

# Optimal Antithrombotic Regimen After Cryptogenic Stroke: A Systematic Review and Network Meta-Analysis

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## Abstract

Although several antithrombotic strategies have been investigated for the management of cryptogenic strokes, ie, ischemic strokes without known etiologies, an optimal antithrombotic strategy for cryptogenic strokes is unknown. We aim to assess oral antithrombotic agents' comparative efficacy and safety after cryptogenic stroke to identify an optimal treatment.

A systematic review and meta-analysis synthesizing evidence from randomized controlled trials (RCTs) obtained from PubMed, Embase Cochrane, Scopus, and Web of Science until February 2024. We used the random-effects model to report dichotomous outcomes using a risk ratio (RR) with a 95% confidence interval (CI). Frequentist network meta-analysis was conducted using R, version 4.3.1.

Seven RCTs with 15,240 patients were included. None of the OACs showed a significant efficacy in preventing all-cause mortality, stroke recurrence, cardiovascular mortality, and major adverse cardiac events compared to aspirin. Also, safety measures were similar between different OACs and aspirin regarding safety measures, including major bleeding, intracranial hemorrhage, and gastrointestinal bleeding. However, only rivaroxaban significantly increased the incidence of major bleeding (RR: 2.69, CI [1.67, 4.33]).

There was no difference between various OACs and aspirin regarding efficacy and safety outcomes. There is a greater risk of major bleeding with rivaroxaban. Further research is still warranted to define a personalized strategy for selecting antithrombotic strategies after cryptogenic stroke on a case-by-case basis.

## Keywords

brain infarct, ESUS, idiopathic, aspirin, warfarin, apixaban, rivaroxaban, dabigatran

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## Introduction

Cerebrovascular accidents (CVAs), commonly known as strokes, constitute a significant cause of morbidity and mortality worldwide, with more than 795,000 cases in the United States annually.<sup>1</sup> Strokes can be ischemic, hemorrhagic, or

subarachnoid, with the ischemic strokes comprising most of (>60%) stroke cases.<sup>2</sup> Ischemic strokes exhibit marked heterogeneity with more than 100 implicated pathologies.<sup>3</sup> Yet, no definite etiology is identified in 30%–40% of ischemic stroke cases, to which the term cryptogenic stroke is used to refer.<sup>4,5</sup> The Trial

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of Org 10172 defined cryptogenic stroke, in the acute stroke treatment criteria, as the brain infarct not attributed to a definite source of large-vessel atherosclerosis, cardio-embolism, or small-vessel disease in the presence of extensive cardiac, serologic, hematologic, and vascular evaluation, incomplete evaluation, or evidence of more than one competing cause.<sup>6</sup> However, it has been shown that some cryptogenic strokes are caused by a source of cardio-embolism, such as atrial cardiopathy and patent foramen ovale (PFO).<sup>7–9</sup> For instance, PFO is detected in and likely the cause of 50% of cryptogenic stroke cases.<sup>10</sup>

Comprising a significant cause of disability and mortality, research on the management of ischemic stroke is escalating.<sup>11,12</sup> The combination of antiplatelet therapy and stroke risk factor modification, as the mainstay of stroke prevention strategies in patients with stroke of identified cause, has been applied to cryptogenic stroke cases.<sup>13,14</sup> Interestingly, some studies showed a potential benefit from warfarin over aspirin in specific subgroups of cryptogenic stroke patients, which opened the investigations of the superiority of antiplatelets compared to anticoagulants.<sup>14,15</sup> Additionally, percutaneous closure of PFO, in cases with PFO, showed successful results in preventing stroke recurrence in such cases.<sup>16</sup> Although it is hypothesized that anticoagulants can be beneficial in stroke cases with potential sources of emboli, most studies focused on surgical or percutaneous closure of PFO (source of emboli) and antiplatelets instead of comparing antiplatelets to anticoagulants.<sup>17</sup>

Previous systematic reviews and meta-analyses, including five or six randomized clinical trials (RCTs) per each, have shown controversial results concerning the benefit of anticoagulants over antiplatelets in reducing the risk of stroke recurrence and safety issues such as significant bleeding.<sup>18–20</sup> The most recent review of 2282 patients concluded that oral anticoagulants (OACs) were associated with a lower risk of recurrent ischemic stroke compared to antiplatelets and a non-significantly higher risk of significant bleeding.<sup>19</sup> However, two large RCTs were published recently, comprising 1367 patients, and apixaban was compared to aspirin for patients with cryptogenic stroke.<sup>15,21</sup> We, therefore, conducted the systematic review and network meta-analysis of RCTs to provide comprehensive and up-to-date evidence of OACs efficacy and safety compared to antiplatelet therapy in patients with cryptogenic stroke with potential cardiac emboli.

## Methodology

### Protocol Registration

We submitted this systematic review and meta-analysis protocol to PROSPERO with ID: CRD42024519285. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension statement for network meta-analyses<sup>22,23</sup> and the Cochrane Handbook of Systematic Reviews and Meta-Analysis<sup>24</sup> were strictly followed to conduct this review.

### Data Sources & Search Strategy

A comprehensive search was conducted using PubMed (MEDLINE), Scopus, Cochrane Central Register of Controlled

Trials (CENTRAL), Web of Science Core Collection, and EMBASE up to Feb 20, 2024. The search involved customizing terms and keywords in each database with Mesh terms related to cryptogenic and embolic strokes of undetermined etiology and various antithrombotic medications. This search strategy details are highlighted in (Table S1).

### Eligibility Criteria

We included randomized controlled trials (RCTs) that followed the following PICO criteria: population (P): patients with cryptogenic stroke or embolic stroke of undetermined source (ESUS); intervention (I): oral anticoagulant either vitamin K antagonists such as warfarin, or direct oral anticoagulant (DOACs); control (C) another oral anticoagulant or antiplatelets; and outcomes (O): efficacy outcomes including all-cause mortality, cardiovascular mortality, stroke recurrence, major adverse cardiac events (MACE), ischemic stroke, myocardial infarction, and systemic thromboembolism. While the safety outcomes included major bleeding, gastrointestinal bleeding, intracranial hemorrhage, and the incidence of any serious adverse event.

Observational studies, review articles, letters, single-arm clinical trials, animal studies, case series, case reports, comments, and consensus documents were excluded from this study.

### Study Selection

The review process utilized the Covidence web tool to manage records. After removing duplicates, four investigators (A.N., M.Ay., S.R., and M.T.) independently assessed the records. These investigators also performed full-text reviews for records meeting the initial criteria, with any discrepancies resolved through discussion and consensus with M.Ab.

### Data Extraction

Four independent reviewers (A.N., M.Ay., S.R., and M.T.) extracted the following data using a pilot-tested Excel sheet: summary characteristics (first author name, year of publication, country, study design, total participants, intervention and control details, main inclusion criteria, primary outcome, and follow-up duration); baseline characteristics (age, gender, number of patients in each arm, baseline scores, and comorbidities); and outcomes data as previously outlined. Any disagreements among the reviewers were resolved through a consensus conference.

### Risk of Bias

Four reviewers (A.N., M.Ay., S.R., and M.T.) assessed the risk of bias using the Cochrane RoB 2 tool for RCTs.<sup>25</sup> The RoB 2 tool assessed five areas of potential bias in RCTs: randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Any disagreements among the reviewers were resolved through a consensus conference.

## Statistical Analysis

We used R version 4.3.1. to perform a network meta-analysis using a frequentist framework and a random effects model. We pooled dichotomous outcomes using risk ratio (RR) and the corresponding 95% confidence interval (CI). Statistical inconsistency between network arms was evaluated by calculating  $I^2$ . We interpreted the I-square test as follows: not significant for 0%–40%, moderate heterogeneity for 30%–60%, and substantial heterogeneity for 50%–90%, following the Cochrane Handbook (chapter nine). Treatment ranking was determined by calculating the SUCRA (Surface Under the Cumulative Ranking Curve) to assess the probability of each treatment being at each possible rank.<sup>26</sup>

## Results

### Search Results and Study Selection

We identified a total of 4477 records after searching the databases. Three thousand and five duplicates and automatically identified irrelevant records were removed using Covidence, which left 1172 records for title and abstract screening. We excluded 1158 records and screened 14 full-text articles to include seven RCTs (Figure 1).

