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ORIGINAL RESEARCH

Efficacy and Safety of Direct Oral Anticoagulants for Stroke Prevention in Older Patients With Atrial Fibrillation: A Network Meta-Analysis of Randomized Controlled Trials

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BACKGROUND: Although older patients with atrial fibrillation are at heightened risk of thromboembolic and bleeding events, their optimal treatment choice remains uncertain.

METHODS AND RESULTS: This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We searched the PubMed, EMBASE, and Cochrane databases for randomized controlled trials that compared thromboembolic or bleeding outcomes between a direct oral anticoagulant (DOAC) and a vitamin K antagonist (VKA) and reported outcomes for patients aged ≥75 years with atrial fibrillation. The efficacy outcome was the composite of stroke and systemic embolism. Safety outcomes included major bleeding, any clinically relevant bleeding, and intracranial hemorrhage. Each DOAC and VKA was compared pairwise in a network meta-analysis. High- and low-dose regimens and factor IIa and Xa inhibitors were also compared. Seven randomized controlled trials were included in the analysis. Stroke and systemic embolism risks did not differ significantly among DOACs. There were no significant differences in major bleeding between each DOAC and VKA. Intracranial hemorrhage risk was significantly lower with dabigatran, apixaban, and edoxaban than with VKA and rivaroxaban, which had similar risks. High-dose regimens led to lower risks of stroke or systemic embolism compared with VKA and low-dose regimens, with both doses having similar bleeding risks.

CONCLUSIONS: In patients aged ≥75 years with atrial fibrillation, DOACs were associated with fewer thromboembolic events compared with VKA, whereas dabigatran, apixaban, and edoxaban were associated with lower risks of intracranial hemorrhage compared with VKA and rivaroxaban.

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Key Words: atrial fibrillation ■ bleeding ■ direct oral anticoagulants ■ old age ■ stroke

Atrial fibrillation (AF) is the most common sustained arrhythmia in adults worldwide, with a reported lifetime risk of up to 1 in every 3 individuals.[1] AF risk increases with age, especially in those aged >65 years.[2] As the global population continues to age, people living with AF have increased substantially over the past 50 years, reaching almost 60 million globally by 2019, leading to 0.315 million deaths and

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CLINICAL PERSPECTIVE

What Is New?

- In this network meta-analysis comparing direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs) in patients aged ≥75 years with atrial fibrillation, there were no statistically significant differences in stroke or systemic embolism and major bleeding between each DOAC and VKA.
- Rivaroxaban had a greater risk of any bleeding event than VKA, with borderline significance (risk ratio, 1.19 [95% CI, 0.99–1.43]), and a significantly greater risk of intracranial hemorrhage compared with other DOACs.
- High-dose regimens (of dabigatran or edoxaban) led to lower risks of stroke or systemic embolism compared with VKA and low-dose regimens without increasing major bleeding.

What Are the Clinical Implications?

- DOACs should be considered over VKA in stroke prevention for atrial fibrillation in patients aged ≥75 years.
- The choice between each DOAC should be made individually based on thrombotic and bleeding risks.

Nonstandard Abbreviations and Acronyms

DOAC	direct oral anticoagulant
ICH	intracranial hemorrhage
TTR	time in therapeutic range
VKA	vitamin K antagonist

8.39 million disability-adjusted life years lost.[3] An estimated 2.5 million deaths could be attributable to AF between 2030 and 2034.[3] Therefore, AF is an increasingly important global health issue.

One key element of AF management is preventing thromboembolic complications. However, anticoagulation benefits are often offset by increased bleeding risk. Many validated scoring systems for risk stratification[4–6] indicate that specific clinical factors lead to increased thromboembolic and bleeding event risks. For example, advanced age is included in the CHA_2DS_2-VASc stroke score (congestive heart failure, hypertension, age ≥75 [doubled], diabetes mellitus, prior stroke or transient ischemic attack [doubled], vascular disease, age 65–74, and sex category [female])[6] for AF stroke risk and the Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile International Normalized Ratio (INR), Elderly, Drugs or alcohol use (HAS-BLED) score[4] for major bleeding risk. Indeed, an age ≥75 years counts for 2 points in the CHA_2DS_2-VASc score. Older age is associated with elevated ischemic stroke and systemic embolism risks in patients with AF,[7,8] and the proportion of strokes attributable to AF also increases with age.[9] Conversely, the incidence of intracranial hemorrhages (ICHs) during warfarin therapy for stroke prevention is substantially higher in the older population, particularly in those aged >85 years.[10] Stroke prevention in older patients with AF remains a clinical dilemma and challenge.

