



# 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

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## Abstract

The non-vitamin K antagonist oral anticoagulants (NOACs) have been increasingly prescribed in clinical practice for stroke prevention in patients with nonvalvular atrial fibrillation (AF). Direct comparisons between NOACs in trials are lacking, leaving an important clinical decision-making gap. We aimed to perform a systematic review and meta-analysis to summarize the evidence of observational studies for direct comparative effectiveness and safety amongst NOACs in patients with AF. Conference proceedings and electronic databases including MEDLINE, CINAHL, EMBASE and PUBMED were systematically searched. We included observational studies directly comparing individual NOACs in patients with nonvalvular AF who were aged  $\geq 18$  years for stroke prevention. Primary outcome included effectiveness outcome (stroke or systemic embolism) and safety outcome (major bleeding). Data were extracted in duplicated by two reviewers independently. A random-effects meta-analysis was conducted to synthesize the data from included observational studies. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) to rate the overall quality of evidence for each outcome. Fifteen studies were included for qualitative synthesis, twelve studies for meta-analyses. It was found that rivaroxaban and dabigatran were similar with regard to risk of stroke or systemic embolism (Hazard ratio [HR] = 1.00, 95% CI 0.91–1.10; evidence quality: low), but rivaroxaban was associated with higher risk of major bleeding (HR = 1.39, 95% CI 1.28–1.50; evidence quality: moderate). Compared with apixaban, a significantly higher risk of major bleeding was observed with rivaroxaban (HR = 1.71, 95% CI 1.51–1.94; evidence quality: low). Apixaban was associated with lower risk of major bleeding, in comparison with dabigatran (HR = 0.80, 95% CI 0.68–0.95; evidence quality: low). No differences in risk of stroke or systemic embolism was observed between rivaroxaban versus apixaban, and apixaban versus dabigatran. In this study, apixaban was found to have the most favorable safety profile amongst the three NOACs. No significant difference was observed in risk of stroke or systemic embolism between the NOACs. Such findings may provide some decision-making support for physicians regarding their choices amongst NOACs in patients with AF.

*Registration* PROSPERO (identifier: CRD42016052908).

**Keywords** Non-vitamin K antagonist oral anticoagulant · Stroke · Major bleeding · Atrial fibrillation · Direct comparison

## Abbreviations

NOACs Non-vitamin K antagonist oral anticoagulants  
AF Atrial fibrillation

GRADE Grading of Recommendations Assessment, Development and Evaluation  
HR Hazard ratio  
CI Confidence interval  
RCT Randomized controlled trial  
MI Myocardial infarction

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Extended author information available on the last page of the article

## Introduction

Atrial fibrillation (AF) is a highly prevalent, age-related cardiac arrhythmia and independently increases the risk of stroke by five fold [1, 2]. The use of antithrombotic prophylaxis remains the mainstay to prevent stroke in patients with nonvalvular AF [3, 4]. The non-vitamin K antagonist oral anticoagulants (NOACs) have been increasingly prescribed in clinical practice, due to their advantages over warfarin such as the decreased need for monitoring, fewer food and drug interactions, and more predictable pharmacodynamic effect [5–7].

The efficacy and safety of NOACs compared with warfarin have been presented in respective multicenter Phase III randomized controlled trials (RCTs) [8–11]. However, no head-to-head comparison between NOACs is available from RCTs; therefore there is a lack of direct clinical outcome evidence to inform physicians and patients on the choice amongst NOACs. Some studies employed the RCT data to conduct indirect comparison analyses for relative effect estimates between NOACs by using the common comparator arm (warfarin) in all the trials [12–18]. Nevertheless, the utility and credibility of their results are limited given the difference in populations, outcomes, study methodology and designs, and time in therapeutic range in warfarin groups between the respective RCTs [19, 20]. Besides, whether and how NOACs in real-world circumstances would show different effectiveness-safety profiles from those in the ideal RCT settings, and whether similar comparative effectiveness-safety profiles would be observed amongst NOACs, remains to be further explored. Observational studies provide a platform for direct comparative evaluation amongst NOACs in heterogeneous populations in real-world clinical practice, which could supply some evidence to physicians to aid in decision-making regarding their choices amongst NOACs.

In this study, we aimed to conduct a systematic review and meta-analysis to summarize the evidence of direct comparison from observational studies for the comparative effectiveness and safety between NOACs in patients with nonvalvular AF.

## Methods

We conducted this study based on guidance from the Cochrane Handbook of Systematic Reviews and reported results according to PRISMA (the Preferred Reporting Items for Systematic Reviews and Meta-analyses) recommendations [21, 22]. The study protocol was registered in PROSPERO (Prospective Register of Ongoing Systematic Reviews; identifier: CRD42016052908).

## Search strategy

We searched the following electronic databases to identify eligible observational studies: MEDLINE, CINAHL and EMBASE from Jan 1st, 2009 to November 30th, 2016, because the first NOAC (dabigatran) in AF was reported for licensing in 2009 [10]. We also updated the PUBMED search from November 2016 up to August 3rd, 2017. We used descriptors including synonyms for observational studies, NOACs, stroke or bleeding, and atrial fibrillation in the search (detailed terms for search were presented in Supplemental Table 1). Reference lists of included studies and other review or editorial articles were also searched for relevant reports. No language restriction was used. Three conference proceedings were searched for unpublished and ongoing studies: American College of Cardiology (2009–2016), European Society of Cardiology (2009–2016), and International Society on Thrombosis and Haemostasis (2009–2016).

## Study eligibility criteria

Case-control and cohort studies directly comparing individual NOACs in patients with nonvalvular AF who were aged  $\geq 18$  years for stroke prevention were eligible for inclusion. We focused on factor Xa inhibitors (rivaroxaban, edoxaban, and apixaban) and the direct thrombin inhibitor (dabigatran). Therefore the comparisons amongst NOACs included dabigatran versus rivaroxaban, dabigatran versus apixaban, dabigatran versus edoxaban, rivaroxaban versus apixaban, rivaroxaban versus edoxaban, and apixaban versus edoxaban.

If data from the same participants were published in multiple reports or at different time points, we chose the study with the largest sample size and longest follow-up. We excluded studies if their objectives were not comparative effectiveness or safety profiles of NOACs, or if they could not provide data on comparative effectiveness or safety amongst NOACs in patients with AF. Moreover, some studies may compare one NOAC (e.g., dabigatran) with a combination of the other NOACs (e.g., rivaroxaban and apixaban). These studies were not included if no data on direct comparison (e.g., dabigatran vs. rivaroxaban, or dabigatran vs. apixaban) could be isolated or extracted. Furthermore, we excluded studies comparing NOACs in patients for cardioversion or ablation of AF, because of their short-term treatment duration and follow-up.