### Characteristics of Included Studies

This study involves seven RCTs<sup>15,16,21,27–30</sup> with 15,240 patients. Three trials investigated warfarin as an intervention,<sup>16,28,29</sup> while four trials investigated DOACs, either dabigatran, rivaroxaban, or apixaban.<sup>15,21,27,30</sup> All the included trials used aspirin as a control. Further details are highlighted in (Table 1) about the included trials' characteristics and in (Table 2) about the included patients' baseline data.

### Risk of Bias

Three of the included RCTs, including the RE-SPECT ESUS trial, NAVIGATE ESUS, and ARCADIA trial,<sup>15,27,30</sup> demonstrated an overall low risk of bias. However, ATTICUS showed overall some concerns due to the open-label treatments.<sup>21</sup> Also, PICSS<sup>29</sup> showed some concerns due to a lack of information about allocation concealment. Finally, CLOSE<sup>16</sup> and Shariat et al<sup>28</sup> exhibited a high risk of bias mainly due to the open-label assessment of outcomes.<sup>16,28</sup> The risk of bias in the included studies is detailed in (Figure 2).

### DOACs Versus Warfarin Versus Aspirin

#### Efficacy Outcomes

**All-Cause Mortality.** Based on the analysis of six RCTs, compared to aspirin, there was no significant difference observed between aspirin and warfarin (RR: 2.31 with 95% CI (0.29, 18.26),  $P = .43$ ) or DOACs (RR: 1.11 with 95% CI (0.87, 1.42),  $P = .39$ ) (Figure 3A). After ranking the treatment

arms, warfarin has the highest risk, followed by DOACs and aspirin (Table 3). Low heterogeneity was observed ( $I^2 = 0\%$ ).

**Cardiovascular Mortality.** Based on the analysis of four RCTs, compared to aspirin, no significant difference was observed between aspirin and DOACs (RR: 1.11 with 95% CI (0.71, 1.74),  $P = .65$ ) or warfarin (RR: 1.09 with 95% CI (0.02, 53.44),  $P = .96$ ) (Figure 3B). After ranking the treatment arms, DOACs had the highest risk, followed by warfarin and aspirin (Table 3). Low heterogeneity was observed ( $I^2 = 14.9\%$ ).

**Stroke Recurrence.** Based on the analysis of five RCTs, compared to aspirin, no significant difference was observed between aspirin and DOACs (RR: 0.95 with 95% CI (0.83, 1.09),  $P = .47$ ) or warfarin (RR: 0.31 with 95% CI (0.09, 1.03),  $P = .06$ ) (Figure 3C). After ranking the treatment arms, aspirin had the highest risk, followed by DOACs and warfarin (Table 3). Low heterogeneity was observed ( $I^2 = 0\%$ ).

**Major Adverse Cardiac Events.** Based on the analysis of five RCTs, compared to aspirin, no significant difference was observed between aspirin and DOACs (RR: 0.98 with 95% CI (0.87, 1.10),  $P = .73$ ) or warfarin (RR: 0.91 with 95% CI (0.62, 1.33),  $P = .61$ ) (Figure 3D). After ranking the treatment arms, aspirin had the highest risk, followed by DOACs and warfarin (Table 3). Low heterogeneity was observed ( $I^2 = 0\%$ ).

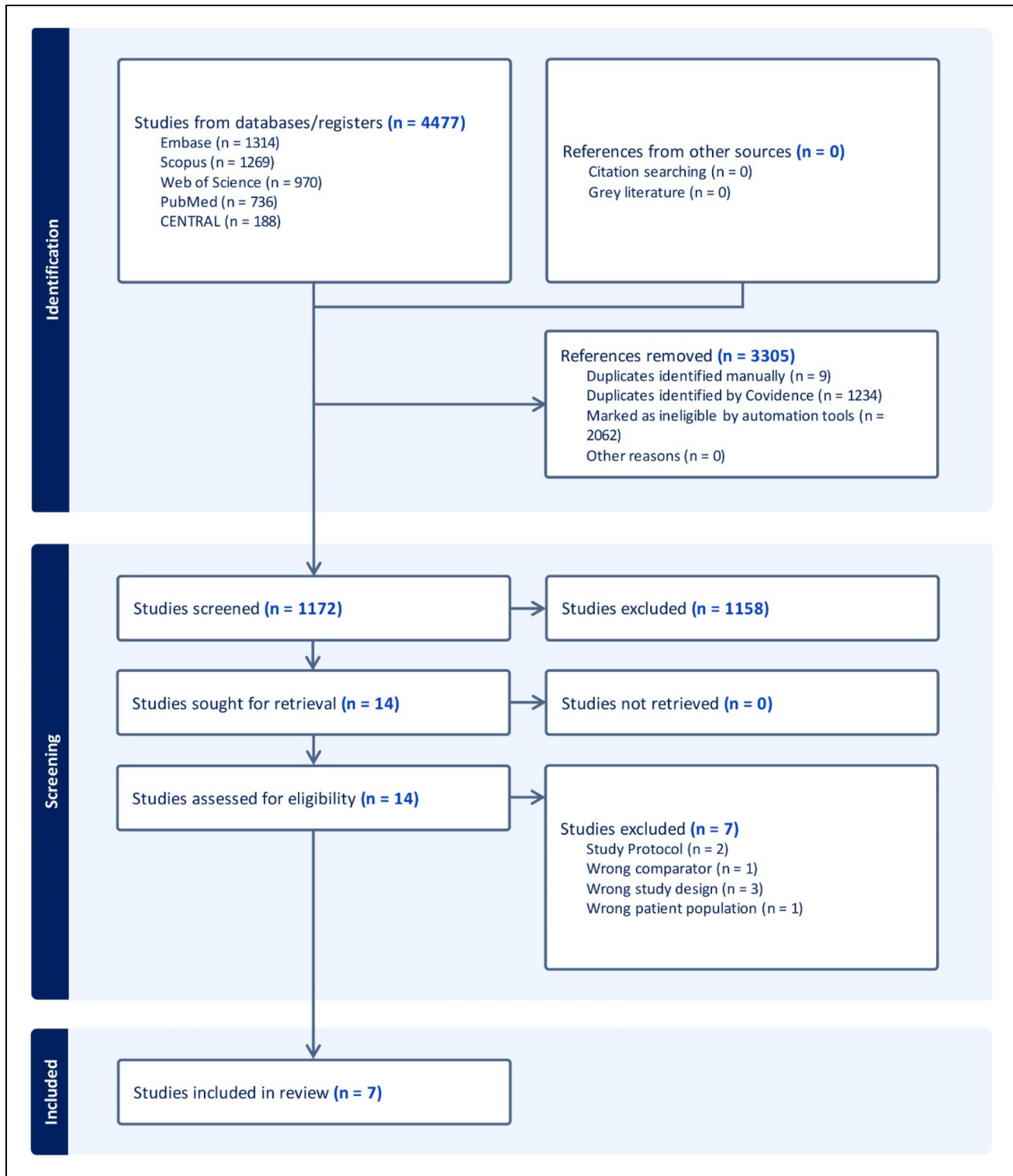
**Ischemic Stroke.** Based on the analysis of four RCTs, compared to aspirin, no significant difference was observed between aspirin and DOACs (RR: 0.92 with 95% CI (0.79, 1.06),  $P = .23$ ) or warfarin (RR: 0.13 with 95% CI (0.01, 2.21),  $P = .16$ ) (Figure S1-A). After ranking the treatment arms, aspirin had the highest risk, followed by DOACs and warfarin (Table 3). Low heterogeneity was observed ( $I^2 = 0\%$ ).

