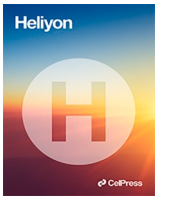
Heliyon 9 (2023) e21740

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Effect of edoxaban compared with other oral anticoagulants for stroke prevention in patients with atrial fibrillation: A meta-analysis

Bailin Zhang [a,1], Winglam Cheng [b,1], Wulamiding Kaisaier [b,1], Zhenbang Gu [b], Wengen Zhu [b,*], Qiuhua Jiang [a,**]

[a] Department of Neurosurgery, Ganzhou People's Hospital, Ganzhou, Jiangxi 341000, China
[b] Department of Cardiology, the First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong, 510080, China

ARTICLE INFO

Keywords:
Atrial fibrillation
Anticoagulants
Edoxaban
Vitamin K antagonists
Warfarin

ABSTRACT

Background and aim: Current observational studies have compared the effectiveness and safety of edoxaban with other oral anticoagulants in patients with AF, but the results are still disputed. This meta-analysis was conducted to compare the effect of edoxaban in patients with AF.
Methods: We performed systematic research from the PubMed, EMBASE, and Cochrane Library databases until November 2022 to obtain relevant observational studies. Adjusted risk ratios (RRs) and 95 % confidence intervals (CIs) of the outcomes were collected and pooled by a ran dom-effects model. This study was prospectively registered in PROSPERO (CRD42022314222).
Results: A total of 17 observational studies were included in this meta-analysis. Compared with vitamin K antagonists, edoxaban was associated with lower risks of stroke or systemic embolism (RR = 0.67, 95 % CI:0.61–0.74), major bleeding (RR = 0.54, 95 % CI:0.44–0.67), and intracranial hemorrhage (RR = 0.51, 95 % CI:0.29–0.90). Compared with dabigatran or rivaroxaban, edoxaban was associated with reduced risks of stroke or systemic embolism (dabigatran [RR = 0.76, 95 % CI:0.66–0.87]; rivaroxaban [RR = 0.81, 95 % CI:0.70–0.94]) and major bleeding (dabigatran [RR = 0.82, 95 % CI:0.69–0.98]; rivaroxaban [RR = 0.81, 95 % CI:0.70–0.94]). Compared with apixaban, edoxaban was associated with a reduced risk of stroke or systemic embolism (RR = 0.87, 95 % CI:0.79–0.97), but had similar risks of bleeding events.
Conclusions: Our current evidence suggested that edoxaban might have superior effectiveness and/or safety outcomes than vitamin K antagonists, dabigatran, rivaroxaban, and apixaban for stroke prevention in patients with AF.

* Corresponding author.
** Corresponding author.
E-mail addresses: ZBL_DOC@163.com (B. Zhang), cheng227@mail2.sysu.edu.cn (W. Cheng), wulamid@mail2.sysu.edu.cn (W. Kaisaier), 1306680982@qq.com (Z. Gu), zhuwg6@mail.sysu.edu.cn (W. Zhu), jiangqh1968@126.com (Q. Jiang).
[1] **Co-first authorship:** Bailin Zhang, Winglam Cheng, Wulamiding Kaisaier.

https://doi.org/10.1016/j.heliyon.2023.e21740
Received 7 March 2023; Received in revised form 26 October 2023; Accepted 26 October 2023
Available online 3 November 2023

1. Introduction

Atrial fibrillation (AF), the most common arrhythmia in adults, is a well-known risk factor for ischemic stroke and mortality [[1,2]]. The predominant goal of AF management is the prevention of non-fatal or fatal thromboembolic events; therefore, oral anticoagulants (OAC) are recommended as the first-line medication in AF guidelines. Compared with the non-anticoagulant treated group, an approximately 64 % reduction in stroke incidence was observed in AF patients with vitamin K antagonists (VKAs) [[3]]. In recent years, non-vitamin K oral anticoagulants (NOACs) have been considered a superior alternative for VKAs such as warfarin due to their convenient administration, fewer drug interactions, and no need for anticoagulation monitoring [[4]]. As such, current guidelines have recommended NOACs as the preferred anticoagulation drug in patients with AF [[5]].

Previous pivotal randomized clinical trials (RCTs) demonstrated that NOACs were non-inferior in the effectiveness and safety outcomes, or even superior to VKAs in patients with AF [6–9]. Similar findings were found in several real-world studies [[10]]. In addition, the comparisons between different subtypes of NOACs were performed in several observational studies. Compared with dabigatran or rivaroxaban, apixaban was associated with a lower risk of major bleeding, but they had no difference in stroke or systemic embolism (SSE) [[11]]. Dabigatran was correlated to reduced risks of major bleeding and SSE compared with rivaroxaban [[11]]. Nevertheless, the effect of edoxaban compared with other OACs is still inconclusive.

Edoxaban, an oral, once-daily, direct inhibitor of factor Xa, is the last marketed NOAC [[12,13]]. Giugliano et al. [[9]]. conducted an RCT to compare high-dose (60 mg once-daily) and low-dose (30 mg once-daily) edoxaban with VKAs in AF patients with moderate to high stroke risk, suggesting that edoxaban was non-inferior to VKAs in preventing SSE and major bleeding. Furthermore, a meta-analysis of RCTs [[14]] demonstrated that compared with VKAs, edoxaban was associated with lower risks of major or clinically relevant nonmajor bleeding, intracranial hemorrhagic events, and had similar risks of gastrointestinal bleeding events and all-cause mortality in the mixed population with AF, venous thromboembolism, or pulmonary embolism [[14]]. With the wide application of edoxaban in clinical practice, several observational studies have assessed the effectiveness and safety outcomes of edoxaban compared with VKAs or other NOACs in patients with AF. The Edoxaban Treatment in routine cliNical prActice (ETNA) program, a prospective, observational noninterventional study, including 26823 patients from Europe, Japan, and other Asian countries, reported the routine clinical use of edoxaban for stroke prevention in AF patients [[15,16]]. Therefore, we performed a systematic review and meta-analysis by including observational cohort studies, aiming to (1) investigate the incidence of stroke and bleeding outcomes in edoxaban users, and (2) evaluate the effectiveness and safety outcomes of edoxaban compared with VKAs or other NOACs among AF patients.

2. Methods

This systematic review and meta-analysis were carried out according to the Cochrane Handbook for Systematic Reviews of Interventions. The results were presented based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement. This study was prospectively registered in **PROSPERO (CRD42022314222)**. It was not necessary to provide ethical approval, because only published studies we have involved.

2.1. Data sources and searches

We performed systematical research on the PubMed, EMBASE, and Cochrane Library databases until November 2022 for studies exploring the effectiveness and safety outcomes of edoxaban in AF patients. The following search terms were used: (1) “atrial fibrillation” OR “atrial flutter”, and (2) “edoxaban” (Supplementary Table 1).

2.2. Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) observational cohort studies that involved edoxaban treatment in non-valvular AF patients, and (2) studies reporting at least one of the effectiveness or safety outcomes during treatment with edoxaban in AF patients. The effectiveness outcomes included SSE, ischemic stroke, myocardial infarction, and all-cause death, whereas the safety outcomes included major bleeding, intracranial hemorrhage, and gastrointestinal bleeding. We excluded studies restricted to AF patients with certain interventions (e.g. ablation, heart valve replacement) or specific diseases (e.g. diabetes mellitus, severe renal impairment). Studies with less than 100 patients were excluded.

