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Original Article

Direct oral anticoagulants compared with other strategies in patients with atrial fibrillation and stroke or transient ischemic attack: Systematic review

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Background: For patients with atrial fibrillation and a prior stroke or transient ischemic attack (TIA), the risk-benefit of direct oral anticoagulants (DOACs) compared to alternative treatment approaches has not been firmly established. We conducted a systematic review of randomized controlled trials (RCTs) to investigate efficacy and safety of DOACs vs warfarin and DOACs vs aspirin or placebo in patients with AF and a prior stroke or TIA.
Methods: We searched PubMed, EMBASE, and Cochrane Central Register of Controlled Trials from January 1, 2000, to January 31, 2023, to find RCTs. Risk ratio (RR) with 95 % CI measured the association of DOACs vs warfarin, and DOACs vs aspirin or placebo, with clinical outcomes. Primary efficacy outcome was stroke or systemic embolism and primary safety outcome was ICH.
Results: We identified 7 RCTs with 19,111 patients with AF and a prior stroke or TIA, of which 5 trials compared DOACs with warfarin and 2 trials compared DOACs vs aspirin or placebo. Compared with warfarin, DOACs were associated with a lower risk of stroke or systemic embolism (RR, 0.85; 95 % CI, 0.75—0.97) and ICH (RR, 0.53; 95 % CI, 0.41—0.68). Compared with aspirin or placebo, DOACs were associated with a reduced risk of stroke or systemic embolism (RR, 0.33; 95 % CI, 0.19—0.58) and risk of ICH did not differ between apixaban and aspirin.
Conclusions: This contemporary evaluation of the literature indicates that DOACs, rather than other antithrombotic agents or no treatment, should be used in patients with AF and a prior stroke or TIA.

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Introduction

Patients with atrial fibrillation (AF) are at an increased risk of ischemic stroke.[1,2] The most powerful predictor of stroke in patients with AF is a history of stroke or transient ischemic attack (TIA).[2–4] Therefore, prevention of recurrent stroke in patients with AF and a prior ischemic stroke or TIA is a major focus of cerebrovascular care. Adjusted-dose warfarin is effective for the prevention of stroke in these patients, but its use is limited by a narrow therapeutic range, food and drug interactions, life-long coagulation monitoring, and high risk of intracranial and systemic bleeding.[5] Due to these limitations of warfarin, substantial proportions of patients with AF at high risk of stroke, do not take warfarin, but instead either take aspirin or do not take any antithrombotic drug at all.[6]

Direct oral anticoagulants (DOACs) do not require routine coagulation monitoring. Moreover, a meta-analysis of four major phase III trials demonstrated that compared with warfarin, DOACs were associated with reductions in stroke or systemic embolic events, as well as intracranial hemorrhage.[7] In patients with AF for whom warfarin therapy was unsuitable, the AVERROES trial showed that apixaban 5 mg twice daily compared with aspirin reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial hemorrhage.[8] In very elderly Japanese patients with AF for whom standard doses of oral anticoagulants were unsuitable, the ELDERCARE-AF trial showed that edoxaban 15 mg once daily compared with placebo reduced the risk of stroke or systemic embolism without significantly increasing major bleeding or intracranial hemorrhage.[9] A narrative review suggested that DOACs were favored over warfarin due to their improved efficacy and better safety for secondary stroke prevention in patients with AF,[10] but that narrative review did not include J-ROCKET AF[11] and ELDERCARE-AF[9] trials.

Assessment of the risk-benefit profile of DOACs is crucial in patients with AF and a prior stroke or TIA because these patients are at high risk of recurrent stroke,[2] and of bleeding from anticoagulation therapy, particularly intracranial hemorrhage.[12] We therefore conducted a systematic review and meta-analysis of randomized controlled trials to investigate efficacy and safety of DOACs compared with warfarin and DOACs compared with aspirin or placebo in patients with AF and a prior stroke or TIA.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline was used for abstracting data and validity of this systematic review and meta-analysis.[13] The protocol was registered with PROSPERO (CRD42023400765).

Search strategy

We searched Pubmed, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1, 2000, to January 31, 2023, with the terms *"novel oral anticoagulants"* or *"non-vitamin K antagonist oral anticoagulants"* or *"direct oral anticoagulants"* or *"dabigatran"* or *"rivaroxaban"* or *"apixaban"* or *"edoxaban"* AND *"atrial fibrillation"* AND *"stroke"* or *"cerebrovascular event"* or *"transient ischemic attack"* AND *"recurrent"* or *"secondary prevention"* or *"previous"* or *"prior"* or *"history"* or *"systemic embolism"*. We restricted the search to studies in humans and randomized controlled trials and did not apply language restrictions. Two investigators (K.-H.L. and W.-T.H.) independently screened and identified potential trials, and discrepancies were resolved by discussion with a third investigator (M.L.).

