ORIGINAL RESEARCH ARTICLE

Safety and Effectiveness of Direct Oral Anticoagulants Versus Warfarin in Patients with Venous Thromboembolism using Real-World Data: A Systematic Review and Meta-Analysis

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Abstract

Background Direct oral anticoagulants (DOACs) have shown comparable efficacy and a superior safety profile in clinical trials for patients with venous thromboembolism (VTE). However, further study is needed to assess DOACs' effectiveness and safety compared to warfarin in a real-world context. Thus, this meta-analysis compares the effectiveness and safety of warfarin and DOACs in patients with VTE.

Method A systematic review of the literature using PubMed and EMBASE was conducted from inception until June 2024. We examined observational studies that compared safety and effectiveness between DOACs and warfarin when used in treating VTE and reported adjusted hazard ratios (HRs) and/or odds ratios (ORs) for recurrent VTE, major bleeding, clinically relevant non-major bleeding, gastrointestinal bleeding, intracranial hemorrhage, and death from any cause. We then estimated the pooled effect using the random-effects model for meta-analysis.

Results A total of 25 studies were included in the current meta-analysis. DOAC therapy was associated with significantly lower risks of recurrent VTE (HR 0.76, 95% confidence interval [CI] 0.69–0.85), major bleeding (HR 0.77, 95% CI 0.72–0.83), clinically relevant non-major bleeding (HR 0.82, 95% CI 0.77–0.88), and gastrointestinal bleeding (HR 0.75, 95% CI 0.68–0.83) compared to warfarin. However, no statistically significant difference was observed in all-cause mortality between the two groups (HR 0.96, 95% CI 0.83–1.10).

Conclusion This meta-analysis found that DOACs are associated with a significant reduction in VTE recurrence in addition to the known favorable safety profile when compared to warfarin.

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Graphical Abstract

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PEER-REVIEWED FEATURE

Safety and Effectiveness of Direct Oral Anticoagulants Versus Warfarin in Patients with Venous Thromboembolism: A Systematic Review and Meta-Analysis

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25 Studies ▸▸▸ 680695 patients were included in the comparative analysis ▸▸▸ DOACs (Rivaroxaban, dabigatran, apixaban and edoxaban) 277548 | Warfarin 403147

The Newcastle-Ottawa Scale score was 8–9

23% reduction in the risk of major bleeding

24% reduction in the risk of recurrent VTE events

18% and 25% reduction in clinically relevant non-major bleeding and gastrointestinal bleeding, respectively

Warfarin — DOACs

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Conclusion: This meta-analysis found that DOACs are associated with a significant reduction in VTE recurrence in addition to the known favorable safety profile when compared to warfarin.

DOACs direct oral anticoagulants, *VTE* venous thromboembolism

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This graphical abstract represents the opinions of the authors. For a full list of declarations, including funding and author disclosure statements, and copyright information, please see the full text online.

Key Points

This was a systematic review and meta-analysis synthesizing 25 observational studies, including 681,022 participants, and investigating the efficacy and safety of direct oral anticoagulants (DOACs) versus warfarin.

DOACs were superior to warfarin in preventing venous thromboembolism recurrence.

DOACs were associated with better safety outcomes such as major bleeding, clinically relevant non-major bleeding, and gastrointestinal bleeding.

1 Introduction

Venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism (PE), is a well-known cause of disability and mortality, with a global incidence exceeding 10 million cases annually [1]. Accordingly, it is the third most common cardiovascular disease after acute myocardial infarction and stroke and is associated with enormous short- and long-term morbidities [2]. In addition to the current high prevalence of VTE, it is expected to exceed 1.8 million cases in the United States (US) alone by 2050 [3]. About two-thirds of reported VTE cases are diagnosed as DVT episodes that often develop in the deep leg veins. Others present with PE when clots travel through the heart to the pulmonary arteries [4]. Besides its effects on the population's health, VTE imposes serious negative economic impacts [5]. In terms of treatment, VTE events have been successfully managed for decades using anticoagulants (ACs) to suppress the synthesis or function of various clotting factors [6].

Anticoagulation, the cornerstone of VTE treatment, is recommended for a duration of at least 3 months in most patients with DVT and/or PE [9]. The goal of AC therapy is to avoid fatal PE, prevent recurrence, and lower the risk of long-term problems, such as post-thrombotic syndrome, long-term exertional dyspnea, or chronic thromboembolic pulmonary hypertension. Guidelines recommend the use of AC over three phases: an initial phase (first week from diagnosis), a long-term phase (the following 3–6 months), and an extended phase, where anticoagulation therapy, in some circumstances, must be extended indefinitely for patients who exhibit a high risk of thrombosis and a low risk of bleeding [7–10].

For many years, warfarin has served as the unchallenged AC option for the management of patients with acute VTE events in the long-term phase [6]. However, the necessity for parenteral AC in the initial treatment phase, the need for frequent monitoring and dose adjustment, and the existence of many drug–drug and drug–food interactions are major drawbacks to using warfarin in practice [11]. In light of those limitations, direct oral ACs (DOACs) are recognized as a good alternative, allowing for fixed-dose administration and less frequent monitoring.

Multiple randomized clinical trials (RCTs) have been conducted to compare DOACs to warfarin in terms of safety and efficacy [12–17]. Each of these reports highlights the superiority of using any DOAC agent compared to warfarin in terms of efficacy. Despite the valuable evidence that RCTs provide, strict inclusion and exclusion criteria constrain their utility. In contrast, real-world data (RWD) offer a supplementary source of evidence, capturing the complexities and diversity present in real-world settings, including individuals who may not meet the criteria or be subject to the controlled conditions imposed in RCTs. Accordingly, we performed this systematic review and meta-analysis to bridge the gap by assessing the actual effectiveness and safety of DOACs compared to warfarin using data from real-world practice settings.
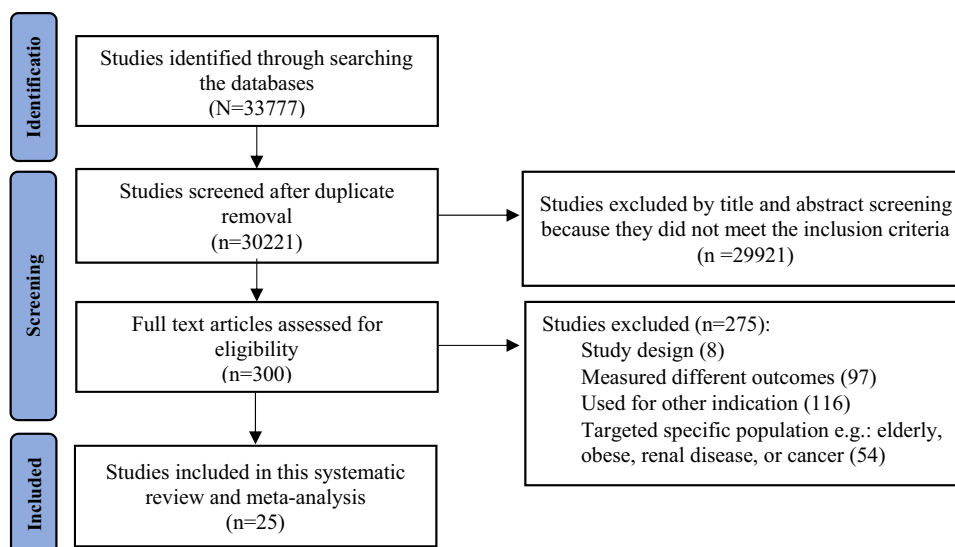
2 Methods

