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REVIEW ARTICLE

Efficacy and Safety of Direct Oral Anticoagulants (DOACs) Versus Warfarin in Atrial Fibrillation Patients with Prior Stroke: a Systematic Review and Meta-analysis

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Abstract

Background The purpose of this meta-analysis was to compare efficacy and safety of direct oral anticoagulants (DOACs) to warfarin for secondary stroke prevention among adult patients with atrial fibrillation and prior stroke.

Methods Major repositories were screened for randomized controlled trials (RCTs), RCT subgroups, and observational studies (OBSs, divided in claims and non-claims). Occurrences of ischemic stroke or transient ischemic attack, systemic embolism, all-cause mortality, intracranial hemorrhage (ICH), and major bleeding were outcomes of interest. Hazard ratios (HRs) and their confidence intervals (95%CIs) were pooled using random-effects models for each study design. Claims studies were analyzed separately from non-claims, while RCT subgroups were grouped with OBSs (non-claims) as the randomization was broken.

Results Of 8647 articles, 20 were included (one RCT, six RCT subgroups, nine claims, and four non-claims). Comparing DOACs to warfarin, pooled HRs (95%CI) were consistently in favor of DOACs although some did not reach statistical significance: for ischemic stroke, 0.84 (0.66–1.07) in claims; 0.90 (0.77–1.06) in non-claims and RCT subgroups; for systemic embolism, 0.77 (0.62–0.96) in claims; 0.86 (0.77–0.96) in non-claims and RCT subgroups; for all-cause mortality, 0.57 (0.33–0.99) in claims; 0.87 (0.79–0.96) in non-claims and RCT subgroups; for ICH, 0.72 (0.39–1.33) in claims; 0.51 (0.38–0.67) in non-claims and RCT subgroups; and for major bleeding, 0.86 (0.71–1.03) in claims; 0.90 (0.76–1.08) for non-claims and RCT subgroups.

Conclusion DOACs were associated with better efficacy and safety profiles than warfarin in atrial fibrillation patients with prior stroke, more specifically a lower risk of systemic embolism, all-cause mortality, and ICH.

Keywords Stroke · Secondary prevention · Atrial fibrillation · Anticoagulants · Direct oral anticoagulants · Warfarin · Meta-analysis

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Introduction

In the USA, more than 690,000 adults experience an ischemic stroke each year and about 240,000 US adults may experience a transient ischemic stroke. Patients who suffered from initial ischemic stroke or transient ischemic attack (TIA) have a high risk of future ischemic stroke, 3 to 4% annually [1].

Direct oral anticoagulants (DOACs) are a relatively new class of medications used mainly for prevention of thromboembolism in patients with non-valvular atrial fibrillation and for treatment of acute venous thromboembolism [2, 3]. The more traditional anticoagulants are warfarin, heparin, and low molecular weight heparins (LMWH) [4, 5]. Warfarin is a vitamin K antagonist and is considered the standard of care for stroke prevention in atrial fibrillation patients [1, 2]. Heparin is considered a short-term therapy in the management of specific patients with acute ischemic stroke and high-risk cardiac conditions [5]. Traditional anticoagulants such as warfarin require regular blood monitoring of the international normalized ratio (INR), food interaction considerations, and monitoring of the possible risk of bleeding. DOACs might be more convenient medications to take if the patient were a suitable candidate [2, 3], as they may require no laboratory monitoring and may reduce the risk of bleeding when taken for stroke prevention [3, 6].

With the publication of the 2019 updated acute stroke management guidelines, the American Stroke Association did not recommend the use of urgent anticoagulation as a treatment of patients with acute ischemic stroke, with the goal of preventing early recurrent stroke, halting neurological worsening, or improving outcomes after acute ischemic stroke [7]. In addition, the usefulness of thrombin inhibitors (e.g., dabigatran) and the safety and usefulness of factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban) for the treatment of patients with acute ischemic stroke are not well established, needing further clinical trials [7]. Initiation of oral anticoagulation is recommended between 4 and 14 days after the onset of neurological symptoms [7].

Although the use of DOACs for patients with atrial fibrillation and venous thromboembolism is supported by systematic reviews and meta-analyses [3, 8, 9], no systematic review and meta-analysis has examined DOACs for stroke prevention in the specific subpopulation of patients with a history of stroke, taking into consideration both randomized controlled trials (RCTs) and comparative observational studies (OBSs). The purpose of the present meta-analysis was therefore to investigate the efficacy and safety of all available DOACs versus warfarin for stroke prevention in patients with atrial fibrillation and a history of previous stroke or TIA.

Methods

Search Strategy and Study Selection

Studies for this meta-analysis were collected from four electronic databases: PubMed, Embase (via Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library, and ClinicalTrials.gov. Keywords included stroke along with warfarin and its variation, and DOACs and its variations (Appendix 1 in the Supplementary Information). The search included articles published up to June 16, 2021. The search strategy followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist, undergoing two levels of screening (title/abstract and full-text) by four reviewers (EB, KU, MZ, YT) [10, 11]. Covidence (www.covidence.org) was used to streamline the review process and ensure high quality at all stages of data management. Disagreements were resolved by discussion or by consulting senior authors. The present study complies with the 1975 Declaration of Helsinki. Ethics committee approval was not sought for this meta-analysis, as it was solely based on already published data.

Study Selection

According to the pre-defined study protocol, studies were included if they were (i) RCTs or comparative OBSs comparing DOAC to warfarin to assess the safety and/or efficacy in adult patients (≥ 18 years) with atrial fibrillation at screening with prior stroke (TIA, ischemic stroke, or any kind of hemorrhagic stroke [12, 13] after the initial period when the risk of thrombosis outweighed the risk of bleeding); (ii) studies reporting data on at least one of the following efficacy outcomes: ischemic stroke or TIA, systemic embolism, and all-cause mortality; or one of the safety outcomes defined as major bleeding or intracranial hemorrhage (ICH); and (iii) studies with sample size ≥ 5. Conference abstracts, non-human studies, and non-English studies were excluded.