2.3. Study selection and data extraction

Data extraction was conducted by two independent investigators. We first screened the titles and abstracts to select potential studies, and the full text was screened in the subsequent phase. Disagreements were resolved through discussion with a third investigator. If two or more studies use the same database, we would include the study with the longest follow-up or the largest sample size. The extracted data mainly included the study characteristics (first author and publication year), baseline characteristics (geographical characteristic, data source, study design, inclusion period, patient age and sex, sample size and the number of events in each group, follow-up time), and effectiveness and safety outcomes.

Table 1
Baseline characteristics of the included studies.

Included studies	Location	Data source and study type	Dose of Edoxaban	Sample size(n)	Age (years)	Female (%)	Renal function (CrCl; ml/min)	CHA2DS2-VASc	HAS-BLEED	Included for analyzing EDO vs VKAs	Included for analyzing EDO vs other NOACs
Cerdá et al., 2019	Spain	The University Hospital Vall d'Hebron from Barcelona (Spain),01/2015–09/2017, prospective	EDO EDO60 EDO30	103 83 20	78.7 78.0 81.8	46.6 51.8 25	62.3 ± 18.0 65.1 ± 18.5 51.2 ± 22.3	4.2 ± 1.5 3.9 ± 1.5 4.3 ± 1.5	NA	No	No
Russo et al., 2019	Italy	Atrial Fibrillation Research Database shared by 6 Italian cardiologic centers, prospective	EDO60	130	80.5	45.0	NA	3.8 ± 1.1	2.9 ± 1.0	No	No
Kohsaka et al., 2020	Japan	MDV, 03/2011–07/2018, retrospective	EDO	12262	76.3	43.5	NA	3.8 ± 1.9	NA	Yes; INR 1.6 ± 0.7	No
Nielsen et al., 2021	Denmark	Danish nationwide registries database, 07/2016–11/2018, retrospective	EDO EDO60 EDO30	2285 1642 643	75.1 73.0 80.5	43.4 38.2 56.6	66.7 ± 18.0* 72.0 ± 14.2* 53.8 ± 19.9*	3.5 ± 1.7 3.2 ± 1.7 4.2 ± 1.7	2.4 ± 1.1 2.3 ± 1.1 2.6 ± 1.2	No	No
Köhler et al., 2022	Germany	DRESDEN NOAC registry prospective 01/01/2016–31/08/2021	EDO EDO60 EDO30	1258 955 303	74.7 72.9 80.3	42.5 38.1 56.4	NA	3.7 ± 1.6 3.4 ± 1.6 4.5 ± 1.5	1.7 ± 0.8 1.6 ± 0.8 1.8 ± 0.9	No	No
Caterinaet al. 2021	Europe, Japan, Korea, Taiwan	ETNA-AF Program	EDO	26823	75	41.8	68.7 ± 28.34	3.2 ± 1.5	2.4 ± 1.1	No	No
Kirchhof et al., 2022	Europe	ETNA-AF-Europe	EDO EDO 60 EDO 30	13133 10036 3097	73.6 71.8 79.5	43.3 39.4 55.9	74.3 ± 30.4 82.1 ± 29.1 50.4 ± 19.7	3.2 ± 1.4 3.0 ± 1.4 3.9 ± 1.3	2.5 ± 1.1 2.4 ± 1.1 2.9 ± 1.1	No	No
Yamashita et al., 2021	Japan	ETNA-AF Program	EDO EDO60 EDO30	11111 2750 6645	74.2 67.4 77.4	40.6 12.3 56.8	63.9 ± 25.8 86.4 ± 25.2 52.5 ± 18.9	3.5 ± 1.6 2.7 ± 1.5 3.9 ± 1.6	2.0 ± 1.0 1.7 ± 1.0 2.1 ± 0.9	No	No
Choi et al., 2021	Korea, Taiwan	ETNA-AF Program	EDO EDO60 EDO30	2677 1304 1373	72.2 NA NA	40.3 NA NA	60.6 [47.1–76.9]	3.1 ± 1.4	2.2 ± 1.0	No	No
Lee et al., 2018	Korea	Korean National Health Insurance Service database, 01/2014–12/2016, retrospective	EDO	4200	70.8	45.9	NA	3.24 ± 1.62	NA	Yes; INR not reported	No
Chan et al., 2019	Taiwan	Taiwan's National Health Insurance Research Database, 06/2012–12/2017, retrospective	EDO	4577	74.7	42.8	NA	3.6 ± 1.6	2.6 ± 1.1	Yes; INR not reported	No
Crocetti et al., 2021	Italy	the Milan Health Protection Agency, 01/01/2017–31/12/2019, retrospective	EDO	1725	78.7	54.6	NA	4.5 ± 1.6	NA	Yes; INR not reported	No

(*continued on next page*)

Table 1 (*continued*)

Included studies	Location	Data source and study type	Dose of Edoxaban	Sample size(n)	Age (years)	Female (%)	Renal function (CrCl; ml/min)	CHA2DS2-VASc	HAS-BLEED	Included for analyzing EDO vs VKAs	Included for analyzing EDO vs other NOACs
Nielsen et al., 2021	Denmark	Danish nationwide registries database, 06/2016–11/2018, retrospective	EDO60	1772	72.2	38.6	75.5 ± 14.5*	3.0 [2.0–4.0]	2.0 [1.0–3.0]	No	No
			EDO30	537	82.8	64.6	53.3 ± 18.9*	4.0 [3.0–5.0]	2.0 [2.0–3.0]		
Lee et al., 2019	Korea	Korean Health Insurance Review and Assessment database, 01/2015–12/2017, retrospective	EDO	15496	71.1	44.5	NA	3.58 ± 1.38	2.61 ± 1.01	Yes; INR not reported	Yes
Enomoto et al., 2021	Japan	JMDC database,03/2011–06/2017, retrospective	EDO	382	58.0	15.4	NA	NA	NA	No	Yes
Marston et al., 2021	Germany	DADB, 01/2013–12/2017, retrospective	EDO	1236	72.3	40.0	NA	4.02 ± 1.86	2.34 ± 1.05	YES; INR not reported	YES
Lau et al., 2022	France, Germany, the United Kingdom,the United States	Five standardized electronic health care databases, 01/01/2010–31/12/2017, retrospective	EDO	12722	NA	NA	NA	NA	NA	No	Yes

AF = atrial fibrillation; VKAs = vitamin K antagonists; NOACs = non-vitamin K oral anticoagulants; EDO = edoxaban; EDO30mg = edoxaban 30 mg once daily; EDO60mg = edoxaban 60 mg once daily; NA = not available; INR=International Normalized Ratio.

*Estimated glomerular filtration rate (mL/min/1.73 m^2).

2.4. Quality assessment

The Newcastle-Ottawa Scale (NOS) item was used to assess the quality score of observational studies. The NOS tool included 3 domains with a total of 9 points: the selection of cohorts (0–4 points), the comparability of cohorts (0–2 points), and the assessment of the outcomes (0–3 points). An NOS of ≤6 points indicates a low quality [[17,18]].

