Daiichi-Sankyo and is a speaker for Bayer, Bristol Myers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. The other authors report no conflicts.

Supplemental Materials

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REFERENCES

- Lip G, Freedman B, De Caterina R, Potpara TS. Stroke prevention in atrial fibrillation: past, present and future. Comparing the guidelines and practical decision-making. *Thromb Haemost*. 2017;117:1230–1239. doi: 10.1160/TH16-11-0876
- January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Ellnor PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the heart rhythm society in collaboration with the society of thoracic surgeons. *Circulation*. 2019;140:R665. doi: 10.1016/j.jacc.2019.01.011
- Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H, Heidbuchel H, Hendriks J, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962. doi: 10.1093/eurheartj/ehw210
- Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, Lane DA, Ruff CT, Turakhia M, Werring D, et al. Antithrombotic therapy for atrial

- fibrillation CHEST guideline and expert panel report. *Chest*. 2018;154:1121–1201. doi: 10.1016/j.chest.2018.07.040
5. Li G, Lip GYH, Holbrook A, Chang Y, Larsen TB, Sun X, Tang J, Mbuagbaw L, Witt DM, Crowther M, et al. Direct comparative effectiveness and safety between non-vitamin K antagonist oral anticoagulants for stroke prevention in nonvalvular atrial fibrillation: a systematic review and meta-analysis of observational studies. *Eur J Epidemiol*. 2019;34:173–190. doi: 10.1007/s10654-018-0415-7
 6. Douros A, Durand M, Doyle CM, Yoon S, Reynier P, Filion KB. Comparative effectiveness and safety of direct oral anticoagulants in patients with atrial fibrillation: a systematic review and meta-analysis of observational studies. *Drug Safety*. 2019;42:1135–1148. doi: 10.1007/s40264-019-00842-1
 7. Bai Y, Shi XB, Ma CS, Lip G. Meta-analysis of effectiveness and safety of oral anticoagulants in atrial fibrillation with focus on apixaban. *Am J Cardiol*. 2017;120:1689–1695. doi: 10.1016/j.amjcard.2017.07.072
 8. Proietti M, Romanazzi I, Romiti GF, Farcomeni A, Lip G. Real-world use of apixaban for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. *Stroke*. 2018;49:98–106. doi: 10.1161/STROKEAHA.117.018395
 9. Xue Z, Zhou Y, Wu C, Lin J, Liu X, Zhu W. Non-vitamin K antagonist oral anticoagulants in Asian patients with atrial fibrillation: evidences from the real-world data. *Heart Fail Rev*. 2020;25:957–964. doi: 10.1007/s10741-019-09878-y
 10. Allan V, Ramagopalan SV, Mardekian J, Jenkins A, Li X, Pan X, Luo X. Propensity score matching and inverse probability of treatment weighting to address confounding by indication in comparative effectiveness research of oral anticoagulants. *J Comp Eff Res*. 2020;9:603–614. doi: 10.2217/ce-2020-0013
 11. Rutherford OW, Jonasson C, Ghanima W, Söderdahl F, Halvorsen S. Comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in atrial fibrillation: a nationwide cohort study. *Eur Heart J - Cardiovasc Pharmacother*. 2020;6:75–85. doi: 10.1093/ehjcp/pvz086
 12. Fralick M, Colacci M, Schneeweiss S, Huybrechts KF, Lin KJ, Gagne JJ. Effectiveness and safety of apixaban compared with rivaroxaban for patients with atrial fibrillation in routine practice. *Ann Intern Med*. 2020;172:463. doi: 10.7326/M19-2522