Selection of Commercial Claims Studies

For outcomes that had more than one claims study conducted in the same country, only the claims study with the largest number of participants was included for that specific analysis. This was done in order to ensure no overlap in participants included in the final meta-analysis [14], as previously done in our preceding work [15]. Reasons for exclusion of some claims studies are provided in Appendix 2 in the Supplementary Information. To further circumvent double counting of participants in the meta-analysis, studies based on insurance claims were analyzed separately from the non-claims studies.

Data Extraction

Eligible studies had the following data extracted independently by four reviewers (EB, KU, MZ, YT) and reported for each treatment arm when provided: (i) patient characteristics including age, medication use, comorbidities, number of patients eligible for warfarin and DOAC treatment, and gender distribution; (ii) study characteristics such as design, total number of patients at enrolment, and outcome category; (iii) treatment characteristics including dose of warfarin and DOAC, and median follow-up period; and (iv) effect size of all of the above-mentioned safety and efficacy outcomes.

Data Analysis

Hazard ratios (HRs) and their 95% confidence intervals (CIs) were extracted from original studies and then pooled to compare efficacy and safety between DOAC and warfarin groups. RCT subgroups were grouped with the OBSs (non-claims) as once the randomization was broken, the two subgroups being compared were no longer exchangeable, their subsequent results were underpowered, subject to confounding, and the multiple analyses conducted were prone to inflating type I error [16]. For OBSs that used more than one treatment arm compared to the same participants in the reference category, only one arm with the largest sample size compared to the reference group was included in the analysis to avoid artificially inflating the power. Another commonly used approach to handle a multiple-treatment arm study is to split the placebo into the number of active treatment arms being compared to it; however, while this is feasible in a randomized controlled trial where randomization eliminates confounding, this is not feasible in an observational setting where the point estimates provided are derived from a multivariable-adjusted model; hence, relying only on the counts in each group to derive the point estimate will lead to an unadjusted point estimate, which tends to be a biased point estimate. Moreover, because the goal of our research question was to compare DOACs to warfarin head-to-head and not to compare all pairwise comparisons within DOACs, a network meta-analysis was beyond the scope of our research question posed in this manuscript. Pooled effect estimates were analyzed by the random-effects model using the DerSimonian–Laird method, which takes into account the within and between study variation [17]. Heterogeneity was assessed using the Cochrane Q test ($p < 0.1$) and the I^2 value [18]. Comprehensive Meta-Analysis version 3 (Biostat Inc., Englewood, NJ, USA) software was used to meta-analyze the selected studies. Unless otherwise indicated, a p value < 0.05 was considered statistically significant.

Bias and Quality Assessment

The quality of RCTs was assessed with the Cochrane Collaboration tool for assessing risk of bias [19], which assigns low, high, or unclear risk of bias based on the process of sequence generation, allocation concealment, blinding, data collection, and outcome reporting. For OBSs, the Newcastle–Ottawa Scale (NOS) [20] was used to assess the quality based on selection of study groups, their comparability, and outcome assessment in the studies. The score can range between 0 (worst score) and 9 (best score). Because all of our outcomes emanated from fewer than 10 studies, assessing small study bias through funnel plots [21] or other statistical tests [22] was not feasible.

Results

Search Results and Characteristics

A total of 8647 publications were identified from PubMed ($n = 1180$), Embase ($n = 6672$), Cochrane Library ($n = 738$), and ClinicalTrials.gov ($n = 57$) up to June 16, 2021. After removing 1333 duplicates, 7314 articles were subjected to title and abstract screening, of which 519 were selected for full-text review. Twenty-four [23–46] studies were selected for systematic review (Table 1). For meta-analysis, four studies [43–46] were excluded as they were redundant claims or duplicate data, leaving 20 studies that met the inclusion criteria and underwent data extraction (Fig. 1). Among the twenty studies included for meta-analysis, one RCT [23], six RCT subgroups [24–29], nine retrospective claims analyses [30–38], and four prospective cohort (non-claims) studies [39–42] were identified.

The triple AXEL study by Hong et al. [23] was the only RCT that had our research question as the main analysis and directly compared DOAC to warfarin for 183 eligible atrial fibrillation patients with prior acute ischemic stroke or TIA. The mean participants' age was 70.6 years in warfarin and 70.2 years in the DOAC group. Out of six RCT subgroups, five [24, 26–29] used subgroups of patients who had atrial fibrillation with previous stroke or TIA from large anticoagulation therapy trials, including the J-ROCKET [47], ROCKET [48], RE-LY [49], ARISTOTLE [50], and ENGAGE AF TIMI 48 [51] trials. Similarly, Mao et al. [25] focused on anticoagulation usage in a subgroup of patients with prior stroke; however, the study did not mention the type of prior stroke. Notably, the trial subgroup by Diener et al. [29] had two arms of dabigatran with two different doses (110 mg and 150 mg) compared to the same reference group (warfarin); we only extracted the multivariate point estimate for the standard dose (150 mg of dabigatran) to avoid double counting participants in the