**Myocardial Infarction.** Based on the analysis of four RCTs, compared to aspirin, no significant difference was observed between aspirin and warfarin (RR: 2.18 with 95% CI (0.04, 111.51),  $P = 0.70$ ) or DOACs (RR: 0.93 with 95% CI (0.56, 1.52),  $P = .76$ ) (Figure S1-B). After ranking the treatment arms, warfarin had the highest risk, followed by aspirin and DOACs (Table 3). Low heterogeneity was observed ( $I^2 = 16.1\%$ ).

**Combined Systemic Thromboembolism.** Based on the analysis of five RCTs, compared to aspirin, no significant difference was observed between aspirin and DOACs (RR: 1.00 with 95% CI (0.84, 1.20),  $P = .96$ ) or warfarin (RR: 0.53 with 95% CI (0.25, 1.13),  $P = .10$ ) (Figure S1C). After ranking the treatment arms, aspirin had the highest risk, followed by DOACs and warfarin (Table 3). Low heterogeneity was observed ( $I^2 = 0\%$ ).

#### Safety Outcomes

**Major Bleeding.** Based on the analysis of six RCTs, compared to aspirin, no significant difference was observed between aspirin and warfarin (RR: 2.29 with 95% CI (0.70, 7.51),  $P = .17$ ) or DOACs (RR: 1.58 with 95% CI (0.92,



**Figure 1.** PRISMA flow chart of the screening process.

2.70),  $P = .10$ ) (Figure 4A). After ranking the treatment arms, warfarin had the highest risk, followed by DOACs and aspirin (Table 3). High heterogeneity was observed ( $I^2 = 50.2\%$ ).

*Gastrointestinal Bleeding.* Based on the analysis of four RCTs, compared to aspirin, no significant difference was observed between aspirin and DOACs (RR: 1.26 with 95% CI (0.73, 2.19),  $P = .41$ ) or warfarin (RR: 1.36 with 95% CI

**Table 1.** Summary Characteristics of the Included RCTs.

Study ID	Study Design	Country	Total Participants	Intervention (OACs)				Control			
				Drug	Dose/Times of administration	Treatment Duration	Drug	Dose/Times of administration	Treatment Duration	Primary Outcome	Follow-up duration
Diener et al 2019 (RE-SPECT ESUS) <sup>27</sup>	Multicenter, double-blinded RCT	International	5390	dabigatran	150 mg or 110 mg twice daily	A minimum of 6 months and a maximum of 3.5 years	Aspirin	100 mg once daily	A minimum of 6 months and a maximum of 3.5 years	Recurrent stroke of any type	Median of 19 months
Geisler et al 2023 (ATTICUS) <sup>21</sup>	Multicenter, open-label, blinded-outcome RCT	Germany	352	apixaban	5 mg twice daily	12 months	Aspirin	100 mg once daily	N/A	New ischemic lesion on diffusion-weighted or fluid-attenuated inversion recovery brain MRI	12 months
Hart et al 2018 (NAVIGATE ESUS) <sup>30</sup>	Multicenter, double-blinded RCT	International	7213	rivaroxaban	15 mg once daily	N/A	Aspirin	100 mg once daily	N/A	Recurrent stroke of any type	Median of 11 months
Homma et al 2002 (PICSS) <sup>29</sup>	Multicenter, double-blinded RCT	USA	630	warfarin	2 mg daily	N/A	Aspirin	325 mg daily	N/A	Recurrent ischemic stroke	24 months
Kamel et al 2024 (ARCADIA) <sup>15</sup>	Multicenter, double-blinded RCT	USA	1015	apixaban	5 mg or 2.5 mg, twice daily	N/A	Aspirin	81 mg once daily	N/A	Recurrent stroke of any type	1.8 ± 1.3 years
Mas et al 2017 (CLOSE) <sup>16</sup>	Multicenter, open-label, RCT	Germany and France	596	warfarin	Goal to achieve INR 2-3	N/A	Aspirin	75 mg	N/A	Fatal or nonfatal stroke	5.2 ± 2.1 years
Shariat et al 2012 <sup>28</sup>	Single-center, single-blinded RCT	Iran	44	warfarin	Started at 2.5 mg orally once daily and then adjusted to achieve an INR target of 2 to 3	18 months	Aspirin	80 mg orally 3 times daily	N/A	Recurrence of ischemic event or death due to any cause	14.6 ± 3.7 months

Abbreviations: RCT, randomized controlled trial; INR, international normalized ratio; MRI, magnetic resonance imaging; N/A, not available; OACs, oral anticoagulants.

**Table 2.** Baseline Characteristics of the Participants.

Study ID	ARM	Number of patients in each group	Age (Years) Mean (SD)	Gender (Male) N. (%)	Renal disease	BMI, Mean (SD) CAD or IHD	NIHSS, mean (SD)	Comorbidities N. (%)						
								DM	TIA	Smoking	DVT or PE	N/A		
Diener et al 2019 (RE-SPECT ESUS) <sup>27</sup>	dabigatran	2695	64.5 ± 11.4	1694 (62.9)		27.2 ± 5.0	1 ± 1.48	117 (4.3)	1996 (74.1)	301 (11.2)	475 (17.6)	458 (17.0)	N/A	
Geisler et al 2023 (ATTICUS) <sup>21</sup>	aspirin	63.9 ± 11.4	1709 (63.4)	27.3 ± 5.0		1 ± 1.48	N/A	639 (23.7)	124 (4.6)	276 (10.2)	500 (18.6)	433 (16.1)	N/A	
	apixaban	178	68.6 ± 11.1	92 (51.6)		27.7 ± 5.2	1.33 ± 2.24	3 (1.7)	153 (86.0)	10 (5.6)	12 (6.7)	24 (13.5)	27 (15.2)	5 (2.8)
Hart et al 2018 (NAVIGATE ESUS) <sup>30</sup>	aspirin	68.3 ± 9.8	89 (51.1)	27.7 ± 4.9		1.33 ± 2.24	N/A	48 (27.6)	4 (2.3)	17 (9.8)	30 (17.2)	26 (14.9)	4 (2.3)	N/A
	rivaroxaban	3609	N/A	2232		27.1 ± 4.9	1	N/A	2782	889	N/A	620	756	N/A
Homma et al 2002 (PICSS) <sup>29</sup>	aspirin	3604	2204	27.3 ± 5.1		1	N/A	917	N/A	N/A	643	728	N/A	N/A
	warfarin	203	57.9 ± 13.3	120		28.1 ± 5.0	N/A	N/A	108	N/A	N/A	N/A	55	N/A
Kamel et al 2024 (ARCADIA) <sup>15</sup>	aspirin	398	212	28.7 ± 6.4		N/A	N/A	127	N/A	N/A	N/A	117	N/A	N/A
	apixaban	507	67.8 ± 10.8	235 (46.3)		N/A	1 ± 0.3	36 (7.1)	396 (78.1)	58 (11.4)	97 (19.1)	230 (45.4)	N/A	
Mas et al 2017 (CLOSE) <sup>16</sup>	aspirin	68.2 ± 11.0	229 (45.1)	N/A		1 ± 0.3	N/A	159 (31.3)	35 (6.9)	46 (9.1)	100 (19.7)	200 (39.4)	N/A	N/A
	warfarin	187	43.8 ± 9.5	104 (55.6)		20 ± 10.7	N/A	N/A	15 (8.0)	2 (1.1)	N/A	N/A	54 (28.9)	4 (2.1)
Shariat et al 2012 <sup>28</sup>	aspirin	44.18 ± 10.5	244 (59.65)	51 ± 27		N/A	N/A	16 (3.9)	N/A	N/A	N/A	119 (29.09)	7 (1.71)	N/A
	warfarin	21	60.6 ± 4.3	10 (47.6)		N/A	N/A	N/A	9 (42.9)	N/A	5 (23.8)	N/A	7 (33.3)	N/A
aspirin	23	63.0 ± 4.7	18 (78.3)	N/A		N/A	N/A	3 (13)	N/A	4 (17.4)	10 (43.5)	N/A	N/A	N/A

Abbreviations: BMI, body mass index; NIHSS, National Health Institute Stroke Severity Score; AF, atrial fibrillation; HTN, hypertension; HF, heart failure; DM, diabetes mellitus; CAD, coronary heart disease; IHD, ischemic heart disease; TIA, transient ischemic attack; DVT, deep vein thrombosis; PE, pulmonary embolism.