2.1 Search Strategy and Databases

A systematic literature search was conducted using PubMed and EMBASE from inception through June 2024 to identify observational studies that compared the outcomes of using DOACs versus warfarin in patients with acute VTE. The literature search was limited to peer-reviewed articles published in English. The search terms included venous thromboembolism, VTE, deep venous thromboembolism, DVT, pulmonary embolism, PE, rivaroxaban, edoxaban, apixaban, dabigatran, DOACs, vitamin K antagonists, VKA, and warfarin.

2.2 Study Selection, Data Extraction, and Quality Assessment

Studies were included if they were observational (i.e., non-randomized), evaluated DOACs and warfarin for acute VTE management, reported VTE recurrence, and/or noted bleeding-related outcomes. Case reports, economic evaluations, RCTs, and other study designs not reporting analyses of RWD were excluded. Studies were also excluded if their participants were restricted to patients who were morbidly obese, had active cancer, and/or had end-stage renal disease, including hemodialysis. In addition, studies that evaluated

Fig. 1 Flow diagram for studies included in the systematic review and meta-analysis

Identification

Studies identified through searching the databases
(N=33777)

Screening

Studies screened after duplicate removal
(n=30221)

Studies excluded by title and abstract screening because they did not meet the inclusion criteria
(n =29921)

Full text articles assessed for eligibility
(n=300)

Studies excluded (n=275):
    Study design (8)
    Measured different outcomes (97)
    Used for other indication (116)
    Targeted specific population e.g.: elderly, obese, renal disease, or cancer (54)

Included

Studies included in this systematic review and meta-analysis
(n=25)

both atrial fibrillation and VTE patients were excluded if they did not report the VTE patients' outcomes separately.

Initially, four researchers (WAA, SAA, SMA, and AMA) independently screened the studies under consideration for eligibility based on titles and abstracts. The Rayyan software was used to combine the search results and remove duplicates [18]. All identified studies were assessed for final inclusion based on a full-text review by two other senior authors (MSA and ARA), and any disagreements were resolved by consensus among these two senior authors. Four investigators (WAA, SAA, SMA, and AMA) extracted the following data from the included studies into an Excel sheet: the primary author's last name, year of publication, number of centers, patients' baseline characteristics, study arms, study period, key inclusion and exclusion criteria, and the reported effectiveness and safety outcomes with their related definitions. Two additional investigators (RSA and MAA) checked and validated the extracted data.

2.3 Data Synthesis and Analysis

The effectiveness outcome of the analysis estimated the risk of VTE recurrence among the DOACs group relative to the use of warfarin via the hazard ratio (HR) or odds ratio (OR) with a corresponding 95% confidence interval (CI). The safety outcomes included major bleeding, clinically relevant non-major bleeding, intracranial hemorrhage, gastrointestinal bleeding, and all-cause mortality. The meta-analysis was performed with a random-effects model using Comprehensive Meta-Analysis (CMA) software version 3. Forest plots were used to summarize the results, including the heterogeneity I^2 statistics using the restricted maxim likelihood method (REML) [19]. We also ran a sensitivity analysis by eliminating one study at a time to examine the effect on the pooled analysis and heterogeneity score when a

substantial degree of heterogeneity was detected ($I^2 > 75\%$). Publication bias was assessed via Egger's test. Lastly, this meta-analysis was prepared in accordance with the preferred reporting system for meta-analysis of observational studies (MOOSE) [20].

2.4 Quality Assessment and Publication Bias

The Newcastle–Ottawa Scale (NOS), which consists of eight criteria encompassing three domains—selection, comparability, and outcome—is a useful tool for assessing the quality of nonrandomized studies. The NOS scale has a maximum of nine stars, with low-quality studies receiving one to three stars, average-level studies receiving four to six stars, and high-quality studies receiving seven to nine stars [21]. Two of the team's investigators (WAA and SMA) independently applied the NOS scale to rate the quality of the included studies independently, and any disagreements were resolved by consensus among these two authors.

3 Results

3.1 Study Selection and Baseline Characteristics

A total of 33,777 publications were initially identified from the PubMed ($n = 10,351$) and EMBASE ($n = 23,426$) databases. After removing 3556 duplicates, the remaining 30,221 articles were subjected to title and abstract screening. Among the latter, 300 were selected for full-text review, and 275 studies were excluded at this stage for various reasons. Ultimately, the selection process yielded 25 studies to be included in the current meta-analysis [22–46]. Figure 1 presents the flowchart for the literature retrieval process. The sample sizes for the included studies ranged between 107

Table 1 Characteristics of studies included in the meta-analysis

Study Primary author	Year/country	Design	Number of patients	Age (years), mean ± SD		Male sex, n (%)		Type of DOACs	Follow-up	Main effectiveness outcome	Main safety outcome
				DOACs (Mean ± SD or median (IQR))	Warfarin	DOACs	Warfarin				
Basto [22]	2018/US	Retrospective cohort study	107	63.6 ± 12.4	61.1 ± 13.9	40 (95.2)	59 (90.8)	APX, RIV, & DAB	1 and 3 months	Time to discharge, and ED visit or readmission	Major bleeding, CRNM bleeding, and Minor bleeding
Coleman [23]	2017/US	Retrospective cohort study	**45,851**	Age ≥ 60 (43.2%)	Age ≥ 60 (42.5%)	(51.2)	(50.8)	RIV	12 months	Recurrent VTE	Major bleeding, GI bleeding, and Intracranial bleeding
Jun [24]	2017/Canada	Retrospective cohort study	59,525	62.8 ± 13.8	64.7 ± 13.3	5822 (46.6)	21,805 (46.4)	APX, RIV, & DAB	3 months	None	Major bleeding All-cause mortality
Sindet-Pedersen [25]	2017/Denmark	Retrospective cohort study	12,318	60 (52–76)	(53–76) 60	2921 (54.0)	3746 (54.2)	RIV	3 and 6 months	Recurrent VTE	Major bleeding, GI bleeding, and Intracranial bleeding
Larsen [26]	2017/Denmark	Retrospective cohort study	**4679**	62.6 ± 17.4	62.6 ± 17.0	958 (55)	1770 (55)	RIV	3 and 6 months	Recurrent VTE	Major bleeding, GI bleeding, and Intracranial bleeding All-cause mortality
Badreldin [27]	2018/US	Retrospective cohort study	441	62.2 ± 17.6	61.6 ± 15.1	156 (59.8)	94 (52.2)	APX, RIV, DAB, & EDX	3 and 6 months	Recurrent VTE	Major bleeding, GI bleeding, and Intracranial bleeding
Roetker [28]	2018/US	Retrospective cohort study	62,431	APX: 64.0 ± 16 RIV: 59.0 ± 16	65 ± 16	APX (47.7) RIV (50.7)	(48.4)	APX & RIV	3 and 6 months	None	All-cause mortality

