

The efficacy and safety of edoxaban versus warfarin in preventing clinical events in atrial fibrillation: A systematic review and meta-analysis

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ABSTRACT

Atrial fibrillation (AF) is the most common type of arrhythmia. Warfarin reduces the incidence and mortality of strokes in patients with AF. Edoxaban reduces the bleeding risk in patients with AF. This study evaluates the efficacy and safety of edoxaban versus warfarin in preventing clinical events in patients with AF through a meta-analysis of randomized controlled trials (RCTs). RCTs were retrieved from medical literature databases. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated to compare the primary and safety endpoints. In total, five articles (10 trial comparisons) containing 24,836 patients were retrieved. Of these patients, 16,268 (65.5%) received edoxaban and 8,568 (34.5%) received warfarin. Compared with warfarin, edoxaban significantly reduced the incidence of cardiovascular death (CVD), major bleeding, and non-major bleeding (RR: 0.86, 95% CI: 0.80–0.93, I^2 : 0.0%; RR: 0.65, 95% CI: 0.59–0.71, I^2 : 75.6%; and RR: 0.80, 95% CI: 0.77–0.84, I^2 : 79.3%, respectively). Edoxaban did not increase the incidence of stroke, systemic embolic events, myocardial infarction, and adverse events compared with warfarin (RR: 1.00, 95% CI: 0.90–1.11, I^2 : 42.8%; RR: 1.00, 95% CI: 0.67–1.49, I^2 : 0.0%; RR: 1.08, 95% CI: 0.93–1.27, I^2 : 0.0%; RR: 1.00, 95% CI: 0.91–1.10, I^2 : 46.4%, respectively). This meta-analysis indicated that compared with warfarin, edoxaban can significantly reduce the incidence of CVD and major and non-major bleeding. The anticoagulant effect and safety of edoxaban may be better than those of warfarin.

Key words: edoxaban, warfarin, atrial fibrillation, meta-analysis

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia observed in outpatient clinics; with the increase in the aging population, the occurrence of AF is also increasing (1). Some studies have found an association between AF and embolism, stroke, myocardial infarction (MI), and cardiovascular death (CVD) (2-4). The most serious complication of AF is embolism, where the dislodged thrombus can be carried to different parts of the body via the blood circulation, leading to the occurrence of various systemic complications such as stroke, pulmonary embolism, and even death (5). AF increases the incidence of

stroke by 4–5 times in all age groups, with a significant increasing trend with age (6). Presently, the relationship between AF and MI is unclear (7). However, in outpatient clinics, AF complicated with MI is common, and acute MI commonly leads to cardiogenic shock (8). Thus, AF is an independent risk factor for mortality in patients with coronary heart disease. Embolism is the main cause of death and disability in patients with AF (9); therefore, standardized anticoagulation therapy is an important aspect in comprehensively treating patients with AF.

Warfarin, (9) a widely used coumarin anticoagulant, inhibits the synthesis of coagulation factors II, VII, IX, and X in the liver and is a vitamin K antagonist, thus inhibiting the formation of

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HIGHLIGHTS

- This is the first study focusing on patients with AF in a meta-analysis of the efficacy and safety of edoxaban versus warfarin. No specific meta-analysis comparing edoxaban and warfarin exists. Our article fills this gap. Compared with warfarin, edoxaban can significantly reduce the incidence of CVD and major and non-major bleeding. The anticoagulant effect and safety of edoxaban may be better than those of warfarin.

thrombi *in vivo* (10). When administering warfarin, measuring the international standardized ratio (INR) regularly is necessary, aiming for 2–3 times the control value (11). This ensures a better antithrombotic effect and a lower risk of bleeding. Studies have shown that warfarin can significantly reduce the incidence and mortality of stroke in patients with AF, but individual differences may lead to different effective doses of warfarin (12, 13). Frequent measurement of INR levels is necessary to adjust to the appropriate warfarin dosage (14).

Edoxaban, the free base of DU-176b, is a highly specific direct inhibitor of coagulation factor Xa (15). In the coagulation process, activated coagulation factor Xa activates prothrombin to thrombin, and thrombin cleaves fibrin monomer to fibrin to form a thrombus (16). As a new oral anticoagulant (NOAC), edoxaban inhibits thrombus formation by selective and reversible direct inhibition of factor Xa (17). Studies have shown that edoxaban significantly reduces the risk of bleeding in patients with AF (18). However, its role in reducing the incidence of CVD, MI, systemic embolism events (SEE), and stroke in patients with AF is controversial.

Thus, we performed this meta-analysis to compare the effects and safety of edoxaban with those of warfarin in preventing clinical events in patients with AF to provide evidence for clinical use.

Methods**Search strategy**

Two researchers searched for published articles comparing the efficacy and safety of edoxaban with those of warfarin in preventing clinical events in patients with AF following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The RCTs were systematically searched in databases such as PubMed, Embase, Cochrane Library, Web of Science, and Google Scholar, with no restrictions on language or publication date (from inception to April 11, 2019). The following keywords and Medical Subject Heading terms were used: “atrial fibrillation”; “atrial fibrillations”; “fibrillation, atrial”; “fibrillations, atrial”; “auricular fibrillation”; “auricular fibrillations”; “fibrillation, auricular”; “fibrillations, auricular”; “persistent atrial fibrillation”; “atrial fibrillation, persistent”; “atrial fibrillations, persistent”; “fibrillation, persistent atrial”; “fibrillations,

persistent atrial”; “persistent atrial fibrillations”; “familial atrial fibrillation”; “atrial fibrillation, familial”; “atrial fibrillations, familial”; “familial atrial fibrillations”; “fibrillation, familial atrial”; “fibrillations, familial atrial”; “paroxysmal atrial fibrillation”; “atrial fibrillation, paroxysmal”; “atrial fibrillations, paroxysmal”; “fibrillation, paroxysmal atrial”; “fibrillations, paroxysmal atrial”; and “paroxysmal atrial fibrillations” in combination with atrial fibrillation. “Apo-Warfarin”; “Aldocumar”; “Warfarin”; “Warfant”; “4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-1-benzopyran-2-one”; “Gen-Warfarin”; “Marevan”; “Coumadin”; “warfarin potassium”; “potassium, warfarin”; “warfarin sodium”; “sodium, warfarin”; “Coumadine”; and “Tedicumar” were used in combination with warfarin. “edoxaban,” “DU-176b,” “edoxaban tosylate,” and “DU-176” were used in combination with edoxaban. Additional relevant studies were retrieved from reviews, meta-analyses, and other literature. Two authors screened and double-reviewed the retrieved studies. If disputes were encountered, they were resolved by consulting a third author.