Study selection and data extraction

Criteria for inclusion of a study were as follows: (1) the study design was a randomized controlled trial; (2) all or an identifiable subset of participants had AF and a history of stroke or TIA; (3) the active treatment arm included a DOAC; (4) the comparator arm included either warfarin, aspirin, or placebo; and (5) recurrent stroke or systemic embolism was reported as an endpoint. Criteria for exclusion of a study were as follows: (1) the study compared one DOAC with another DOAC; or (2) stroke or systemic embolism was either not prespecified or adjudicated major (primary or secondary) endpoint.

We extracted characteristics of each trial, which included: patient age, sex, number of patients in active and comparator groups, duration of follow-up, and number of recurrent stroke or systemic embolism and other outcomes in DOACs vs comparators (warfarin, aspirin, or placebo). Two investigators independently abstracted the data and any discrepant judgments were resolved by referencing the original report.

Study quality assessment

Since all of the included studies were randomized controlled trials, we assessed the overall bias (e.g. bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result) by using the RoB-2 tool.[14]

Statistical analysis

The primary efficacy outcome was stroke or systemic embolism. The primary safety outcome was intracranial

hemorrhage because intracranial hemorrhage during follow-up was a strong predictor of poor long-term functional outcome after ischemic stroke or TIA.[15] The secondary outcomes were stroke, hemorrhage stroke, ischemic stroke, disabling or fatal stroke, death from cardiovascular causes, death from any cause, major bleeding, and gastrointestinal bleeding.

The analysis plan was performed on an intention-to-treat basis. There were 2 arms of DOACs in RE-LY (i.e. dabigatran 150 mg or 110 mg twice daily)[16] and ENGAGE AF-TIMI 48 (i.e. edoxaban 60/30 mg or 30/15 mg once daily)[17] trials respectively and only higher-dose arms of DOACs (i.e. dabigatran 150 mg or edoxaban 60/30 mg) were used for pooled analysis to avoid counting patients from comparator group repeatedly. Patients with modified standard doses, such as 15 mg of rivaroxaban and 2.5 mg of apixaban according to the dose-reduction criteria of original trials were included in the pooled analysis.

We computed the fixed-effects estimate based on the Mantel-Haenszel method. Risk ratio (RR) with 95 % confidence interval (CI) was used as a measure of the association of DOACs vs comparators (warfarin, aspirin, or placebo) with the efficacy and safety outcomes. All p-values were from 2-sided tests and results were deemed statistically significant if $p < 0.05$. Heterogeneity was significant if either the p-value of $\chi 2$ was < 0.05 or the I^2 statistic was > 70 %. Grading of Recommendations, Assessment, Development and Evaluations (GRADE) was used to evaluate summaries of evidence for the primary and secondary outcomes.[18,19] Publication bias was estimated visually by funnel plots.[20] We used Review Manager Software Package (RevMan version 5.4, The Cochrane Collaboration, London, UK) for meta-analysis.

Results

We identified 15 full articles for detailed assessment, of which 8 did not meet the inclusion criteria; therefore, the final analysis included 7 randomized controlled trial (Supplemental Fig. 1).[9,11,21–25] The characteristics of the included trials are shown in Table 1.[9,11,21–25] Overall, 19,111 patients with AF and a prior stroke or TIA were enrolled. Among the 7 included trials, 5 compared DOACs with warfarin[11,21–24] and 2 compared DOACs with aspirin[25] or placebo.[9] The RoB-2 for the included trials is summarized in Supplementary Table.

Primary efficacy outcome: recurrent stroke or systemic embolism

For patients with AF and a prior stroke or TIA, pooled results from the fixed-effects model showed that DOACs compared with warfarin were associated with a reduced risk of recurrent stroke or systemic embolism (RR, 0.85; 95 % CI, 0.75–0.97; P = 0.010)[11,21–24] and DOACs compared with aspirin or placebo were associated with a reduced risk of recurrent stroke or systemic embolism (RR, 0.33; 95 % CI, 0.19–0.58; P < 0.001)[9,25] (Fig. 1).