Table 1 (continued)

Study Primary author	Year/country	Design	Number of patients	Age (years), mean ± SD		Male sex, n (%)		Type of DOACs	Follow-up	Main effectiveness outcome	Main safety outcome
				DOACs Mean ± SD or median (IQR)	Warfarin	DOACs	Warfarin				
Weycker [29]	2018/US	Retrospective cohort study	35,756	60.0 ± 16.0	60.0 ± 16.0	9282 (51.9)	9279 (51.9)	APX	~ 5 months	Recurrent VTE	Major bleeding (including GI and intracranial bleeding), and CRNM bleeding
Al Khateep [30]	2019/Egypt	Prospective cohort study	200	NR	NR	NR	NR	RIV	6 months	Recurrent VTE Major opposed cardiovascular events	Major bleeding and CRNM bleeding All-cause mortality
Kohn [43]	2019/US	Retrospective cohort study	36,853	Age ≥ 60 (43.5%)	Age ≥ 60 (41.7%)	(53.9)	(51.6)	RIV	12 months	Recurrent VTE	Major bleeding, GI bleeding, and Intracranial bleeding
Costa [31]	2020/US	Retrospective cohort study	4939	50 (39–62)*	51 (40, 64)*	(43.6)	(43.6)	RIV	3, 6, and 12 months	Recurrent VTE	Major bleeding, Intracranial bleeding GI bleeding and genitourinary bleeding
Dawwas [32]	2020/US	Retrospective cohort study	36,907	58.9 ± 16.3	59.3 ± 15.8	3911 (48.3)	13,814 (47.9)	APX	1 month	Recurrent VTE	Major bleeding and minor bleeding
Guo [41]	2020/US	Retrospective cohort study	25,193	52.7 ± 12.7	52.4 ± 13.1	6554 (50.6)	7214 (53.8)	APX	6 months	Recurrent VTE	Major bleeding (including GI and intracranial bleeding), and CRNM bleeding All-cause hospitalization

Table 1 (continued)

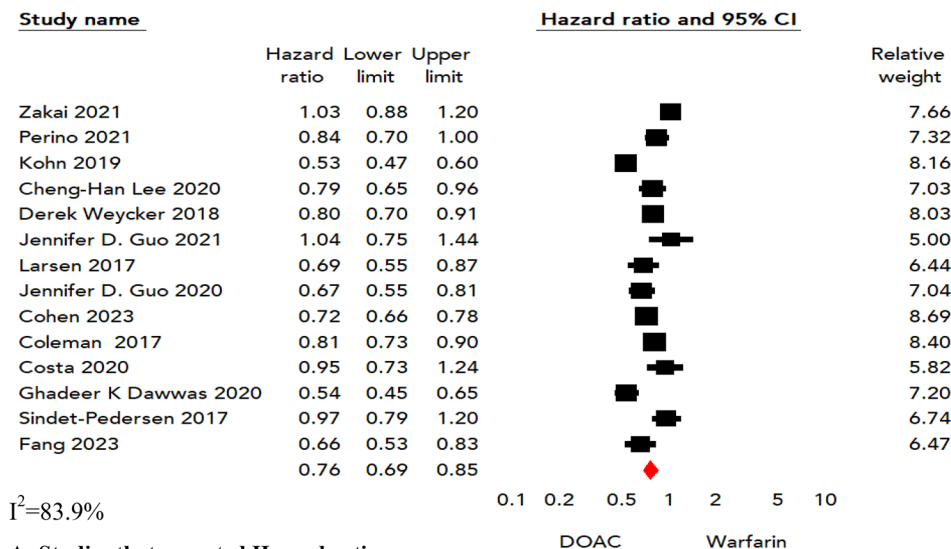| Study Primary author	Year/country	Design	Number of patients	Age (years), mean ± SD DOACs Mean ± SD or median (IQR)	Warfarin	Male sex, n (%) DOACs	Warfarin	Type of DOACs	Follow-up	Main effectiveness outcome	Main safety outcome
Huang [33]	2020/China	Retrospective cohort study	128	58.08 ± 14.5	52.5 ± 14.8	41 (47.6)	20 (47.6)	RIV	1, 3, and 6 months	Absorption of thrombus	Major bleeding, severe bleeding, and mild bleeding
Lee [34]	2020/Taiwan	Retrospective cohort study	7294	68.78 ± 16.03	68.19 ± 16.10	1576 (43.2)	1633 (44.8)	APX, RIV, & EDX	~ 16 months	Recurrent VTE	Major bleeding including intracranial bleeding, and major GI bleeding; All-cause mortality
Guo [42]	2021/US	Retrospective cohort study	37,799	77.7 ± 8.1	77.5 ± 8.1	4726 (37.8)	9192 (36.4)	APX	6 months	Recurrent VTE	Major bleeding (including GI and intracranial bleeding) CRNM bleeding
Naqvi [35]	2021/Pakistan	Retrospective cohort study	161	60.02 ± 10.5	55.50 ± 14.7	27 (50)	13 (43.3)	RIV	NR	Length of stay in hospital	Major bleeding and minor bleeding
Zakai [36]	2021/US	Retrospective cohort study	25,419	APX: 60.1 ± 14.4 RIV: 58.8 ± 13.9	61.5 ± 15.2	APX: 1926 (52) RIV: 3000 (52.9)	2606 (51.3)	APX & RIV	6 months	Recurrent VTE	None
Perino [37]	2021/US	Retrospective cohort study	51,871	64.5 ± 13.1		48,758 (94.0)		APX, RIV, DAB, & EDX	6 months	Recurrent VTE	Major bleeding and CRNM bleeding
Pham [38]	2022/US	Retrospective cohort study	6509	56.6 ± 17.2	57.9 ± 17.6	(51)	(49)	APX & RIV	6 months	Proximal DVT, PE, MI, and stroke	Major bleeding; All-cause mortality
Cohen [39]	2023/US	Retrospective cohort study	155,119	NR	NR	27,410 (45.09)	42,590 (45.15)	APX	6 months	Recurrent VTE	Major bleeding, and CRNM bleeding