Table 1 Characteristics of the studies included in the meta-analysis

Study, country	Study design; single vs multicentre study	Quality of risk/NOS score	Type of prior stroke; timing of stroke	Number of patients taking DOAC	Number of patients taking warfarin	Efficacy outcomes reported	Safety outcomes reported	Median follow-up period
RCT studies ($n=1$)								
Hong KS, 2017 South Korea	RCT; Multicentre	Low risk	Ischemic; 5 days prior to therapy	Rivaroxaban: 101	94	Ischemic stroke/TIA	ICH	4 weeks
Subgroup of RCT ($n=6$)								
Rost NS, 2016 Multinational (ENGAGE AF-TIMI 48)	RCT; Multicentre	Low risk	Ischemic stroke; beyond 1 month prior to therapy	Endoxaban (60 mg): 7036	7036	Ischemic stroke/TIA, Systemic embolism, All-cause mortality	ICH, Major bleeding	2.8 years
Mao L, 2014	RCT; Single center	At risk	NR; beyond 7 days prior to therapy	Rivaroxaban (15 mg/10 mg): 88	86	Systemic embolism	NR	NR
Tanahashi N, 2013 Japan	RCT; Multicentre	Low risk	Ischemic; beyond or equal to 3 months prior to therapy	Rivaroxaban (15 mg/10 mg): 408	405	Ischemic stroke/TIA, Systemic embolism, All-cause mortality	Major bleeding	NR
Hankey GJ, 2012 Multinational (ROCKET AF)	RCT; Multicentre	Low risk	Ischemic; beyond 3 months prior to therapy	Rivaroxaban (20 mg/15 mg): 3754	3714	Ischemic stroke/TIA, Systemic embolism, All-cause mortality	ICH, Major bleeding	676 days
Easton JD, 2012 Multinational (ARISTOTLE trial)	RCT; Multicentre	Low risk	Ischemic; beyond 7 days prior to therapy	Apixaban (5 mg/2.5 mg): 9120	9081	Ischemic stroke/TIA, Systemic embolism, All-cause mortality	ICH, Major bleeding	1.8 years
Diener HC, 2010 US (RE-LY trial)	RCT; Multicentre	At risk	Ischemic; beyond 6 months prior to therapy	Dabigatran (150 mg): 1233	1195	Ischemic stroke/TIA, Systemic embolism, All-cause mortality	ICH, Major bleeding	2 years
Claims studies ($n=13$ for systematic review and $n=9$ for meta-analysis)								
Lin SF, 2020 Taiwan	Retrospective cohort-claims; Multicentre	8	Ischemic 92% Hemorrhage 8%; NR	81,818	83,190	Ischemic stroke/TIA	ICH	2.2 years
† Tsai C, 2020, Taiwan	*Retrospective cohort-claims; Multicentre*	*7*	*Hemorrhagic; NR*	*3493*	*1047*	*Ischemic stroke/TIA, All-cause mortality*	*ICH, Major bleeding*	*NR*
† Lee SR, 2019, Korea	*Retrospective cohort-claims; Multicentre*	*7*	*Hemorrhagic; NR*	*3278*	*2434*	*Ischemic stroke/TIA, All-cause mortality*	*ICH*	*0.6 years*
Nielsen PB, 2019 UK	Retrospective cohort-claims; Multicentre	9	Hemorrhagic; 109 days prior to therapy	348	274	Ischemic stroke/TIA	ICH	1 year
Xian Y, 2019 USA	Retrospective cohort-claims; Multicentre	8	Ischemic; NR	Apixaban: 960 Dabigatran: 1239 Rivaroxaban: 1842	7621	Ischemic stroke/TIA, All-cause mortality	Major bleeding	973.5 days
Jung H, 2019 Korea	Retrospective cohort-claims; Multicentre	8	NR; NR	728	437	All-cause mortality	NR	16 months

Table 1 (continued)

Study, country	Study design; single vs multicentre study	Quality of risk/NOS score	Type of prior stroke; timing of stroke	Number of patients taking DOAC	Number of patients taking warfarin	Efficacy outcomes reported	Safety outcomes reported	Median follow-up period
Yoshimura S, 2018 Japan	Retrospective cohort-claims; Multicentre	8	Ischemic; 7 days prior to therapy	Apixaban: 25 Dabigatran: 203 Rivaroxaban: 238	650	Ischemic stroke/TIA, Systemic embolism, All-cause mortality	Major bleeding	700 days
Lip GYH, 2018, USA	Retrospective cohort-claims; Multicentre	9	NR; NR	Apixaban: 12517	12517	Systemic embolism	NR	NR
Cho MS, 2018 Korea	Retrospective cohort-claims; Multicentre	9	NR; NR	5427	1587	Ischemic stroke/TIA, Systemic embolism	ICH, Major bleeding	NR
† Coleman CI, 2017, USA	*Retrospective cohort-claims; Multicentre*	*8*	*NR; NR*	*2064*	*2604*	*Ischemic stroke/TIA*	*ICH, Major bleeding*	*0.6 years*
† Lip GYH, 2016, USA	*Retrospective cohort-claims; Multicentre*	*7*	*NR; NR*	*16625*	*12713*	*NR*	*Major bleeding*	*NR*
Lauffenburger JC, 2015, USA	Retrospective cohort-claims; Multicentre	7	NR; NR	1495	4710	NR	ICH	12 months
Larsen TB, 2014 Denmark	Retrospective cohort-claims; Multicentre	7	Ischemic; NR	Dabigatran (150 mg): 646	1825	Ischemic stroke/TIA	NR	12.6 months
Non-claims studies ($n=4$)								
Poli D, 2020 Italy	Prospective cohort; Multicentre	5	Hemorrhagic; NR	178	166	NR	ICH	1.2 years
Yokoyama M, 2019 Japan	Prospective cohort; Multicentre	8	Ischemic; NR	56	6	All-cause mortality	ICH	NR
Wilson D, 2018, UK, Netherlands	Prospective cohort; Multicentre	8	Ischemic; NR	542	894	NR	ICH	12 months
Nakase T, 2018 Japan	Prospective cohort; NR	2	Ischemic; NR	Apixaban: 65 Dabigatran: 73 Rivaroxaban: 49	48	Ischemic stroke/TIA, All-cause mortality	ICH	1 year