2.5. Statistical analysis

First, the percentages with 95 % confidence intervals (CIs) were used to express the incidence rates of effectiveness and safety events in patients with AF. Events reported by the individual studies were pooled under the random-effects models. Second, the risk ratios (RRs) and 95 % CIs (adjusted, propensity score matching, or inverse probability of treatment weighting) were used to assess the effectiveness and safety outcomes of edoxaban compared with VKAs or other NOACs in AF patients. The RRs were converted to the natural logarithms and standard errors and pooled by a random effects model using an inverse variance method. For each outcome, we only performed the pooled analysis if the number of included studies was more than 2. We did not perform a multiple treatment meta-analysis due to the variability between the included observational studies, such as the different baseline characteristics between groups. The publication bias was assessed using the funnel plot.

All the analyses were performed using the Review Manager version 5.4 software (the Cochrane Collaboration 2014, Nordic Cochrane Centre Copenhagen, Denmark), and the MetaXL program (version 3.5, www.epigear.com). $P < 0.05$ was taken as statistically significant.

3. Results

3.1. Study selection

The flowchart of the literature retrieval is presented in Supplementary Fig. 1. A total of 5108 studies were initially identified through electronic searches in the databases of PubMed, Embase, and Cochrane Library. There were 3172 studies after duplication removal. And then, 3145 studies were excluded in the process of the title and abstract screenings. After the full-text screenings (n = 27), 9 studies were excluded because (1) one study did not report outcomes of edoxaban; (2) four studies included AF patients with certain interventions or specific diseases (3) one study with a sample size less than 100; and (4) three studies used overlapping databases. Among the remaining 18 studies, we further excluded the pivotal trial by Giugliano et al. [[9]]. Finally, 17 observational studies [[16,19–34]] were included in our meta-analysis.

The baseline characteristics of the included studies are shown in Table 1. Although some studies extracted data from the same database, they included different outcomes for analysis. For instance, the data from two studies by Lee et al. [[27,31]] were both obtained from the Korean National Health Insurance Service database, but the outcomes they reported were different (ischemic stroke,

Table 2
Incidence rates of effectiveness and safety events in patients with atrial fibrillation.

Subgroup	Number of studies	Total	Events	Event rates (95%CI)
Edoxaban				
stroke or systemic embolism	7	53,689	856	1.7 % (1.3–2.1 %)
ischemic stroke	8	74,449	783	1.1 % (0.9–1.4 %)
myocardial infarction	3	25,165	125	0.3 % (0.0–0.8 %)
intracranial hemorrhage	8	84,886	279	0.3 % (0.3–0.4 %)
major bleeding	12	88,521	1153	1.6 % (1.2–2.0 %)
gastrointestinal bleeding	4	39,922	513	1.1 % (0.4–2.1 %)
all-cause death	7	71,440	2476	3.7 % (1.8–6.1 %)
Edoxaban 60 mg				
stroke or systemic embolism	3	13,734	200	1.9 % (1.0–3.1 %)
ischemic stroke	5	15,808	160	1.1 % (0.7–1.6 %)
myocardial infarction	3	14,083	76	0.3 % (0.0–0.8 %)
intracranial hemorrhage	5	15,938	58	0.3 % (0.1–0.5 %)
major bleeding	8	16,980	297	1.7 % (0.8–2.8 %)
gastrointestinal bleeding	2	4522	29	0.6 % (0.0–1.6 %)
all-cause death	5	17,540	596	2.0 % (0.4–4.4 %)
Edoxaban 30 mg				
stroke or systemic embolism	3	10,012	223	2.2 % (1.7–2.7 %)
ischemic stroke	5	11,745	182	1.5 % (1.0–2.0 %)
myocardial infarction	3	11,082	49	0.4 % (0.0–1.1 %)
intracranial hemorrhage	5	11,639	67	0.6 % (0.5–0.7 %)
major bleeding	7	12,160	260	2.4 % (1.5–3.4 %)
gastrointestinal bleeding	2	7182	70	1.2 % (0.4–2.3 %)
all-cause death	5	14,033	855	5.8 % (1.2–13.0 %)

intracranial hemorrhage, gastrointestinal bleeding, and major bleeding in one of the studies [[31]], whereas all-cause death in another study [[27]]). The methodological quality of the observational studies was assessed with the NOS tool (Supplementary Table 2). All the observational studies scored 7 or above, indicating relatively high quality.

3.2. Incidence of effectiveness and safety events in edoxaban users

As shown in Table 2, in AF patients treated with edoxaban, the incidence rate was 1.7 % (95 % CI 1.3–2.1 %) for SSE, 1.1 % (95 % CI 0.9–1.4 %) for ischemic stroke, 0.3 % (95 % CI 0–0.8 %) for myocardial infarction, 3.7 % (95 % CI 1.8–6.1 %) for all-cause death, 1.6 % (95 % CI 1.2–2.0 %) for major bleeding, 0.3 % (95 % CI 0.3–0.4 %) for intracranial hemorrhage, and 1.1 % (95 % CI 0.4–2.1 %) for gastrointestinal bleeding. We further divided the population into two subgroups based on the edoxaban dose (60 mg and 30 mg). Incidence rates of effectiveness and safety outcomes in these two subgroups are shown in Table 2.