Table 1 (continued)

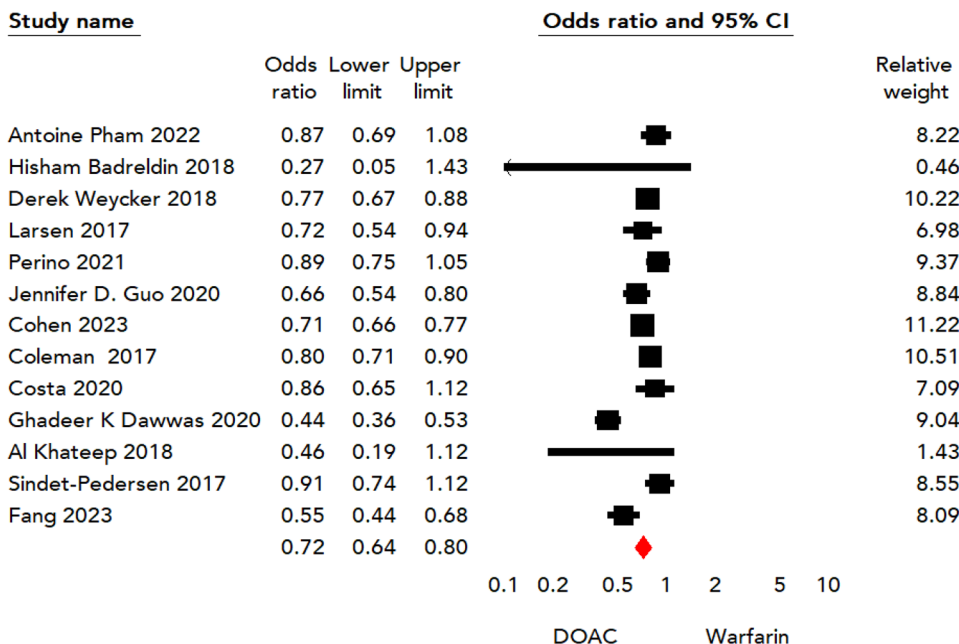| Study Primary author	Year/country	Design	Number of patients	Age (years), mean ± SD		Male sex, n (%)		Type of DOACs	Follow-up	Main effectiveness outcome	Main safety outcome
				DOACs — Mean ± SD or median (IQR)	Warfarin	DOACs	Warfarin				
Ingason [40]	2023/Iceland	Retrospective cohort study	7081	APX: 72.7 ± 13.2, RIV: 68.7 ± 13.0, DAB: 70.1± 13.6	66.8 ± 16.8	APX: 1119 (53.3), RIV: 1844 (59.4), DAB: 270 (57.0)	746 (53.2)	APX, RIV, & DAB	APX: ~ 13 months, RIV: ~ 19 months, DAB: ~ 20 months, Warfarin: ~ 18 months	None	GI bleeding
Ramos-Isaza [44]	2023/Colombia	Retrospective cohort study	505	RIV: 60 ± 18.59	61.6 ±19.82	116 (55.5)	126 (60.3)	RIV	12 months	Survival at 6 and 12 months	Major bleeding and new episode of VTE.
Fang [45]	2023/California	Retrospective cohort study	18,495	≤ 54: 443 (20.8), 55–64: 431 (20.2), 65–74: 619 (29.0), 75–84: 459 (21.5), ≥ 85: 182 (8.5)	≤ 54: 4085 (25.0), 55–64: 3484 (21.3), 65–74: 3956 (24.2), 75–84: 3283 (20.1), ≥ 85: 1553 (9.5)	1152 (54.0)	8370 (51.2)	DAB, RIV, & APX	6 months	Recurrent VTE	Hospitalization for hemorrhage and all-cause death.
Glise Sandbla [46]	2023/Sweden	Retrospective cohort study	45,114	APX: 65.7 (16.4), RIV: 64.5 (16.8), DAB: 65.5 (16.9), EDX: 65.5 (16.9)	67.1 (16.4)	APX: 10,570 (54.2%), RIV: 10,142 (55.7%), DAB: 333 (51.9%), EDX: 106 (48.2%)	3511 (53.5%)	APX, RIV, DAB, & EDX	6 months	Major bleeding	GI bleeding, and Intracranial bleeding

APX apixaban, *CRNM* clinically relevant non-major, *DAB* dabigatran, *DOAC* direct oral anticoagulant, *DVT* deep vein thrombosis, *EDX* edoxaban, *GI* gastrointestinal, *MI* myocardial infarction, *NR* not reported, *PE* pulmonary embolism, *RIV* rivaroxaban, *US* United States, *VTE* venous thromboembolism, *IQR* interquartile range, *SD* Standard deviation

* Reported as median (25,75% range)

Fig. 2 Comparison of the risk of recurrent VTE for patients on DOACs compared to patients on warfarin using random-effects model. **A** Studies that reported hazard ratios ($I^2 = 83.9\%$). **B** Studies that reported number of events per arm ($I^2 = 78.48\%$). *CI* confidence interval, *DOAC* direct oral anticoagulant

Study name	Hazard ratio	Lower limit	Upper limit	Hazard ratio and 95% CI	Relative weight
Zakai 2021	1.03	0.88	1.20		7.66
Perino 2021	0.84	0.70	1.00		7.32
Kohn 2019	0.53	0.47	0.60		8.16
Cheng-Han Lee 2020	0.79	0.65	0.96		7.03
Derek Weycker 2018	0.80	0.70	0.91		8.03
Jennifer D. Guo 2021	1.04	0.75	1.44		5.00
Larsen 2017	0.69	0.55	0.87		6.44
Jennifer D. Guo 2020	0.67	0.55	0.81		7.04
Cohen 2023	0.72	0.66	0.78		8.69
Coleman 2017	0.81	0.73	0.90		8.40
Costa 2020	0.95	0.73	1.24		5.82
Ghadeer K Dawwas 2020	0.54	0.45	0.65		7.20
Sindet-Pedersen 2017	0.97	0.79	1.20		6.74
Fang 2023	0.66	0.53	0.83		6.47
	0.76	0.69	0.85		

0.1 0.2 0.5 1 2 5 10
DOAC   Warfarin

$I^2 = 83.9\%$

A- Studies that reported Hazard ratios

Study name	Odds ratio	Lower limit	Upper limit	Odds ratio and 95% CI	Relative weight
Antoine Pham 2022	0.87	0.69	1.08		8.22
Hisham Badreldin 2018	0.27	0.05	1.43		0.46
Derek Weycker 2018	0.77	0.67	0.88		10.22
Larsen 2017	0.72	0.54	0.94		6.98
Perino 2021	0.89	0.75	1.05		9.37
Jennifer D. Guo 2020	0.66	0.54	0.80		8.84
Cohen 2023	0.71	0.66	0.77		11.22
Coleman 2017	0.80	0.71	0.90		10.51
Costa 2020	0.86	0.65	1.12		7.09
Ghadeer K Dawwas 2020	0.44	0.36	0.53		9.04
Al Khateep 2018	0.46	0.19	1.12		1.43
Sindet-Pedersen 2017	0.91	0.74	1.12		8.55
Fang 2023	0.55	0.44	0.68		8.09
	0.72	0.64	0.80		