Inclusion and exclusion criteria

The inclusion criteria were as follows: RCTs that involved edoxaban and warfarin; studies that allocated patients into two groups (edoxaban and warfarin groups); and all patients who had been diagnosed with AF according to the international diagnostic guidelines. Exclusion criteria were as follows: retrospective trials, animal experiments, non-RCTs, reviews, series and case reports, studies with erroneous or incomplete data, studies with results that were not focused on patients with AF, studies with patients with low coagulation function, and studies with patients allergic to edoxaban or warfarin.

Endpoints

The primary endpoints for this study were CVD, stroke, SEE, and MI. The safety endpoints included major bleeding, non-major bleeding (life-threatening bleeding, clinically relevant non-major bleeding, minor bleeding, any overt bleeding, etc.), and other adverse events (AEs).

Data extraction

Two authors independently reviewed the contents of the retrieved studies. The primary and safety endpoints were extracted by the authors and verified by a third author. The data extracted included the following primary information: the first author’s name, year of publication, test type/region, sample size, sex ratio, average age, intervention, CHADS-2 score [congestive heart failure, hypertension, age >75 years, diabetes (all 1 point each); previous stroke (2 points)], type of AF, follow-up time, and endpoints measured in each study. If the contents of the studies needed clarification, the first author of the study was contacted. Disagreements were resolved through consensus or by consulting a third author.

Risk-of-bias assessments

The methodological quality of the included studies was estimated independently by two authors based on the Cochrane

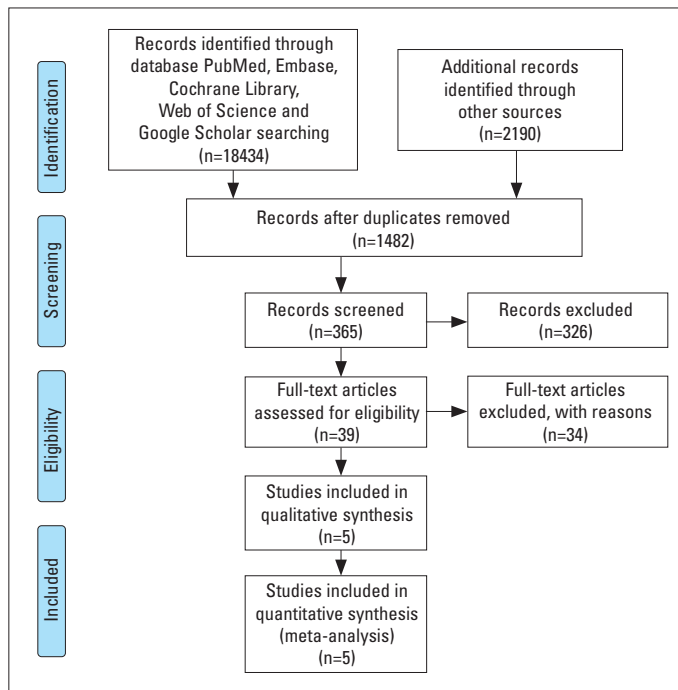


Figure 1. Flow diagram of the study selection process.

Risk-of-Bias criteria. Each quality item was graded as low risk, high risk, or no clear risk. The seven items used to assess bias in each trial included randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases.

Statistical analysis

Stata (version 12.0; Stata Corp, College Station, Texas) was used to analyze and pool the individual research results. The pooled results were presented as risk ratios (RR) and 95% confidence intervals (CI) with two-sided *p* values. *P* values of <0.05 were used to denote statistical significance. Heterogeneity was evaluated using the *I*² test. Heterogeneity was considered small when *I*² <50% and substantial when *I*² >50%. A funnel plot was generated to examine publication bias and to explore the sources of heterogeneity, if more than 10 studies were included to assess this endpoint. Subgroup analysis was performed according to the dosage of edoxaban (30 mg, 60 mg, and others according to the administration dose of edoxaban per day).

Results

Studies retrieved and characteristics

In total, 18,434 relevant studies were enrolled according to the PRISMA guidelines. The titles and abstracts of the studies were screened to exclude irrelevant studies. Furthermore, we eliminated the unsuitable studies by reading the full text of the articles. Finally, five studies (19–23) (10 trial comparisons) were included according to the inclusion and exclusion criteria with