Primary safety outcome: intracranial hemorrhage

For patients with AF and a prior stroke or TIA, pooled results from the fixed-effects model showed that DOACs compared with warfarin were associated with a reduced risk of intracranial hemorrhage (RR, 0.53; 95 % CI, 0.41–0.68; P < 0.001)[11,21–24] and risk of intracranial hemorrhage did not differ between apixaban and aspirin (RR, 0.77; 95 % CI, 0.21–2.84; P = 0.690)[25] (Fig. 2).

Secondary outcomes

For patients with AF and a prior stroke or TIA, pooled results showed that DOACs compared with warfarin were associated with a reduced risk of recurrent stroke (RR, 0.86; 95 % CI, 0.75–0.97; P = 0.020)[11,21–24] and apixaban compared with aspirin was associated with a reduced risk of recurrent stroke (RR, 0.32; 95 % CI, 0.16–0.64; P = 0.001)[25] (Fig. 3).

For patients with AF and a prior stroke or TIA, pooled results showed that DOACs compared with warfarin were associated with a reduced risk of hemorrhagic stroke (RR, 0.51; 95 % CI, 0.37–0.69; P < 0.001)[11,21–24] and risk of hemorrhagic stroke did not differ between apixaban and aspirin (RR, 0.24; 95 % CI, 0.03–2.14; P = 0.200)[25] (Supplemental Fig. 2).

For patients with AF and a prior stroke or TIA, pooled results showed that risk of ischemic stroke was not significantly different between DOACs and warfarin (RR, 0.96; 95 % CI, 0.84–1.11; P = 0.610)[11,21–24] and apixaban compared with aspirin was associated with a reduced risk of ischemic stroke (RR, 0.32; 95 % CI: 0.15–0.67; P = 0.003)[25] (Supplemental Fig. 3).

For patients with AF and a prior stroke or TIA, pooled results showed that risk of disabling or fatal stroke was not significantly different between DOACs and warfarin (RR, 0.86; 95 % CI, 0.72–1.03; P = 0.100)[21–24] and apixaban compared with aspirin was associated with a reduced risk of disabling or fatal stroke (RR, 0.29; 95 % CI, 0.13–0.67, P = 0.004)[25] (Supplemental Fig. 4).

For patients with AF and a prior stroke or TIA, pooled results showed that risk of death from any cause was not significantly different between DOACs and warfarin (RR, 0.91; 95 % CI, 0.83–1.00; P = 0.060) and between apixaban and aspirin (RR, 0.78; 95 % CI, 0.45–1.35; P = 0.370)[25] (Supplemental Fig. 5).

For patients with AF and a prior stroke or TIA, pooled results showed that death from cardiovascular causes was not significantly different between DOACs and warfarin (RR, 0.91; 95 % CI, 0.81–1.03; P = 0.130) and death from cardiovascular causes did not differ between apixaban and aspirin (RR, 0.77; 95 % CI, 0.40–1.46; P = 0.420)[25] (Supplemental Fig. 6).

For patients with AF and a prior stroke or TIA, pooled results showed that DOACs compared with warfarin were associated with a reduced risk of major bleeding (RR, 0.88; 95 % CI, 0.78–0.99; P = 0.030)[11,21–24] and the risk of major bleeding was not significantly different between apixaban and aspirin (RR, 1.22; 95 % CI, 0.56–2.65; P = 0.620)[25] (Fig. 4).

Table 1 Characteristics of included trials.

DOACs vs. Warfarin

Source	Population	Countries	Treatment Group		Sample size	Men, %	Mean age, y	HTN, %	DM, %	CHADS2 score	Treatment duration, y
			DOACs	Warfarin							
RE-LY[21]	Subgroup of AF patients with a prior stroke or TIA	44 countries	Dabigatran 150 mg twice daily	Warfarin	2428	62	71	77	22	≥3 (89 %)	2
ROCKET AF[23]	Subgroup of AF patients with a prior stroke or TIA	45 countries	Rivaroxaban 20/15 mg once daily	Warfarin	7468	61	71	85	25	4 (IQR:3—5)	2.5
J-ROCKET AF[11]	Subgroup of AF patients with a prior stroke, TIA, or non-CNS systemic embolism	Japan	Rivaroxaban 15/10 mg once daily	Warfarin	813	83	70	71	25	3.48 ± 0.92 (SD)	2.5
ARISTOTLE[22]	Subgroup of AF patients with a prior stroke or TIA	39 countries	Apixaban 5/2.5 mg twice daily	Warfarin	3436	63	70	83	26	≥3 (92 %)	1.8
ENGAGE AF-TIMI 48[24]	Subgroup of AF patients with a prior stroke or TIA	46 countries	Edoxaban 60/ 30 mg once daily	Warfarin	3967	62	70	86	27	4-6 (67 %)	2.8