0.1 0.2 0.5 1 2 5 10
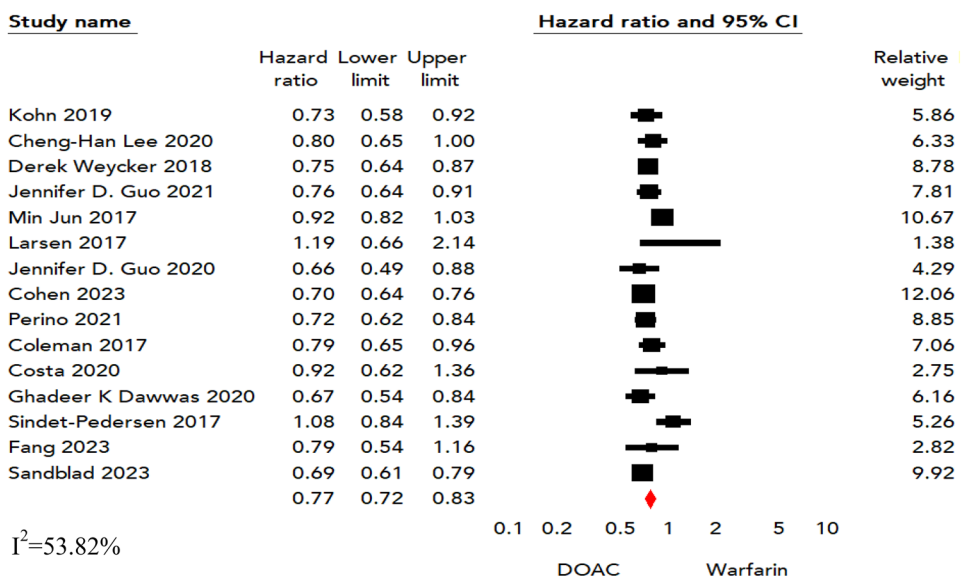DOAC   Warfarin

$I^2 = 78.48\%$

B- Studies that reported number of events per arm

and 155,119 patients, and 680,695 patients were included in the analysis. All included studies were retrospective in nature except for one prospective study. Most of the studies were conducted in the US using data retrieved from hospitals or claims (Table 1). The NOS score for all included studies was eight or nine stars (Figure S1, see the electronic supplementary material); additionally, the results from conducting Egger's test for all outcomes did not suggest a potential for publication bias (Table S1).
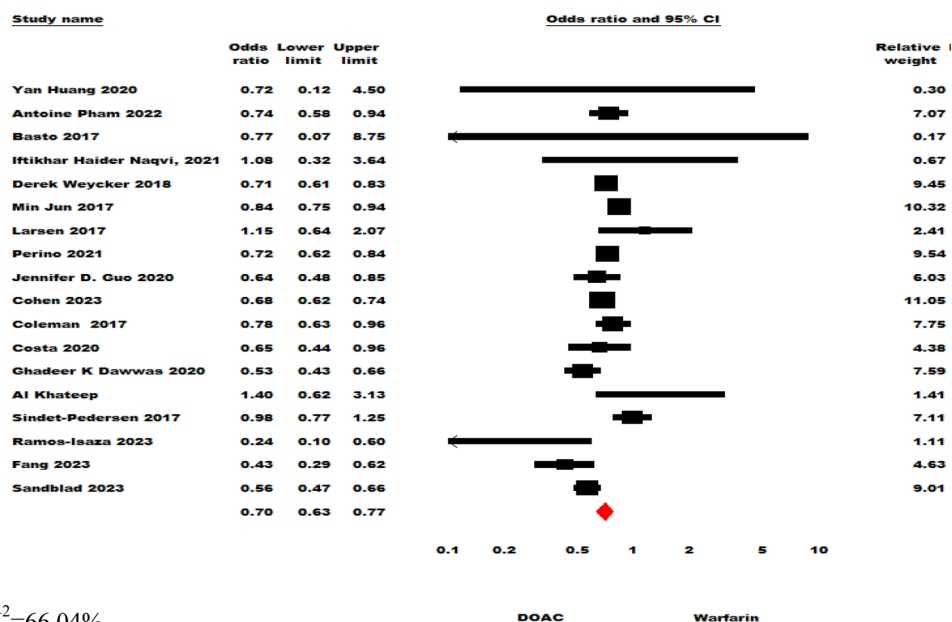
3.2 Effectiveness Outcomes

The use of DOACs for the treatment of acute VTE was associated with a 24% reduction in the risk of recurrent VTE events compared to the use of warfarin (HR 0.76, 95% CI 0.69–0.85), but a significant degree of heterogeneity was observed ($I^2 = 83.9\%$). Likewise, the incidence of recurrent VTE in patients treated with DOACs was lower compared to patients treated with warfarin based on studies that reported the number of events per arm (OR 0.72, 95% CI 0.64–0.80;

Fig. 3 Comparison of the risk of major bleeding for patients on DOACs compared to patients on warfarin using random-effects model. **A** Studies that reported hazard ratios ($I^2 = 53.82\%$) **B** Studies that reported number of events per arm ($I^2 = 66.04\%$). *CI* confidence interval, *DOAC* direct oral anticoagulant

A- Studies that reported Hazard ratios

Study name	Hazard ratio	Lower limit	Upper limit	Relative weight
Kohn 2019	0.73	0.58	0.92	5.86
Cheng-Han Lee 2020	0.80	0.65	1.00	6.33
Derek Weycker 2018	0.75	0.64	0.87	8.78
Jennifer D. Guo 2021	0.76	0.64	0.91	7.81
Min Jun 2017	0.92	0.82	1.03	10.67
Larsen 2017	1.19	0.66	2.14	1.38
Jennifer D. Guo 2020	0.66	0.49	0.88	4.29
Cohen 2023	0.70	0.64	0.76	12.06
Perino 2021	0.72	0.62	0.84	8.85
Coleman 2017	0.79	0.65	0.96	7.06
Costa 2020	0.92	0.62	1.36	2.75
Ghadeer K Dawwas 2020	0.67	0.54	0.84	6.16
Sindet-Pedersen 2017	1.08	0.84	1.39	5.26
Fang 2023	0.79	0.54	1.16	2.82
Sandblad 2023	0.69	0.61	0.79	9.92
	0.77	0.72	0.83	