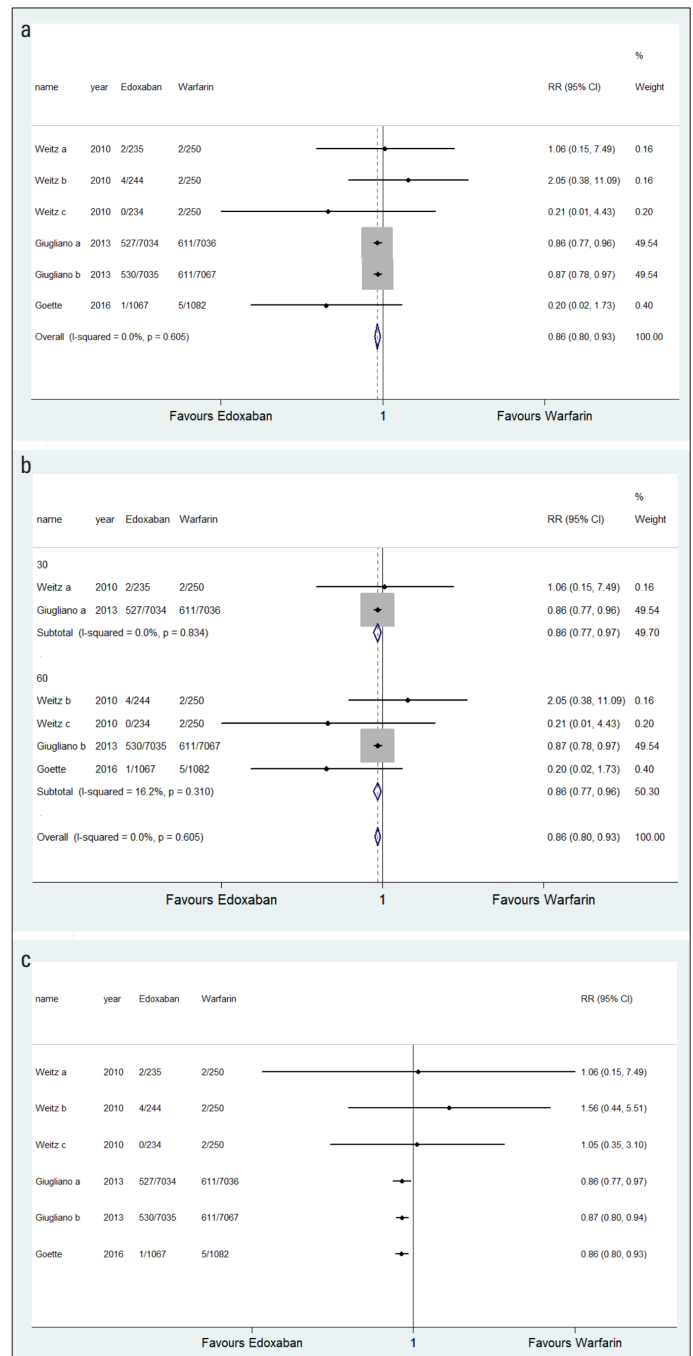


Figure 2. a-c. a. Comparison of CVD between the edoxaban group and the warfarin group. b. Comparison of CVD between the edoxaban group and the warfarin group (subgroup analysis according to edoxaban dosage). c. Comparison of CVD between the edoxaban group and the warfarin group (cumulative meta-analysis). RR - risk ratio

24,836 patients (Fig. 1). Moreover, 16,268 patients (65.5%) were randomized into the edoxaban group and 8,568 (34.5%) to the warfarin group. All studies included in this meta-analysis were RCTs. The basic characteristics of the individuals from the trials are described in Table 1.

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

Author	Year	Testtype/ region	Sample size		Women, No. (%)		Average age (years)		Intervention		CHADS ₂ score (mean)		Type of AF	Follow- up	Endpoints
			Edoxaban	Warfarin	Edoxaban	Warfarin	Edoxaban	Warfarin	Edoxaban	Warfarin	Edoxaban	Warfarin			
Chung et al. ^a (19)	2010	Multicentre	79	75	28 (35.4)	28 (37.3)	64.9	64.5	30 mg qd	Adjusted based on INR values	2.0	1.8	Non-valvular AF	3 months	Major bleeding, Non-major bleeding, AEs
Chung et al. ^b (19)	2010	Multicentre	80	75	25 (31.2)	28 (37.3)	65.9	64.5	60 mg qd	Adjusted based on INR values	1.9	1.8	Non-valvular AF	3 months	Major bleeding, Non-major bleeding, AEs
Weitz et al. ^a (20)	2010	Multicentre	235	250	95 (40.4)	99 (39.6)	65.2±8.3	66.0±8.5	30 mg qd	Adjusted based on INR values	N/A	N/A	Non-valvular AF	12 weeks	CVD, Stroke, MI, SEE, Major bleeding, Non-major bleeding, AEs
Weitz et al. ^b (20)	2010	Multicentre	244	250	94 (38.5)	99 (39.6)	64.8±8.8	66.0±8.5	30 mg bid	Adjusted based on INR values	N/A	N/A	Non-valvular AF	12 weeks	CVD, Stroke, MI, SEE, Major bleeding, Non-major bleeding, AEs
Weitz et al. ^c (20)	2010	Multicentre	234	250	79 (33.7)	99 (39.6)	64.9±8.8	66.0±8.5	60 mg qd	Adjusted based on INR values	N/A	N/A	Non-valvular AF	12 weeks	CVD, Stroke, MI, SEE, Major bleeding, Non-major bleeding, AEs
Yamashita et al. ^a (21)	2011	Japan	130	125	21 (16.0)	22 (17.0)	69.4	68.8	30 mg qd	Adjusted based on INR values	1.9	2.2	Non-valvular AF	12 weeks	Major bleeding, Non-major bleeding, AEs
Yamashita et al. ^b (21)	2011	Japan	134	125	25 (18.6)	22 (17.0)	69.5	68.8	45 mg qd	Adjusted based on INR values	2.1	2.2	Non-valvular AF	12 weeks	Major bleeding, Non-major bleeding, AEs
Giugliano et al. ^a (22)	2013	Multicentre	7034	7036	2730 (38.8)	2641 (37.5)	72	72	30 mg qd	Adjusted based on INR values	2.8±1.0	2.8±1.0	N/A	2.8 years	CVD, Stroke, MI, SEE, Major bleeding, Non-major bleeding, AEs
Giugliano et al. ^b (22)	2013	Multicentre	7035	7036	2669 (37.9)	2641 (37.5)	72	72	60 mg qd	Adjusted based on INR values	2.8±1.0	2.8±1.0	N/A	2.8 years	CVD, Stroke, MI, SEE, Major bleeding, Non-major bleeding, AEs
Goette et al. (23)	2016	Multicentre	1067	1082	374 (34.0)	382 (35.0)	64.3	64.2	60 mg qd	Adjusted based on INR values	2.6	2.6	Non-valvular AF	58 days	CVD, Stroke, MI, SEE, Major bleeding, Non-major bleeding, AEs

a, b and c represent different doses of Edoxaban compared with a same dose of Warfarin in a study.
CVD - cardiovascular death, SEE - systemic embolism events, MI - myocardial infarction, AEs - adverse events

Table 2. Assessment of methodological quality of included study

Study	Random allocation	Hidden distribution	Blind method	Incomplete outcome data	Selective reporting of results	Other bias	Quality grade
Chung et al. (19)	Randomized	No clear	Double-blind	Low	Low	Low	B
Weitz et al. (20)	Randomized	No clear	Double-blind	Low	Low	Low	A
Yamashita et al. (21)	Randomized	No clear	Double-blind	Low	Low	Low	B
Giugliano et al. (22)	Randomized	No clear	Double-blind	Low	Low	Low	A
Goette et al. (23)	Randomized	No clear	Blinded-endpoint evaluation	Low	Low	Low	A

Literature quality evaluation

The Cochrane Risk-of-Bias criteria were used to evaluate the quality of the retrieved studies, which were assessed by two authors. All five studies (19–23) described random sequence generation and allocation concealment, blinding of participants and personnel, and blinding of outcome assessment. None described other biases. The literature quality score is shown in Table 2.

Primary endpoints

The incidence of CVD

Three studies (19, 20, 22) (six trial comparisons) reported CVD. In total, 1,064 of 15,849 patients in the edoxaban group and 618 of 8,368 patients in the warfarin group developed CVD. The results showed that edoxaban could significantly reduce the incidence of CVD compared with warfarin (6.7% vs. 7.4%) (RR=0.86, 95% CI=0.80–0.93, $I^2=0.0\%$) (Fig. 2a). The fixed effects model was applied. The heterogeneity was low. Subgroup analysis was performed according to the dosage of edoxaban and showed that edoxaban significantly reduced the incidence of CVD at 30 and 60 mg dosages compared with warfarin (RR=0.86, 95% CI=0.77–0.97 and RR=0.86, 95% CI=0.77–0.96, respectively) (Fig. 2b). The cumulative meta-analysis result is shown in Figure 2c.