DOACs vs. Aspirin or Placebo

Source	Population	Countries	Treatment Group		Sample size	Men, %	Mean Age, y	HTN, %	DM, %	CHADS2 score	Treatment duration, y
			DOACs	Aspirin or Placebo							
AVERROES[25]	Subgroup of AF patients with a prior stroke or TIA; not suitable for warfarin	36 countries	Apixaban 5/2.5 mg twice daily	Aspirin 81—324 mg	764	56	72	81	20	≥3 (93 %)	1.1
ELDERCARE-AF[9]	Subgroup of AF patients with a prior stroke or TIA; ≥80 years; not considered to be appropriate candidates for OACs at doses approved for stroke prevention	Japan	Edoxaban 15 mg once daily	Placebo	236	NA (43 in whole trial)	NA (87 in whole trial)	NA (82 in whole trial)	NA (23 in whole trial)	NA	1.3

AF: atrial fibrillation, DM: diabetes mellitus, DOACs: direct oral anticoagulants, HTN: hypertension, NA: not available, OACs: oral anticoagulants, TIA: transient ischemic attack.
Trial name: RELY: Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke. ROCKET AF: Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack. J-ROCKET AF: Rivaroxaban versus Warfarin in Japanese Patients with Nonvalvular Atrial Fibrillation for the Secondary Prevention of Stroke. ARISTOTLE: Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack. ENGAGE AF-TIMI 48: Outcomes with Edoxaban Versus Warfarin in Patients with Previous Cerebrovascular Events. AVERROES: Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack. ELDERCARE-AF: Low-Dose Edoxaban in Very Elderly Patients with Atrial Fibrillation.

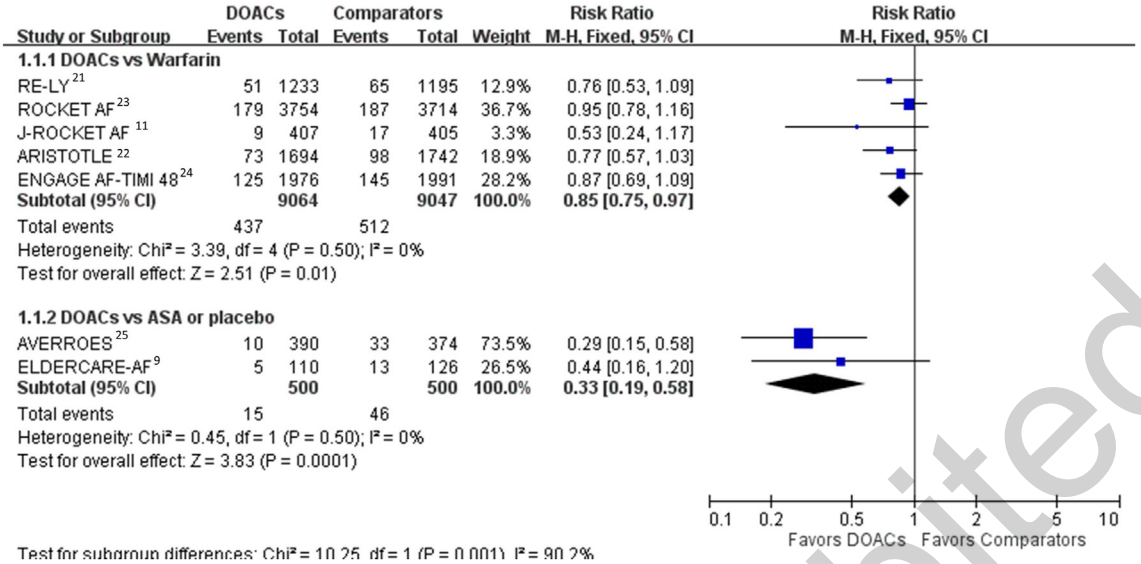

Figure 1 Title: Risk of Recurrent Stroke or Systemic Embolism Legends: Risk ratio (RR) with 95 % confidence interval (CI) of recurrent stroke or systemic embolism with direct oral anticoagulants (DOACs) vs warfarin and DOACs vs aspirin or placebo in patients with atrial fibrillation and a prior stroke or transient ischemic attack.

For patients with AF and a prior stroke or TIA, pooled results showed that the risk of gastrointestinal bleeding was not significantly different between DOACs and warfarin (RR, 1.15; 95 % CI, 0.83—1.60; P = 0.390)[11,21–24] and the risk of gastrointestinal bleeding was not significantly different between apixaban and aspirin (RR, 0.77; 95 % CI, 0.21—2.84; P = 0.690)[25] (Supplemental Fig. 7).