RCT, randomized controlled trial; *DOAC*, direct oral anticoagulant; *ICH*, intracranial hemorrhage; *NOS*, Newcastle–Ottawa Scale; *NR*, not reported; *TIA*, transient ischemic attack

†The fours studies in italics were systematically reviewed but not included in the meta-analysis

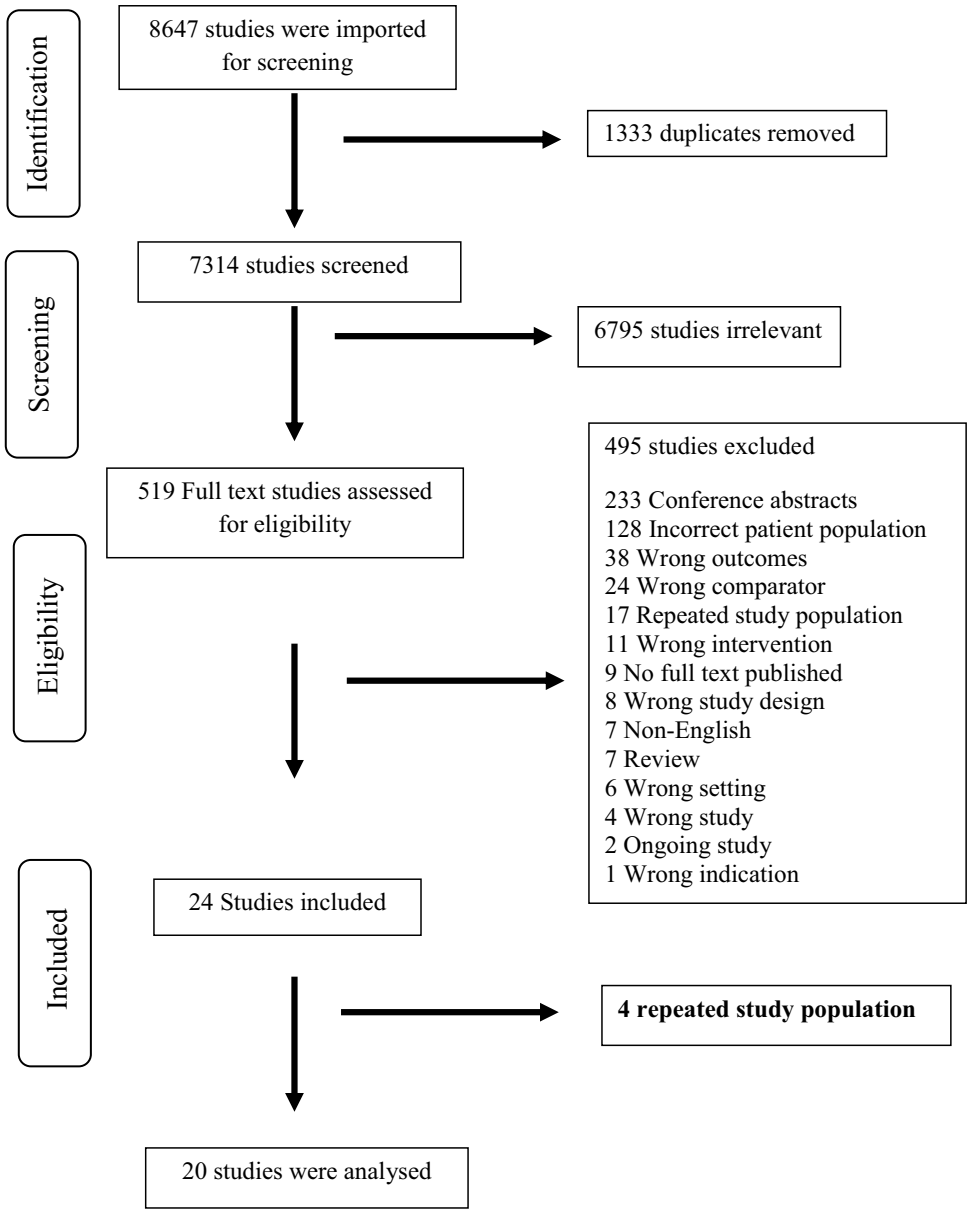

Fig. 1 Study selection process of the identified articles

reference category. For all six RCT subgroups, the mean age was between 68 and 80 in both groups; the median follow-up period was between 4 weeks and 3 years for both warfarin and DOAC arms. According to the Cochrane Collaboration's tool for assessing risk of bias [19], the trials by Diener et al. [29] and Mao et al. [25] were assessed to be at risk of bias due to their open-label characteristics. On the other hand, the RCT by Hong et al. [23] and another four RCT subgroups [24, 26–28] were rated as having a low risk of bias (Table 1). In order to measure the patients' stroke risk, the RCT used $CHADS_2$ VASc score, while the subgroup trials used $CHADS_2$Score. The most commonly reported comorbidity in the RCT [23] was hypertension followed by diabetes and hyperlipidemia. In the subgroup trials [24–29], the commonly reported comorbidities were hypertension, diabetes, and heart failure.