**Figure 2.** Quality assessment of risk of bias in the included trials. The upper panel presents a schematic representation of risks (low = green, unclear = yellow, and high = red) for specific types of biases of each of the studies in the review. The lower panel presents risks (low = green, unclear = yellow, and high = red) for the subtypes of biases of the combination of studies included in this review.

(0.29, 6.40),  $P = .70$ ) (Figure 4B). After ranking the treatment arms, DOACs had the highest risk, followed by warfarin and aspirin (Table 3). Low heterogeneity was observed ( $I^2 = 0\%$ ).

**Intracranial Hemorrhage.** Based on the analysis of five RCTs, compared to aspirin, no significant difference was observed between aspirin and DOACs (RR: 1.12 with 95% CI (0.31, 4.04),  $P = .86$ ) or warfarin (RR: 1.09 with 95% CI (0.01, 82.41),  $P = .97$ ) (Figure 4C). After ranking the treatment arms, DOACs had the highest risk, followed by warfarin and aspirin (Table 3). High heterogeneity was observed ( $I^2 = 70.7\%$ ).

**Any Serious Adverse Events.** Based on the analysis of three RCTs, compared to aspirin, no significant difference was

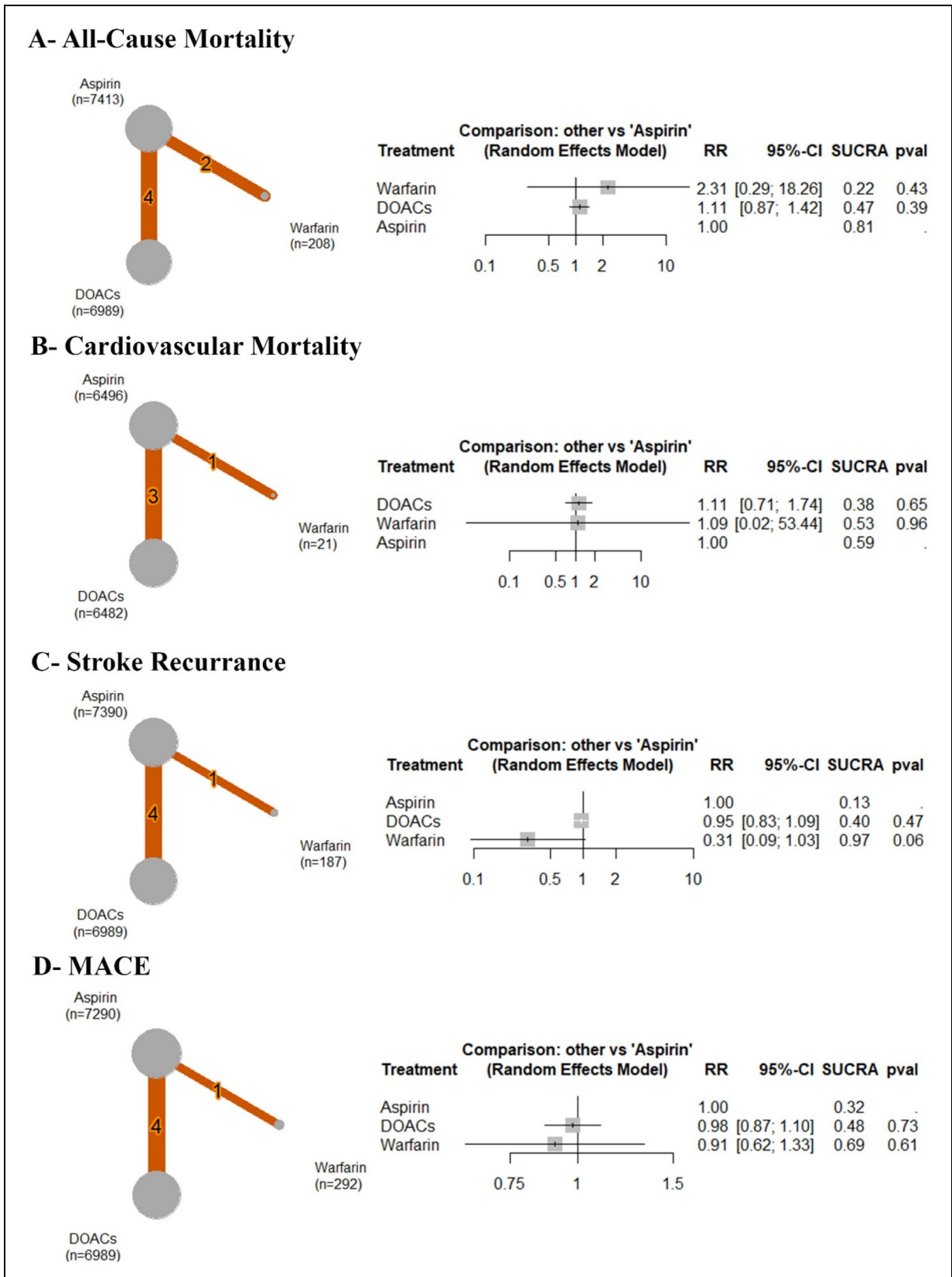
observed between aspirin and DOACs (RR: 1.03 with 95% CI (0.92, 1.16),  $P = 0.60$ ) or warfarin (RR: 0.99 with 95% CI (0.75, 1.31),  $P = .94$ ) (Figure 4D). After ranking the treatment arms, DOACs had the highest risk, followed by warfarin and aspirin (Table 3). High heterogeneity was observed ( $I^2 = 62.9\%$ ).

### Individual DOACs Versus Warfarin Versus Aspirin

#### Efficacy Outcomes

**All-Cause Mortality.** Based on the analysis of six RCTs, compared to aspirin, there was no significant difference observed between aspirin and warfarin (RR: 2.31 with 95%





**Figure 3.** Forest and network plots of the efficacy outcomes, comparing warfarin versus DOACs versus aspirin. DOACs: direct oral anticoagulants, MACE: major adverse cardiac events, RR: risk ratio, CI: confidence interval.



**Table 3.** Ranking Table row for DOACs Versus Warfarin Versus Aspirin Network meta-Analysis.

<b>All-Cause Mortality.</b>		
Warfarin		
2.08 (0.26; 16.65)	DOACs	
2.31 (0.29; 18.26)	1.11 (0.87; 1.42)	Aspirin
<b>Cardiovascular Mortality.</b>		
DOACs		
1.02 (0.02; 50.97)	Warfarin	
1.11 (0.71; 1.74)	1.09 (0.02; 53.44)	Aspirin
<b>Stroke Recurrence.</b>		
Aspirin		
1.05 (0.92; 1.20)	DOACs	
3.20 (0.97; 10.60)	3.05 (0.91; 10.17)	Warfarin
<b>MACE.</b>		
Aspirin		
1.02 (0.91; 1.15)	DOACs	
1.10 (0.75; 1.61)	1.08 (0.72; 1.61)	Warfarin
<b>Ischemic Stroke.</b>		
Aspirin		
1.09 (0.95; 1.26)	DOACs	
7.78 (0.45; 134.15)	7.14 (0.41; 123.46)	Warfarin
<b>Myocardial Infarction.</b>		
Warfarin		
2.18 (0.04; 111.51)	Aspirin	
2.36 (0.04; 124.31)	1.08 (0.66; 1.77)	DOACs
<b>Combined Systemic Thromboembolism.</b>		
Aspirin		
1.00 (0.83; 1.19)	DOACs	
1.89 (0.89; 4.00)	1.89 (0.87; 4.11)	Warfarin
<b>Any Serious Adverse Events.</b>		
DOACs		
1.04 (0.77; 1.41)	Warfarin	
1.03 (0.92; 1.16)	0.99 (0.75; 1.31)	Aspirin
<b>Major Bleeding.</b>		
Warfarin		
1.45 (0.40; 5.35)	DOACs	
2.29 (0.70; 7.51)	1.58 (0.92; 2.70)	Aspirin
<b>Gastrointestinal Bleeding.</b>		
DOACs		
0.93 (0.18; 4.79)	Warfarin	
1.26 (0.73; 2.19)	1.36 (0.29; 6.40)	Aspirin
<b>Intracranial Hemorrhage.</b>		
DOACs		
1.03 (0.01; 93.16)	Warfarin	
1.12 (0.31; 4.04)	1.09 (0.01; 82.41)	Aspirin