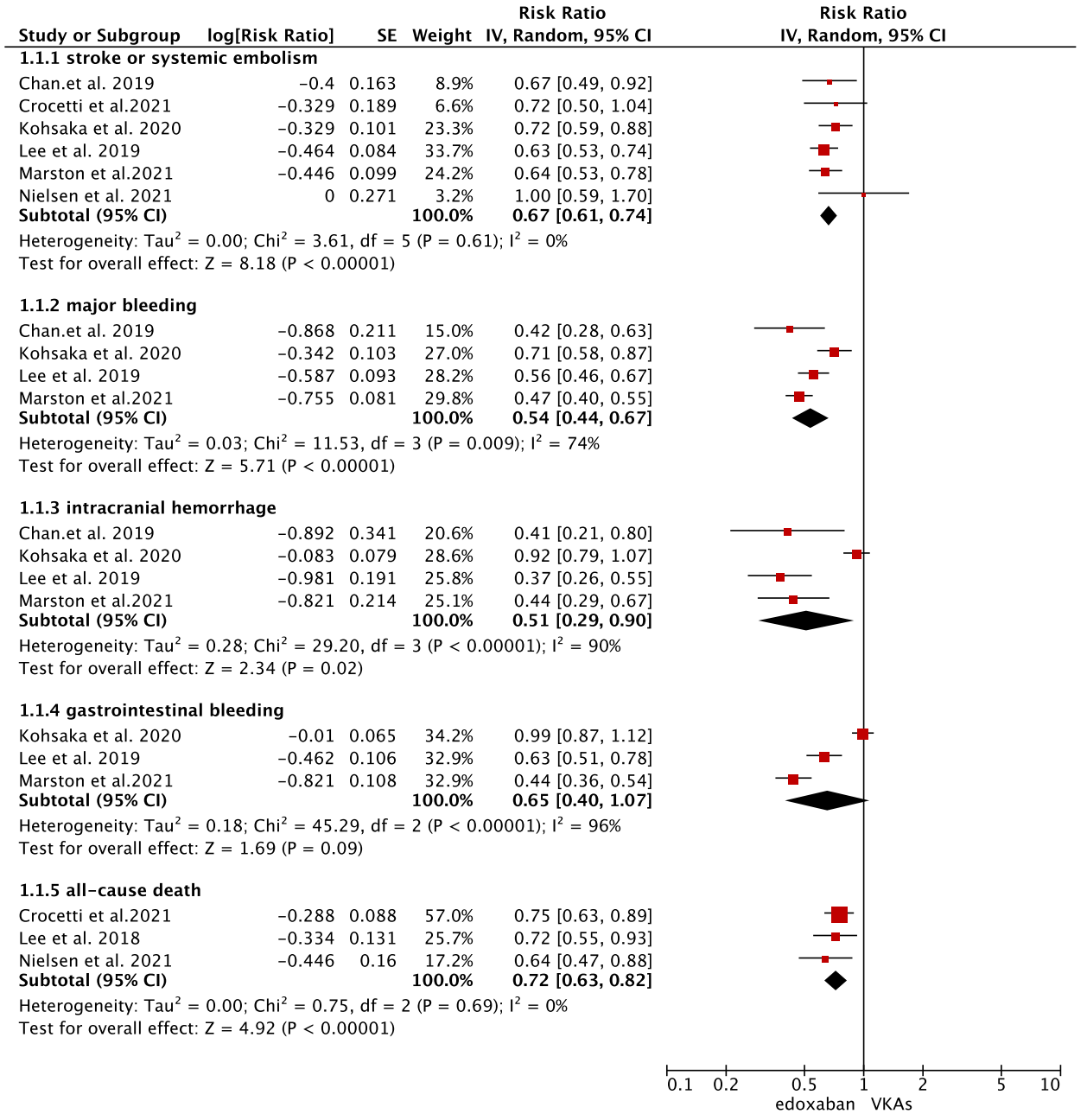


Fig. 1. Effectiveness and safety data of edoxaban compared with vitamin K antagonists in atrial fibrillation patients.

3.3. Effectiveness and safety outcomes between edoxaban and VKAs

As shown in Fig. 1, compared with VKAs, edoxaban was associated with reduced risks of SSE (RR = 0.67, 95 % CI:0.61–0.74; P < 0.00001), all cause-death (RR = 0.72, 95 % CI:0.63–0.82; P < 0.00001), major bleeding (RR = 0.54, 95 % CI:0.44–0.67; P < 0.00001), and intracranial hemorrhage (RR = 0.51, 95 % CI:0.29–0.90; P = 0.02). However, there was a comparable rate of gastrointestinal bleeding (RR = 0.65, 95 % CI:0.40–1.07; P = 0.09) between edoxaban and VKAs.

3.4. Effectiveness and safety outcomes between edoxaban and dabigatran

As shown in Fig. 2, compared with dabigatran use, the use of edoxaban was associated with reduced risks of SSE (RR = 0.76, 95 % CI:0.66–0.87; P < 0.0001) and major bleeding (RR = 0.82, 95 % CI:0.69–0.98; P = 0.02), but they had similar risks of intracranial hemorrhage (RR = 0.83, 95 % CI:0.60–1.15; P = 0.26) and gastrointestinal bleeding (RR = 0.86, 95 % CI:0.65–1.15; P = 0.31).

3.5. Effectiveness and safety outcomes between edoxaban and apixaban

Compared with apixaban, edoxaban was associated with a reduced risk of SSE (RR = 0.87, 95 % CI:0.79–0.97; P = 0.009) (Fig. 3). However, there were no differences in incidence rates of major bleeding (RR = 1.03, 95 % CI:0.90–1.17; P = 0.69), intracranial hemorrhage (RR = 0.91, 95 % CI:0.54–1.54; P = 0.73), and gastrointestinal bleeding (RR = 1.17, 95 % CI:1.00–1.37; P = 0.05) between edoxaban and apixaban in AF patients.

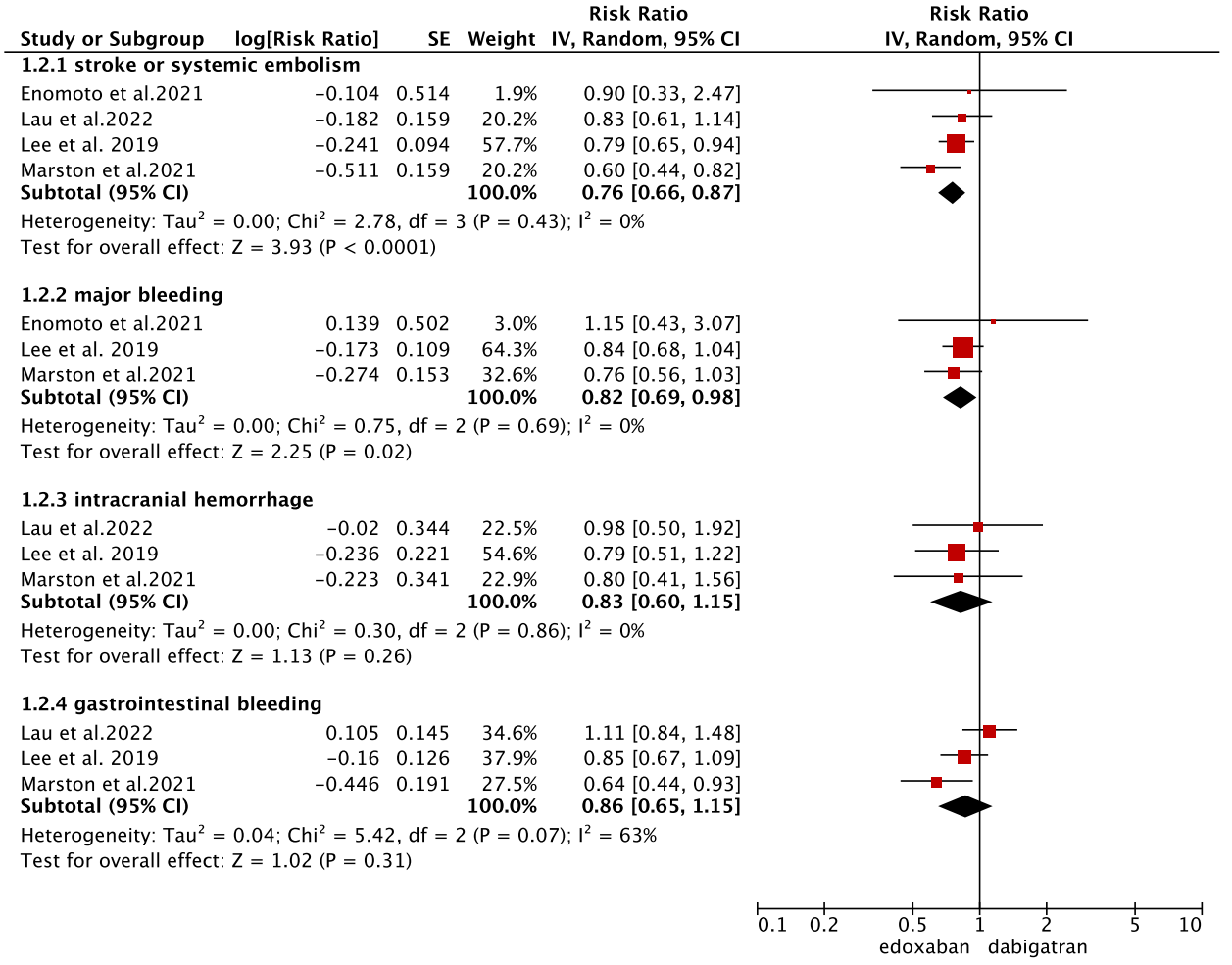


Fig. 2. Effectiveness and safety data of edoxaban compared with dabigatran in atrial fibrillation patients.