Since the pivotal RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial[11] in 2009, the introduction of direct oral anticoagulants (DOACs) has revolutionized stroke prevention in AF, with all DOACs showing superior or noninferior efficacy and safety compared with vitamin K antagonists (VKAs). However, slight discrepancies remain between the results of each drug's landmark trial. More important, patients aged ≥75 years represent only a limited proportion of the study population in each trial. As previously noted, although older patients are at heightened risk of thromboembolic and bleeding events, their optimal treatment choice remains uncertain. Several DOACs have published data on their efficacy and safety in the older population.[12,13] However, direct comparisons between DOACs are lacking in these patients. This study aimed to compare the efficacy and safety of different DOACs in patients aged ≥75 years through a network meta-analysis, with particular foci on various bleeding outcomes and the subgroup of very old patients.

METHODS

This study's protocol was registered with PROSPERO (proprietary) (registration number CRD42022329557) and followed throughout the entire study period. This meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The data that support the findings of this study are available from the corresponding author on reasonable request. Because this study used public use data sets that involve deidentified data, it was waived from Institutional Review Board approval in our institution and informed consent.

Data Sources and Search Strategies

We searched the PubMed, EMBASE, and Cochrane databases for studies published between the date of database inception and February 10, 2023, that met the following inclusion criteria: (1) articles published in English; (2) randomized controlled trials (RCTs) that compared a DOAC with a VKA; (3) enrolled patients with AF; (4) event-driven studies that reported thromboembolic or bleeding outcomes; and (5) studies that reported outcomes for patients aged ≥75 years. Secondary analyses

of RCTs were included. Abstracts, letters, reviews, meta-analyses, and gray literature were excluded. Search keywords included *direct oral anticoagulants*, *DOACs*, *novel oral anticoagulants*, *NOACs*, *dabigatran*, *rivaroxaban*, *apixaban*, *edoxaban*, *warfarin*, *vitamin K antagonist*, *atrial fibrillation*, *randomized controlled trial*, *clinical trial*, *controlled clinical trial*, *stroke*, *systolic embolism*, *bleeding*, *major bleeding*, *intracranial hemorrhage*, and their synonyms and related keywords. Search results, including all titles and abstracts, were independently assessed by 2 authors (D.S.-H.L. and J.-K.L.) to identify eligible studies. The full texts of selected publications were further inspected to confirm eligibility. All disagreements on the qualification of studies were resolved through discussion and consensus. Details of the search strategy are provided in Table S1.

Outcomes

This study's outcomes of interest included efficacy and safety outcomes. The efficacy outcome was the composite of stroke and systemic embolism. The safety outcomes were major bleeding, clinically relevant bleeding, and ICH. Major bleeding was defined in most trials according to the International Society on Thrombosis and Hemostasis definition, which includes clinically overt bleeding with any 1 of the following: (1) a decrease in the hemoglobin level of ≥2 g/dL; (2) requiring transfusion of ≥2 units of packed red cells; (3) occurring at a critical site (ie, intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal); and (4) resulting in death. Clinically relevant nonmajor bleeding was defined as any clinically overt bleeding that does not meet the criteria for major bleeding but resulted in hospital admission, physician-guided medical or surgical treatment, or a change in antithrombotic therapy (including study drug) for bleeding. ICH included hemorrhagic strokes and subdural or subarachnoid hemorrhages.

Data Extraction

Two authors (D.S.-H.L. and J.-K.L.) extracted data from all enrolled studies and independently assessed the bias risk for each study using the Cochrane Risk of Bias tool. Any discordances in the evaluation were resolved by discussion. Data were extracted using a standardized format and included the following: the trial name, the publication year, the DOAC type used in the intervention arm, the DOAC dose used in the intervention arm, the VKA type used in the control arm, the total number of patients, the major inclusion criteria of study participants, the efficacy and safety outcomes reported by the study, the follow-up length, the participants' demographic and clinical characteristics (including age and sex), and the age strata adopted in the subgroup analyses (Table[11,14–19]). The sample size, the number of events, and the incidence of events (per 1000 patient-years) in each age category in each treatment arm were extracted. If the number of events was not provided in the study, the risk ratio (RR) estimates, including the hazard ratios or incidence rate ratios, and their corresponding 95% CIs were extracted.

Statistical Analysis

Most studies reported hazard or incidence rate ratios with 95% CIs. We calculated relative risk and its 95% CI using sample size and the numbers of events for the few studies without reported hazard or incidence rate ratios. The comparisons of outcomes among the different DOACs used a frequentist approach and restricted maximum likelihood multivariate meta-analysis.[20] Pooled RRs were summarized using the random-effect model in which between-study variance was allowed and estimated. Pairwise comparisons among treatment (dabigatran, rivaroxaban, apixaban, and edoxaban) and control groups used visual forest plots rather than tables. The variance of the pooled effect sizes was described using the tau (τ) statistics, which represent the SD of the true effect sizes.

For studies that reported the results of 2 DOAC doses, the high- and low-dose arms were compared. Furthermore, factor IIa and factor Xa inhibitors were compared. Finally, the above comparisons among treatment groups were repeated for the major bleeding outcome in the subgroup of very old patients (aged ≥80 years). Because no studies had directly compared any 2 DOACs (eg, apixaban versus edoxaban), this network meta-analysis did not evaluate inconsistency (incoherence) between direct and indirect effects. In addition, intransitivity was not assessed because potential modification factors were not obtainable in study-level meta-analyses. The network meta-analysis was performed using the statistical package netmeta (version 2.7-0; updated on December 22, 2022) in the R statistical software (version 4.2.1). A 2-sided $P<0.05$ was considered statistically significant.