Abbreviations: DOACs, direct oral anticoagulants; MACE, major adverse cardiac events.

CI (0.29, 18.26),  $P = .43$ ) or rivaroxaban (RR: 1.25 with 95% CI (0.87, 1.79),  $P = .23$ ) or apixaban (RR: 1.24 with 95% CI (0.58, 2.66),  $P = .57$ ), or dabigatran (RR: 0.97 with 95% CI (0.67, 1.39),  $P = .85$ ) (Figure 5A). After ranking the treatment arms, warfarin has the highest risk, followed by rivaroxaban, apixaban, aspirin, and dabigatran (Table 4). Low heterogeneity was observed ( $I^2 = 0\%$ ).

**Stroke Recurrence.** Based on the analysis of five RCTs, compared to aspirin, there was no significant difference observed between aspirin and rivaroxaban (RR: 1.08 with

95% CI (0.87, 1.34),  $P = .47$ ) or apixaban (RR: 0.96 with 95% CI (0.66, 1.39),  $P = .83$ ) or dabigatran (RR: 0.86 with 95% CI (0.70, 1.04),  $P = .11$ ), or warfarin (RR: 0.31 with 95% CI (0.09, 1.03),  $P = .06$ ) (Figure 5B). After ranking the treatment arms, rivaroxaban has the highest risk, followed by aspirin, apixaban, dabigatran, and warfarin (Table 4). Low heterogeneity was observed ( $I^2 = 0\%$ ). Compared to warfarin, rivaroxaban was significantly associated with an increased incidence of stroke recurrence (RR: 3.46 with 95% CI (1.03, 11.67) (Table 4).

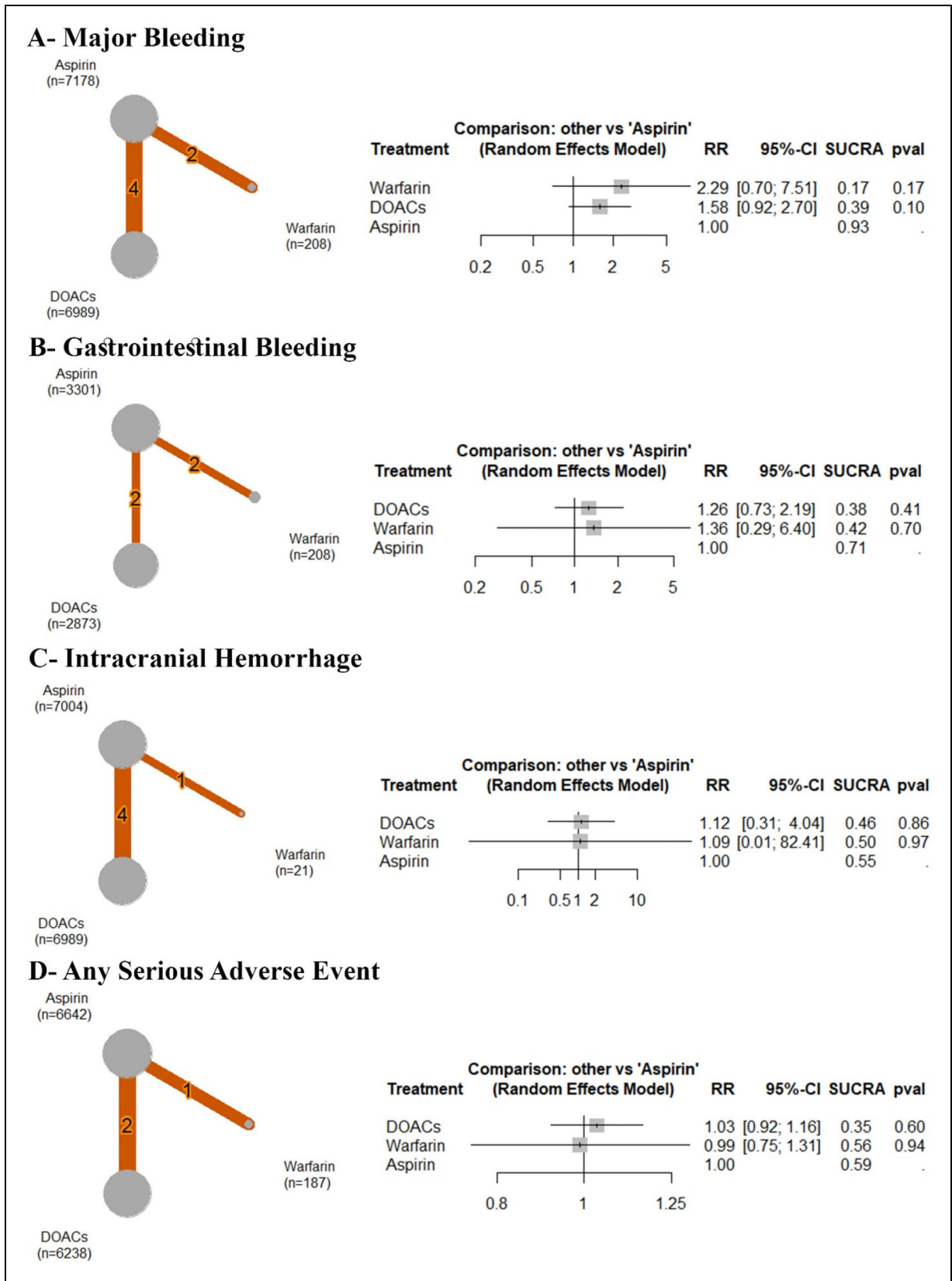
**Major Adverse Cardiac Events.** Based on the analysis of five RCTs, compared to aspirin, there was no significant difference observed between aspirin and rivaroxaban (RR: 1.06 with 95% CI (0.88, 1.28),  $P = .55$ ) or apixaban (RR: 1.04 with 95% CI (0.77, 1.39),  $P = .80$ ) or warfarin (RR: 0.91 with 95% CI (0.62, 1.33),  $P = .61$ ), or dabigatran (RR: 0.89 with 95% CI (0.75, 1.07),  $P = .21$ ) (Figure 5C). After ranking the treatment arms, rivaroxaban has the highest risk, followed by apixaban, aspirin, warfarin, and dabigatran (Table 4). Low heterogeneity was observed ( $I^2 = 0\%$ ).

**Combined Systemic Thromboembolism.** Based on the analysis of five RCTs, compared to aspirin, there was no significant difference observed between aspirin and rivaroxaban (RR: 1.07 with 95% CI (0.87, 1.32),  $P = .16$ ) or apixaban (RR: 0.90 with 95% CI (0.62, 1.31),  $P = .45$ ) or dabigatran (RR: 0.60 with 95% CI (0.26, 1.37),  $P = .75$ ), or warfarin (RR: 0.53 with 95% CI (0.25, 1.13),  $P = .84$ ) (Figure 5D). After ranking the treatment arms, rivaroxaban has the highest risk, followed by aspirin, apixaban, dabigatran, and warfarin (Table 4). Low heterogeneity was observed ( $I^2 = 0\%$ ).