 13. Bonde AN, Martinussen T, Lee CJY, Lip GYH, Staerk L, Bang CN, Bhattacharya J, Gislason G, Torp-Pedersen C, Olesen JB, et al. Rivaroxaban versus apixaban for stroke prevention in atrial fibrillation. *Circulation: Cardiovascular Quality and Outcomes*. 2020;13. doi: 10.1161/CIRCOUTCOMES.119.006058
 14. Villines TC, Ahmad A, Petrini M, Tang W, Evans A, Rush T, Thompson D, Oh K, Schwartzman E. Comparative safety and effectiveness of dabigatran vs. rivaroxaban and apixaban in patients with non-valvular atrial fibrillation: a retrospective study from a large healthcare system. *Eur Heart J Cardiovasc Pharmacother*. 2019;5:80–90. doi: 10.1093/ehjcp/pvy044
 15. Meng SW, Lin TT, Liao MT, Chen HM, Lai CL. Direct comparison of low-dose dabigatran and rivaroxaban for effectiveness and safety in patients with non-valvular atrial fibrillation. *Acta Cardiol Sin*. 2019;35:42–54. doi: 10.6515/ACS.201901_35(1).20180817A
 16. Graham DJ, Baro E, Zhang R, Liao J, Wernecke M, Reichman ME, Hu M, Illoh O, Wei Y, Goulding MR, et al. Comparative stroke, bleeding, and mortality risks in older medicare patients treated with oral anticoagulants for nonvalvular atrial fibrillation. *Am J Med*. 2019;132:596–604. doi: 10.1016/j.amjmed.2018.12.023
 17. Blin P, Dureau Pournin C, Cottin Y, Bénichou J, Mismetti P, Abouefath A, Lassalle R, Droz C, Moore N. Comparative effectiveness and safety of standard or reduced dose dabigatran vs. rivaroxaban in nonvalvular atrial fibrillation. *Clin Pharmacol Ther*. 2019;105:1439–1455. doi: 10.1002/cpt.1318
 18. Lee S, Choi E, Kwon S, Han K, Jung J, Cha M, Oh S, Lip GYH. Effectiveness and safety of contemporary oral anticoagulants among Asians with nonvalvular atrial fibrillation. *Stroke*. 2019;50:2245–2249. doi: 10.1161/STROKEAHA.119.025536
 19. Gupta K, Trocio J, Keshishian A, Zhang Q, Dina O, Mardekian J, Rosenblatt L, Liu X, Hede S, Nadkarni A, et al. Real-world comparative effectiveness, safety, and health care costs of oral anticoagulants in nonvalvular atrial fibrillation patients in the U.S. department of defense population. *J Manag Care Spec Pharm*. 2018;24:1116–1127. doi: 10.18553/jmcp.2018.17488
 20. Andersson NW, Svanström H, Lund M, Pasternak B, Melbye M. Comparative effectiveness and safety of apixaban, dabigatran, and rivaroxaban in patients with non-valvular atrial fibrillation. *Int J Cardiol*. 2018;268:113–119. doi: 10.1016/j.ijcard.2018.03.047
 21. Amin A, Keshishian A, Trocio J, Dina O, Le H, Rosenblatt L, Liu X, Mardekian J, Zhang Q, Baser O, et al. A real-world observational study of hospitalization and health care costs among nonvalvular atrial fibrillation patients prescribed oral anticoagulants in the U.S. medicare population. *J Manag Care Spec Pharm*. 2018;24:911–920. doi: 10.18553/jmcp.2018.24.9.911
 22. Lip GYH, Keshishian A, Kamble S, Pan X, Mardekian J, Horblyuk R, Hamilton M. Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. *Thromb Haemostasis*. 2017;116:975–986. doi: 10.1160/TH16-05-0403
 23. Lai CL, Chen HM, Liao MT, Lin TT, Chan KA. Comparative effectiveness and safety of dabigatran and rivaroxaban in atrial fibrillation patients. *J Am Heart Assoc*. 2017;6. doi: 10.1161/JAHA.116.005362
 24. Adeboye G, Sylwestrzak G, Barron JJ, White J, Rosenberg A, Abarca J, Crawford G, Redberg R. Major bleeding risk during anticoagulation with warfarin, dabigatran, apixaban, or rivaroxaban in patients with nonvalvular atrial fibrillation. *J Manag Care Spec Ph*. 2017;23:968. doi: 10.18553/jmcp.2017.23.9.968