$I^2 = 53.82\%$

B- Studies that reported number of events per arm

Study name	Odds ratio	Lower limit	Upper limit	Relative weight
Yan Huang 2020	0.72	0.12	4.50	0.30
Antoine Pham 2022	0.74	0.58	0.94	7.07
Basto 2017	0.77	0.07	8.75	0.17
Iftikhar Haider Naqvi, 2021	1.08	0.32	3.64	0.67
Derek Weycker 2018	0.71	0.61	0.83	9.45
Min Jun 2017	0.84	0.75	0.94	10.32
Larsen 2017	1.15	0.64	2.07	2.41
Perino 2021	0.72	0.62	0.84	9.54
Jennifer D. Guo 2020	0.64	0.48	0.85	6.03
Cohen 2023	0.68	0.62	0.74	11.05
Coleman 2017	0.78	0.63	0.96	7.75
Costa 2020	0.65	0.44	0.96	4.38
Ghadeer K Dawwas 2020	0.53	0.43	0.66	7.59
Al Khateep	1.40	0.62	3.13	1.41
Sindet-Pedersen 2017	0.98	0.77	1.25	7.11
Ramos-Isaza 2023	0.24	0.10	0.60	1.11
Fang 2023	0.43	0.29	0.62	4.63
Sandblad 2023	0.56	0.47	0.66	9.01
	0.70	0.63	0.77	

$I^2 = 66.04\%$

$I^2 = 78.48\%$). The forest plots for the effectiveness outcomes are displayed in Fig. 2.

3.3 Safety Outcomes

The use of DOAC agents was significantly associated with a 23% reduction in the risk of major bleeding compared to warfarin (HR 0.77, 95% CI 0.72–0.83); however, as with the risk of recurrent VTE events, high heterogeneity was found ($I^2 = 53.82\%$). Similarly, the risk of major bleeding events in patients treated with DOACs was lower compared to patients treated with warfarin based on studies reporting the number of events per arm (OR 0.70, 95% CI 0.63–0.77;

$I^2 = 66.04\%$). The forest plots for major bleeding are presented in Fig. 3.

Compared to warfarin, DOACs were significantly associated with a lower risk of clinically relevant non-major bleeding (HR 0.82, 95% CI 0.77–0.88; $I^2 = 75.5\%$). This outcome was also observed in studies reporting the number of events per arm (OR 0.82, 95% CI 0.72–0.94; $I^2 = 92.2\%$). Figure 4 presents the forest plots for the clinically relevant non-major bleeding.
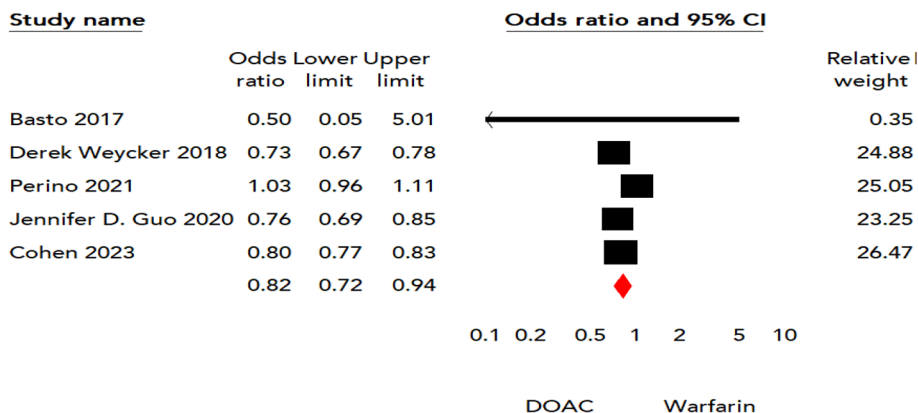
The risk of gastrointestinal bleeding was also lower in the DOACs group compared to the warfarin group (HR 0.75, 95% CI 0.68–0.83) and exhibited no heterogeneity ($I^2 = 0\%$). Similarly, studies reporting the number of events per arm

Fig. 4 Comparison of the risk of clinically relevant non-major bleeding for patients on DOACs compared to patients on warfarin using random-effects model. **A** Studies that reported hazard ratios ($I^2 = 75.48\%$). **B** Studies that reported number of events per arm ($I^2 = 92.19\%$). *CI* confidence interval, *DOAC* direct oral anticoagulant
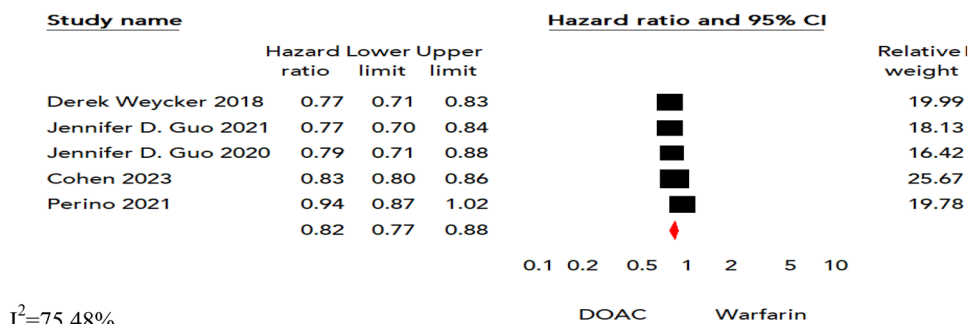
A- Studies that reported Hazard

B- Studies that reported number of events per arm

also demonstrated a lower risk (OR 0.69, 95% CI 0.60–0.81, $I^2 = 18.73\%$). The results for gastrointestinal bleeding can be found in Fig. 5.

The risk of intracranial hemorrhage was significantly lower in the DOACs group compared to the warfarin group (HR 0.69, 95% CI 0.52–0.91; $I^2 = 38.9\%$). However, no significant differences were observed in the incidence of intracranial hemorrhage among studies reporting the number of events per arm (OR 0.69, 95% CI 0.53–0.91; $I^2 = 2.39\%$). For the forest plots for the risk of intracranial hemorrhage, please see Fig. 6.

Four studies reported the HR for all-cause mortality in patients receiving DOACs and warfarin, and no significant difference was found in the risk of all-cause mortality between the two groups (HR 0.96, 95% CI 0.83–1.10). In addition, six studies reported the number of events per arm, with no significant difference in the incidence of all-cause mortality among patients treated with DOACs or warfarin (OR 0.75, 95% CI 0.61–0.94). The forest plots for all-cause mortality are illustrated in Fig. 7.