Among the claims studies [30–38], the sample size ranged between 340 and 16,000. Lip et al. [35] had three arms (apixaban, dabigatran, and rivaroxaban) compared to warfarin; only the arm with the largest number of participants was included in the meta-analysis. Larsen et al. [38] included two arms (dabigatran 150 mg and dabigatran 110 mg) compared to warfarin; only the standard dose (dabigatran 150 mg) was included in the analysis. The median follow-up ranged from 1 to 2 years. The NOS score ranged from 7 to 9 (Table 1). All of the claims studies adjusted for at least three covariates and up to ten (Appendix 3 in the Supplementary Information). Among

the non-claims studies [39–42], the sample size ranged between 6 and 900 participants. The median follow-up was 1 year. The NOS score ranged between 2 and 8 (Table 1). While two studies [40, 41] adjusted for two covariates, two other studies [39, 42] did not adjust for any (Appendix 3 in the Supplementary Information). For both claims and non-claims studies, the commonly reported comorbidities were diabetes, hypertension, and heart failure. In order to measure patients' stroke risk and bleeding risk at baseline, the most common assessment tools used were $CHADS_2$Score, CHA_2DS_2 VASc Score, and HAS-BLED Score.

In all of the 20 studies included in the meta-analysis (RCT, RCT subgroups, claims, and non-claims studies), patients had atrial fibrillation and history of transient ischemic stroke, ischemic stroke, or any kind of hemorrhagic stroke at baseline; however, five [25, 33, 35–37] of the 20 studies did not specifically report the type of stroke the patients had. In the RCT [23], ischemic stroke had occurred 5 days before the anticoagulation therapy was initiated. In subgroups of RCTs, the timing of the anticoagulation varied across studies. Rost NS et al. [24] included ischemic stroke patients beyond 1 month prior to therapy. Mao L et al. [25] and Easton JD et al. [28] included stroke patients beyond 7 days prior to therapy. Tanahashi N et al. [26] and Hankey GJ et al. [27] included ischemic stroke patients beyond 3 months prior to therapy. Diener HC et al. [29] included ischemic stroke patients beyond 6 months prior to therapy. As for claims studies, only two reported the timing of stroke: Nielsen [31] (109 days prior to therapy) and Yoshimura [34] (7 days prior to therapy) (Table 1). None of the non-claims studies reported the timing of the studies; however, Wilson D et al. [40] reported that the timing was not controlled and depended on best clinical judgment according to standard practice.

Efficacy Outcomes

Ischemic Stroke or Transient Ischemic Attack Events

One RCT [23], five RCT subgroups [24, 26–29], six claims [30–32, 34, 36, 38], and one non-claim study [41] had sufficient data to analyze ischemic stroke or TIA. Comparing DOACs to warfarin in atrial fibrillation patients with history of stroke, the HR for ischemic stroke or TIA was trending in favor of DOACs (< 1) for all subgroups, yet was not statistically significant in both claims (pooled HR: 0.84; 0.66–1.07; $I^2 = 87.4\%$; p heterogeneity < 0.01) and non-claims and RCT subgroups (HR: 0.90; 0.77–1.06; $I^2 = 0\%$; p heterogeneity: 0.75) (Table 2; Fig. 2). There was only one RCT [23] analyzed separately from the other OBS studies showing a similar trend favoring DOACs.

Systemic Embolism Events

Six RCT subgroups [24–29] and three observational claims studies [34–36] had sufficient data to analyze systemic embolism. Comparing DOACs to warfarin, the pooled HR for systemic embolism was statistically significantly in favor of DOACs in both claims (pooled HR: 0.77; 0.62–0.96; $I^2 = 55.4\%$; p heterogeneity: 0.11) and non-claims and RCT subgroups (pooled HR: 0.86; 0.77–0.96; $I^2 = 21.9\%$; p heterogeneity: 0.27) (Table 2; Fig. 3).

All-Cause Mortality

Five RCT subgroups [24, 26–29], three claims [32–34], and two non-claims studies [39, 41] had sufficient data to analyze all-cause mortality. Comparing DOACs to warfarin in patients with history of stroke, pooled HR for all-cause mortality was trending in favor of DOACs (< 1) for all subgroups. It was statistically significant in claims (pooled HR: 0.57; 0.33–0.99; $I^2 = 90.9\%$; p heterogeneity < 0.01) and non-claims and RCT subgroups (pooled HR: 0.87; 0.79–0.96; $I^2 = 0\%$; p heterogeneity: 0.86) (Table 2; Fig. 4).

Safety Outcomes

Intracranial Hemorrhage Events

Thirteen studies, one RCT [23], four RCT subgroups [24, 27–29], four claims [30, 31, 36, 37], and four non-claims [39–42], provided data on ICH. Comparing DOACs to warfarin in atrial fibrillation patients with a history of stroke, the pooled HR was trending in favor of DOACs (< 1) but was not statistically significant in claims (pooled HR: 0.72; 0.39–1.33; $I^2 = 10.9\%$; p heterogeneity 0.35); yet it was statistically significant in non-claims and RCT subgroups (pooled HR: 0.51; 0.38–0.67; $I^2 = 94.3\%$; p heterogeneity: < 0.01) (Table 2; Fig. 5).

Major Bleeding Events

Eight studies including five RCT subgroups [24, 26–29] and three claims [32, 34, 36] provided data on major bleeding events. Comparing DOACs to warfarin in atrial fibrillation patients with a history of stroke, the pooled HR was trending in favor of DOACs (< 1) but did not reach statistical significance in both claims (pooled HR: 0.86; 0.71–1.03; $I^2 = 2.46\%$; p heterogeneity: 0.36) and non-claims and RCT subgroups (pooled HR: 0.90; 0.76–1.08; $I^2 = 51.8\%$; p heterogeneity: 0.08) (Table 2; Fig. 6).