 25. Abraham NS, Noseworthy PA, Yao X, Sangaralingham LR, Shah ND. Gastrointestinal safety of direct oral anticoagulants: a large population-based study. *Gastroenterology*. 2017;152:1014–1022. doi: 10.1053/j.gastro.2016.12.018
 26. Lin J, Trocio J, Gupta K, Mardekian J, Lingohr-Smith M, Menges B, You M, Nadkarni A. Major bleeding risk and healthcare economic outcomes of non-valvular atrial fibrillation patients newly-initiated with oral anticoagulant therapy in the real-world setting. *J Med Econ*. 2017;20:952–961. doi: 10.1080/13696998.2017.1341902
 27. Norby FL, Bengtson LGS, Lutsey PL, Chen LY, MacLehose RF, Chamberlain AM, Rapson I, Alonso A. Comparative effectiveness of rivaroxaban versus warfarin or dabigatran for the treatment of patients with non-valvular atrial fibrillation. *Bmc Cardiovasc Disor*. 2017;17. doi: 10.1186/s12872-017-0672-5
 28. Gorst-Rasmussen A, Lip GYH, Bjerregaard Larsen T. Rivaroxaban versus warfarin and dabigatran in atrial fibrillation: comparative effectiveness and safety in Danish routine care. *Pharmacoepidem Dr S*. 2016;25:1236–1244. doi: 10.1002/pds.4034
 29. Noseworthy PA, Yao X, Abraham NS, Sangaralingham LR, McBane RD, Shah ND. Direct comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in non-valvular atrial fibrillation. *Chest*. 2016;150:1302–1312. doi: 10.1016/j.chest.2016.07.013
 30. Schneeweiss S, Gagne JJ, Patrick AR, Choudhry NK, Avorn J. Comparative efficacy and safety of new oral anticoagulants in patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2012;5:480–486. doi: 10.1161/CIRCOUTCOMES.112.965988
 31. Silverio A, Di Maio M, Protà C, De Angelis E, Radano I, Citro R, Carrizzo A, Ciccarelli M, Vecchione C, Capodanno D, et al. Safety and efficacy of non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: systematic review and meta-analysis of 22 studies and 440 281 patients. *Eur Heart J Cardiovasc Pharmacother*. 2019. doi: 10.1093/ehjcp/pvz073
 32. Hill NR, Sandler B, Bergrath E, Milenković D, Ashaye AO, Farooqui U, Cohen AT. A systematic review of network meta-analyses and real-world evidence comparing apixaban and rivaroxaban in nonvalvular atrial fibrillation. *Clinical Applied Thrombosis/Hemostasis*. 2020;26:1146323188. doi: 10.1177/1076029619898764
 33. Sun Z, Liu Y, Zhang Y, Guo X, Xu Y. Differences in safety and efficacy of oral anticoagulants in patients with non-valvular atrial fibrillation: a bayesian analysis. *Int J Clin Pract*. 2019:e13308. doi: 10.1111/ijcp.13308
 34. Liao XZ, Fu YH, Ma JY, Zhu WG, Yuan P. Non-vitamin K antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and peripheral artery disease: a systematic review and meta-analysis. *Cardiovasc Drugs Ther*. 2020;34:391–399. doi: 10.1007/s10557-020-06962-6
 35. Xue Z, Zhou Y, Wu C, Lin J, Liu X, Yu P, Zhu W. Dose-response relationship of cardiorespiratory fitness with incident atrial fibrillation. *Heart Fail Rev*. 2020;25:419–425. doi: 10.1007/s10741-019-09871-5
 36. Zhou Y, Ma J, Zhu W. Efficacy and safety of direct oral anticoagulants versus warfarin in patients with atrial fibrillation across BMI categories: a systematic review and meta-analysis. *Am J Cardiovasc Drug*. 2020;20:51–60. doi: 10.1007/s40256-019-00362-4