Among studies reporting HR and OR for the risk of recurrent VTE and clinically relevant non-major bleeding, significant heterogeneity was seen ($I^2 > 75\%$). According to the sensitivity analysis, the pooled estimates did

not differ significantly from the primary analyses (Figures S2–S5). However, eliminating Kohn et al. and Zakai et al. from studies reporting HRs (HR 0.77, 95% CI 0.70–0.84, $I^2 = 67.3\%$; not presented in figures), and eliminating Dawwas et al. from studies reporting ORs (OR 0.76, 95% CI 0.70–0.82, $I^2 = 55.36\%$) for the risk of recurrent VTE reduced the heterogeneity to less than 75%. Similarly, excluding Perino et al. from studies reporting HRs (HR 0.80, 95% CI 0.77–0.84; $I^2 = 37.0\%$) and ORs (OR 0.77, 95% CI 0.72–0.82; $I^2 = 50.7\%$) for the risk of clinically relevant non-major bleeding reduced heterogeneity to less than 75%.

4 Discussion

Warfarin has traditionally been the primary therapeutic agent for managing VTE; however, the limitations associated with its use have highlighted the viability of DOACs as an alternative. According to the results of clinical trials, DOACs have demonstrated comparable efficacy and a superior safety profile to warfarin. Furthermore, real-world studies have uncovered compelling evidence supporting the superiority of DOACs, as demonstrated in

Fig. 5 Comparison of the risk of gastrointestinal bleeding for patients on DOACs compared to patients on warfarin using random-effects model. **A** Studies that reported hazard ratios ($I^2 = 0\%$). **B** Studies that reported number of events per arm ($I^2 = 18.73\%$). *CI* confidence interval, *DOAC* direct oral anticoagulant
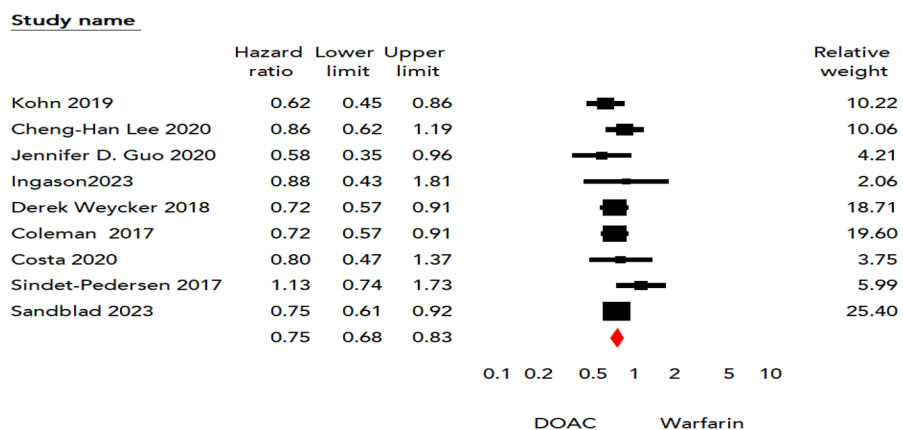
$I^2=0\%$

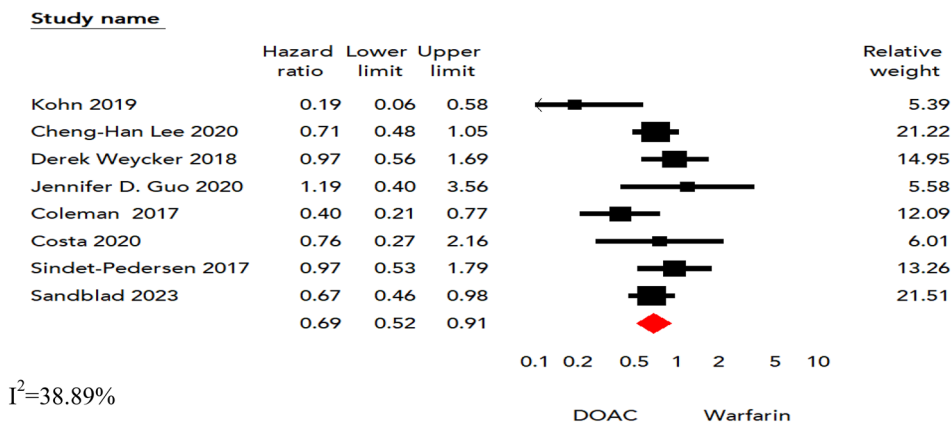**A- Studies that reported Hazard ratios**
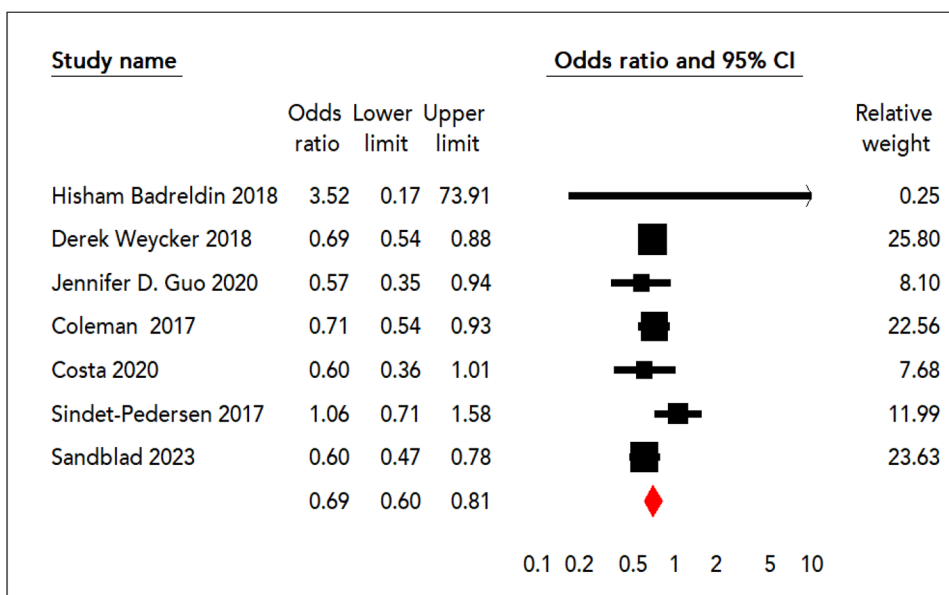
$I^2=18.73\%$

B- Studies that reported number of events per arm

this systematic review and meta-analysis, which aimed to assess the effectiveness and safety of DOACs versus warfarin in real-world practice. In comparison to warfarin, we found the use of DOACs to be significantly associated with a reduced risk of recurrent VTE, major bleeding, clinically relevant non-major bleeding, gastrointestinal bleeding, and intracranial hemorrhage.