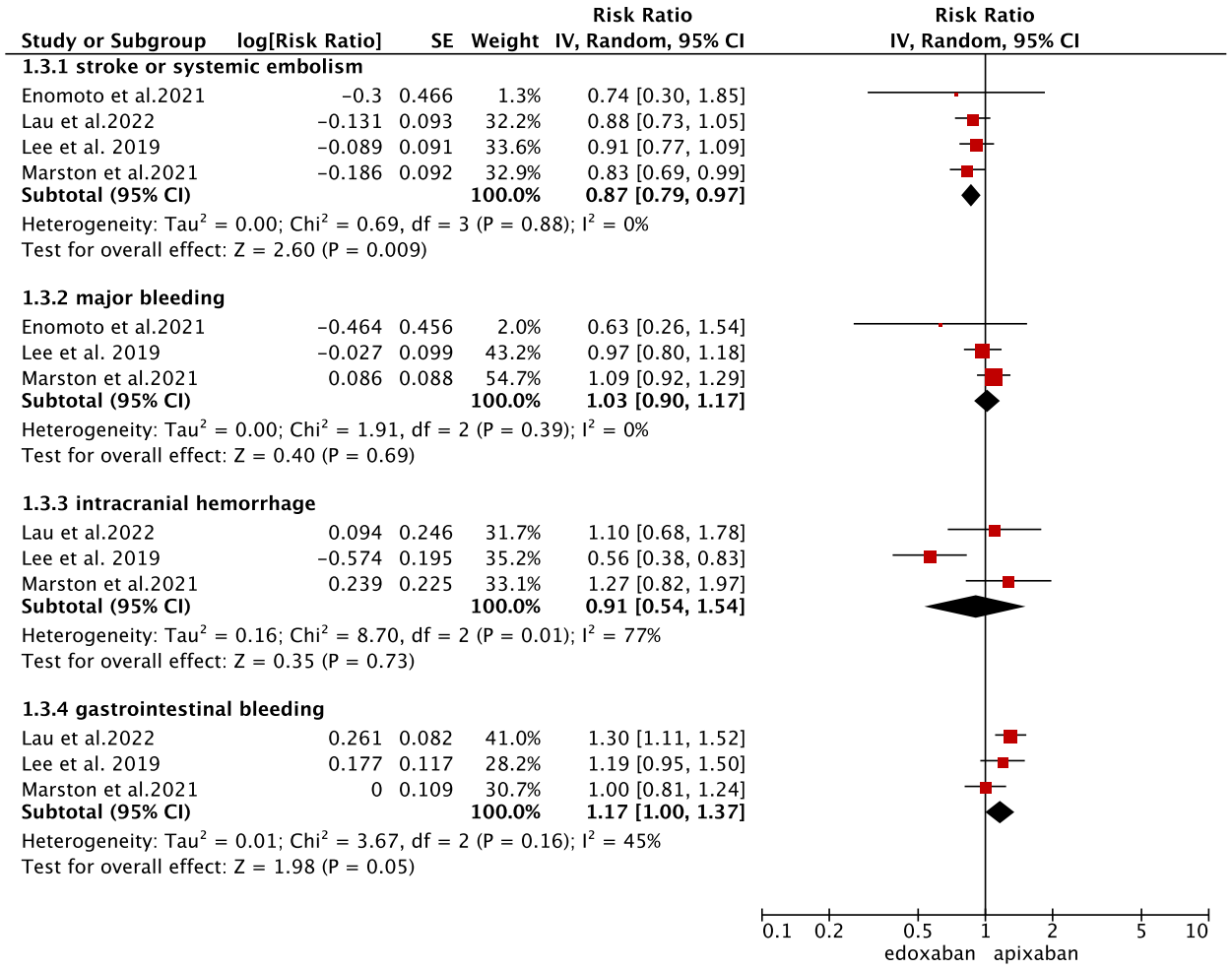


Fig. 3. Effectiveness and safety data of edoxaban compared with apixaban in atrial fibrillation patients.

3.6. Effectiveness and safety outcomes between edoxaban and rivaroxaban

As presented in Fig. 4, compared with rivaroxaban use, the use of edoxaban was associated with reduced risks of SSE (RR = 0.81, 95 % CI:0.70–0.94; P = 0.005) and major bleeding (RR = 0.73, 95 % CI:0.65–0.82; P < 0.000001). However, they had similar risks of intracranial hemorrhage (RR = 0.78, 95 % CI:0.50–1.21; P = 0.27) and gastrointestinal bleeding (RR = 0.81, 95 % CI:0.60–1.09; P = 0.16).

3.7. Publication bias

For the observational studies, the publication bias was assessed by the funnel plots (Supplementary Figs. 2–5). Of note, the results of the publication bias should be treated with caution since the number of included studies for each outcome was less than 10.

4. Discussion

In our current meta-analysis, the main findings were as follows: (1) compared with VKAs, edoxaban was associated with lower risks of SSE, all-cause death, major bleeding, and intracranial hemorrhage; (2) compared with dabigatran or rivaroxaban, edoxaban was correlated with reduced risks of SSE and major bleeding; and (3) compared with apixaban, edoxaban was associated with a reduced risk of SSE, but they had similar risks of bleeding events. Overall, edoxaban had superior effectiveness and/or safety outcomes than VKAs or other NOACs (dabigatran, rivaroxaban, and apixaban), demonstrating that edoxaban might be the preferred option for anticoagulation in AF patients.

Edoxaban is an oral, direct inhibitor of factor Xa. It is rapidly absorbed, and absolute oral bioavailability was almost 62 % [[35]]. The anticoagulant effect of edoxaban begins rapidly after drug ingestion, with plasma concentrations peaking 1 or 2 h after oral