Summaries of evidence for the primary and secondary outcomes are presented in Table 2.

Publication bias

There was no obvious publication bias shown in the funnel plot (Supplemental Fig. 8).

Discussion

The present meta-analysis, comprising 7 randomized controlled trials with 19,111 patients with AF and a prior stroke or TIA, revealed that DOACs compared with warfarin were associated with a 15 % reduced risk of recurrent stroke or systemic embolism and a 47 % reduced risk of intracranial hemorrhage. Also, DOACs compared with aspirin or placebo were associated with a 67 % reduced risk of recurrent stroke or systemic embolism and risk of intracranial hemorrhage did not differ between apixaban and aspirin. These findings support the notion that DOACs should be preferred over warfarin in patients with AF and a prior stroke or TIA, which is in line with

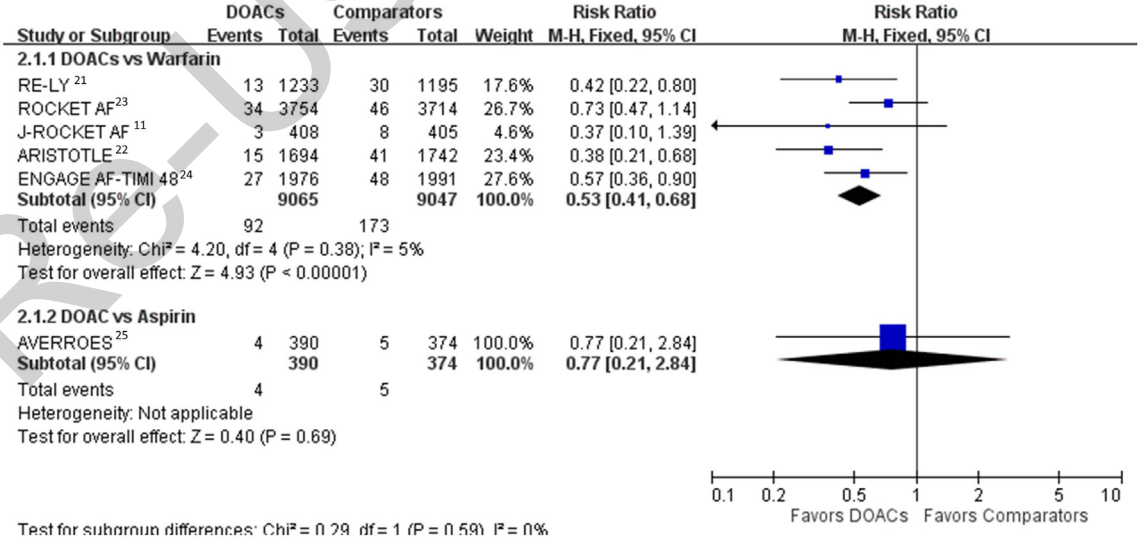

Figure 2 Title: Risk of Intracranial Hemorrhage Legends: Risk ratio (RR) with 95 % confidence interval (CI) of intracranial hemorrhage with direct oral anticoagulants (DOACs) vs warfarin and DOACs vs aspirin or placebo in patients with atrial fibrillation and a prior stroke or transient ischemic attack.