## Outcomes

In this study, the primary outcomes included the effectiveness outcome (a composite of stroke or systemic

embolism) and the safety outcome (a composite of major bleeding). Given that the included studies may define primary outcomes differently, we adopted the definitions from the included individual studies and presented their definitions in Table 1. Our secondary outcomes were myocardial infarction (MI) and all-cause mortality.

### Data extraction and individual study quality assessment

Two reviewers (G.L. and Y.C.) independently screened and chose eligible studies for inclusion. We used the Kappa statistic to quantify the agreement between the two reviewers [23]. Disagreement was addressed by discussion between the two reviewers, with a third arbiter available if no consensus could be reached. The two reviewers extracted data independently including information on study design, patient characteristics, anticoagulant information, outcome assessment, follow-up period, and comparative treatment effect estimates.

The Cochrane Collaboration ROBINS-I (Risk of Bias In Non-randomized Studies- of Interventions) evaluation tool was used to assess the individual observational study quality [24]. Each study was rated as either low, moderate, serious, or critical risk of bias, according to the domains of confounding, participant selection, intervention classification, departure from intended intervention, missing data, outcome measures, and selective reporting.

### Statistical analyses

We performed a random-effects meta-analysis to synthesize the data by pooling the results of the cohort and case-control studies, respectively. We used the adjusted hazard ratios (HRs) for cohort studies and odds ratios (ORs) for case-control studies for meta-analyses. Treatment effect estimates were reported with pooled HRs and ORs for cohort studies and case-control studies respectively, each with 95% confidence intervals (CIs).

Data on the composite outcomes may not be extracted in some studies, because they may only report individual components of the composite outcomes (e.g., they presented results for stroke and systemic embolism respectively). For these studies, we only pooled data on stroke for effectiveness outcome, and intracranial hemorrhage (ICH) for safety outcome respectively, to avoid duplicate counting of the same patients with multiple events in the meta-analyses [25]. Likewise, if multiple doses of a NOAC were studied and not combined, we included data only on the highest dose for meta-analysis.

Statistical heterogeneity for included studies was estimated using the  $I^2$  statistic, in which a  $p$  value of less than 0.1 or an  $I^2$  of over 50% indicated significant heterogeneity

[21]. To explain heterogeneity in primary outcomes, for each comparison amongst NOACs, we conducted the following three predefined subgroup analyses by: (1) individual component of composite outcomes (i.e., stroke and systemic embolism for effectiveness outcome, and ICH and major gastrointestinal (GI) bleeding for safety outcome, respectively), (2) lengths of follow-up (where the median follow-up was used to categorize studies as having long- or short follow-up), and (3) different CHADS<sub>2</sub> (> 2 vs. ≤ 2) or CHA<sub>2</sub>DS<sub>2</sub>-VASc (> 3 vs. ≤ 3) scores, and HAS-BLED scores (> 2 vs. ≤ 2). Three sensitivity analyses were performed to evaluate the robustness of our main results by: (1) employing a fixed-effects model for the meta-analysis, (2) only including low-risk-of-bias studies for analysis, and (3) only pooling data on standard doses of NOACs (150 mg b.i.d. for dabigatran, 20 mg o.d. for rivaroxaban, 5 mg b.i.d. for apixaban, and 60 mg o.d. for edoxaban).

### Assessment of publication bias and quality of a body of evidence across included studies

We used the Begg's rank correlation and Egger's regression tests for primary outcomes to evaluate potential publication bias statistically [21]. Funnel plots were also constructed for visual inspection of asymmetry. The quality of a body of evidence for this study was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool [26]. The quality of evidence across included studies could be categorized as very low, low, moderate, or high, based on the judgement about the study design, directness of evidence, precision of results, inconsistency of results or unexplained heterogeneity, and publication bias [26].

## Results

There were 1449 records included for screening. After title and abstract screening and duplicate removal, we assessed a total of 92 full-text articles for eligibility with an interrater Kappa statistic of 0.80 (95% CI 0.63–0.97) between the assessors. Fifteen studies (nine full texts [20, 27–34] and six abstracts [35–40]) were eligible to be included for qualitative synthesis, among which there were twelve studies (seven full texts [20, 28, 30–34] and five abstracts [35, 37–40]) included for quantitative synthesis (Supplemental Figure 1).

Table 1 shows characteristics of the fifteen included studies. Most studies ( $n = 14$ ) were retrospective cohort designs using data from electronic health databases, while only one study was prospective cohort research [34]. Thirteen studies focused on NOAC-naïve users. All the primary outcome measures were identified from ICD-9-

**Table 1** Patients' characteristics of included studies

References	Country	Study design	Data source	Study period	Comparison	Population characteristics			CHADS <sub>2</sub> score	
						Name of NOAC (dose)	All new NOAC-users?	Sample size (% for females)		Age: years
<i>Full texts (n = 9)</i>										
Al-Khalili et al. [27]	Sweden	Retrospective cohort	Stockholm Heart Center (a cardiology outpatient clinic)	2011 Dec–2015 Jan	Rivaroxaban versus Apixaban; Dabigatran; Rivaroxaban versus Dabigatran	Rivaroxaban	Yes	282 (50%)	Mean 73	Median 3 <sup>c</sup>
						Apixaban		251 (49%)	Mean 73	Median 3 <sup>c</sup>
						Dabigatran		233 (49%)	Mean 72	Median 3 <sup>c</sup>
Chan et al. [28]	China	Retrospective cohort	Taiwan National Health Insurance Research Database	2013 Feb–2013 Dec	Rivaroxaban versus dabigatran	Rivaroxaban (10, 15 and 20 mg once daily)	No; some patients had experience with ≥ 1 of study drugs	3916 (46%)	Mean 76	Mean 4.12 <sup>c</sup>
						Dabigatran (110 and 150 mg twice daily)		5921 (42%)	Mean 75	Mean 4.08 <sup>c</sup>
Deitelzweig et al.* (a) [29]	USA	Retrospective cohort	Premier Hospital Database	2012 Jan–2014 Mar	Rivaroxaban versus Apixaban; Apixaban versus Dabigatran	Rivaroxaban	Unknown; all patients received a NOAC in their first hospitalization due to AF (index hospitalization)	37,754 (49%)	Mean 72.3	Mean 2.04
						Apixaban		4138 (51%)	Mean 73.6	Mean 2.19
						Dabigatran		32,838 (46%)	Mean 71.9	Mean 2.09
Deitelzweig et al.* (b) [29]	USA	Retrospective cohort	Cerner Health Facts Hospital Database	2012 Jan–2014 Aug	Rivaroxaban versus Apixaban; Apixaban versus Dabigatran	Rivaroxaban	Unknown (same as above in Deitelzweig et al. [29] (a))	6635 (48%)	Mean 72.1	Mean 2.06
						Apixaban		1813 (51%)	Mean 74.9	Mean 2.35
						Dabigatran		5753 (45%)	Mean 72.4	Mean 2.15
Graham et al. [20]	USA	Retrospective cohort	Medicare databases	2011 Nov–2014 Jun	Rivaroxaban versus dabigatran	Rivaroxaban (20 mg once daily)	Yes	66,651 (47%)	N/A (all patients were ≥ 65 years)	Median 2
						Dabigatran (150 mg twice daily)		52,240 (47%)		Median 2