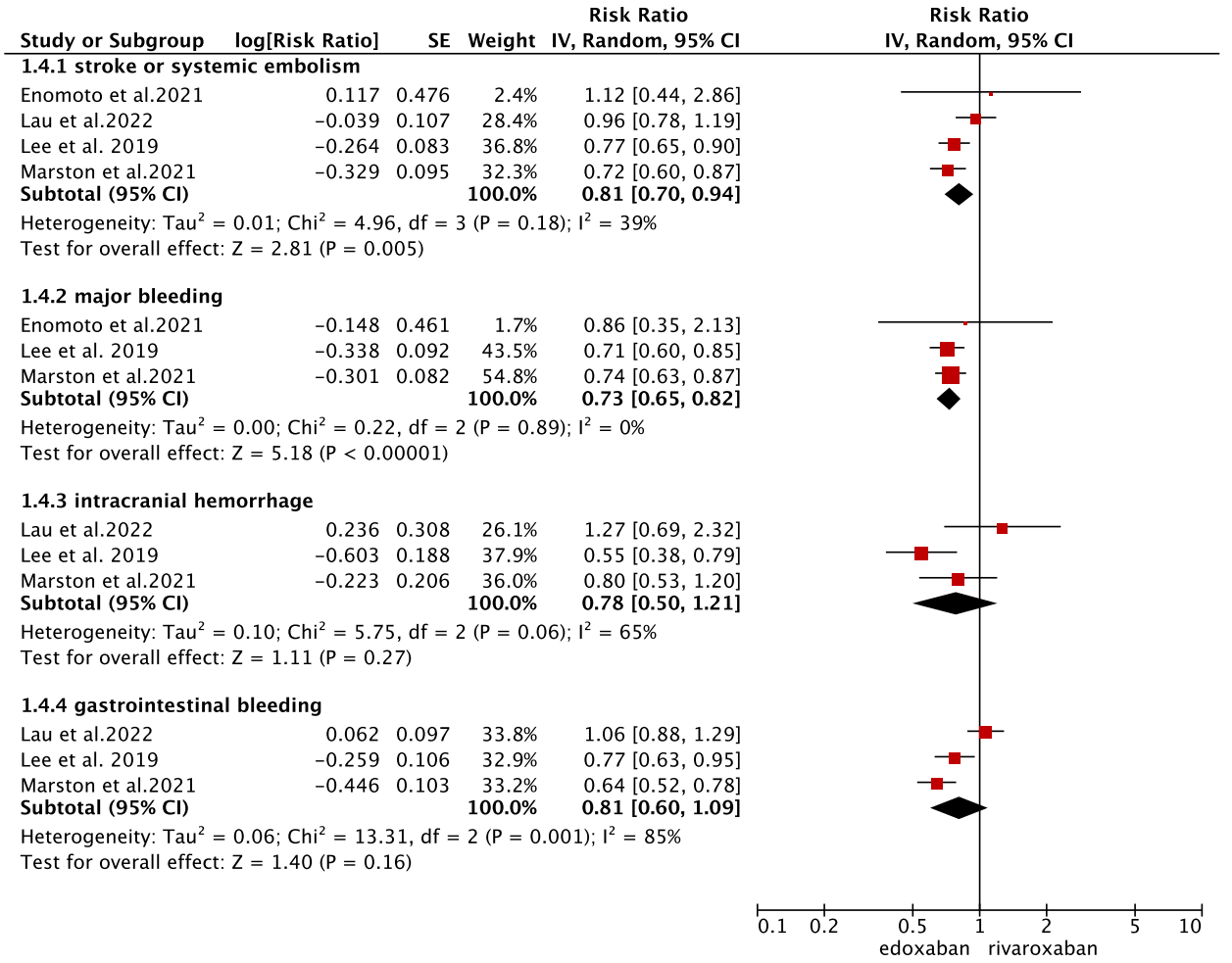


Fig. 4. Effectiveness and safety data of edoxaban compared with rivaroxaban in atrial fibrillation patients.

administration [[36]]. Compared with VKAs, edoxaban has more advantages (e.g., wide therapeutic window, few drug-drug interactions, lack of interactions with food). The pivotal ENGAGE AF-TIMI 48 trial by Giugliano et al. [[9]] has demonstrated that edoxaban was non-inferior to warfarin in preventing stroke risk, and had a significantly lower risk of major bleeding. After that, the high-dose edoxaban (60/30 mg) was approved for stroke prevention in patients with AF. In addition, several observational studies [[21,28,31]] suggested that compared with the VKA-treated population, the allocation of edoxaban was significantly associated with decreased risks of SSE and major bleeding in AF patients. In real-world settings, edoxaban 30 mg is recommended in AF patients who have at least 1 dose reduction criteria: renal impairment (CrCl 30–50 ml/min), body weight ≤60 kg, or concomitant use of a potent phosphorylated glycoprotein inhibitor.

Chen et al. demonstrated that compared with VKAs, edoxaban was associated with reduced risks of major or clinically relevant nonmajor bleeding events, any bleeding events, and intracranial bleeding events via performing a meta-analysis of phase III RCTs [[14]]. However, in this meta-analysis, the targeted population was those with AF, venous thromboembolism, or pulmonary embolism [[14]]. Another meta-analysis by Liang et al. found that edoxaban could significantly reduce the incidence rates of cardiovascular death and major or non-major bleeding [[37]]. However, the unbalanced sample size and substantial heterogeneity across the included studies were the major limitations of Liang et al., which might affect the findings [[38]]. Our current meta-analysis first included observational studies and found that compared with VKAs, edoxaban was associated with reduced risks of SSE, all-cause death major bleeding, and intracranial hemorrhage in patients with AF. For AF patients, Gencer et al. [[39]] systemically analyzed the effectiveness and safety outcomes of edoxaban versus VKAs in the high-risk subgroups. The primary outcome for this analysis was a net clinical outcome, namely a composite of SSE, major bleeding, or death. Compared with VKAs, higher-dose edoxaban regimen (HDER) and lower-dose edoxaban regimen (LDER) were associated with a significant reduction of a net clinical outcome in 7 and 8 of the 12 high-risk subgroups, respectively [[39]]. In addition, the occurrence of a net clinical outcome with LDER was less than HDER, but Gencer et al. [[39]] did not further analyze this difference. Steffel et al. [[40]] compared the net clinical outcome of LDER versus HDER of the ENGAGE AF TIMI-48 trial, and also found that the occurrence of net clinical outcome was less frequent with LDER. It was

probably because HDER reduced the occurrence of SSE, but the occurrence of disabling/fatal non-hemorrhagic stroke was not different between HDER and LDER, and LDER significantly reduced the occurrence of major bleeding.

In current guidelines, NOACs were recommended as the first-line medication to prevent stroke in AF patients. However, which NOAC is the best remains unknown. Focusing on comparing the effectiveness and safety outcomes among different NOAC subtypes, some correlated RCTs were insufficient to provide more powerful evidence. In an indirect analysis performed by Skjøth et al. [[41]], the effectiveness and safety outcomes of edoxaban were compared with other NOACs using multiple RCTs, suggesting that edoxaban 60 mg shared similar risks of SSE with apixaban, rivaroxaban, and dabigatran 110 mg, but compared with dabigatran 150 mg, edoxaban was associated with a higher risk of SSE. From the safety perspective, compared with edoxaban, apixaban, and dabigatran had a comparable risk of major bleeding, but rivaroxaban showed an increased risk of major bleeding. In our current meta-analysis by including observational studies, compared with dabigatran or rivaroxaban, edoxaban had reduced risks of SSE and major bleeding, and compared with apixaban, edoxaban had a reduced risk of SSE but shared similar bleeding risks. Our findings were not entirely consistent with those of Skjøth et al. [[41]], which might be due to the differences in the patient populations and study designs.

The Global ETNA-AF program is the largest prospective non-interventional program to evaluate the effect of edoxaban in routine clinical practice for AF patients. The study elaborated that AF patients treated with edoxaban had a low incidence of stroke, intracranial hemorrhage, and other major bleeding events. De Caterina et al. [[42]] applied the propensity-score matching method to adjust key baseline characteristics, and compared the effectiveness and safety of edoxaban between clinical practice and RCTs. They found consistent effectiveness findings with the ENGAGE AF-TIMI 48 trial, but a lower rate of bleeding events in the ETNA observational study. Moreover, by comparing the results of 2nd follow-up period with 1st follow-up period, the event rates of ischemic stroke and major bleeding were lower in the 2nd year. Although there was a slight increase in all-cause deaths in the 2nd year, this difference was not statistically significant [[43]]. To our knowledge, renal function is a criterion influencing the dose selection of NOACs. There is insufficient evidence to prove that the use of NOACs reduces renal function. At least 89.9 % of patients treated with edoxaban did not experience worsening renal function during the 2 years of follow-up from the ETNA-AF-Europe study. Furthermore, intracranial hemorrhage rates are low in patients with and without worsening renal function [[44]].