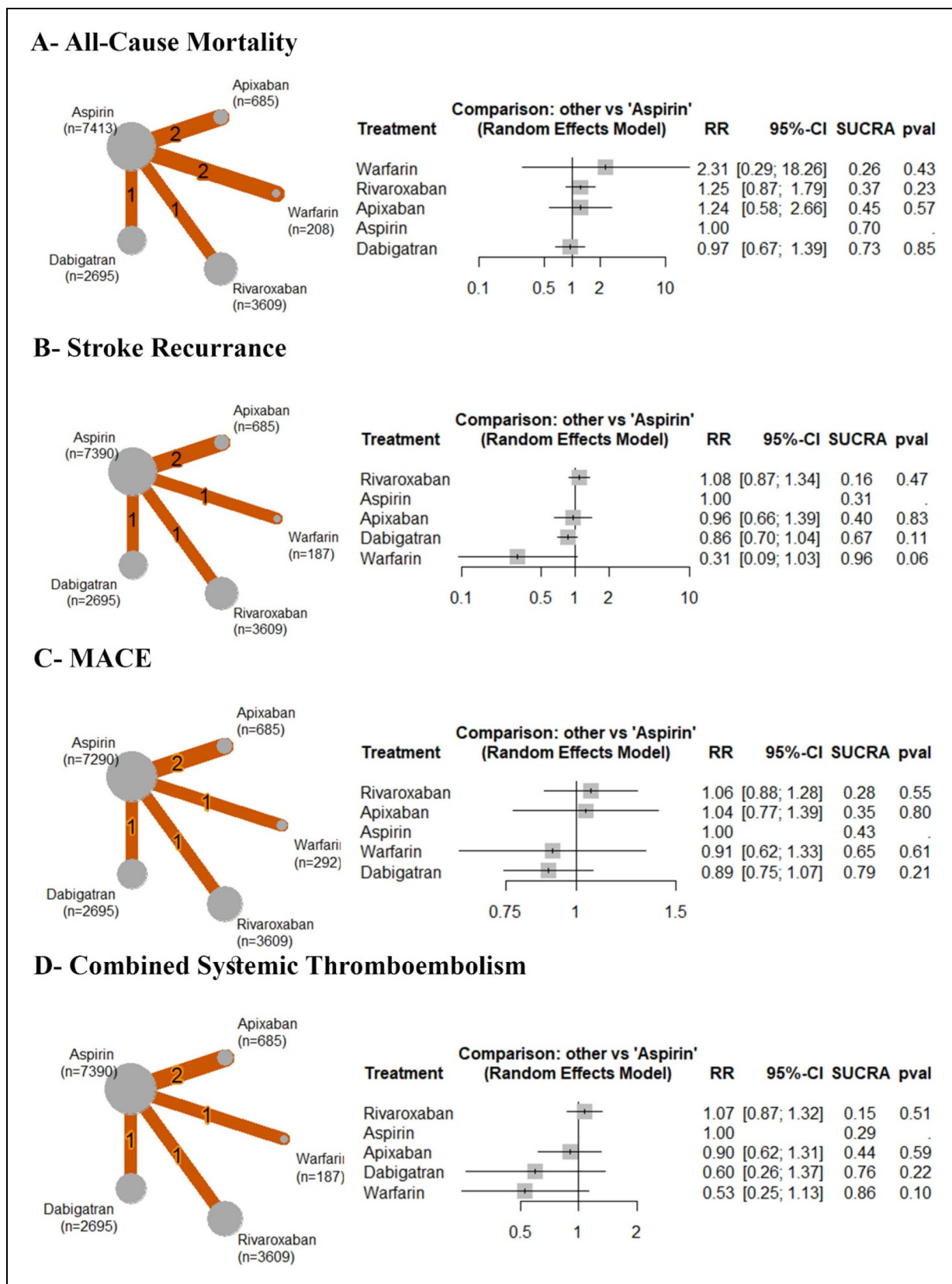
**Safety Outcomes**

**Major Bleeding.** Based on the analysis of six RCTs, compared to aspirin, rivaroxaban was significantly associated with an increased incidence of major bleeding (RR: 2.69 with 95% CI (1.67, 4.33),  $P < 0.01$ ); however, there was no significant difference observed between aspirin and warfarin (RR: 2.30 with 95% CI (0.83, 6.40),  $P = .11$ ) or dabigatran (RR: 1.20 with 95% CI (0.87, 1.67),  $P = .27$ ), or apixaban (RR: 1.00 with 95% CI (0.32, 3.08),  $P = 1.00$ ) (Figure 6A). After ranking the treatment arms, rivaroxaban has the highest risk, followed by warfarin, dabigatran, apixaban, and aspirin (Table 4). Low heterogeneity was observed ( $I^2 = 0\%$ ). Compared to dabigatran, rivaroxaban was significantly associated with an increased incidence of major bleeding (RR: 2.24 with 95% CI (1.26, 3.99) (Table 4).

**Gastrointestinal Bleeding.** Based on the analysis of four RCTs, compared to aspirin, there was no significant difference observed between aspirin and apixaban (RR: 2.93 with 95% CI (0.12, 71.50),  $P = .51$ ) or dabigatran (RR: 1.23 with 95% CI (0.70, 2.15),  $P = .47$ ), or warfarin (RR: 1.36 with 95% CI (0.29, 6.40),  $P = .70$ ) (Figure 6B). After ranking the treatment arms, apixaban has the highest risk, followed by warfarin,



**Figure 4.** Forest and network plots of the safety outcomes, comparing warfarin versus DOACs versus aspirin. DOACs: direct oral anticoagulants, RR: risk ratio, CI: confidence interval.



**Figure 5.** Forest and network plots of the efficacy outcomes, comparing various OACs versus aspirin. OACs: oral anticoagulants, RR: risk ratio, CI: confidence interval.