Table 2 Pooled hazard ratios (HRs) of efficacy and safety outcomes from studies comparing DOACs to warfarin in patients with a history of stroke, for each study design

Outcomes	RCTs Pooled HR (95%CI); no. of studies; *p* heterogeneity; I^2 value	Claims studies Pooled HR (95% CI); no. of studies; *p* heterogeneity; I^2 value	Non-claims and RCT subgroups Pooled HR (95% CI); no. of studies; *p* heterogeneity; I^2 value
Efficacy outcomes			
Ischemic stroke/transient ischemic attack	DL: 0.93 (0.06–14.5); 1 study *p* hetero: NA; I^2: NA	DL: 0.84 (0.66–1.07); 6 studies; *p* hetero: 0.00; I^2: 87.4%	DL: 0.90 (0.77–1.06); 6 studies; *p* hetero: 0.75; I^2: 0%
Systemic embolism	NA	**DL: 0.77 (0.62–0.96)**; 3 studies; *p* hetero: 0.11; I^2: 55.4%	**DL: 0.86 (0.77–0.96)**; 6 studies; *p* hetero: 0.27; I^2: 21.9%
All-cause mortality	NA	**DL: 0.57 (0.33–0.99)**; 3 studies; *p* hetero: 0.00; I^2: 90.9%	**DL: 0.87 (0.79–0.96)**; 7 studies; *p* hetero: 0.86; I^2: 0%
Safety outcomes			
Intracranial hemorrhage events	DL: 1.10 (0.70–1.72); 1 study *p* hetero: NA; I^2: NA	DL: 0.72 (0.39–1.33); 4 studies; *p* hetero: 0.35; I^2: 10.9%	**DL: 0.51 (0.38–0.67)**; 8 studies; *p* hetero: 0.00; I^2: 94.3%
Major bleeding events	NA	DL: 0.86 (0.71–1.03); 3 studies; *p* hetero: 0.36; I^2: 2.46%	DL: 0.90 (0.76–1.08); 5 studies; *p* hetero: 0.08; I^2: 51.8%

DOAC, direct oral anticoagulant; *DL*, DerSimonian and Laird; *CI*, confidence interval; *NA*, not available

Values in bold are statistically significant

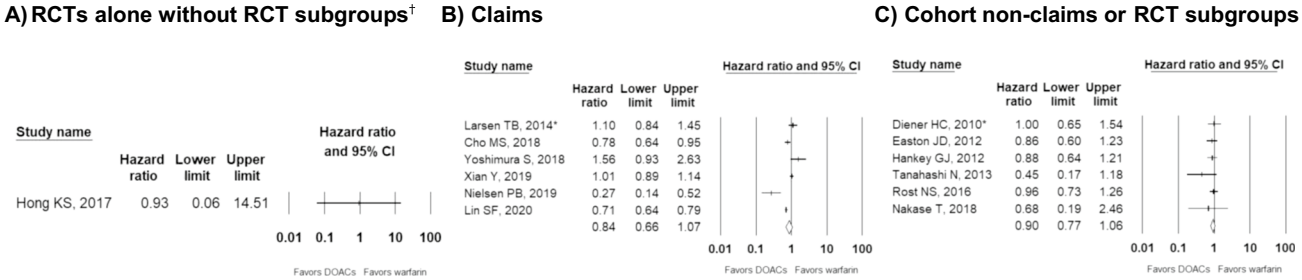

Fig. 2 Efficacy outcome: ischemic stroke for each study design separately ((**A**) RCTs; (**B**) Claims; (**C**) Cohort non-claims or RCT subgroups). (**B**) and (**C**) *(150 mg dabigatran); †Only one RCT had our research question as the main analysis and directly compared warfarin to DOAC in eligible patients with prior acute ischemic stroke or TIA

Sensitivity Analyses

A sensitivity analysis including only the studies reporting ischemic stroke as previous event led to results that were not materially different from the main analysis (Appendix 4 in the Supplementary Information). Additionally, in an attempt to assess the robustness of our results for outcomes with high heterogeneity ($I^2 > 40\%$), a one-study-removal analysis did not reveal any of the included studies to be an outlier, which further confirmed the robustness of our pooled point estimates (Appendix 5 in the Supplementary Information).

Discussion

The objective of the present study was to assess the efficacy and safety of all DOACs compared to warfarin in the treatment of patients with atrial fibrillation and prior stroke or

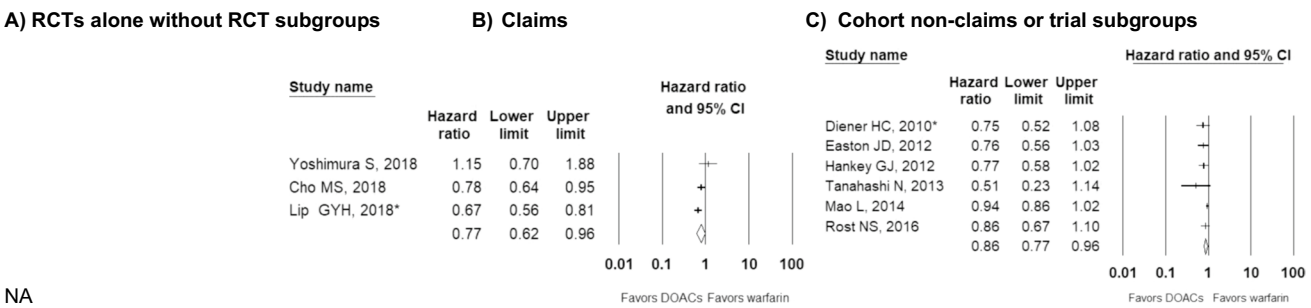

Fig. 3 Efficacy outcome: systemic embolism for each study design separately ((**A**) RCTs; (**B**) Claims; (**C**) Cohort non-claims or trial subgroups). (**B**) *(Apixaban); (**C**) *(150 mg dabigatran); NA, not applicable