Although RCTs and observational studies have demonstrated that edoxaban has similar effectiveness and a better safety profile than VKAs, the data from previous studies were insufficient, and our current study made the evidence more credible. In addition, our present study was the first meta-analysis to compare the effectiveness and safety of edoxaban with other NOACs. Most of the published studies on edoxaban have focused on its comparison with VKAs. The use of NOACs is now increasingly common in patients with AF, and physicians' choice of drugs should be based on more clinical evidence. Since the direct comparisons of efficacy and safety between NOAC and NOAC in RCT are lacking, real-world studies may serve as a complementary resource to provide reliable evidence for edoxaban in clinical decisions.

5. Limitations

There were some limitations in this meta-analysis. First, because the most included studies were observational studies and several confounding factors might exist, we could only evaluate the associations rather than causal relationships. For example, concomitant medication inherently influenced the risk-benefit balance of anticoagulation, and this set of data was typically poorly presented in observational studies [45]. The results of our study should be interpreted cautiously due to the limited powerful evidence. Second, due to insufficient data, we did not perform the subgroup analysis based on baseline patient characteristics such as AF type and NOAC dose. Third, we did not include observational studies which only focused on the specific populations with AF in this meta-analysis (e.g. diabetes mellitus or severe renal impairment). Further research is needed to confirm the findings of this study and to explore potential differences in specific patient populations such as acute coronary syndrome [46]. Finally, although we compared the effectiveness and safety outcomes of edoxaban with VKAs or other NOACs, some outcomes could not be assessed due to insufficient data. In addition, the international normalized ratio (INR) or the time in the therapeutic range (TTR) for warfarin users was not considered due to the limited data, which might affect the pooled results between edoxaban and VKAs.

6. Conclusions

Our current evidence of this meta-analysis suggested that edoxaban had superior effectiveness and/or safety outcomes than VKAs, dabigatran, rivaroxaban, and apixaban for stroke prevention in patients with AF. Further high-quality studies could confirm our findings.

Funding sources

This study was funded by the Guangdong Natural Science Foundation (2023A1515012798) .

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Bailin Zhang: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **Winglam Cheng:** Conceptualization, Data curation, Formal analysis, Resources, Software, Writing – original draft. **Wulamiding Kaisaier:** Data curation, Formal analysis, Resources, Software, Visualization. **Zhenbang Gu:** Data curation, Formal analysis, Methodology, Software, Visualization. **Wengen Zhu:** Conceptualization, Data curation, Project administration, Supervision, Validation, Writing – review & editing. **Qiuhua Jiang:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e21740.

References

[1] G.Y. Lip, D.A. Lane, Stroke prevention in atrial fibrillation: a systematic review, JAMA 313 (19) (May 19 2015) 1950–1962.
[2] R.B. Schnabel, X. Yin, P. Gona, et al., 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study, Lancet 386 (9989) (Jul 11 2015) 154–162.
[3] R.G. Hart, L.A. Pearce, M.I. Aguilar, Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation, Ann Intern Med. Jun 19 146 (12) (2007) 857–867.
[4] M. Bradley, E.C. Welch, E. Eworuke, D.J. Graham, R. Zhang, T.Y. Huang, Risk of stroke and bleeding in atrial fibrillation treated with apixaban compared with warfarin, J Gen Intern Med. Dec 35 (12) (2020) 3597–3604.
[5] G. Hindricks, T. Potpara, N. Dagres, et al., 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC, Eur Heart J. Feb 1 42 (5) (2021) 373–498.
[6] S.J. Connolly, M.D. Ezekowitz, S. Yusuf, et al., Dabigatran versus warfarin in patients with atrial fibrillation, N. Engl. J. Med. 361 (12) (Sep 17 2009) 1139–1151.
[7] M.R. Patel, K.W. Mahaffey, J. Garg, et al., Rivaroxaban versus warfarin in nonvalvular atrial fibrillation, N Engl J Med. Sep 8 365 (10) (2011) 883–891.
[8] C.B. Granger, J.H. Alexander, J.J. McMurray, et al., Apixaban versus warfarin in patients with atrial fibrillation, N Engl J Med. Sep 15 365 (11) (2011) 981–992.
[9] R.P. Giugliano, C.T. Ruff, E. Braunwald, et al., Edoxaban versus warfarin in patients with atrial fibrillation, N Engl J Med. Nov 28 369 (22) (2013) 2093–2104.
[10] F. Liu, Y. Yang, W. Cheng, J. Ma, W. Zhu, Reappraisal of non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients: a systematic review and meta-analysis, Front Cardiovasc Med 8 (2021), 757188.
[11] W. Zhu, Z. Ye, S. Chen, et al., Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients, Stroke. Apr 52 (4) (2021) 1225–1233.
[12] A. Corsini, N. Ferri, M. Proietti, G. Boriani, Edoxaban and the issue of drug-drug interactions: from pharmacology to clinical practice, Drugs. Jul 80 (11) (2020) 1065–1083.
[13] A.J. Camm, H. Bounameaux, Edoxaban: a new oral direct factor xa inhibitor, Drugs 71 (12) (Aug 20 2011) 1503–1526.
[14] H.B. Chen, J. Xiu, Y.H. Li, T.H. Yu, The risk of bleeding and all-cause mortality with edoxaban versus vitamin K antagonists: a meta-analysis of phase III randomized controlled trials, Thromb. Res. 194 (Oct 2020) 82–90.
[15] R. De Caterina, G. Agnelli, P. Laeis, et al., The global Edoxaban Treatment in routine cliNical prActice (ETNA) noninterventional study program: rationale and design, Clin Cardiol. Dec 42 (12) (2019) 1147–1154.
[16] R. De Caterina, Y.H. Kim, Y. Koretsune, et al., Safety and effectiveness of edoxaban in atrial fibrillation patients in routine clinical practice: one-year follow-up from the global noninterventional ETNA-AF program, J Clin Med. Feb 3 10 (4) (2021).
[17] W. Zhu, R. Wan, F. Liu, et al., Relation of body mass index with adverse outcomes among patients with atrial fibrillation: a meta-analysis and systematic review, J Am Heart Assoc. Sep 9 5 (9) (2016).
[18] Y. Zhou, J. Ma, W. Zhu, Efficacy and safety of direct oral anticoagulants versus warfarin in patients with atrial fibrillation across BMI categories: a systematic review and meta-analysis, Am J Cardiovasc Drug 20 (2020) 51–60.
[19] M. Cerdá, J.J. Cerezo-Manchado, E. Johansson, et al., Facing real-life with direct oral anticoagulants in patients with nonvalvular atrial fibrillation: outcomes from the first observational and prospective study in a Spanish population, J Comp Eff Res. Feb 8 (3) (2019) 165–178.
[20] V. Russo, E. Attena, C. Mazzone, et al., Real-life performance of edoxaban in elderly patients with atrial fibrillation: a multicenter propensity score-matched cohort study, Clin Ther. Aug 41 (8) (2019) 1598–1604.
[21] S. Kohsaka, J. Katada, K. Saito, et al., Safety and effectiveness of non-vitamin K oral anticoagulants versus warfarin in real-world patients with non-valvular atrial fibrillation: a retrospective analysis of contemporary Japanese administrative claims data, Open Heart 7 (1) (2020), e001232.
[22] P.B. Nielsen, T.B. Larsen, F. Skjøth, M. Søgaard, G.Y.H. Lip, Effectiveness and safety of edoxaban in patients with atrial fibrillation: data from the Danish Nationwide Cohort, Eur Heart J Cardiovasc Pharmacother. Jan 7 (1) (2021) 31–39.
[23] C. Köhler, L. Tittl, S. Marten, et al., Effectiveness and safety of edoxaban therapy in daily-care patients with atrial fibrillation. Results from the DRESDEN NOAC REGISTRY, Thromb Res. Jul 215 (2022) 37–40.
[24] P. Kirchhof, L. Pecen, A. Bakhai, et al., Edoxaban for stroke prevention in atrial fibrillation and age-adjusted predictors of clinical outcomes in routine clinical care, Eur Heart J Cardiovasc Pharmacother (Dec 15 (2022) 47–57.
[25] T. Yamashita, Y. Koretsune, T. Nagao, K. Shiosakai, Safety and effectiveness of edoxaban in Japanese patients with nonvalvular atrial fibrillation: final report of a two-year postmarketing surveillance study (ETNA-AF-Japan), J Arrhythm. Apr 37 (2) (2021) 370–383.
[26] E.K. Choi, W.S. Lin, G.S. Hwang, et al., Clinical events with edoxaban in south Korean and Taiwanese atrial fibrillation patients in routine clinical practice, J Clin Med. Nov 16 (22) (2021) 10.
[27] S.R. Lee, E.K. Choi, K.D. Han, J.H. Jung, S. Oh, G.Y.H. Lip, Edoxaban in asian patients with atrial fibrillation: effectiveness and safety, J. Am. Coll. Cardiol. 72 (8) (Aug 21 2018) 838–853.