Table 1 (continued)

References	Country	Study design	Data source	Study period	Comparison	Population characteristics				
						Name of NOAC (dose)	All new NOAC-users?	Sample size (% for females)	Age: years	CHADS <sub>b</sub> score
Gorst-Rasmussen et al. [30]	Denmark	Retrospective cohort	Danish National Prescription Registry, Danish National Patient Register, and Danish Civil Registration System	2012 Feb–2014 Jul	Rivaroxaban versus dabigatran	Rivaroxaban (20 mg once daily) Dabigatran (150 mg twice daily)	Yes	1629 (49%)	Mean 72.8	Mean 1.5
Hernandez and Zhang [33]	USA	Retrospective cohort	Medicare Part D data from the Centers for Medicare and Medicaid Services	2010–2013	Rivaroxaban versus dabigatran	Rivaroxaban (20 mg once daily) Dabigatran (150 mg twice daily)	Yes	5799 (54%)	Mean 75.4	Mean 3.29
Li et al. [34]	China	Prospective cohort	Hospital-based AF registry in Queen Mary Hospital, Hong Kong	2008 Jan–2014 Dec	Rivaroxaban versus dabigatran	Rivaroxaban Dabigatran	Yes	669 (40%)	Mean 73.3	Mean 2.5
Lip et al. [31]	USA	Retrospective cohort	Truven MarketScan <sup>®</sup> Commercial and Medicare supplemental US claims database	2013 Jan–2014 Dec	Rivaroxaban versus dabigatran	Rivaroxaban Dabigatran	Yes	4657 (36%)	Mean 66.3	Mean 1.6
					Rivaroxaban versus apixaban	Rivaroxaban Apixaban	Yes	4657 (35%)	Mean 66.5	Mean 1.6
					Rivaroxaban versus dabigatran	Rivaroxaban Apixaban	Yes	7399 (39%)	Mean 68.3	Mean 1.7
					Apixaban versus dabigatran	Apixaban Dabigatran	Yes	7399 (39%)	Mean 68.4	Mean 1.8
							Yes	4407 (36%)	Mean 67.0	Mean 1.6
								4407 (36%)	Mean 66.9	Mean 1.7

Table 1 (continued)

References	Country	Study design	Data source	Study period	Comparison	Population characteristics			CHADS <sub>b</sub> score	
						Name of NOAC (dose)	All new NOAC-users?	Sample size (% for females)		Age: years
Noseworthy et al. [32]	USA	Retrospective cohort	Optum Labs Data Warehouse	2010 Oct–2015 Feb	Rivaroxaban versus dabigatran	Rivaroxaban	Yes	15,787 (40%)	Median 70	Median 4 <sup>3</sup>
					Dabigatran		15,787 (41%)	Median 71	Median 4 <sup>3</sup>	
					Rivaroxaban versus apixaban	Rivaroxaban	Yes	6565 (46%)	Median 73	Median 4 <sup>3</sup>
					Apixaban		6565 (46%)	Median 73	Median 4 <sup>3</sup>	
					Apixaban versus dabigatran	Apixaban	Yes	6542 (46%)	Median 73	Median 4 <sup>3</sup>
					Dabigatran		6542 (46%)	Median 73	Median 4 <sup>3</sup>	
<i>Abstracts (n = 6)</i>										
Adeboyeje et al. [39]	USA	Retrospective cohort	A US commercial claims database	2010 Nov–2015 Feb	Rivaroxaban versus Dabigatran;	Rivaroxaban	Yes	8398	Mean 67	N/A
					Dabigatran versus Apixaban;	Apixaban		3689	Mean 69	
					Rivaroxaban versus Apixban	Dabigatran		8539	Mean 66	
Amin et al. [38]	USA	Retrospective cohort	Optum Research Database	2013 Jan–2014 Dec	Dabigatran versus Apixaban;	Rivaroxaban	Yes	8740	N/A	Mean 4.0 <sup>3</sup>
					Rivaroxaban versus Apixban	Apixaban		3762	Mean 4.2 <sup>3</sup>	
					Dabigatran versus Apixaban	Dabigatran		2677	Mean 4.0 <sup>3</sup>	
					Apixaban versus Apixban	Apixaban		833		
Deitelzweig et al. [35]** (a)	USA	Retrospective cohort	Humana Medicare Advantage Database	2009 Jul–2014 Sep	Dabigatran versus Apixaban;	Rivaroxaban	Yes	7667	N/A	N/A
					Rivaroxaban versus Apixban	Apixaban		2028	Mean 75.5	
					Dabigatran versus Apixban	Dabigatran		5644	N/A	
Deitelzweig et al. [40]** (b)	USA	Retrospective cohort	PharMetrics Plus data.	2012 Jan–2014 Jan	Dabigatran versus Apixaban;	Rivaroxaban	Yes	6167	Mean 63.4	Mean 1.8
					Rivaroxaban versus Apixban	Apixaban		833		
						Dabigatran		2150		

Table 1 (continued)

References	Country	Study design	Data source	Study period	Comparison	Population characteristics				
						Name of NOAC (dose)	All new NOAC-users? <sup>a</sup>	Sample size (% for females)	Age: years	CHADS <sub>2</sub> score
Lai et al. [36]	China	Retrospective cohort	A Taiwan Medical Center	2013 Mar–2013 Oct	Rivaroxaban versus Dabigatran	Rivaroxaban (15 mg once daily) Dabigatran (110 mg twice daily)	Yes	57 (47%)	Mean 74.8	Mean 3.0
Lin (2015) [37]	USA	Retrospective cohort	Humedica Electronic Health Record Database	2013 Jan–2014 Jun	Dabigatran versus Apixaban; Rivaroxaban versus Apixban	Rivaroxaban Apixaban Dabigatran	Yes	6407 2038 2440	N/A	N/A
References	Population characteristics			Outcome measures <sup>a</sup>			Follow-up period	Primary statistical analysis used		
	HAS-BLED score <sup>2</sup>	Baseline Charlson-comorbidity index	Baseline renal dysfunction: %	Baseline non-study antiplatelet use: %	Effectiveness endpoint definition	Safety endpoint definition				
<i>Full texts</i>										
Al-Khalili et al. [27]	N/A	N/A	10%	29%	N/A	Major bleeding defined according to the ISTH (International Society of Thrombosis and Hemostasis) criteria	Median 432 days Median 348 days	Multivariable Cox survival regression		
			12%	40%			Median 367 days			
			10%	36%						
Chan et al. [28]	Mean 3.11 Mean 3.12	N/A	22%	41%	Hospital discharge diagnoses for ischemic stroke and systemic embolism	Major bleeding required hospitalization, including ICH, GI bleeding and other critical site bleeding	N/A	Multivariable Cox survival regression		
			22%	45%						