RESULTS

Search Results

The initial search identified 1217 citations. After a critical assessment of these articles according to the prespecified criteria, 13 studies published from 7 RCTs were included in the analysis (n=79 003 patients; Figure 1).

Study Characteristics

Details of the 7 included studies are listed in the Table. The main results of these RCTs were published between 2009 and 2021. All 7 RCTs compared a DOAC with a VKA in patients with AF, consistent

Table. Study-Level Characteristics of Included RCTs

Name of trial	Year	Intervention arms	Control arm	No. of participants	Inclusion criteria	Median follow-up, y	Mean/ median age, y	Female sex, %	Age category	Efficacy outcomes extracted in this meta-analysis	Safety outcomes extracted in this meta-analysis
RE-LY[11]	2009	Dabigatran 110 mg twice daily Dabigatran 150 mg twice daily	Warfarin	18 113	Patients with atrial fibrillation with at least 1 additional risk factor for stroke	2	71	36.3	<65 65–74 75–79 80–84 ≥85	Stroke or systemic embolism	Major bleeding Intracranial hemorrhage
ARISTOTLE[14]	2011	Apixaban 5 mg twice daily	Warfarin	18 201	Patients with atrial fibrillation with at least 1 additional risk factor for stroke	1.8	70	35.5	<65 65–74 ≥75 ≥80	Stroke or systemic embolism	Major bleeding All bleeding events Intracranial hemorrhage
ROCKET AF[15]	2011	Rivaroxaban 20 mg once daily	Warfarin	14 264	Patients with atrial fibrillation with moderate-to-high risk for stroke	1.9	73	39.7	<75 ≥75	Stroke or systemic embolism	Major bleeding Major and nonmajor clinically relevant bleeding events Intracranial hemorrhage
J-ROCKET AF[16]	2012	Rivaroxaban 15 mg only daily	Warfarin	1280	Patients with atrial fibrillation with at least 1 additional risk factor for stroke	2.5	71.1	17.1	<75 ≥75	Stroke or systemic embolism	Major bleeding Major and nonmajor clinically relevant bleeding events
ENGAGE AF-TIMI 48[17]	2013	Edoxaban 60 mg only daily Edoxaban 30 mg only daily	Warfarin	21 105	Patients with atrial fibrillation with a CHADS2 score of ≥2	2.8	72	38.4	<65 65–74 ≥75	Stroke or systemic embolism	Major bleeding Intracranial hemorrhage
AUGUSTUS[18]	2019	Apixaban 5 mg twice daily	Any VKA	4614	Patients with atrial fibrillation with acute coronary syndrome or those who underwent percutaneous coronary intervention within 14 d of randomization	0.5	70.7	29.1	<65 65–79 ≥80	Stroke or systemic embolism	Major and nonmajor clinically relevant bleeding events
ENVISAGE-TAVI AF[19]	2021	Edoxaban 60 mg only daily Edoxaban 30 mg only daily	Any VKA	1426	Patients with atrial fibrillation status after transcatheter aortic valve replacement	1.5	82.1	48.7	<85 ≥85	NA	Major bleeding

ARISTOTLE indicates Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; AUGUSTUS, Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation; CHADS2, chronic heart failure, hypertension, diabetes and age >74 years, previous history of stroke or transient ischemic attack (TIA) (doubled); ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48; ENVISAGE-TAVI AF, Edoxaban versus Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation-Atrial Fibrillation; J-ROCKET, Rivaroxaban versus warfarin in Japanese patients with atrial fibrillation; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; NA, not applicable; RCT, randomized controlled trial; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; and VKA, vitamin K antagonist.