Stroke

Three studies (20, 22, 23) (six trial comparisons) reported strokes. In total, 647 of 15,849 patients in the edoxaban group and 324 of 8,368 patients in the warfarin group had stroke. The results showed that no significant differences were observed between the edoxaban and warfarin groups (4.1% vs. 3.9%, respectively) (RR=1.00, 95% CI=0.90–1.11, $I^2=42.8\%$) (Fig. 3a). The fixed effects model was applied. The heterogeneity was low. Subgroup analysis was performed according to the dosage of edoxaban, which showed that no significant differences at 30 and 60 mg dosages were observed between the edoxaban and warfarin groups (RR=1.13, 95% CI=0.97–1.30 and RR=0.87, 95% CI=0.75–1.02, respectively) (Fig. 3b). The cumulative meta-analysis result is shown in Figure 3c.

SEEs

Three studies (20, 22, 23) (six trial comparisons) reported SEE. In total, 47 of 15,849 patients in the edoxaban group and 24 of 8,368 patients in the warfarin group had an SEE. The results showed no

significant differences between the edoxaban and warfarin groups (0.3% vs. 0.3%, respectively) (RR=1.00, 95% CI=0.67–1.49, $I^2=0.00\%$) (Fig. 4a). The fixed effects model was applied. The heterogeneity was low. Subgroup analysis was performed according to the dosage of edoxaban, which showed that no significant differences at 30 and 60 mg dosages were observed between the edoxaban and warfarin groups (RR=1.30, 95% CI=0.76–2.23 and RR=0.72, 95% CI=0.39–1.32, respectively) (Fig. 4b). The cumulative meta-analysis result is shown in Figure 4c.

Myocardial infarction

Three studies (20, 22, 23) (six trial comparisons) reported MI. In total, 309 of 15,849 patients in the edoxaban group and 144 of 8,368 patients in the warfarin group had MI. No significant differences were observed between the edoxaban and warfarin groups (1.9% vs. 1.7%, respectively) (RR=1.08, 95% CI=0.93–1.27, $I^2=0.0\%$) (Fig. 5a). The fixed effects model was applied. The heterogeneity was low. Subgroup analysis was performed according to the dosage of edoxaban and showed that no significant differences at 30 and 60 mg dosages were observed between the edoxaban and warfarin groups (RR=1.21, 95% CI=0.97–1.51 and RR=0.96, 95% CI=0.76–1.21, respectively) (Fig. 5b). The cumulative meta-analysis result is shown in Figure 5c.

Safety endpoints

Major bleeding

Five studies (19–23) (10 trial comparisons) reported major bleeding. In total, 683 of 16,268 patients in the edoxaban group and 532 of 8,568 patients in the warfarin group experienced major bleeding. The result showed that edoxaban could significantly reduce the incidence of major bleeding compared with warfarin (4.2% vs. 6.2%, respectively) (RR=0.65, 95% CI=0.59–0.71, $I^2=75.6\%$) (Fig. 6a). The fixed effects model was applied. Subgroup analysis was performed according to the dosage of edoxaban and revealed that edoxaban significantly reduced the incidence of major bleeding at 30 and 60 mg dosages compared with warfarin (RR=0.48, 95% CI=0.42–0.56 and RR=0.81, 95% CI=0.71–0.91, respectively) (Fig. 6b). The cumulative meta-analysis result is shown in Figure 6c.

Non-major bleeding

Five studies (19–23) (10 trial comparisons) reported non-major bleeding. In total, 3,552 of 16,268 patients in the edoxa-

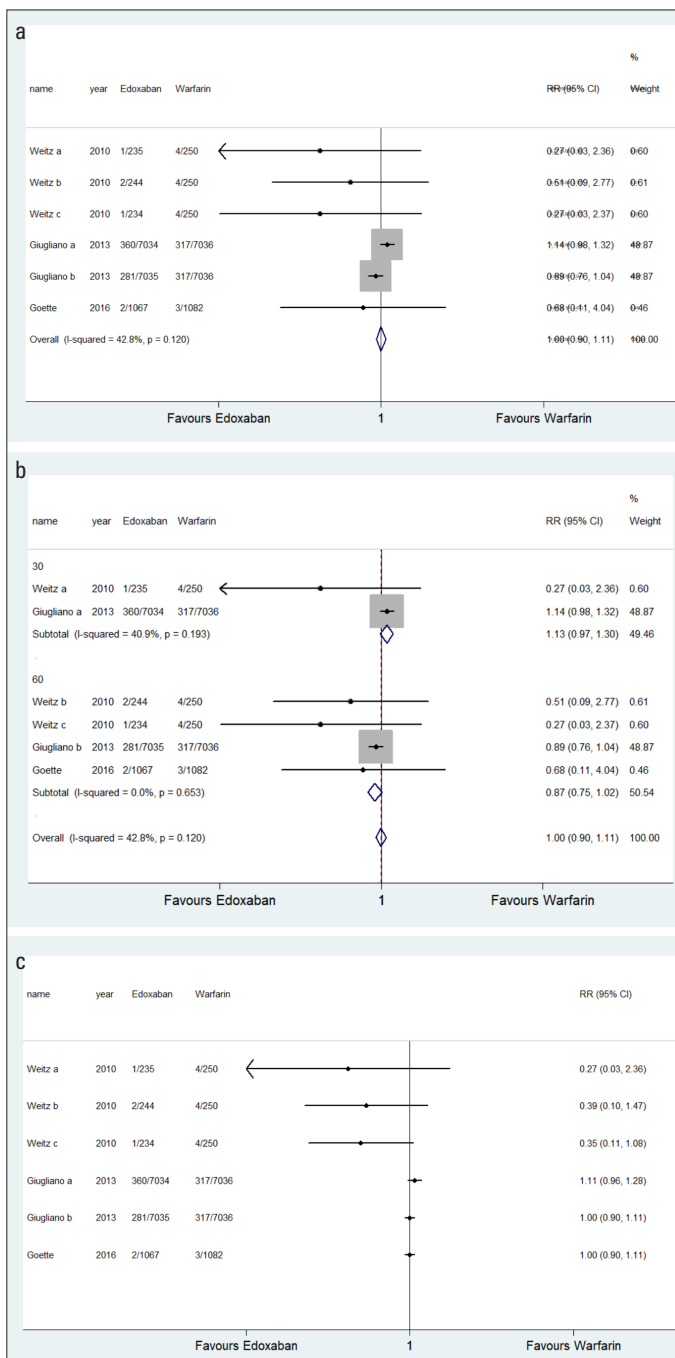


Figure 3. a-c. a. Comparison of stroke between the edoxaban group and the warfarin group. b. Comparison of stroke between the edoxaban group and the warfarin group. (subgroup analysis according to edoxaban dosage). c. Comparison of stroke between the edoxaban group and the warfarin group. (cumulative meta-analysis).