Table 1 (continued)

References	Population characteristics			Outcome measures <sup>a</sup>		Follow-up period	Primary statistical analysis used
	HAS-BLED score <sup>2</sup>	Baseline Charlson-Deyo comorbidity index	Baseline renal dysfunction: %	Baseline non-study antiplatelet use: %	Effectiveness endpoint definition		
Deitelzweig et al.* (a) [29]	Mean	2.35	2.09 <sup>d</sup>	N/A	N/A	N/A	Multivariable logistic regression
	Mean	2.56	2.35 <sup>d</sup>				
	Mean	2.33	2.12 <sup>d</sup>				
Deitelzweig et al.* (b) [29]	Mean	2.31	2.39 <sup>d</sup>	N/A	N/A	N/A	Multivariable logistic regression
	Mean	2.50	2.71 <sup>d</sup>				
	Mean	2.37	2.47 <sup>d</sup>				
Graham et al. [20]	Median	2	N/A	11%	15%	Mean 111 days	Propensity score method (inverse probability of treatment weighting)
	Median	2		13%	13%	Mean 108 days	
Gorst-Rasmussen et al. [30]	Mean	2.3	N/A	1.5%	44.0% <sup>e</sup>	Median 1.08 years	Propensity score method (covariate adjustment)
	Mean	1.9	N/A	1.1%	36.1% <sup>e</sup>	Median 1.08 years	
Hernandez and Zhang [33]	N/A	N/A	N/A	28.6%	6.1%	Mean 251 days	Propensity score method (inverse probability of treatment weighting)
	N/A	N/A	N/A	26.3%	7.1%	Mean 385 days	
Li et al. [34]	Mean	2.0	N/A	0.4%	N/A	Mean 651 days	Multivariable Cox survival regression
	Mean	2.0	N/A	0.9%	N/A		

Table 1 (continued)

References	Population characteristics				Outcome measures <sup>a</sup>		Follow-up period	Primary statistical analysis used
	HAS-BLED score <sup>2</sup>	Baseline Charlson-Deyo comorbidity index	Baseline renal dysfunction: %	Baseline non-study antiplatelet use: %	Effectiveness endpoint definition	Safety endpoint definition		
Lip et al. [31]	Mean 1.9	Mean 1.6	7.2%	N/A	N/A	Major bleeding defined as bleeding requiring hospitalisation during the period of drug use or within 30 days after the last days of supply of the treatment prescription. Using hospital claims	Mean 173 days	Propensity score method (matching)
	Mean 2.0	Mean 1.6	7.2%				Mean 177 days	
	Mean 2.1	Mean 1.7	7.9%				Mean 182 days	
	Mean 2.2	Mean 1.8	8.5%				Mean 148 days	
	Mean 2.0	Mean 1.6	6.6%				Mean 146 days	
	Mean 2.0	Mean 1.6	7.4%				Mean 179 days	
	Median 2	Median 2	13.3%	10.8% <sup>f</sup>	Inpatient admission for stroke (ischemic and hemorrhagic stroke) and systemic embolism	Inpatient admission for major bleeding including ICH, GI bleeding and major bleeding from other sites	N/A	Propensity score method (matching)
Noseworthy et al. [32]	Median 2	Median 2	13.7%	11.1% <sup>f</sup>				
	Median 2	Median 2	19.0%	11.7% <sup>f</sup>				
	Median 2	Median 2	19.1%	12.3% <sup>f</sup>				
	Median 2	Median 2	18.8%	12.2% <sup>f</sup>				
	Median 2	Median 2	18.3%	11.9% <sup>f</sup>				
	Median 2	Median 2	18.3%	11.9% <sup>f</sup>				
<i>Abstracts</i>								
Adeboyeje et al. [39]	N/A	N/A	N/A	N/A	Effectiveness outcome defined as a composite of thromboembolic event or stroke	All Major bleeding required hospitalization	N/A	Propensity score method (inverse probability of treatment weighting)
Amin et al. [38]	N/A	N/A	N/A	N/A		Major bleeding events identified by the Cunningham algorithm plus additional major bleeding sites	N/A	Multivariable Cox survival regression

Table 1 (continued)

References	Population characteristics			Outcome measures <sup>a</sup>			Follow-up period	Primary statistical analysis used
	HAS-BLED score <sup>2</sup>	Baseline Charlson-Deyo comorbidity index	Baseline renal dysfunction: %	Baseline non-study antiplatelet use: %	Effectiveness endpoint definition	Safety endpoint definition		
Deitelzweig (2015) <sup>*,**</sup> (a) [35]	N/A	N/A	N/A	N/A	N/A	All bleeding events required a hospitalization	N/A	Multivariable Cox survival regression
Deitelzweig et al. [40] <sup>**, (b)</sup>	N/A	N/A	N/A	N/A	N/A	Major bleeding not specified	N/A	Multivariable Cox survival regression
Lai (2014) [36]	N/A	N/A	N/A	N/A	N/A	Major bleeding including cerebral, respiratory, gastrointestinal and urinary hemorrhage	Median 136 days Median 177 days	Multivariable Cox survival regression
Lin (2015) [37]	N/A	N/A	N/A	N/A	N/A	Major bleeding not specified	N/A	Multivariable Cox survival regression

<sup>a</sup>This study was presented by study (a) and (b) because it reported separate findings for the two databases and no combined data could be extracted

<sup>\*\*</sup>These two studies were attached with (a) and (b) to avoid confusion because they were from the same first author and published in the same year

<sup>b</sup>Outcomes were identified from ICD-9-CM or ICD-10-CM codes

<sup>c</sup>Modified HAS-BLED score ranged from 0 to 8 because labile international normalized ratio was not applicable to NOAC users

<sup>d</sup>Data were for CHA2DS2-VASc score

<sup>e</sup>Data were for Charlson comorbidity index

<sup>f</sup>Data were for aspirin use only

<sup>g</sup>Data were for antiplatelet or NSAID use

CM or ICD-10-CM codes. All fifteen studies investigated comparisons between rivaroxaban and dabigatran (number of patients: 337,661), nine studies [27, 29, 31, 32, 35, 37–40] for rivaroxaban versus apixaban (number of patients: 128,548), and nine studies [27, 29, 31, 32, 35, 37–40] for apixaban versus dabigatran (number of patients: 100,724). No studies provided data on edoxaban, reflecting its very recent approval. For rivaroxaban versus dabigatran, the included studies were conducted in USA ( $n = 10$ ), China ( $n = 3$ ), Denmark ( $n = 1$ ) and Sweden ( $n = 1$ ). Patients had a median age of approximately 72 years, with a median CHADS<sub>2</sub> score of 2 and a median HAS-BLED score of 2. The follow-up period varied from 110 days to 400 days. Studies with data on rivaroxaban versus apixaban or apixaban versus dabigatran were performed in USA ( $n = 8$ ) and Sweden ( $n = 1$ ). Patients' median age was 73 years, median CHADS<sub>2</sub> score 2 and median HAS-BLED score 2. Only one study provided data on follow-up period of approximately 160 days [31].