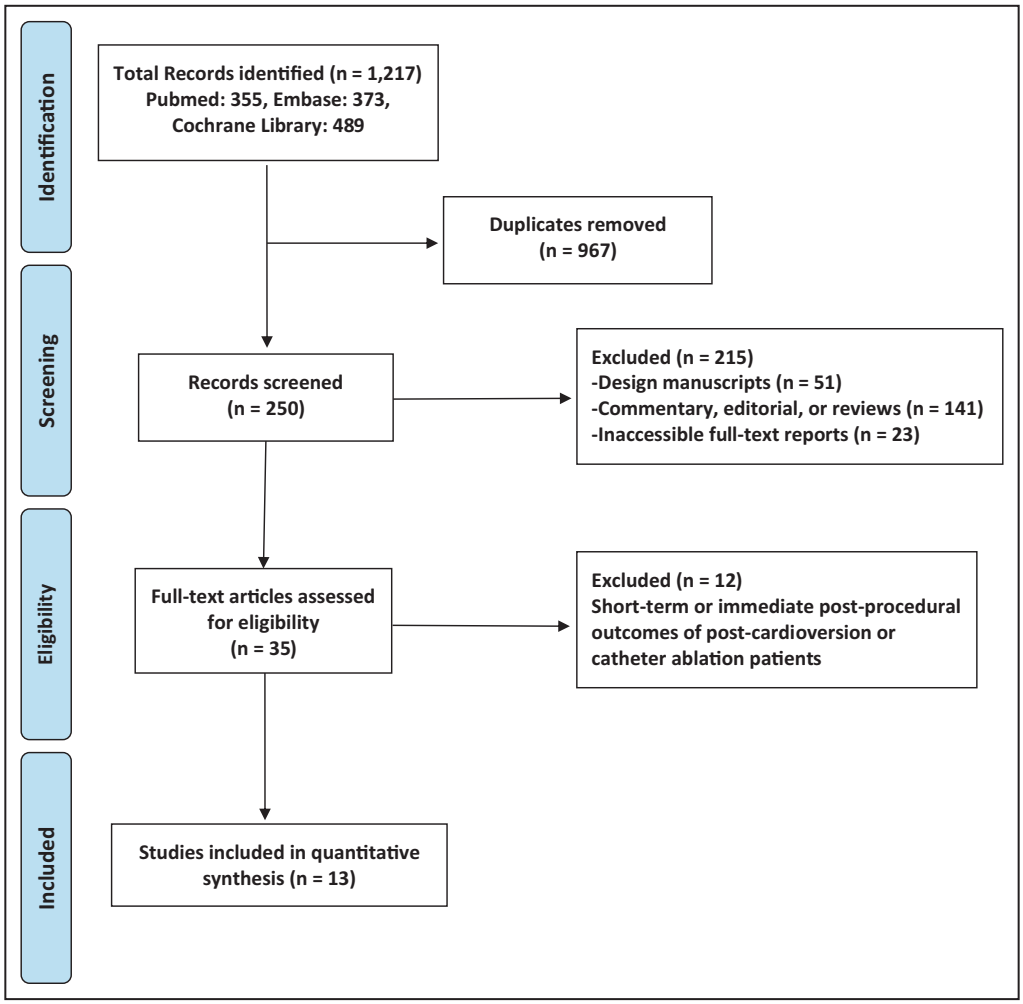

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart for study identification, inclusion, and exclusion.

with our inclusion criteria. One study evaluated the safety and efficacy of dabigatran (RE-LY),[11] 2 apixaban (ARISTOTLE [Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation] and AUGUSTUS [Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation]),[14,18] 2 rivaroxaban (ROCKET-AF [Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation] and J-ROCKET [Rivaroxaban versus warfarin in Japanese patients with atrial fibrillation]),[15,16] and 2 edoxaban (ENGAGE AF-TIMI 48 [Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48] and ENVISAGE-TAVI AF [Edoxaban versus Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation-Atrial Fibrillation]).[17,19] Only 3 RCTs on dabigatran[11] or edoxaban[17,19] evaluated the safety and efficacy of 2 different doses. Most RCTs reported safety and efficacy outcomes, except for ENVISAGE-TAVI AF,[19] which reported only safety outcomes. Five RCTs enrolled patients with AF at increased stroke risk,[11,14–17] 1 enrolled patients with AF and acute coronary syndrome or those who recently underwent percutaneous coronary intervention,[18] and 1 included patients with AF who received transcatheter aortic valve replacement.[19]

Bias Risk

A low bias risk was identified for all 7 included RCTs after assessment with the Cochrane Risk of Bias tool. The detailed results of the risk-of-bias assessments are provided in Table S2.

Efficacy Outcome: Stroke or Systemic Embolism

The network diagram is shown in Figure S1A. Across all DOACs investigated, there were no statistically