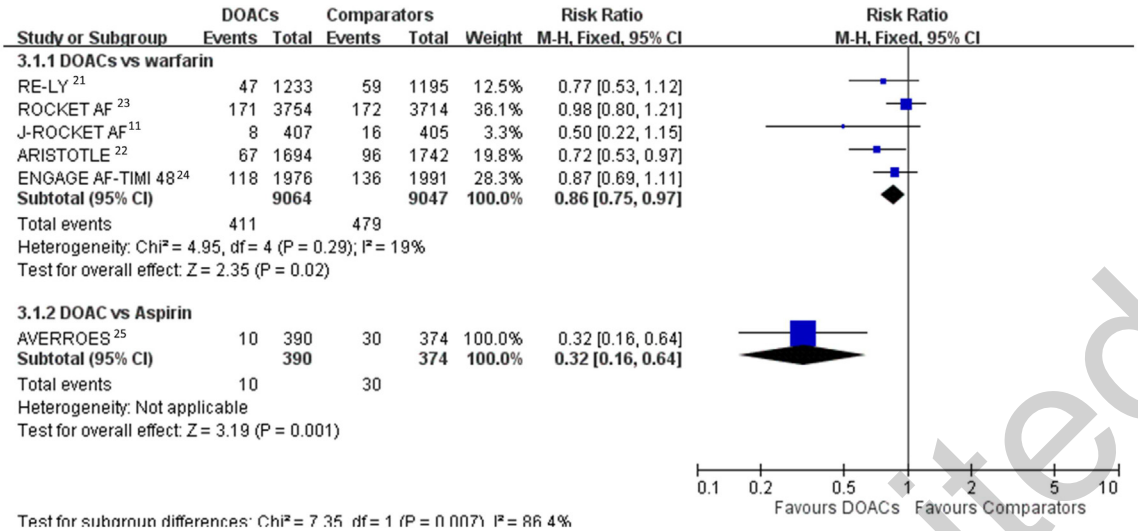

Figure 3 Title: Risk of Recurrent Stroke Legends: Risk ratio (RR) with 95 % confidence interval (CI) of recurrent stroke with direct oral anticoagulants (DOACs) vs warfarin and DOACs vs aspirin or placebo in patients with atrial fibrillation and a prior stroke or transient ischemic attack.

expert consensus guidelines from the European Heart Association,[26] European Stroke Association,[27] and Asia Pacific Heart Rhythm Society.[28]

In many countries, only about half to two-thirds of patients with AF received treatment with warfarin before DOACs were available.[29] Hesitation to use warfarin may not always be unreasonable in AF patients because intracranial hemorrhage during follow-up is a strong predictor of poor long-term functional outcome after ischemic stroke or TIA.[15] In patients with AF and a prior stroke or TIA, apixaban compared with aspirin was not associated with an increased risk of intracranial hemorrhage[25] and in patients with embolic stroke of undetermined source, dabigatran compared with aspirin was not associated with an increased risk of intracranial hemorrhage.[30] On the other hand, a 15-mg to 20-mg dose of rivaroxaban once daily compared with aspirin may be associated with a substantially increased risk of intracranial hemorrhage.[31] Therefore certain DOACs such as apixaban might be the most reasonable treatment strategy for patients with AF and a prior stroke who are not suitable for warfarin, considering their comparable risk of intracranial hemorrhage and substantially lower risk of recurrent stroke and systemic embolism with aspirin or placebo.

For patients with AF and a prior stroke or TIA, a balanced risk assessment of both recurrent stroke and intracranial hemorrhage should be done simultaneously, and as such, the current meta-analysis evaluated recurrent stroke or systemic embolism as the primary efficacy outcome, and intracranial hemorrhage as the primary safety outcome.

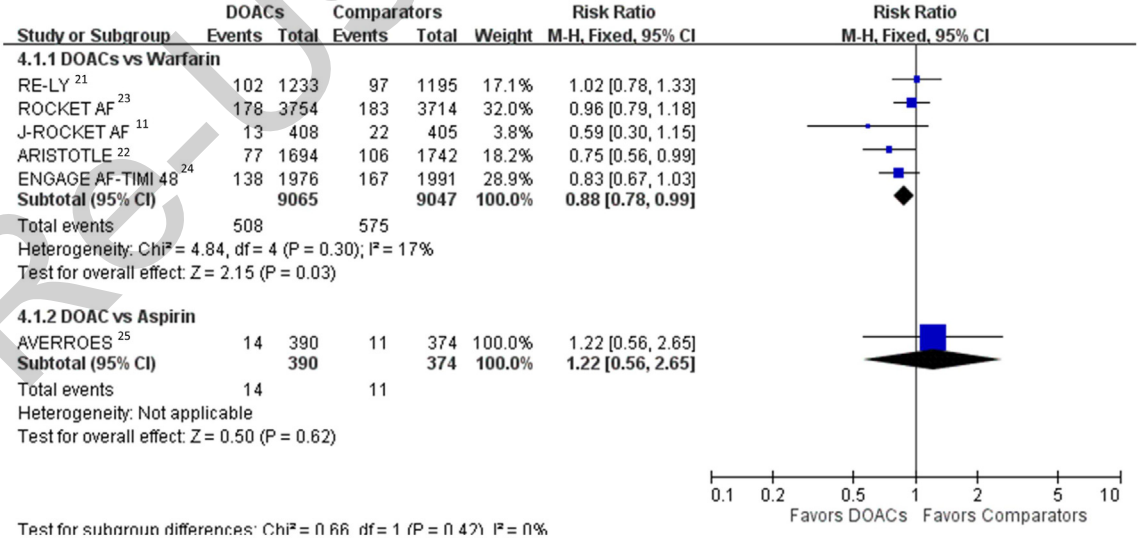

Figure 4 Title: Risk of Major Bleeding Legends: Risk ratio (RR) with 95 % confidence interval (CI) of major bleeding with direct oral anticoagulants (DOACs) vs warfarin and DOACs vs aspirin or placebo in patients with atrial fibrillation and a prior stroke or transient ischemic attack.