RR - risk ratio

ban group and 2,216 of 8,568 patients in the warfarin group experienced non-major bleeding. The results showed that edoxaban could significantly reduce the incidence of non-major bleeding compared with warfarin (21.8% vs. 25.9%, respectively) (RR=0.80, 95% CI=0.77–0.84, $I^2=79.3%$) (Fig. 7a). The fixed effects model was applied. Subgroup analysis was

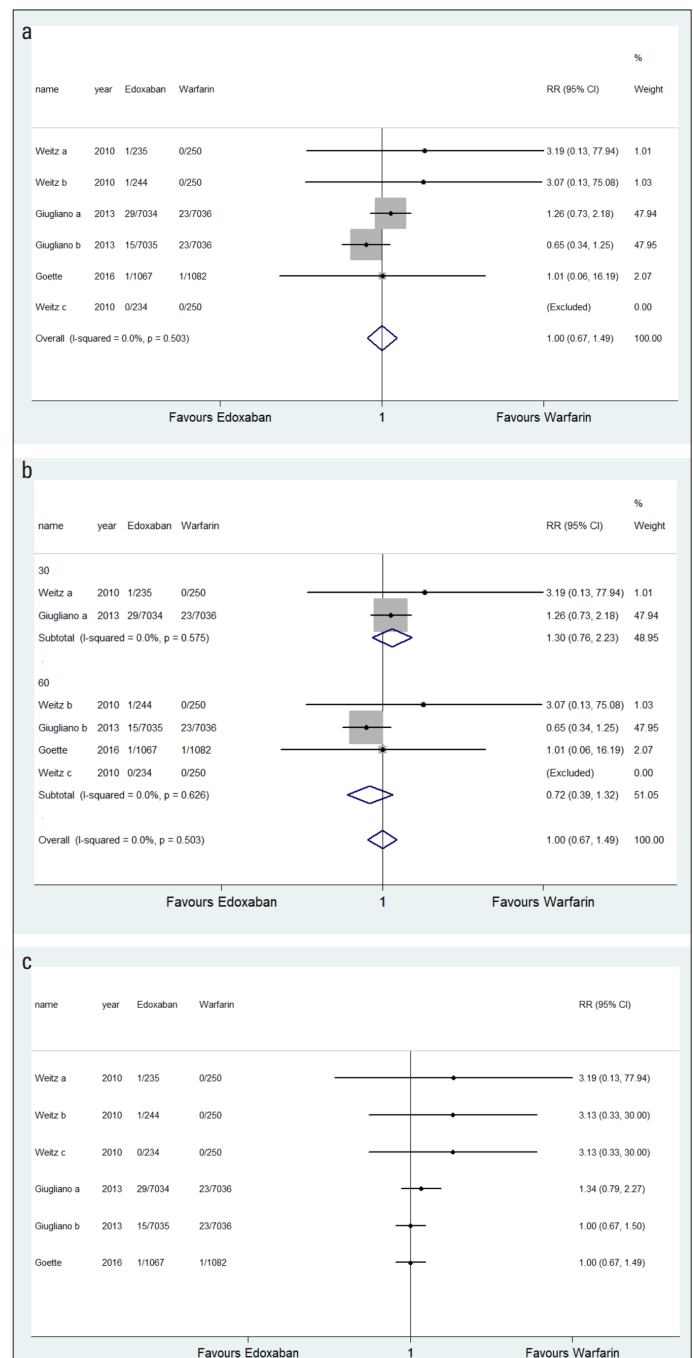


Figure 4. a-c. a. Comparison of SEE between the edoxaban group and the warfarin group. b. Comparison of SEE between the edoxaban group and the warfarin group. (subgroup analysis according to edoxaban dosage). c. Comparison of SEE between the edoxaban group and the warfarin group. (cumulative meta-analysis).

RR - risk ratio

performed according to the dosage of edoxaban, which showed that edoxaban significantly reduced the incidence of non-major bleeding at 30 and 60 mg dosages compared with warfarin (RR=0.71, 95% CI=0.67–0.75 and RR=0.89, 95% CI=0.85–0.94, respectively) (Fig. 7b). The cumulative meta-analysis result was shown in Figure 7c.