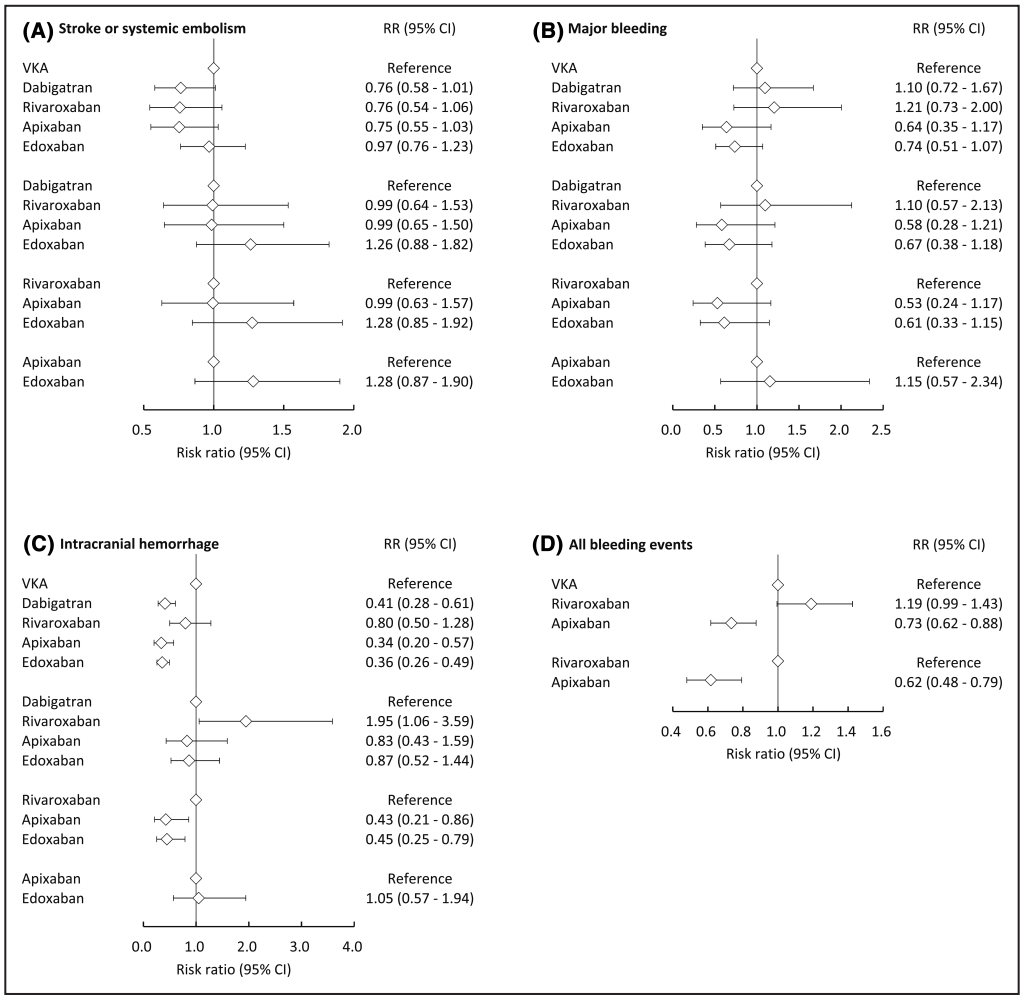

Figure 2. Forest plot illustrating the pairwise comparison among treatment groups (direct oral anticoagulants and vitamin K antagonist [VKA]) on the risks of ischemic stroke or systemic embolism (A), major bleeding (B), intracranial hemorrhage (C), and all bleeding events (D).
RR indicates risk ratio.

significant differences in stroke or systemic embolism risks (Figure 2A). Dabigatran, rivaroxaban, and apixaban had substantially but nonsignificantly lower risks than the control (VKA). However, there was a trend toward lower efficacy with edoxaban, which performed similarly to VKA in the included trials (RR, 0.97 [95% CI, 0.76–1.23]). The τ statistic was 0.133.

Safety Outcomes: Bleeding Events

All DOACs had reported outcomes for major bleeding and ICH compared with VKA. Only rivaroxaban and apixaban had reported outcomes for all bleeding events. There were no statistically significant differences in major bleeding between each DOAC and VKA (Figure 2B). However, there was a trend toward lower major bleeding risk with apixaban (RR, 0.64 [95% CI, 0.35–1.17]) and edoxaban (RR, 0.74 [95% CI, 0.51–1.07]). The τ statistic was 0.288. Moreover, dabigatran (RR, 0.41 [95% CI, 0.28–0.61]), apixaban (RR, 0.34 [95% CI, 0.20–0.57]), and edoxaban (RR, 0.36 [95% CI, 0.26–0.49]) had significantly lower ICH risks than VKA and rivaroxaban, which had similar ICH risks (RR, 0.80 [95% CI, 0.50–1.28]; Figure 2C). The τ statistic was 0. Apixaban had significantly lower risks for all bleeding events than VKA (RR, 0.73 [95% CI, 0.62–0.88]; Figure 2D). Rivaroxaban had a greater risk of any bleeding event than VKA, with borderline significance (RR, 1.19 [95% CI, 0.99–1.43]). The overall I^2 values of these comparisons were 83%, 0%, and 29%, respectively. The τ statistic was 0.088.

Comparison of Efficacy and Safety Outcomes Between Low- and High-Dose Regimens

The network diagram is shown in Figure S1B. High-dose regimens showed superior efficacy in stroke or systemic embolism prevention compared with VKA (RR, 0.77 [95% CI, 0.68–0.87]) and low-dose regimens