**Table 4.** Ranking Table row for Individual OACs Versus Warfarin Versus Aspirin Network meta-Analysis.

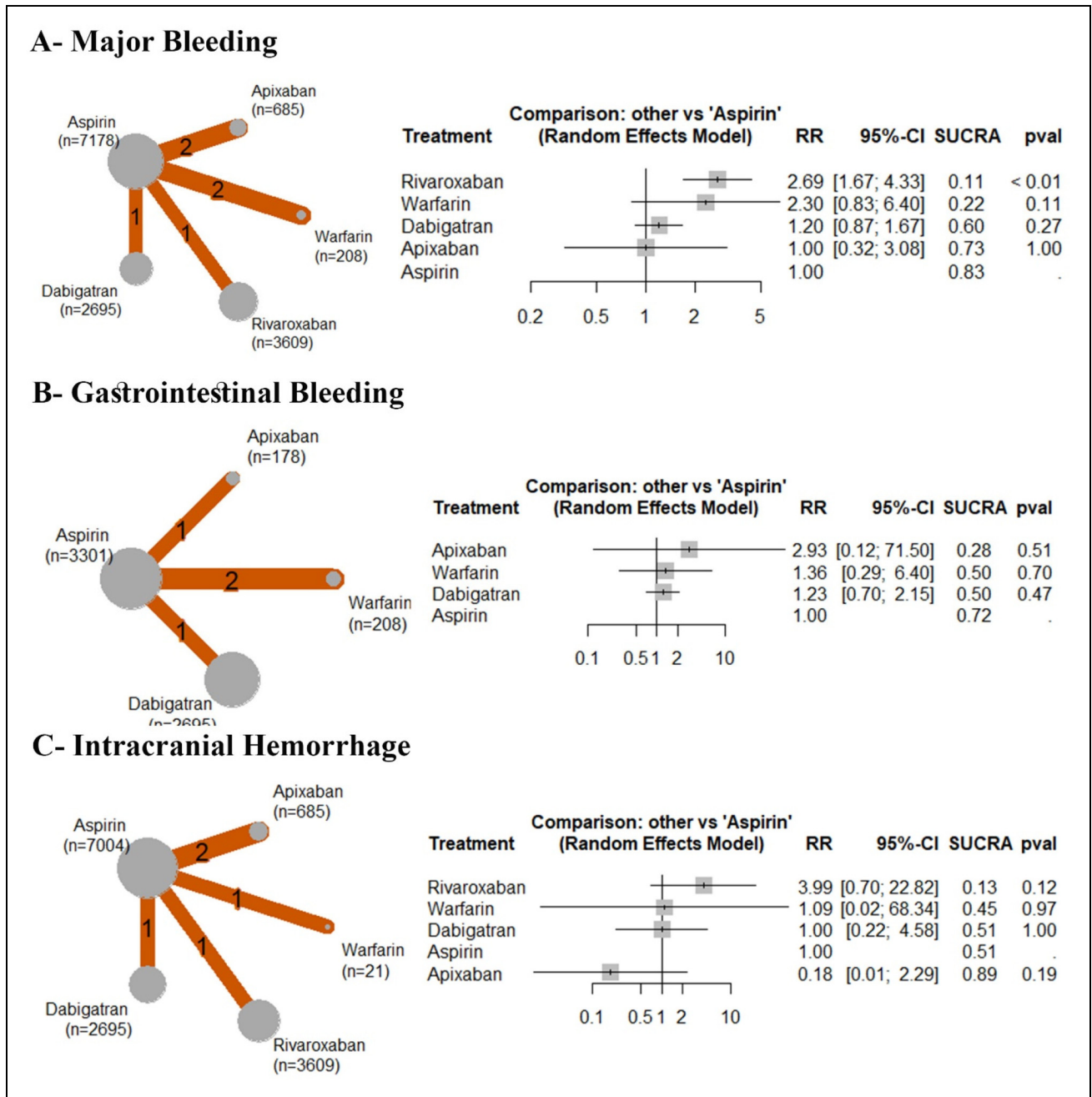
<b>All-Cause Mortality.</b>					
Warfarin					
1.85 (0.23; 15.09)					
1.86 (0.21; 16.80)					
2.31 (0.29; 18.26)					
2.40 (0.29; 19.52)					
Rivaroxaban					
	1.00 (0.43; 2.33)				
	1.25 (0.87; 1.79)				
	1.29 (0.77; 2.16)				
Apixaban					
		1.24 (0.58; 2.66)			
		1.29 (0.55; 2.99)			
Aspirin					
			1.04 (0.72; 1.49)		
Dabigatran					
<b>Stroke Recurrence.</b>					
Rivaroxaban					
1.08 (0.87; 1.34)					
1.13 (0.74; 1.72)					
1.26 (0.95; 1.68)					
3.46 (1.03; 11.67)					
Aspirin					
	1.04 (0.72; 1.51)				
	1.17 (0.96; 1.42)				
	3.20 (0.97; 10.60)				
Apixaban					
		1.12 (0.74; 1.70)			
		3.07 (0.88; 10.75)			
Dabigatran					
			2.74 (0.81; 9.20)		
Warfarin					
<b>MACE.</b>					
Rivaroxaban					
1.02 (0.72; 1.45)					
1.06 (0.88; 1.28)					
1.17 (0.76; 1.79)					
1.19 (0.91; 1.54)					
Apixaban					
	1.04 (0.77; 1.39)				
	1.14 (0.71; 1.85)				
	1.16 (0.82; 1.64)				
Aspirin					
		1.10 (0.75; 1.61)			
		1.12 (0.94; 1.34)			
Warfarin					
			1.02 (0.67; 1.55)		
Dabigatran					
<b>Combined Systemic Thromboembolism.</b>					
Rivaroxaban					
1.07 (0.87; 1.32)					
1.19 (0.77; 1.83)					
1.79 (0.76; 4.19)					
2.02 (0.93; 4.42)					
Aspirin					
	1.11 (0.76; 1.61)				
	1.67 (0.73; 3.80)				
	1.89 (0.89; 4.00)				
Apixaban					
		1.50 (0.61; 3.72)			
		1.70 (0.73; 3.95)			
Dabigatran					
			1.13 (0.37; 3.46)		
Warfarin					
<b>Major Bleeding.</b>					
Rivaroxaban					
1.17 (0.38; 3.62)					
2.24 (1.26; 3.99)					
2.70 (0.79; 9.16)					
2.69 (1.67; 4.33)					
Warfarin					
	1.91 (0.65; 5.60)				
	2.30 (0.50; 10.56)				
	2.30 (0.83; 6.40)				
Dabigatran					
		1.21 (0.37; 3.90)			
		1.20 (0.87; 1.67)			
Apixaban					
			1.00 (0.32; 3.08)		
Aspirin					
<b>Gastrointestinal Bleeding.</b>					
Apixaban					
2.16 (0.06; 75.01)					
2.39 (0.09; 61.18)					
2.93 (0.12; 71.50)					
Warfarin					
	1.11 (0.21; 5.75)				
	1.36 (0.29; 6.40)				
Dabigatran					
		1.23 (0.70; 2.15)			
Aspirin					
<b>Intracranial Hemorrhage.</b>					
Rivaroxaban					
3.65 (0.04; 325.00)					
3.99 (0.39; 40.40)					
3.99 (0.70; 22.82)					
22.10 (1.01; 481.37)					
Warfarin					
	1.09 (0.01; 89.64)				
	1.09 (0.02; 68.34)				
	6.05 (0.05; 775.39)				
Dabigatran					
		1.00 (0.22; 4.58)			
		5.53 (0.29; 106.95)			
Aspirin					
			5.53 (0.44; 70.20)		
Apixaban					

dabigatran, and aspirin (Table 4). Low heterogeneity was observed ( $I^2 = 0\%$ ).

**Intracranial Hemorrhage.** Based on the analysis of five RCTs, compared to aspirin, there was no significant difference observed between aspirin and rivaroxaban (RR: 3.99 with 95% CI (0.70, 22.82),  $P = .12$ ) or warfarin (RR: 1.09 with 95% CI (0.02, 68.34),  $P = .97$ ) or dabigatran (RR: 1.00 with 95% CI (0.22, 4.58),  $P = 1.00$ ), or apixaban (RR: 0.18 with 95% CI (0.01, 2.29),  $P = .19$ ) (Figure 6C). After ranking the treatment arms, rivaroxaban has the highest risk, followed by warfarin, dabigatran, aspirin, and apixaban (Table 3). Low heterogeneity was observed ( $I^2 = 15\%$ ). Compared to apixaban, rivaroxaban was significantly associated with an increased incidence of intracranial hemorrhage (RR: 22.10 with 95% CI (1.01, 481.37) (Table 4).