Among all the included studies, eight used multivariable survival regression, six propensity score method, and one multivariable logistic regression to quantify comparative evaluation amongst NOACs, respectively (Table 1). Study quality was evaluated for the nine full texts. Seven studies were rated as low-risk-of-bias for effectiveness and safety outcomes [20, 28, 29, 31, 32]. There was one study [30] rated as moderate-risk-of-bias for stroke or systemic embolism because it did not provide information on missing data and it measured transient ischemic attack as a component of effectiveness outcome. One study [27] was graded as moderate-risk-of-bias for safety outcomes because of the potential selective reporting and no information on missing data.

### Rivaroxaban versus dabigatran

Figure 1 and Table 2 display results of comparative effectiveness and safety between rivaroxaban and dabigatran. Seven studies that provided data on HRs were synthesized, while the other study [29] that reported adjusted ORs was not included for meta-analyses. No significant difference in risk of stroke or systemic embolism was found between rivaroxaban and dabigatran (HR = 1.00, 95% CI 0.91–1.10,  $p = 0.97$ ; Fig. 1a). There was marginally significant heterogeneity observed for risk of stroke or systemic embolism ( $I^2 = 44%$ ,  $p$  value = 0.1). Compared with dabigatran, rivaroxaban was significantly associated with increased risk of major bleeding (HR = 1.39, 95% CI 1.28–1.50,  $p < 0.001$ ; Fig. 1b). Regarding secondary outcomes, no significant difference was found in risk of MI between rivaroxaban and dabigatran (HR = 0.87, 95% CI 0.72–1.05,  $p = 0.15$ ; Supplemental Figure 2), while a higher risk of all-cause death was found with rivaroxaban

(HR = 1.28, 95% CI 1.14–1.43,  $p < 0.001$ ; Supplemental Figure 3). No statistically significant heterogeneity was found for risks of major bleeding, MI and death, with all the  $I^2$  of  $< 50%$  and  $p$  values of  $> 0.1$ .

Likewise, as shown in Table 2, rivaroxaban was non-significantly associated with risk of stroke, but significantly associated with increased risk of major GI bleeding, compared with dabigatran. However, no significant association was observed for ICH ( $p = 0.46$ ). Similar results were found in the subgroup analysis by HAS-BLED score ( $p$  values  $> 0.05$  for subgroup differences; Table 3). Sensitivity analyses also yielded similar results to the main analyses (Table 3).

### Rivaroxaban versus apixaban

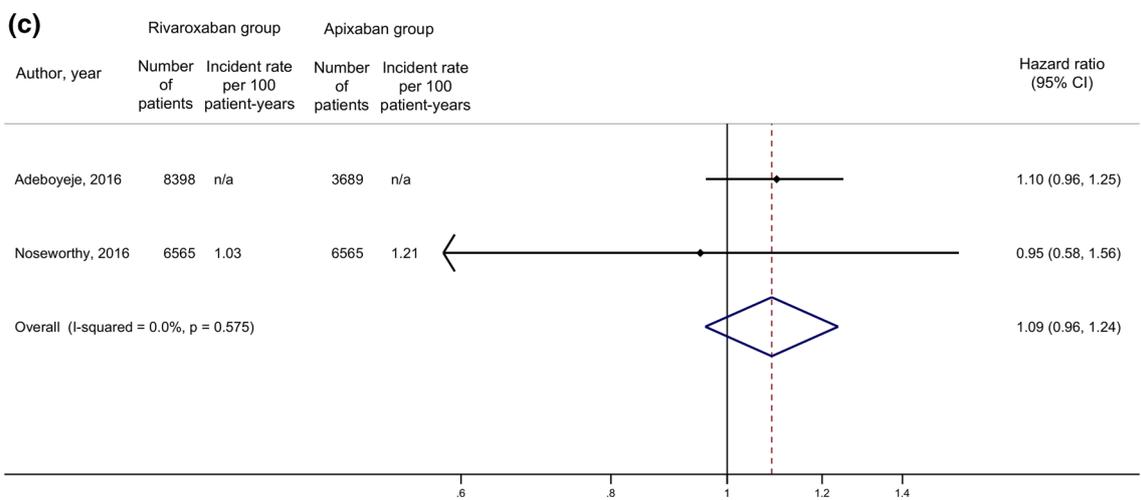
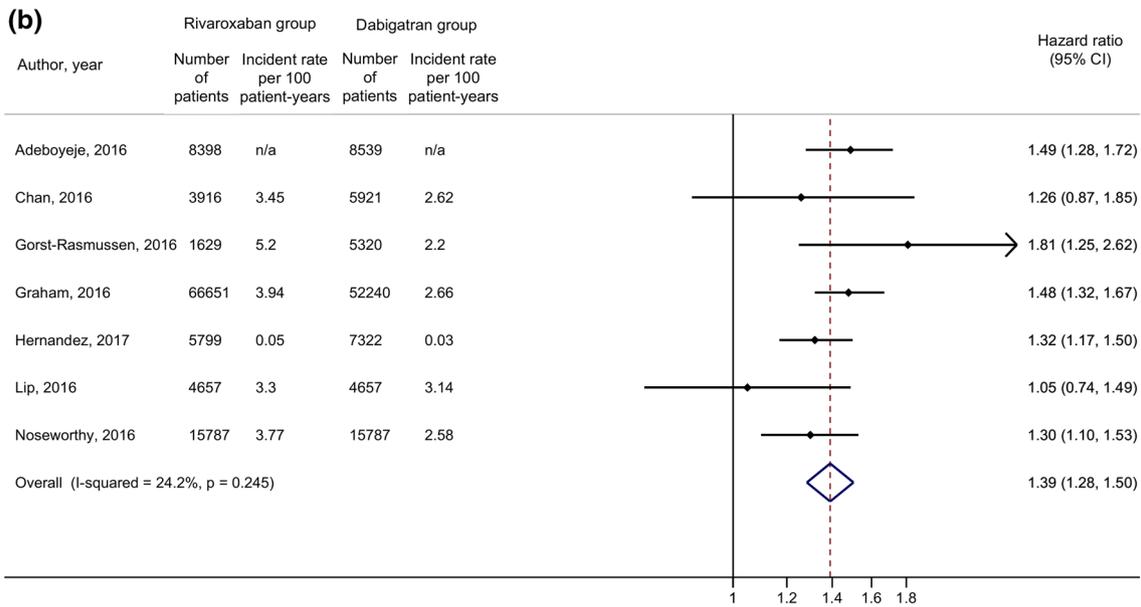
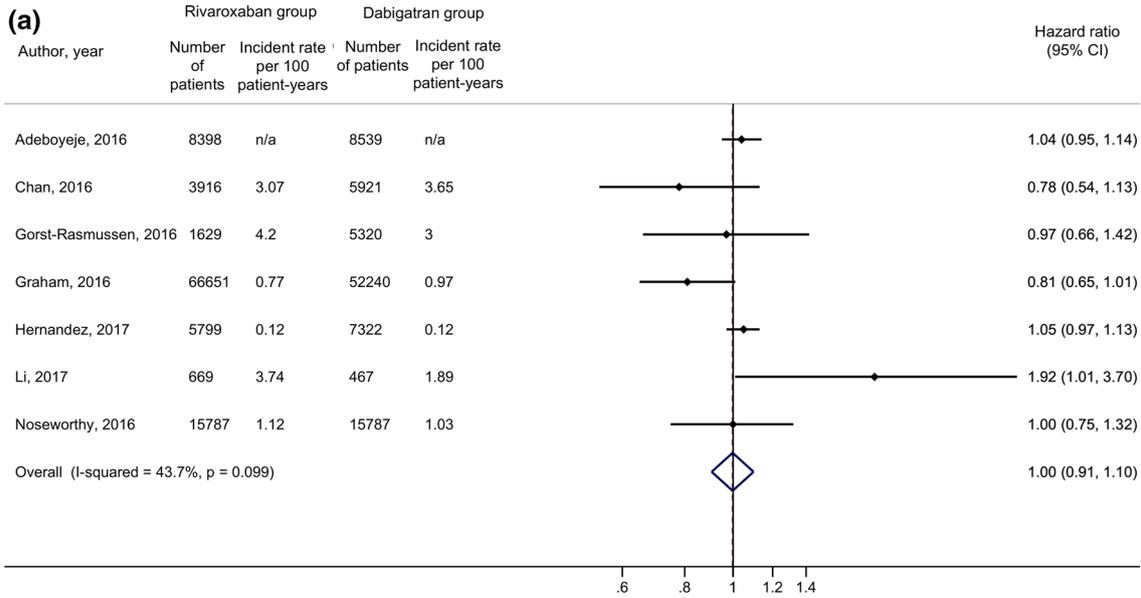
Compared with apixaban, no difference in risk of stroke or systemic embolism was found in rivaroxaban (HR = 1.09, 95% CI 0.96–1.24,  $p = 0.19$ ; Fig. 1c and Table 2). However a significantly higher risk of major bleeding was observed in rivaroxaban (HR = 1.71, 95% CI 1.51–1.94,  $p < 0.001$ ; Fig. 1d and Table 2) with significant heterogeneity found ( $I^2 = 56%$ ,  $p = 0.04$ ). No analyses for effectiveness outcomes or subgroup analyses were conducted due to insufficient studies or data available. Similar results were found in sensitivity analyses (Table 3).