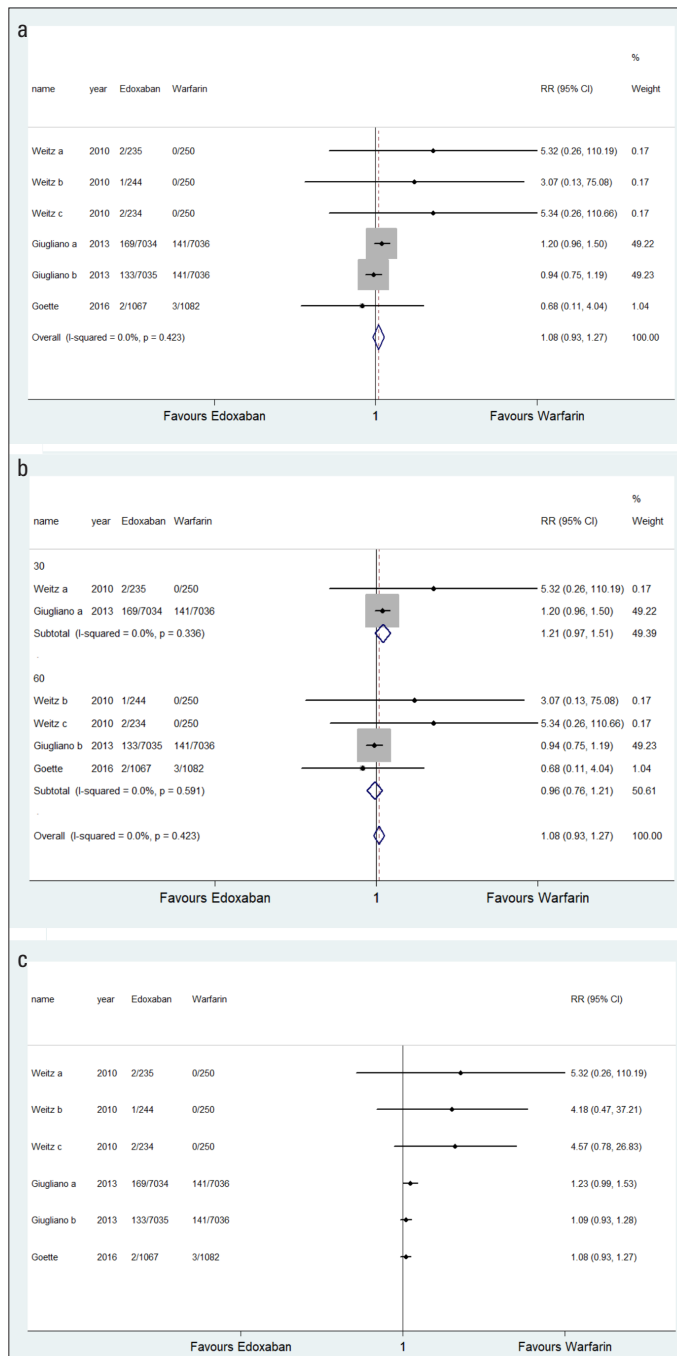


Figure 5. a-c. Comparison of MI between the edoxaban group and the warfarin group. **b.** Comparison of MI between the edoxaban group and the warfarin group (subgroup analysis according to edoxaban dosage). **c.** Comparison of MI between the edoxaban group and the warfarin group (cumulative meta-analysis).

RR - risk ratio

Adverse events

Four studies (19–21, 23) (eight trial comparisons) reported AEs. In total, 557 of 2,199 patients in the edoxaban group and 451 of 1,532 patients in the warfarin group had AEs. No significant differences were observed between the edoxaban and warfarin groups (25.3% vs. 29.4%, respectively) (RR=1.00, 95% CI=0.91–

1.10, I²=46.4%) (Fig. 8a). The fixed effects model was applied. Subgroup analysis was performed according to the dosage of edoxaban, which showed that no significant differences at 30 and 60 mg dosages were observed between the edoxaban and warfarin groups (RR=1.03, 95% CI=0.85–1.25 and RR=1.00, 95% CI=0.90–1.11, respectively) (Fig. 8b). The cumulative meta-analysis result is shown in Figure 8c.

Publication bias and sensitivity analysis

The funnel plot showed that there was bias among retrieved articles (Figs. 6d and 7d). The results of the sensitivity analysis are shown in Figures 6e and 7e.

Discussion

Warfarin is the most commonly used traditional anticoagulant in patients with AF (24). However, due to its narrow therapeutic window and interactions with several drugs and foods, warfarin is more likely to fail to meet the appropriate INR ratio than to cause bleeding events. Time in therapeutic range (TTR) of INR, which was used to evaluate the effectiveness and safety of warfarin anticoagulation, is approximately half were suboptimal (25, 26). Edoxaban is a NOAC recently approved by the US Food and Drug Administration following dabigatran, rivaroxaban, and apixaban (27). In many clinical studies, edoxaban is superior to warfarin in preventing SEEs and reducing the risk of bleeding (28). However, there are still inconsistent conclusions with respect to prevention of strokes and SEEs (29) owing to incomplete research, the small sample size of studies, and limitations in the clinical reference value.

This is the first meta-analysis to compare the efficacy and safety of edoxaban with those of warfarin in preventing clinical events in patients with AF. The results of this meta-analysis show that the incidences of CVD, major bleeding, and non-major bleeding in the edoxaban group was significantly lower than that in the warfarin group. Edoxaban did not increase the incidence of stroke, SEE, MI, and AEs compared with warfarin.

Subgroup analyses were performed according to the dosage of edoxaban and showed that edoxaban did not increase the incidence of stroke, SEE, MI, or AEs at 30 mg, 60 mg, 120 mg, or other dosages compared with warfarin; edoxaban significantly reduced the incidence of CVD, major bleeding, and non-major bleeding at 30 and 60 mg dosages compared with warfarin. However, in other dosage groups (45 and 120 mg), the result was the opposite. No significant differences at a 120-mg dosage were observed between the edoxaban and warfarin groups when evaluating AEs; edoxaban can significantly decrease the incidence of major and non-major bleeding at other dosage levels compared with warfarin. This reversal of edoxaban's effect may be due to its current suggested dosage (30 or 60 mg). The commonly used dosage of edoxaban is 60 mg a day, and a dosage of 30 mg a day might be only prescribed if the patient has complications such as kidney disease, a low body weight, or taking some specific drugs, such as ciclosporin, dronedarone, erythromycin, and ketoconazole (30). However, in one trial by