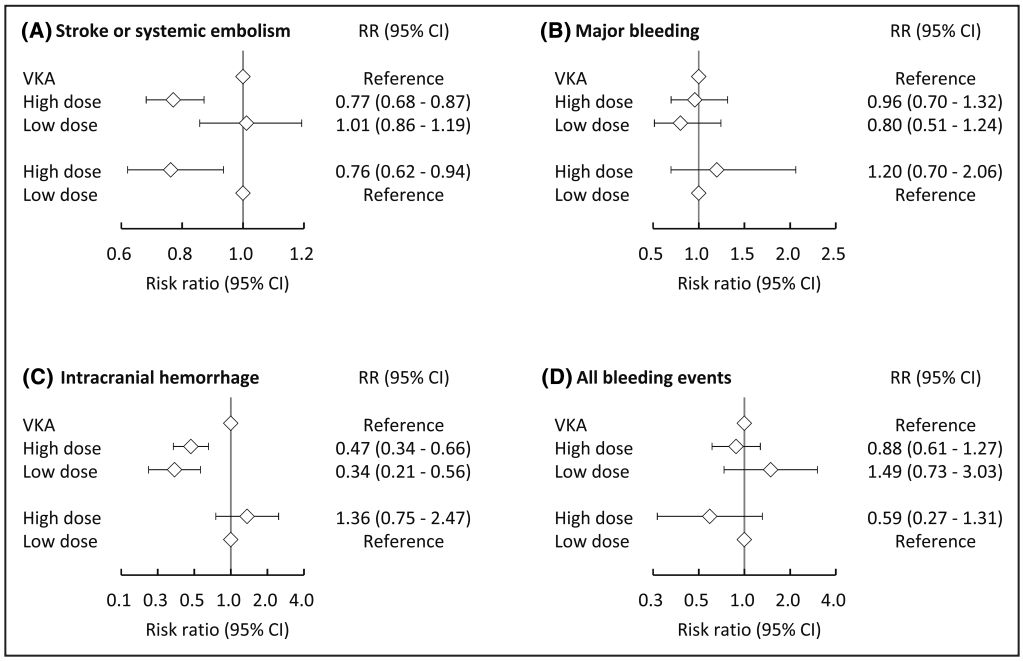

Figure 3. Forest plot illustrating the pairwise comparison among high-dose direct oral anticoagulant (DOACs), low-dose DOACs, and vitamin K antagonist (VKA) on the risks of ischemic stroke or systemic embolism (A), major bleeding (B), intracranial hemorrhage (C), and all bleeding events (D). Data comparing 2 different doses are available only for dabigatran and edoxaban.
RR indicates risk ratio.

(RR, 0.76 [95% CI, 0.62–0.94]; Figure 3A). Both high- and low-dose regimens had similar major (Figure 3B) and any (Figure 3D) bleeding risks to VKA but were associated with significantly lower ICH risks (high-dose regimen versus VKA: RR, 0.47 [95% CI, 0.33–0.66]; low-dose regimen versus VKA: RR, 0.34 [95% CI, 0.21–0.56]; Figure 3C). The τ statistics of the above comparisons were 0, 0.336, 0.234, and 0.306, respectively.

Comparison of Efficacy and Safety Outcomes Between Factor IIa and Xa Inhibitors

The network diagram is shown in Figure S1C. Both factor IIa and Xa inhibitors led to fewer stroke and systemic embolic events than VKA, albeit only reaching borderline significance (factor IIa versus VKA: RR, 0.76 [95% CI, 0.57–1.02]; factor Xa versus VKA: RR, 0.85 [95% CI, 0.72–1.01]; Figure S2A). Major bleeding risks did not differ significantly between factor IIa inhibitors, factor Xa inhibitors, and VKA (Figure S2B). Similarly, the risks of any bleeding event did not differ significantly between factor Xa inhibitors and VKA (Figure S2D). However, both factor IIa and Xa inhibitors led to fewer ICH events than VKA (factor IIa versus VKA: RR, 0.41 [95% CI, 0.23–0.72]; factor Xa versus VKA: RR, 0.43 [95% CI, 0.30–0.63]; Figure S2C). The τ statistics of the above comparisons were 0.139, 0.305, 0.278, and 0.315, respectively.

Major Bleeding Among Very Old Patients

RCTs on rivaroxaban did not report outcomes for patients aged ≥80 years. Dabigatran, apixaban, edoxaban, and VKA had similar major bleeding risks in patients aged ≥80 years (Figure 4A). Similarly, high- or low-dose regimens had statistically similar incidences of major bleeding to VKA in very old patients (Figure 4B). However, factor Xa inhibitors showed superior safety in terms of major bleeding risk to VKA (RR, 0.72 [95% CI, 0.54–0.97]) and factor IIa inhibitors (RR, 0.58 [95% CI, 0.35–0.99]) in patients aged ≥80 years (Figure 4C). The risk did not significantly differ between factor IIa inhibitors and VKA (RR, 1.24 [95% CI, 0.80–1.91]). The τ statistics of the above comparisons were 0.303, 0.417, and 0.278, respectively.