### Apixaban versus dabigatran

In comparison with dabigatran, apixaban was not significantly associated with decreased risk of stroke or systemic embolism (HR = 0.94, 95% CI 0.83–1.06,  $p = 0.32$ ; Fig. 1e and Table 2), but significantly associated with decreased risk of major bleeding (HR = 0.80, 95% CI 0.68–0.95,  $p = 0.01$ ; Fig. 1f and Table 2). There was significant heterogeneity found for risk of major bleeding:  $I^2 = 61%$ ,  $p = 0.03$ . No analyses for effectiveness outcomes or subgroup analyses were performed. Sensitivity analyses produced similar findings to the main analyses (Table 3).

### Assessment of publication bias and quality of a body of evidence

There was no evidence of publication bias found in the comparison amongst NOACs, with all the  $p$  values of  $> 0.05$  for Begg's and Egger's tests (Supplemental Figures 4–7). The quality of a body of evidence across included studies was rated as low-quality for the effectiveness outcome of rivaroxaban versus dabigatran and for the safety outcomes of rivaroxaban versus apixaban or apixaban versus dabigatran, due to the non-randomized design and unexplained heterogeneity. The evidence for the



◀**Fig. 1** Results of direct comparisons amongst NOACs: **a** results for risk of stroke or systemic embolism comparing rivaroxaban with dabigatran; **b** results for risk of major bleeding comparing rivaroxaban with dabigatran; **c** results for risk of stroke or systemic embolism comparing rivaroxaban with apixaban; **d** results for risk of major bleeding comparing rivaroxaban with apixaban; **e** results for risk of stroke or systemic embolism comparing apixaban with dabigatran; **f** results for risk of major bleeding comparing apixaban with dabigatran

safety outcome of rivaroxaban versus dabigatran was graded as moderate-quality because of the non-randomized design (Supplemental Table 2).

## Discussion

In this systematic review and meta-analysis, we summarized the evidence from observational studies of direct comparative effectiveness and safety amongst NOACs in patients with AF. No significant differences in risk of stroke or systemic embolism were found between rivaroxaban versus dabigatran, rivaroxaban versus apixaban, or apixaban versus dabigatran. Apixaban was found to have the most favorable safety profile amongst the three NOACs.

Apixaban was associated with a lower risk of major bleeding when compared with dabigatran or rivaroxaban (Table 2). This finding may provide some decision-making support for physicians regarding their choices amongst NOACs, especially when considering the equivalent effect of the NOACs on effectiveness outcomes. The evaluated risk of major bleeding and mortality in rivaroxaban compared with dabigatran or apixaban may reflect the true difference in safety outcomes between the three NOACs. The once-daily dosing of rivaroxaban and twice-daily administration of dabigatran might also explain the higher risk of major bleeding in rivaroxaban, given its higher peak in plasma concentrations than dabigatran [20]. However, the observed results (no difference in effectiveness, but better safety) between rivaroxaban and dabigatran or apixaban may also be partly due to selective prescribing. Patients in Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) were older and frailer, required more orthopedic procedures, and had more baseline comorbidities than in RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) or Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) [8–10], therefore physicians may prefer prescribing rivaroxaban to patients at higher risk of adverse health outcomes [30, 32]. In addition, once-daily dosing may be

preferred for patients on other multiple drugs or with memory problems, to decrease pill burden. Although all the included studies used multivariable or propensity score adjustment to estimate the relative effect, the non-randomized design could not fully adjust for the effect of selective prescribing or prevent the potential residual confounding.

The numbers of studies included for quantitative syntheses of the primary outcomes were relatively small (Table 2). Three studies [27, 29, 36] investigating risk of major bleeding could not be used for meta-analyses, because two studies [27, 36] did not provide data on the relative effect and the other study [29] only reported adjusted ORs (rather than HRs). Nevertheless, they consistently reported higher incidence rates of major bleeding during follow-up in rivaroxaban compared with dabigatran or apixaban. Likewise, due to insufficient studies available and suboptimal reporting, no analyses of using standard NOAC doses or subgroup analyses could be conducted for rivaroxaban versus apixaban or apixaban versus dabigatran. Therefore the significant heterogeneity could not be further explored, leading to the quality of a body of evidence being low (Supplemental Table 2).