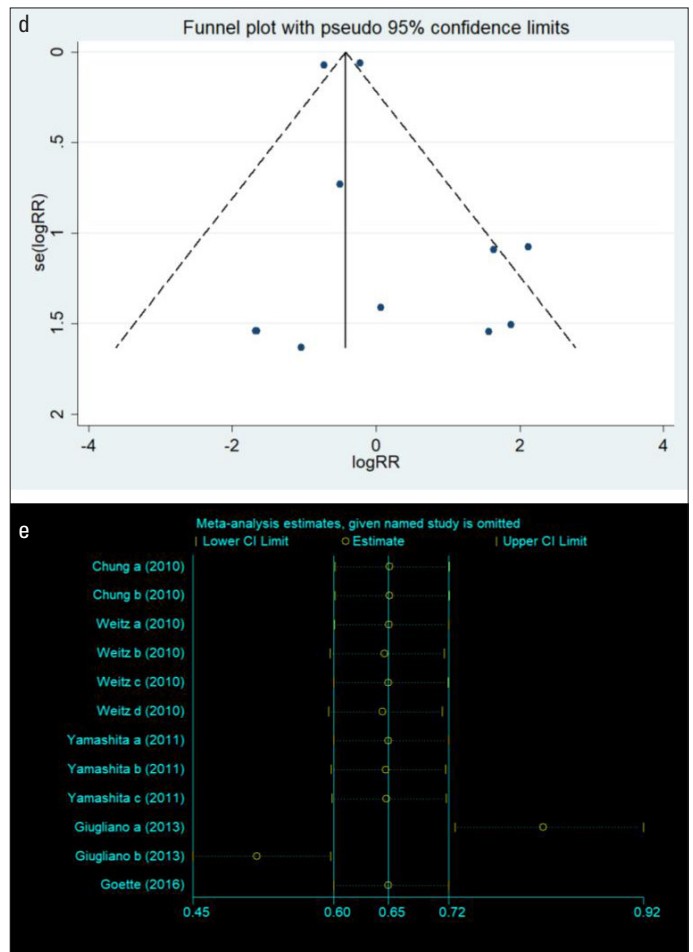
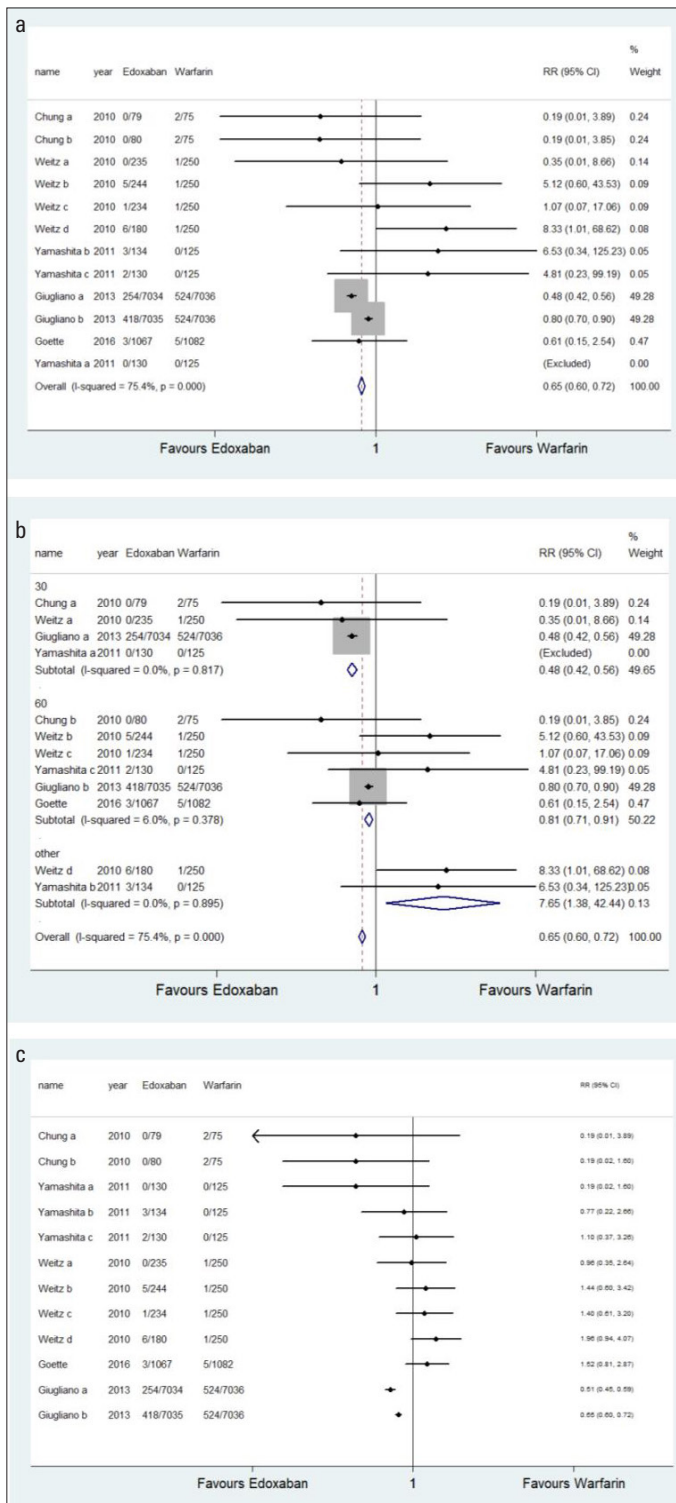


Figure 6. a-e. a. Comparison of major bleeding between the edoxaban group and the warfarin group. b. Comparison of major bleeding between the edoxaban group and the warfarin group (subgroup analysis according to edoxaban dosage). c. Comparison of major bleeding between the edoxaban group and the warfarin group (cumulative meta-analysis). d. Comparison of major bleeding between the edoxaban group and the warfarin group (funnel plot) e. Comparison of major bleeding between the edoxaban group and the warfarin group (sensitivity analysis)
RR - risk ratio

Weitz et al. (20), patients were administered 60-mg edoxaban twice a day—much higher than the usual clinical dosage—which was proven to increase the risk of bleeding and might be a source of heterogeneity to our results.

When evaluating the safety endpoints, we found that the results were highly heterogeneous; therefore, we performed sensitivity analyses to deconstruct the results. The results

showed that after excluding the study by Giugliano et al. (22), the overall effect on major and non-major bleeding was greatly affected, and after excluding the study by Goette et al. (23), the overall effect on AEs was greatly affected. The same results were obtained from the cumulative meta-analysis based on the sample size from small to large. This may be because the sample size in different studies was extremely unbalanced. The weight



of the sample size in the studies by Giugliano et al. (22) and Goette et al. (23) was too large, which directly resulted in the overall effect changing with the results of the two studies.

Presently, there are many meta-analyses and RCTs on NOACs in patients with AF. However, whether NOACs can reduce the incidence of CVD, strokes, SEE, MI, major bleeding, non-major bleeding, and AEs in patients with AF is still unclear.

These studies mention edoxaban as a NOAC; however, no meta-analysis had compared edoxaban with warfarin. A report by Almutairi et al. (31) has shown that edoxaban can significantly reduce the incidence of CVD and MI, and edoxaban and warfarin had no difference in effect on the incidence of SEE, major bleeding, and stroke events. Another study (32) has shown that edoxaban can significantly reduce the incidence of CVD and