Table 2 Grading of Recommendations, Assessment, Development and Evaluations (GRADE) for summary of the quality assessments and summary finding for the efficacy and safety outcomes.

Quality assessment							Summary of findings				
							Event, No./Total, No.		Effect		Quality
Outcomes, No. of studies	Design	Study limitation (Risk of bias)	Inconsistency	Indirectness	Imprecision	Publication bias	DOACs	Control	Relative (95 % CI)	Absolute	
Recurrent stroke or systemic embolism											
DOACs vs warfarin, n = 5	RCT	No serious limitations	No inconsistency	No serious indirectness	No imprecision	Undetected	437/9064	512/9047	0.85 (0.75—0.97)	9 fewer per 1000 (2—14)	High
DOACs vs aspirin or placebo, n = 2	RCT	No serious limitations	No inconsistency	No serious indirectness	Some imprecision	Undetected	15/500	46/500	0.33 (0.19—0.58)	62 fewer per 1000 (39—75)	Moderate
ICH											
DOACs vs warfarin, n = 5	RCT	No serious limitations	No inconsistency	No serious indirectness	No imprecision	Undetected	92/9065	173/9047	0.53 (0.41—0.68)	9 fewer per 1000 (6—11)	High
DOAC vs aspirin, n = 1	RCT	No serious limitations	—	No serious indirectness	Serious imprecision	Undetected	4/390	5/374	0.77 (0.21—2.84)	Not significant	Low
Stroke											
DOACs vs warfarin, n = 5	RCT	No serious limitations	Some inconsistency	No serious indirectness	No imprecision	Undetected	411/9064	479/9047	0.86 (0.75—0.97)	7 fewer per 1000 (2—13)	Moderate
DOAC vs Aspirin, n = 1	RCT	No serious limitations	No inconsistency	No serious indirectness	Some imprecision	Undetected	10/390	30/374	0.32 (0.16—0.64)	54 fewer per 1000 (29—67)	Moderate
Hemorrhagic stroke											
DOACs vs warfarin, n = 5	RCT	No serious limitations	No inconsistency	No serious indirectness	No imprecision	Undetected	57/9064	113/9047	0.51 (0.37—0.69)	6 fewer per 1000 (4—8)	High
DOAC vs Aspirin, n = 1	RCT	No serious limitations	—	No serious indirectness	Serious imprecision	Undetected	1/390	4/374	0.24 (0.03—2.14)	Not significant	Low
Ischemic stroke											
DOACs vs warfarin, n = 5	RCT	No serious limitations	No inconsistency	No serious indirectness	No imprecision	Undetected	362/9064	375/9047	0.96 (0.84—1.11)	Not significant	High
DOAC vs Aspirin, n = 1	RCT	No serious limitations	—	No serious indirectness	Some imprecision	Undetected	9/390	27/374	0.32 (0.15—0.67)	49 fewer per 1000 (24—61)	Moderate

(*continued on next page*)

Table 2 (*continued*)

Quality assessment							Summary of findings				
							Event, No./Total, No.		Effect		Quality
Outcomes, No. of studies	Design	Study limitation (Risk of bias)	Inconsistency	Indirectness	Imprecision	Publication bias	DOACs	Control	Relative (95 % CI)	Absolute	
Disabling or fatal stroke											
DOACs vs warfarin, n = 4	RCT	No serious limitations	No inconsistency	No serious indirectness	No imprecision	Undetected	215/8657	249/8642	0.86 (0.72—1.03)	Not significant	High
DOAC vs aspirin, n = 1	RCT	No serious limitations	—	No serious indirectness	Some imprecision	Undetected	7/390	23/374	0.29 (0.13—0.67)	43 fewer per 1000 (20—53)	Moderate
Death from any cause											
DOACs vs warfarin, n = 4	RCT	No serious limitations	No inconsistency	No serious indirectness	No imprecision	Undetected	756/8657	827/8642	0.91 (0.83—1.00)	Not significant	High
DOAC vs aspirin, n = 1	RCT	No serious limitations	—	No serious indirectness	No imprecision	Undetected	22/390	27/374	0.78 (0.45—1.35)	Not significant	High
Death from cardiovascular causes											
DOACs vs warfarin, n = 4	RCT	No serious limitations	No inconsistency	No serious indirectness	No imprecision	Undetected	494/8657	540/8642	0.91 (0.81—1.03)	Not significant	High
DOAC vs aspirin, n = 1	RCT	No serious limitations	—	No serious indirectness	Some imprecision	Undetected	16/390	20/374	0.77 (0.40—1.46)	Not significant	Moderate
Major bleeding											
DOACs vs warfarin, n = 5	RCT	No serious limitations	Some inconsistency	No serious indirectness	No imprecision	Undetected	508/9065	575/9047	0.88 (0.78—0.99)	8 fewer per 1000 (1—14)	Moderate
DOAC vs aspirin, n = 1	RCT	No serious limitations	—	No serious indirectness	Some imprecision	Undetected	14/390	11/374	1.22 (0.56—2.65)	Not significant	Moderate
Gastrointestinal bleeding											
DOAC vs warfarin, n = 3	RCT	No serious limitations	Serious inconsistency	No serious indirectness	No imprecision	Undetected	77/3335	66/3342	1.15 (0.83—1.60)	Not significant	Low
DOAC vs aspirin, n = 1	RCT	No serious limitations	—	No serious indirectness	Serious imprecision	Undetected	4/390	5/374	0.77 (0.21—2.84)	Not significant	Low