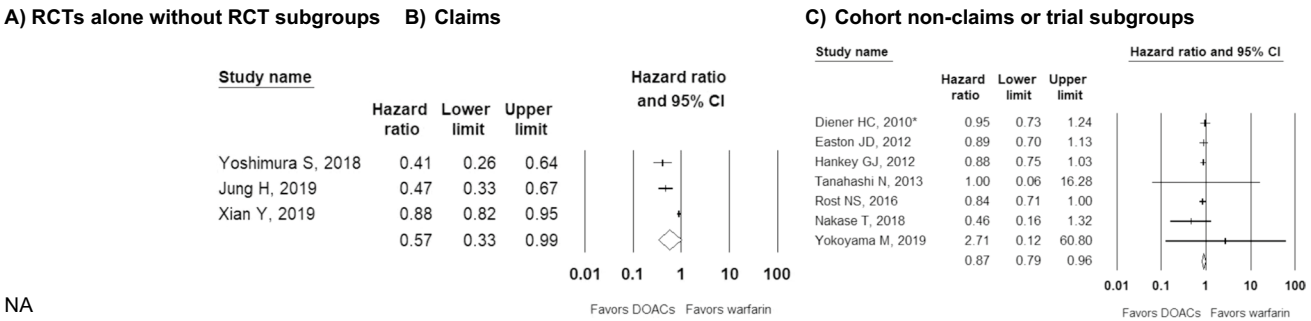

Fig. 4 Efficacy outcome: all-cause mortality for each study design separately ((**A**) RCTs; (**B**) Claims; (**C**) Cohort non-claims or trial subgroups). (**C**) *(150 mg dabigatran); NA, not applicable

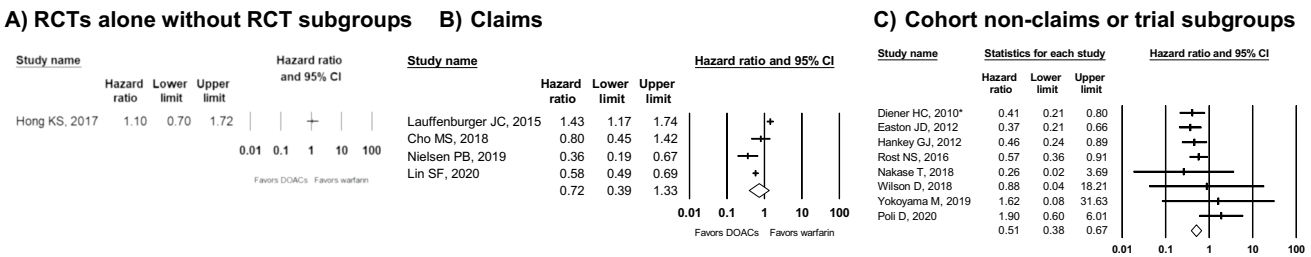

Fig. 5 Safety outcome: intracranial hemorrhage events for each study design separately ((**A**) RCTs; (**B**) Claims; (**C**) Cohort non-claims or trial subgroups). (**C**) *(150 mg dabigatran)

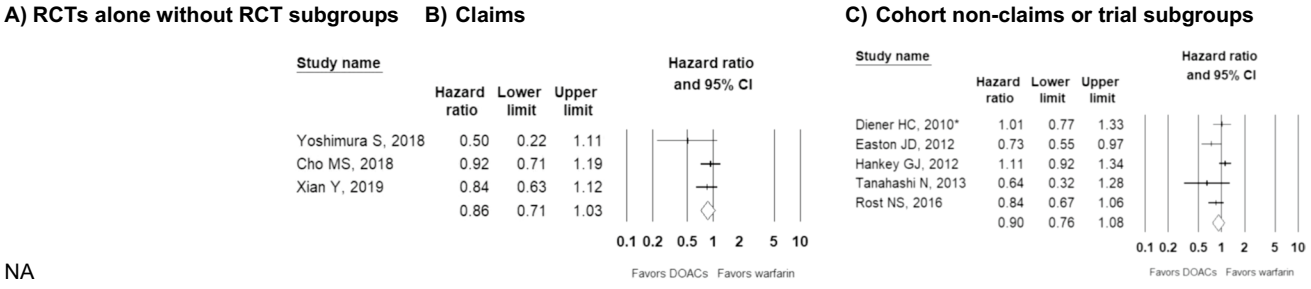

Fig. 6 Safety outcome: major bleeding for each study design separately ((**A**) RCTs; (**B**) Claims; (**C**) Cohort non-claims or trial subgroups). (**C**) *(150 mg dabigatran); NA, not applicable

TIA. Analyses of pooled efficacy data showed DOACs to be more effective than warfarin in reducing systemic embolism and all-cause mortality with pooled HRs reaching statistical significance in both claims and non-claims studies and RCT subgroups. Similarly, safety profile results showed a statistically significantly lower risk of ICH among patients on DOACs compared to warfarin. Other efficacy (ischemic stroke) and safety (major bleeding) outcomes were trending in favor of DOACs with a pooled HR < 1. In general, the value of standard therapy with warfarin was confirmed, but a marginal benefit of DOACs in terms of efficacy and safety, combined to their greater ease of use, might make these newer drugs of first choice in the analyzed patient population.

Several published RCTs [48–51] and OBSs [33, 35–37] demonstrated that DOACs were not inferior to warfarin in the prevention of stroke in patients with non-valvular atrial fibrillation. A number of meta-analyses pooled the available data, confirming the effectiveness and safety of DOACs for the prevention of stroke in patients with non-valvular atrial fibrillation [3, 8, 9, 52–66]. In the high-risk subpopulation of patients with prior stroke, DOACs have been reported to retain an important role [67–73]. Additional OBSs [30, 42] were recently published to address this issue, which highlighted the need for an updated meta-analysis. To our knowledge, no published systematic review has ever presented an up-to-date quantitative analysis utilizing both RCTs and OBSs in this setting, while discerning RCTs from RCT subgroups. Notably, when an RCT is originally designed to address a research question, the two groups become exchangeable because of the randomization process. Nevertheless, when subgroups of patients are taken out of the two arms to be compared separately, randomization is broken, and the two groups are no longer comparable [16]. None of the previous analyses [67–73] took that into account by adjusting for potential confounders; instead, the respective authors considered the studies as RCTs; however, in our meta-analysis, RCT subgroups were treated as OBS non-claims studies.