Three studies summarizing the observational evidence of direct comparisons amongst NOACs have been published [41–43]. Although our findings were in general agreement with their results, the other studies have limitations, either only exploring the comparison between rivaroxaban and dabigatran [42, 43], or only assessing the safety profiles amongst NOACs [41, 43]. There are several studies using data from RCTs to indirectly compare efficacy and safety outcome between NOACs [12–18]. Our study found similar effectiveness but higher risk of major bleeding in rivaroxaban compared with dabigatran, which was not consistent with the indirect comparison studies that showed higher risk of stroke or systemic embolism in rivaroxaban but no difference in major bleeding [12, 13, 15, 18]. Indirect comparison should be interpreted with caution, given that such comparison is essentially observational design across trials and may suffer apparent and latent biases including confounding [21, 44]. Specifically, the difference in the three RCTs (ROCKET-AF, RE-LY, and ARISTOTLE) yielded the indirect comparison questionable and even misleading [19, 45], because it remained unclear whether and to what extent the difference in risk of outcomes could be attributed to the drug alone. Indirect comparison studies can be used to generate hypotheses that are further corroborated ideally in direct comparative RCTs [18]. Given that no such RCT is available currently or in the near future, findings from real-world studies with direct comparative assessment amongst NOACs may assist in decision-making in clinical practice. The large-scale direct design with multivariable or

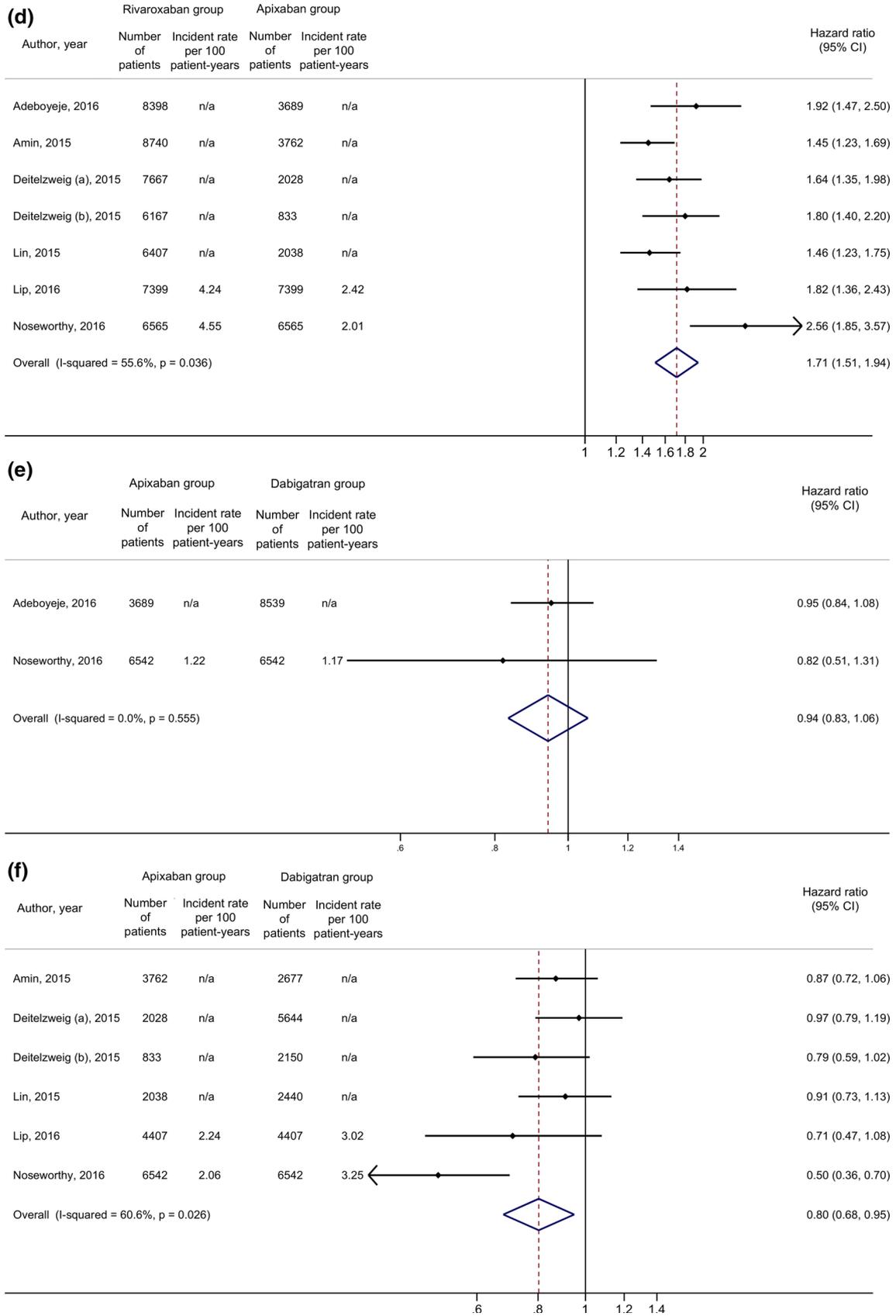


Fig. 1 continued

**Table 2** Results of comparative effectiveness and safety amongst NOACs in patients with AF

Outcome	Rivaroxaban versus Dabigatran		Rivaroxaban versus Apixaban		Apixaban versus Dabigatran	
	Number of studies/patients	Pooled HR (95% CI), <i>p</i> value	Number of studies/patients	Pooled HR (95% CI), <i>p</i> value	Number of studies/patients	Pooled HR (95% CI), <i>p</i> value
Stroke or SE	7/198,445	1.00 (0.91–1.10), 0.97	2/25,217	1.09 (0.96–1.24), 0.19 <sup>b</sup>	2/25,312	0.94 (0.83–1.06), 0.32 <sup>b</sup>
Stroke	4/164,722	1.02 (0.89–1.16), 0.75 <sup>c</sup>	1/13,130	– <sup>a</sup>	1/13,084	– <sup>a</sup>
SE	1/13,121	– <sup>a</sup>	0/0	– <sup>a</sup>	0/0	– <sup>a</sup>
Major bleeding	7/206,623	1.39 (1.28–1.51), < 0.001	7/77,657	1.71 (1.51 – 1.94), < 0.001	6/43,470	0.80 (0.68 – 0.95), 0.01
ICH	4/173,423	1.19 (0.75–1.88), 0.46	1/13,130	– <sup>a</sup>	1/13,084	– <sup>a</sup>
Major GI bleeding	3/141,849	1.26 (1.18–1.36), < 0.001	0/0	– <sup>a</sup>	0/0	– <sup>a</sup>
Myocardial infarction	2/128,728 <sup>b</sup>	0.87 (0.72–1.05), 0.15	0/0	– <sup>a</sup>	0/0	– <sup>a</sup>
All-cause death	4/148,798	1.28 (1.14–1.43), < 0.001	0/0	– <sup>a</sup>	0/0	– <sup>a</sup>