DISCUSSION

In this network meta-analysis, we compared the efficacy and safety of DOACs for preventing stroke or systemic embolism in older patients with AF and reported several findings. First, in patients aged ≥75 years, all DOACs showed similar efficacies in preventing stroke and systemic embolic events, except for edoxaban, which showed nominally decreased efficacy compared with other DOACs. Second, all DOACs had similar major bleeding risks to VKA. Third, rivaroxaban was the only DOAC with a similar ICH risk to VKA, whereas

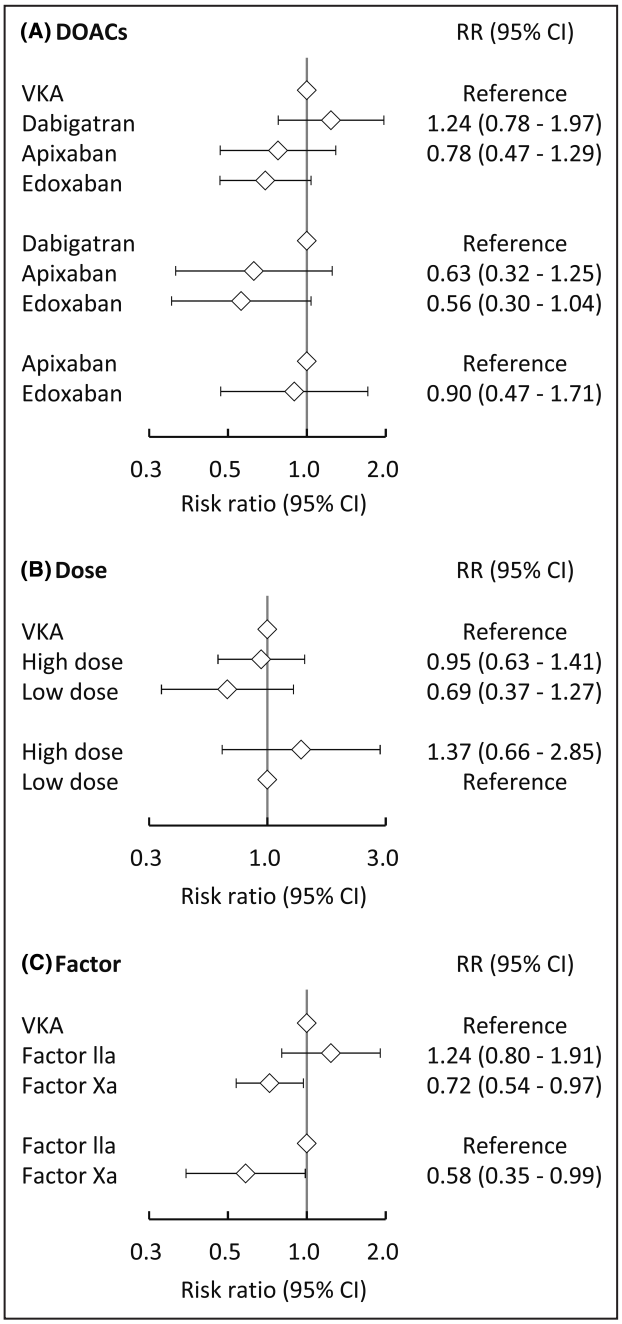

Figure 4. Forest plot illustrating the pairwise comparison on the risk of major bleeding between different treatment groups in the very old population (aged ≥80 years): each direct oral anticoagulant (DOAC) and vitamin K antagonist (VKA) (A), high-dose DOACs, low-dose DOACs, and VKA (B), and factor IIa inhibitors, factor Xa inhibitors, and VKA (C).
RR indicates risk ratio.

all other DOACs had reduced risks. Furthermore, the incidence of all bleeding events was nominally higher with rivaroxaban than with VKA. Fourth, high-dose regimens prevented more embolic events without increased bleeding risk than low-dose regimens or VKA. Finally, factor Xa inhibitors (apixaban and edoxaban) were associated with lower risks of major bleeding in very old patients (aged ≥80 years) compared with factor IIa inhibitors and VKA.

The significance of both AF and stroke increases with age. The AF burden is greatest in the older population, with incidence peaking between 75 and 80 years, and prevalence continuing to increase beyond 90 years.[3] In addition, ischemic stroke and ICH risks are elevated in older patients with AF,[8,10] reflecting the dilemmas in AF management in the older population. Although studies on each DOAC reported varying efficacy and safety in the general population with AF, a prior meta-analysis showed superior efficacy and safety for DOACs compared with warfarin in patients aged ≥75 years.[21] The benefits of DOACs are likely accentuated in older patients, who are at high risk of thromboembolic and bleeding events. In this study, we observed a trend toward lower efficacy with edoxaban, which performed similarly to VKA. On the basis of an RCT's subgroup result, this observation may be underpowered and requires further validation. Recently, an RCT compared reduced-dose edoxaban against a placebo in patients with AF aged ≥80 years and deemed ineligible for standard anticoagulation because of high bleeding risks.[13] Low-dose edoxaban significantly reduced ischemic stroke or systemic embolism, albeit with a nonsignificant increase in major bleeding. These results remained consistent across all age strata in a subsequent post hoc analysis.[22] Similarly, the AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial assessed the effects of a DOAC in patients with AF ineligible for VKA.[12] It compared apixaban with aspirin, reporting greater efficacy for apixaban with similar safety. The benefits of apixaban persisted in this trial's older subgroup.[23] Our study's results suggest superior efficacies for dabigatran, rivaroxaban, and apixaban in preventing ischemic stroke or systemic embolism in AF compared with edoxaban and VKA. However, there was a lack of data directly comparing each DOAC in the older population, and trials focused on vulnerable populations adopted variable controls. Further investigation is needed to shed light on this subject.