Rasmussen et al. [67] and Sardar et al. [69] pooled data from three RCTs [48–50] and reported equivalent effectiveness of DOACs and warfarin, with similar reduction of recurrent stroke and all-cause mortality in patients with previous stroke or TIA. When including more recent studies, all-cause mortality risk remained in favor of DOACs while results on reduction of ischemic stroke or TIA were consistently trending in favor of DOACs compared to warfarin (all HRs were below 1). Previously published pooled analyses also reported a reduction in intracranial bleeding [67, 69], which was at least in part consistent with our results, which showed a statistical significance in non-claims studies and RCT subgroups, but did not reach statistical significance in claims studies. This discrepancy between claims and non-claims OBSs might depend on residual confounding, including dose differences and treatment duration of DOACs among claims OBS, as these studies did not take into consideration, for example, that some patients could have started the therapy in the past before entering the study (prevalent users), while others could have been starting the treatment at baseline (incident users). Other reasons could be due to the inclusion of patients with diverse baseline characteristics that are quite different from the patients included in an RCT subgroup (e.g., type of previous stroke, concomitant medication use, patients with previous comorbidities, older patients).

Examining data from the same three above-mentioned RCTs [48–50], Ntaios et al. reported more favorable efficacy and safety profiles for DOACs compared to warfarin, while using a fixed-effect model when pooling their results [68]. Specifically, the use of DOACs for the secondary prevention of stroke was reported to reduce the risk of systemic embolism and the risk of ICH [68]. These results were consistent with our findings, although we used the random-effects models, known to be more appropriate and more conservative than the fixed-effect models.

A more recent meta-analysis by Ruff et al. considered four phase III RCTs [48–51], including data for edoxaban [70]. In their subgroup analyses, DOACs were found to be more effective in reducing the risk of systemic embolism compared to warfarin in patients with prior stroke or TIA [70], which was congruent with our results. Moreover, the cited study also reported no statistically significant reduction in major bleeding events [70], which was also similar to our findings when considering a broader sample of the same patient population. The recently published meta-analysis by Liu et al. [73] included observational studies; however, prospective cohort non-claims studies [39–42] were not included, patients were double counted by including claims studies with overlapping population, and low and standard dose DOACs were pooled together, all of which may have introduced bias in outcomes' interpretation.

Findings of this meta-analysis need to be taken into consideration in the context of its limitations. Most importantly, regarding the RCT subgroups, none of these studies adjusted for confounding, despite the randomization being broken and subjecting studies to inevitable confounding bias. Even though the prevalence of ischemic stroke is generally higher than of hemorrhagic stroke, some studies did not specifically report the type of stroke patients had previously experienced [25, 33, 35–37]. Moreover, some studies failed to report the time lapse between the stroke and anticoagulation therapy [30, 32, 33, 35–46], which prevented us from assessing the optimal anticoagulation timing for this patient population. We also noted a high level of heterogeneity among the claims studies, which could be due to the clinical heterogeneity across the OBSs mostly, such as differential baseline

risk and quality of care. Lastly, non-English studies were not included, which may weaken the power of our study.

Despite these limitations, strengths and novelty of the present study should be acknowledged. In order to avoid double counting participants in our study, claims were analyzed separately from non-claims studies, while meticulously ensuring there was no overlap in the pooled claims studies conducted in the same country. This can provide useful information on the efficacy of drugs in real-world populations as compared to the controlled environment of RCTs. Moreover, RCT subgroups were combined with OBS studies instead of RCTs as the randomization was no longer applicable among the subgroups compared, which necessitates further adjustment for confounding in such analyses. None of the RCT subgroups conducted such adjustment which could lead to biased estimates.

The implication of this study is to reinforce the possibility of administering DOACs to patients with atrial fibrillation and a history of stroke. However, the need of larger phase III trials or larger cohort studies with appropriate adjustment for confounding remains, as concomitant medications (antiplatelet agents and NSAIDs), comorbidities (e.g., hypertension, cardiac failure), and timing of oral anticoagulation need to be assessed to validate the use of DOAC or warfarin.

Conclusion

DOACs were found to have at least non-inferior and, in some regards, better efficacy and safety profiles than warfarin for secondary prevention in atrial fibrillation patients with a history of stroke or TIA. More specifically, DOACs were statistically significantly associated with a reduction in the risk of systemic embolism, all-cause mortality (in both claims and non-claims studies and RCT subgroups), and ICH (in non-claims studies and RCT subgroups); all other outcomes trended in favor of DOACs in claims studies, non-claims studies, and RCT subgroups. Further phase III clinical trials or well-conducted comparative observational studies are still needed to confirm some of the non-statistically significant efficacy and safety outcomes obtained in this meta-analysis in atrial fibrillation patients with prior stroke.

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Author Contribution JB, MMi, and RM conceived and designed the study. KU, EB, YT, and MZ collected the data. KU and RM performed the analyses. KU and MMa wrote the paper. RM edited the entire manuscript.

Availability of Data and Material Not applicable. The data that were used for the present study were secondary data extracted from previously published papers that are herein referenced; data are available upon request to the corresponding author.

Code Availability Not applicable.

Declarations

Ethics Approval Ethics committee approval was not required for this study, as it is solely based on previously published data.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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