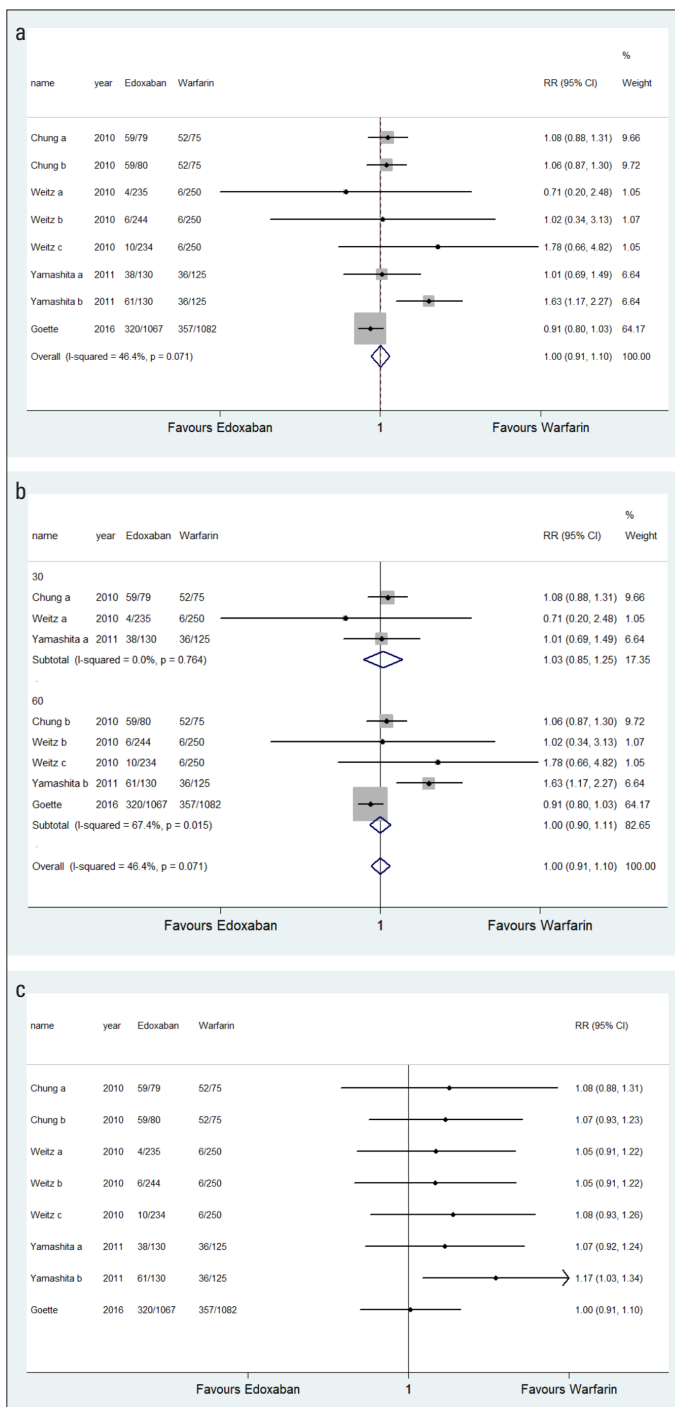


Figure 8. a-c. a. Comparison of AEs between the edoxaban group and the warfarin group. b. Comparison of AEs between the edoxaban group and the warfarin group. (subgroup analysis according to edoxaban dosage). c. Comparison of AEs between the edoxaban group and the warfarin group. (cumulative meta-analysis). RR - risk ratio

major bleeding; however, no difference in the incidence of SEE and stroke events was observed between edoxaban and warfarin (3). However, only one RCT (33) was included in these two meta-analyses. The study by Bruins Slot et al. (34) has reported that factor Xa inhibitors can significantly reduce the incidence

of CVD, stroke, SEE, major bleeding, non-major bleeding, and AEs (except for MI) compared with warfarin. The registration studies, ENGAGE AF-TIMI 48 trial and Hokusai-VTE study, all have confirmed that the efficacy and safety of edoxaban are not lower than those of warfarin, with a superior trend (35). Similarly, a network meta-analysis (36) has reported on the efficacy of five anticoagulants on preventing clinical events in patients with AF and showed that no difference in reducing the incidence of CVD, stroke, SEE, MI, major bleeding, non-major bleeding, and AEs was observed between edoxaban and warfarin. In addition, the dosage of edoxaban is important; however, meta-analyses did not analyze the dose. The ENGAGE AF-TIMI 48 trial (22) has suggested that the clinical benefits of edoxaban at 30 mg and 60 mg doses were consistent. However, according to clinical guidelines, different doses have different effects on patients. Therefore, a systematic review of the clinical use of edoxaban is urgently needed.

NOACs included dabigatran, rivaroxaban, apixaban, and edoxaban, which were all factor Xa inhibitors except for the first one. The study by Lee et al. (37) has demonstrated that the efficacy and safety of edoxaban and rivaroxaban were similar. In addition, the research by Sherrill et al. (38) has supported that a high dose of edoxaban has a similar effect with other NOACs and has a significant advantage in reducing the incidence of hemorrhage as well. The 2016 American College of Cardiology Annual Scientific Sessions (ACC 16) has put forward that compared with other NOACs, edoxaban is an agent with larger renal elimination and should be avoided in patients with a creatinine clearance (CrCl) of more than 95 ml/min. Compared with rivaroxaban, edoxaban seems to be more cost effective according to Miller et al. (39).

The strengths of this meta-analysis are as follows: (1) This is the first study focusing on patients with AF in a meta-analysis of the efficacy and safety of edoxaban versus warfarin. Articles have compared several NOACs to warfarin in preventing clinical events; however, no specific meta-analysis comparing edoxaban and warfarin exists. Our article fills this gap. (2) Five RCTs were retrieved with a sample size of 24,836 patients, which is much larger than previous meta-analysis. (3) Subgroup analyses were conducted according to the dosage of edoxaban to explain the heterogeneity among the included studies and increase the reliability of these results. (4) Sensitivity analyses and cumulative meta-analyses were conducted to deconstruct heterogeneity and explore the influence of sample size on the overall effect. (5) Several different bleeding definitions, other than major bleeding, were observed among the retrieved studies (life-threatening bleeding, clinically relevant non-major bleeding, minor bleeding, any overt bleeding, etc.). Such inconsistent definitions may affect the interpretation of the results. This study used major bleeding and non-major bleeding as the safety endpoints to represent the aforementioned definitions.

Study limitations

The limitations of this study are as follows: (1) We retrieved only five articles, and the sample sizes were unbalanced. The

study by Giugliano et al. (22) accounted for more than 80% of the total sample size. Through sensitivity analysis and cumulative meta-analysis, we are aware that this had a great impact on several endpoints. The RCTs we included lack TTR analyses of warfarin, which might render the result about the effectiveness of the warfarin inaccurate. (2) Several baseline characteristics (i.e., diabetes, hypertension, older age, and other drug use) were not considered, which may have led to a mixed bias. (3) We used the outcome events reported in the retrieved studies to integrate the results of this meta-analysis. Therefore, assessing the effect of these baseline characteristics on the results was difficult. (4) This study could not explore the interactions among the subgroup analysis because of the limitations inherent in the included studies. (5) Although the definition of non-major bleeding as an endpoint was used to summarize all types of bleeding (except for major bleeding) observed among the retrieved studies, the differences may still have impacted the results of our meta-analysis. (6) Large differences in the follow-up duration used were observed among the studies. Therefore, the results on the long-term effect and safety of edoxaban were not comprehensive. (7) Although the assessment of safety endpoints was significantly heterogeneous, due to the shortage of retrieved articles, we still chose a fixed effects model.

Conclusion

This meta-analysis revealed that compared with warfarin, edoxaban can significantly reduce the incidence of CVD, major bleeding, and non-major bleeding in patients with AF. The anti-coagulant effect and safety of edoxaban may be better than those of warfarin.

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