<sup>a</sup>No meta-analysis conducted due to insufficient studies or data available

<sup>b</sup>Fixed-effects model was used due to only two studies included for analysis

<sup>c</sup>Data were for ischemic stroke

**Table 3** Results of subgroup and sensitivity analyses for comparison between NOACs

Analysis	Stroke or SE*	Major bleeding		
	Rivaroxaban versus Dabigatran	Rivaroxaban versus Dabigatran	Rivaroxaban versus Apixaban	Apixaban versus Dabigatran
<i>Subgroup analysis</i> <sup>a</sup>				
HAS-BLED score				
≤ 2	0.78 (0.60–1.02), 0.052 <sup>b</sup>	1.41 (1.13–1.76), 0.002 <sup>b</sup>	– <sup>c</sup>	– <sup>c</sup>
> 2	1.01 (0.80–1.27), 0.95 <sup>b</sup>	1.35 (1.11–1.63), 0.001 <sup>b</sup>	– <sup>c</sup>	– <sup>c</sup>
<i>Sensitivity analysis</i>				
Employing fixed-effects model	1.03 (0.97–1.08), 0.38	1.40 (1.31–1.49), < 0.001	1.65 (1.52–1.79), < 0.001	0.84 (0.76–0.92), < 0.001
Only including low-risk-of-bias studies	1.00 (0.90–1.11), 0.95	1.35 (1.24–1.46), < 0.001	2.11 (1.70–2.63), < 0.001	0.69 (0.48–0.98), 0.039
Using data on standard doses of NOACs	0.96 (0.80–1.15), 0.63	1.45 (1.30–1.61), < 0.001	– <sup>c</sup>	– <sup>c</sup>

\*No syntheses conducted for stroke or SE regarding Rivaroxaban versus Apixaban or Apixaban versus Dabigatran due to only 2 studies included and no data available for subgroup analyses

<sup>a</sup>No subgroup analyses performed by length of follow-up, CHADS<sub>2</sub> (> 2 vs. ≤ 2) score or CHA<sub>2</sub>DS<sub>2</sub>-VASc (> 3 vs. ≤ 3) score because of insufficient studies or data available

<sup>b</sup>Fixed-effects model was used due to only two studies included for analysis

<sup>c</sup>No meta-analysis conducted due to insufficient studies or data available

propensity score adjustment in the relatively homogeneous patients for each individual study may provide more credible evidence than indirect comparison, although an observational study is prone to biases due to its non-randomization and should be interpreted with caution.

Moreover, four included studies evaluated the comparison between NOACs and warfarin and reported consistent findings with the respective trials [28, 30, 31, 37]. This would also support the validity of the included observational studies and our current review. However, further

large-scale, well-designed and transparently-reported observational studies or eventually head-to-head clinical trials are needed to update the evidence and inform decision-making, because of insufficient studies or data available in our study including limited evidence for subgroup evaluations and for risks of MI and death.

## Strengths and limitations

This study is the first systematic review to summarize evidence from observational studies for direct comparison amongst NOACs, to our knowledge. An exhaustive and comprehensive search was conducted to obtain all relevant and most-updated studies. Study processes including screening, data extraction and analyses were performed in duplicate with a good level of agreement. Results from sensitivity analyses supported the robustness of findings from the main analyses.

Some limitations exist in our study. First, the non-randomized comparisons in observational studies may suffer from biases, which could impair the findings and thus weaken the strength of evidence. Secondly, due to limited studies or data, we could not further evaluate the comparative outcomes of interest amongst all NOACs, especially with no data on edoxaban available. Similarly, no analyses could be performed in subgroup populations including patients with or without renal dysfunction, with different sex, at low or high risk of stroke and/or major bleeding, with high or low drug adherence, with or without concomitant over-the-counter antiplatelets, and at different ages. Thirdly, the statistical methods used in the included studies including multivariable regression and propensity score methods were performed to estimate different relative treatment effects. For instance, the propensity score matching was used to estimate effects in the patients who received NOACs; the propensity score covariate adjustment was used for conditional effects within levels of the propensity scores; and the propensity score inverse probability of treatment weighting and the multivariable regression were used to estimate effects in all the patients with AF who were eligible for a NOAC [46]. However no analyses could be conducted to compare the different targeted effects due to the small number of included studies. Furthermore, all the included studies used ICD-9-CM or ICD-10-CM (International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification) codes to identify outcomes and no chart reviews were performed to validate outcome measures, which was a common limitation of observational analyses based on electronic health databases. For example, it was reported that the outcome data (incidences of cardiovascular and bleeding events) identified from medical claims after MI were generally

lower than from physician adjudication [47]. Therefore caution is needed when interpreting such observational studies that depend on the data from electronic health databases alone. Additionally, because the follow-up periods were relatively short ranging from 110 to 400 days (Table 1), little was known about the long-term comparative effectiveness and safety between NOACs in patients with AF in the current study.

## Conclusion

This systematic review and meta-analysis based on observational studies of direct comparative effectiveness and safety amongst NOACs in patients with AF found increased risk of major bleeding with rivaroxaban compared to dabigatran and apixaban. Apixaban was associated with lower risk of major bleeding than dabigatran. No significant difference was observed in risk of stroke or systemic embolism amongst the three NOACs. Such findings may provide some decision-making support for physicians regarding their choices amongst NOACs in patients with AF.

**Author contributions** GL, GYHL, AH and MAHL: conceived and designed the study. GL, YC, LM and LT: acquired data, performed statistical analyses and interpretation, and drafted the manuscript. GYHL, AH, TBL, XS, JT, DMW, MC, and MAHL: provided professional and statistical support, and made several critical revisions to the manuscript. GYHL, AH, LT and MAHL: supervised the study. All authors read and approved the final manuscript. GL acts as the guarantor of this work.

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## Compliance with ethical standards

**Conflict of interest** GYHL has served as a consultant for Bayer, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic and Boehringer Ingelheim and has been on the speaker's bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic. TBL has been on the speakers' bureaus for Bayer, BMS/Pfizer, Roche Diagnostics, and Boehringer- Ingelheim. MC has sat on advisory boards for Janssen, Leo Pharma, Portola, and AKP America; and he has received funding for presentations from Leo Pharma, Bayer, Celgene, Shire, and CSL Behring. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**Availability of data and materials** The data appeared in this study are already publicly available in the literature.

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## Affiliations

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