Bleeding risk is 1 key aspect evaluated in any anticoagulation therapy. In the landmark trials for each DOAC, although they had reduced or similar major bleeding risks to VKA, they all had significantly lower ICH risks.[11,14,15,17] However, this phenomenon was inconsistent in the older population. In this analysis, all DOACs had similar major bleeding risks to VKA in the older population. Dabigatran, apixaban, and edoxaban had significantly lower ICH risks than VKA, whereas rivaroxaban had a similar risk. We also found significantly lower risks of all bleeding events with apixaban and a nominally increased risk with rivaroxaban compared with VKA, just missing statistical significance.

These results suggest a propensity toward bleeding with rivaroxaban use in older patients that was not seen in the general population. Whether this increase in bleeding risk increases with age is unclear. Lower risk of bleeding with DOAC use compared with VKA seems less evident in the older population. An additional factor that should be considered is the time in therapeutic range (TTR) during VKA therapy. In both the RE-LY and ROCKET AF trials, mean patient age increased with center-level TTR.[24,25] Similarly, in the ENGAGE AF-TIMI 48 study, individual TTR was higher in older age groups.[26] Interestingly, meta-analyses have demonstrated that the lower risk of bleeding with DOAC use compared with warfarin is only present in patients from centers with lower center-level TTR.[27] In fact, in the RE-LY[24] and ROCKET AF,[25] there was a trend toward greater risks of major bleeding with DOAC use compared with warfarin among patients with higher individual TTR. As the older subgroup in these trials coincided with subgroups with higher TTR, both of these factors may have contributed to the attenuation of safety benefits of DOACs seen in the current study. VKA remains an available treatment option in cases where DOACs are less suitable or contraindicated. Similar to all post hoc analyses, this study's results should be interpreted cautiously. Our results suggest hypothesis-generating associations and provide the groundwork for future prospective studies.

Two dabigatran and edoxaban doses were evaluated for efficacy and safety in the RE-LY and ENGAGE AF-TIMI 48 trials.[11,17] Both trials reported reduced efficacy but similar safety with lower doses. These findings persisted in the older population, as demonstrated by our analyses. High-dose regimens were associated with significantly lower ischemic stroke or systemic embolism risks than low-dose regimens and VKA. However, high- and low-dose regimens performed similarly across all safety outcomes, even in the older patient. The bleeding risk is a primary concern during anticoagulation in older patients. A previous European survey of reasons for hesitation toward anticoagulation for stroke prevention in AF showed that 11.4% of interviewed physicians considered advanced age a major concern.[28] It is intuitive to opt for lower dosages in patients at high risk of bleeding, such as those of advanced age. However, real-world studies have shown how inappropriate, off-label underdosing was associated with an increased risk of thromboembolic events without a reduction in bleeding risk.[29] Our analysis shows that high-dose dabigatran and edoxaban regimens should be adopted to prevent AF-related embolic events, even in the older population. Furthermore, dose reductions should be based on criteria recommended by drug labels, which differ slightly for each DOAC, and not on the presence of advanced age only.

Limitations

This study had several limitations that should be noted. First, our study's results are based on subgroup data from RCTs. Therefore, direct comparisons between each agent may be underpowered. We conducted a comprehensive literature review and included all studies that met our inclusion criteria to increase statistical power. Nevertheless, conclusions from our results should be treated cautiously. Second, the definition of bleeding events, particularly minor bleeding, differed slightly between trials. The RRs extracted from each RCT may reflect slightly different clinical meanings. Similarly, in the subgroup analysis of very old patients, cutoffs for age strata varied in each trial, with some reporting data in patients aged ≥80 years and others in patients aged >85 years. The number of patients available for analysis was even more limited in this extreme population. Our goal was to provide clinical recommendations in treating older patients and not report conclusions on causality. Finally, none of the comparisons of the 2 primary end points (stroke/systemic embolism and major bleeding) were statistically significant in our analyses. Furthermore, no additional subgroup analysis or meta-regression analyses (eg, to sex or race) was conducted because this was a study-level meta-analysis without individual data of the participants. Further studies focused on older patients are needed to validate our findings.

CONCLUSIONS

In patients aged ≥75 years, using DOACs in AF was associated with lower stroke and systemic embolic event risks and similar bleeding risks to VKA, with a trend toward lower efficacy with edoxaban. The use of rivaroxaban was associated with greater risk of ICH compared with other DOACs. In older patients, high-dose regimens showed superior efficacy in preventing embolic events without increasing bleeding risk compared with low-dose regimens and VKA. Stroke prevention in AF is a clinical issue of increasing significance, and further studies focused on older patients are needed to guide treatment in this high-risk population.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S2
Figures S1–S2

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