DOACs: direct oral anticoagulants, RCT: randomized controlled trials.

The results from the current study do not fully align with the recommendations from the American Heart Association/American Stroke Association latest expert consensus guidelines, which recommend oral anticoagulation (eg, apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin) to reduce the risk of recurrent stroke in patients with AF and stroke or TIA.[32] Although we agree that warfarin might be nearly as effective as DOACs to prevent recurrent stroke, compared to DOACs, warfarin is associated with a substantially higher risk of intracranial hemorrhage, and therefore should probably not be used in patients with AF and a prior stroke or TIA. Also, this meta-analysis might be the first study to pool data from relevant trials to evaluate efficacy of DOACs in patients with AF and a prior stroke or TIA, who are unsuitable for warfarin or standard doses of oral anticoagulants, and it showed that patients randomly assigned to DOACs vs aspirin or placebo had a substantially lower risk of recurrent stroke or systemic embolism. On the other hand, the AVERROES trial showed that risk of intracranial hemorrhage did not differ between apixaban and aspirin. The number of intracranial hemorrhages was not available in the subgroup of patients with a prior stroke or TIA in the ELDERCARE-AF trial, so we could not pool such data from the ELDERCARE-AF and AVERROES trials. Still, there was only 2 intracranial hemorrhages (0.3 %) in the low-dose edoxaban group and 4 intracranial hemorrhages (0.6 %) in the placebo group for the entire ELDERCARE-AF trial,[9] which implies risk of intracranial hemorrhage might not differ significantly between low-dose edoxaban and placebo. Taken together, this currently meta-analysis newly suggests that for patients with AF and a prior stroke or TIA, but unsuitable for warfarin or standard doses of oral anticoagulants, certain or low-dose DOACs are more reasonable treatment strategies than aspirin or avoidance of any antithrombotic agent.

Limitations

There are several limitations to this study. First, the purpose of all included trials was not to primarily evaluate DOACs vs warfarin or DOACs vs aspirin or placebo for patients with ischemic stroke, and we used a subgroup of patients with a history of stroke or TIA for this meta-analysis. The characteristics of the index stroke and the duration between the index stroke and the trial initiation were vague. Second, ELDERCARE-AF trial[9] only provided results of stroke or systemic embolism in patients with a prior stroke or TIA and we could not pool data from the ELDERCARE-AF and AVERROES trials for other outcomes. Third, there was a narrative review exploring this issue.[10] The current study was distinct from the prior narrative review in that 2 trials conducted in Japan were included in this study.[9,11] The results of the current meta-analysis may further the efficacy and safety of DOACs to be used in Asian populations and very elderly who have AF and a prior stroke or TIA.

Conclusion

This meta-analysis of randomized controlled trials suggests that compared to warfarin, DOACs may be associated with a reduced risk of recurrent stroke or systemic embolism, and associated with a substantially reduced risk of intracranial hemorrhage among patients with AF and a prior stroke or TIA. Also, DOACs compared with aspirin or placebo may be associated with a substantially reduced risk of recurrent stroke or systemic embolism and risk of intracranial hemorrhage did not differ between apixaban and aspirin. Considering the high risk of recurrent ischemic stroke without use of oral anticoagulants, as well as the high risk of intracranial hemorrhage with warfarin use, it might be prudent to implement these findings into the routine clinical practice of managing patients with AF and a prior stroke or TIA.

Declaration of competing interest

The authors have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jfma.2023.10.007.

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