## Discussion

Two previous meta-analyses revealed the benefits of using OACs over aspirin in reducing the rate of stroke recurrence without any significant difference in major bleeding.<sup>19,20</sup> On the other hand, another meta-analysis conveyed no net benefit of OACs over antiplatelet therapy in reducing stroke recurrence with a non-significant increase in bleeding risk.<sup>18</sup> The present network meta-analysis comparing warfarin, direct-acting oral anticoagulants (DOACs), and aspirin revealed no significant benefit of anticoagulants over aspirin in mortality rates, stroke recurrence, bleeding, or cardiovascular events. The lack of benefit of anticoagulants over aspirin, especially in preventing recurrent ischemic events or strokes, can have numerous explanations. All the included RCTs showed no superiority of anticoagulation over antiplatelet therapy. The trials included



**Figure 6.** Forest and network plots of the safety outcomes, comparing various OACs versus aspirin. OACs: oral anticoagulants, MACE: major adverse cardiac events, RR: risk ratio, CI: confidence interval.

different anticoagulants, including warfarin, apixaban, dabigatran, and rivaroxaban, compared to aspirin.<sup>15,16,21,27-30</sup>

Strokes constitute a significant cause of morbidity and mortality worldwide, with a high risk of recurrence unless secondary prevention is implied. Proper secondary prevention requires identifying the underlying stroke mechanism and risk factors.<sup>31</sup> Cryptogenic strokes are believed to be caused by cardio-embolism in the context of atrial cardiopathy or PFO.<sup>7,8,17</sup> Since antithrombotic agents comprise a cornerstone in the secondary prevention of stroke cases, many trials

investigated the efficacy of OACs in cryptogenic strokes. For instance, in cases with PFO, closure of the PFO plus antiplatelet therapy was superior to antiplatelet therapy alone but not OACs alone.<sup>16,18,32</sup> Thus, OACs can be hypothesized to be used in cases where only medical treatment is considered.<sup>19</sup> Although there are published meta-analyses on the efficacy and safety of OACs compared to antiplatelets,<sup>18-20</sup> to the authors' knowledge, this is the first network meta-analysis to evaluate the use of different OACs and antiplatelets in cryptogenic strokes with the inclusion of recently published large trials.<sup>15,21</sup>

The primary hypothesis for using anticoagulants is that they would be superior to antiplatelets in cryptogenic stroke due to the presumed embolic origin of stroke, especially in the presence of factors promoting embolism, such as occult AF and PFO.<sup>30</sup> Yet, occult AF was detected in only 3% to 25% of trials where extensive electrocardiographic monitoring was initiated.<sup>15,21,30</sup> Notably, the diagnosis of occult AF requires such patients to crossover to anticoagulant therapy if they were randomized to antiplatelet, which can affect the precision and interpretation of the results.<sup>15</sup> The presence of PFO among patients in some trials did not favor using anticoagulants either.<sup>16,28–30</sup> Indeed, the presence of PFO and co-occurrence of stroke can be debated as to be a cryptogenic stroke. PFO can be found incidentally without clinical implications.<sup>28</sup> Homma et al, comparing warfarin to aspirin in stroke cases, showed higher rates of cryptogenic strokes with the presence and larger size of PFO. However, neither the presence nor the size affected the patients' response to the medical therapy.<sup>29</sup> The indifference between medical treatments in cryptogenic stroke and PFO may suggest that PFO causes the first stroke but does not have any causal role in stroke recurrence.<sup>33</sup> This is consistent with American Heart Association/American Stroke Association guidelines, which state that antiplatelet therapy is reasonable in patients with an ischemic stroke or transient ischemic attack with a PFO.<sup>31</sup>

Although a comprehensive diagnostic evaluation for a source of stroke was required for eligibility for the trials, the heterogeneous underlying sources of the embolic strokes (arterial, cardiogenic, or paradoxical) with variation in the composition of emboli may have resulted in enrolling patients that would not have benefited from anticoagulants.<sup>30</sup> Furthermore, most recurrent strokes occur in the same cerebral arterial territory as the index cryptogenic stroke, a finding that suggests an upstream atherosclerotic source rather than a central cardioembolic source.<sup>34</sup> The lack of benefit of anticoagulation over aspirin in trial participants despite selection for underlying cardiac abnormalities suggests that a substantial proportion of cryptogenic strokes may arise from non-stenosing atherosclerosis.<sup>15</sup>

All anticoagulants have an inherent risk of bleeding in different anatomical sites with variable severity.<sup>35</sup> Despite the non-significant differences, we found that aspirin had lower risks of major bleeding, intracranial hemorrhage (ICH), or gastrointestinal bleeding. Furthermore, warfarin seemed to have higher risks for major bleeding, whereas, for ICH and gastrointestinal bleeding, DOACs ranked first in the risk assessment. Although DOACs are considered more tolerable with a better safety profile than warfarin, controversial results have been published regarding specific bleeding patterns, eg, major bleeding, ICH, and gastrointestinal bleeding, according to the populations' characteristics and comorbidities.<sup>36–38</sup> The clinical decision for either DOACs or warfarin should consider the notable differences between each of DOACs.

Regarding major bleeding and ICH, rivaroxaban had the highest risk, followed by warfarin, while apixaban had lower risks, even lower than aspirin. The trial by Hart et al, comparing

rivaroxaban 15 mg to aspirin 100 mg daily, was early terminated due to the increased bleeding with the rivaroxaban group along with the lack of beneficial effect regarding stroke risk.<sup>30</sup> On the other hand, another recent trial showed that apixaban had a lower incidence of symptomatic ICH, although such a finding is limited to the small number of events.<sup>15</sup> Similarly, a meta-analysis of RCTs and real-world data suggested that apixaban can be safer than rivaroxaban.<sup>19,39</sup>

## Strengths & Limitations

Although this is the first network meta-analysis to evaluate the use of different anticoagulants compared to antiplatelets for patients after cryptogenic stroke with possible sources of PFO in which we implemented frequentist methodology and adhered to the PRISMA recommendations for reviews evaluating randomized trials, it has some limitations. Some studies may differ in defining some outcome measures or diagnostic criteria. Small sample sizes of some studies may reduce the generalizability of the results.<sup>28</sup> Furthermore, the confidence intervals were wide, implying insufficient precision. Thus, our results are suggestive rather than definitive or conclusive. However, we included only RCTs that inherently provide the highest quality of evidence and precise and relevant interpretation, and the implications of such results should be in light of the real-world data. Also, the mean/median follow-up of the included trials was not more than two years.<sup>15,16,21,27–30</sup> Finally, the aspirin dosage differed across the included trials, but most trials used low-dose aspirin (75–100 mg); thus, this is unlikely to affect the results.

## Implications for Future Research

More extensive studies with large sample sizes and long follow-up durations are needed to conclude recommendations for using anticoagulants primarily over antiplatelets in cryptogenic strokes. Continuous monitoring of patients enrolling in all studies of cryptogenic stroke should be considered to reveal any possible occult conditions. More investigation should be performed into the underlying pathophysiology of cryptogenic strokes. Due to the difference in the characteristics of each anticoagulant, future studies may focus on investigating and comparing each extensively, which can lead to more precise and clinically relevant interpretations. So far, there is no sufficient evidence to recommend the use of anticoagulants in cryptogenic strokes with or without PFO.

## Conclusion

There was no difference between various OACs and aspirin regarding efficacy and safety outcomes. Considering the higher risks and costs of anticoagulation, requiring regular laboratory checks and involving an increased probability of intracranial hemorrhage, we propose that anticoagulation has no benefits over antiplatelet therapy in patients with cryptogenic stroke. Further research is still warranted to define a



personalized strategy for selecting antithrombotic strategies after cryptogenic stroke on a case-by-case basis.

## List of Abbreviations

CVAs	Cerebrovascular accidents
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
DOACs	Direct oral anticoagulant
ESUS	Embolic stroke of undetermined source
ICH	Intracranial hemorrhage
MACE	Major adverse cardiac events
OACs	Oral anticoagulants
PFO	Patent foramen ovale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RCTs	Randomized clinical trials
RR	Risk ratio
SUCRA	Surface Under the Cumulative Ranking Curve

## Author Contributions

M.Ab. conceived the idea. M.Ab. designed the research workflow. B.A. and M.Ab. searched the databases. A.N., M.Ay., S.R., and M.T. screened the retrieved records, extracted relevant data, assessed the quality of evidence, and M.Ab. resolved the conflicts. AMA. performed the analysis. H.T., M.Ab., and AMA. wrote the final manuscript. J.R.B., M.Ab., and B.A. supervised the project. All authors have read and agreed to the final version of the manuscript.

## Availability of Data and Materials

The data is available upon reasonable request from the corresponding author.


## Declaration of Conflicting Interests

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## Supplemental Material

Supplemental material for this article is available online.

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