[28] Y.H. Chan, H.F. Lee, L.C. See, et al., Effectiveness and safety of four direct oral anticoagulants in asian patients with nonvalvular atrial fibrillation, Chest. Sep 156 (3) (2019) 529–543.
[29] E. Crocetti, S. Cattaneo, W. Bergamaschi, S. De Servi, A.G. Russo, Effectiveness and safety of non-vitamin K oral anticoagulants in non-valvular atrial fibrillation patients: results of A real-world study in a metropolitan area of northern Italy, J. Clin. Med. 10 (19) (2021) 4536.
[30] P.B. Nielsen, M. Søgaard, M. Jensen, A.G. Ording, G.Y. Lip, Comparative effectiveness and safety of edoxaban versus warfarin in patients with atrial fibrillation: a nationwide cohort study, Int. J. Stroke (Jul 13 2021), 17474930211029441.
[31] S.R. Lee, E.K. Choi, S. Kwon, et al., Effectiveness and safety of contemporary oral anticoagulants among asians with nonvalvular atrial fibrillation, Stroke. Aug 50 (8) (2019) 2245–2249.
[32] A. Enomoto, Y. Mano, Y. Kawano, et al., Comparison of the safety and effectiveness of four direct oral anticoagulants in Japanese patients with nonvalvular atrial fibrillation using real-world data, Biol. Pharm. Bull. 44 (9) (2021) 1294–1302.
[33] X.L. Marston, R. Wang, Y.C. Yeh, et al., Comparison of clinical outcomes of edoxaban versus apixaban, dabigatran, rivaroxaban, and vitamin K antagonists in patients with atrial fibrillation in Germany: a real-world cohort study, Int. J. Cardiol. 346 (2022) 93–99.
[34] W.C.Y. Lau, C.O. Torre, K.K.C. Man, et al., Comparative effectiveness and safety between apixaban, dabigatran, edoxaban, and rivaroxaban among patients with atrial fibrillation : a multinational population-based cohort study, Ann Intern Med. Nov 175 (11) (2022) 1515–1524.
[35] N. Matsushima, F. Lee, T. Sato, D. Weiss, J. Mendell, Bioavailability and safety of the factor xa inhibitor edoxaban and the effects of quinidine in healthy subjects, Clin Pharmacol Drug Dev. Oct 2 (4) (2013) 358–366.
[36] C.E. Cervantes, J.L. Merino, V. Barrios, Edoxaban for the prevention of stroke in patients with atrial fibrillation, Expert Rev Cardiovasc Ther. Apr 17 (4) (2019) 319–330.
[37] X. Liang, W. Xie, Z. Lin, M. Liu, The efficacy and safety of edoxaban versus warfarin in preventing clinical events in atrial fibrillation: a systematic review and meta-analysis, Anatol J Cardiol. Feb 25 (2) (2021) 77–88.
[38] L. Drabik, A. Undas, Unsolved issues of the efficacy and safety of edoxaban, Anatol J Cardiol. Jun 25 (6) (2021) 460.
[39] B. Gencer, A. Eisen, D. Berger, et al., Edoxaban versus Warfarin in high-risk patients with atrial fibrillation: a comprehensive analysis of high-risk subgroups, Am Heart J. May 247 (2022) 24–32.
[40] J. Steffel, C.T. Ruff, O. Yin, et al., Randomized, double-blind comparison of half-dose versus full-dose edoxaban in 14,014 patients with atrial fibrillation, J Am Coll Cardiol. Mar 9 77 (9) (2021) 1197–1207.
[41] F. Skjøth, T.B. Larsen, L.H. Rasmussen, G.Y. Lip, Efficacy and safety of edoxaban in comparison with dabigatran, rivaroxaban and apixaban for stroke prevention in atrial fibrillation. An indirect comparison analysis, Thromb Haemost 111 (5) (May 5 2014) 981–988.
[42] R. De Caterina, R. Wang, L. Shi, et al., Effectiveness and safety of edoxaban in atrial fibrillation patients from the ETNA-AF global registry, Eur. Heart J. 42 (Issue Supplement_1) (October 2021), https://doi.org/10.1093/eurheartj/ehab724.0556 ehab724.0556.
[43] L. Dinshaw, C. Chen, R. De Caterina, et al., Temporal trend of clinical events in patients with atrial fibrillation on edoxaban therapy: results from the non-interventional global ETNA-AF program, Eur. Heart J. 42 (Issue Supplement_1) (October 2021), https://doi.org/10.1093/eurheartj/ehab724.2979 ehab724.2979.
[44] M. Gwechenberger, G. Baron-Esquivias, T.A.C. De Vries, et al., Low rate of worsening renal function after 2 years of treatment with edoxaban in patients from the ETNA-AF-Europe study, Eur. Heart J. 42 (Issue Supplement_1) (October 2021), https://doi.org/10.1093/eurheartj/ehab724.2924 ehab724.2924.
[45] László Szapáry, Dániel Tornyos, Péter Kupó, et al., Combination of antiplatelet and anticoagulant therapy, component network meta-analysis of randomized controlled trials, Front Cardiovasc Med 9 (2022 Dec 8), 1036609.
[46] Asim A. Elnour, András Komócsi, Péter Kupó, et al., The role of direct oral anticoagulant in patients with acute coronary syndrome on single or dual antiplatelet regime: review of opportunities and challenges, Curr Rev Clin Exp Pharmacol 16 (1) (2021) 52–63.