Several previous systematic reviews and meta-analyses also examined the effectiveness and safety of DOACs compared to warfarin. A network meta-analysis reported that patients treated with DOACs for acute VTE events experienced similar efficacy and exhibited a better safety profile than patients treated with warfarin [47]. Another

meta-analysis found that DOACs were associated with a decreased risk of bleeding in acute VTE [48]. In contrast with the present study, the previous meta-analyses pooled available data from RCTs only [47, 48]. Additionally, a network meta-analysis from RWD but in patients with non-valvular atrial fibrillation yielded results that aligned with our findings in patients with VTE, potentially providing some indirect evidence for this comparison; in particular, compared to patients using warfarin, the researchers associated patients using DOACs with better effectiveness outcomes (lower risk of stroke and systemic embolism) and a favorable safety profile (lower risk of major bleeding and intracranial bleeding). However, unlike our findings in patients

Fig. 6 Comparison of the risk of intracranial hemorrhage for patients on DOACs compared to patients on warfarin using random-effects model. **A** Studies that reported hazard ratios ($I^2 = 38.89\%$). **B** Studies that reported number of events per arm ($I^2 = 2.39\%$). *CI* confidence interval, *DOAC* direct oral anticoagulant

Study name	Hazard ratio	Lower limit	Upper limit	Relative weight
Kohn 2019	0.19	0.06	0.58	5.39
Cheng-Han Lee 2020	0.71	0.48	1.05	21.22
Derek Weycker 2018	0.97	0.56	1.69	14.95
Jennifer D. Guo 2020	1.19	0.40	3.56	5.58
Coleman 2017	0.40	0.21	0.77	12.09
Costa 2020	0.76	0.27	2.16	6.01
Sindet-Pedersen 2017	0.97	0.53	1.79	13.26
Sandblad 2023	0.67	0.46	0.98	21.51
	0.69	0.52	0.91	

$I^2=38.89\%$

A- Studies that reported Hazard ratios

Study name	Odds ratio	Lower limit	Upper limit	Relative weight
Derek Weycker 2018	0.92	0.53	1.61	22.82
Jennifer D. Guo 2020	1.17	0.39	3.47	6.07
Coleman 2017	0.39	0.17	0.86	11.22
Costa 2020	0.52	0.19	1.46	6.76
Sindet-Pedersen 2017	0.84	0.47	1.49	21.00
Sandblad 2023	0.59	0.37	0.94	32.13
	0.69	0.53	0.91	

$I^2=2.39\%$

B- Studies that reported number of events per arm

with VTE, all-cause mortality was significantly lower in the DOAC group in that study [49].

The most frequently used DOACs in the current meta-analysis were apixaban and rivaroxaban, and findings from RWD support their use in patients with acute VTE. For instance, a large study from Saudi Arabia reported comparable VTE recurrence rates between apixaban and warfarin, but significantly fewer major bleeding events with apixaban [50]. Another analysis of data concerning hospital resource utilization and costs in the US revealed that apixaban treatment was associated with a shorter hospital stay, lower cost, and reduced risk of major bleeding-related readmissions compared to warfarin [51]. These observational studies collectively support our results that apixaban may be a more favorable option than warfarin in the treatment of acute VTE. Furthermore, the reports of a systematic review and meta-analysis comparing apixaban to warfarin support our finding regarding DOACs' favorable safety profile [52]. In addition, a recently published meta-analysis demonstrated that rivaroxaban could significantly reduce the incidence of VTE and major bleeding events compared to warfarin [53].

However, in a direct comparison using RWD, Aryal et al. found that apixaban and rivaroxaban had equivalent effectiveness in terms of preventing recurrent VTE, while apixaban exhibited a lower risk of both major and minor bleeding [54]. Therefore, our findings support the recommendations in the guidelines from the American Society of Hematology (2020) and the American College of Chest Physicians (2021) [9, 10], which suggest using DOACs over warfarin for VTE therapy except for certain groups, such as cancer patients, where more data are still needed.

This meta-analysis yields noteworthy implications and recommendations for clinical practice. Our findings offer valuable insights into the safety and effectiveness profile for DOACs in real-world settings, revealing that DOACs actually demonstrate favorable effectiveness and a better safety profile in light of the lower risk of recurrent VTE and major bleeding events compared to warfarin. However, it is crucial to consider that the risk of bleeding can alternatively be influenced by individual patient characteristics, comorbidities, and concomitant medications. Consequently, clinicians should exercise caution, carefully assess patient-specific

Fig. 7 Comparison of the risk of all-cause mortality for patients on DOACs compared to patients on warfarin using random-effects model. **A** Studies that reported hazard ratios ($I^2 = 59.25\%$). **B** Studies that reported number of events per arm ($I^2 = 77.87\%$). *CI* confidence interval, *DOAC* direct oral anticoagulant

Study name	Hazard ratio	Lower limit	Upper limit		Relative weight
Cheng-Han Lee 2020	0.84	0.77	0.93		36.44
Min Jun 2017	0.99	0.84	1.16		27.68
Larsen 2017	1.23	0.91	1.67		14.10
Fang 2023	0.96	0.78	1.19		21.79
	0.96	0.83	1.10		

$I^2 = 59.25\%$

A- Studies that reported Hazard ratios

Study name	Odds ratio	Lower limit	Upper limit		Relative weight
Antoine Pham 2022	1.10	0.68	1.779		11.34
Min Jun 2017	0.81	0.69	0.948		22.98
Larsen 2017	0.99	0.68	1.429		14.93
Roetker 2018	0.64	0.57	0.724		24.42
Ramos-Isaza 2023	1.23	0.50	3.044		4.71
Fang 2023	0.51	0.42	0.622		21.62
	0.75	0.61	0.935		

$I^2 = 77.87\%$

B- Studies that reported number of events per arm

factors, and evaluate potential bleeding risks before initiating DOAC-based therapy.

Notably, we must also acknowledge that the current meta-analysis has certain limitations. The considerable variability observed among the included studies with regard to study designs, follow-up period duration, outcomes, and sample sizes potentially might have contributed to the substantial heterogeneity observed in our analysis. Although this systematic review and meta-analysis included data for more than 400,000 patients from observational studies around the globe, only two studies reported the mean International normalized ratio (INR) in the warfarin group. This omission could affect the effectiveness outcomes, as the INR might not have been at the therapeutic target during the treatment period. Therefore, the findings should be used with caution until large direct comparative studies can be conducted, including sub-group analyses, to support this evidence. Perhaps future studies might scrutinize more carefully patient-specific outcomes that could be based on differences in terms of sex, age group, and the presence of other comorbidities.

5 Conclusion

In conclusion, our meta-analysis of real-world studies provides valuable insights into the use of DOACs in clinical practice. The findings suggest that DOACs are generally effective in treating acute VTE events and are associated

with a lower incidence of VTE recurrence compared to warfarin. In addition, DOACs demonstrate a reduced risk of bleeding events, suggesting a favorable safety profile. These findings support the use of DOACs as a viable treatment option for acute VTE management, offering improved outcomes with a lower risk of recurrence and bleeding-related complications.

Declarations

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