IJHOSCR

Original Article

International Journal of Hematology-Oncology and Stem Cell Research

Safety and Efficacy of Direct Oral Anticoagulants Compared to Warfarin in Patients with Venous Thromboembolism and Morbid Obesity

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Received: 16, May, 2024
Accepted: 27, Mar, 2025

ABSTRACT

Introduction: Several guidelines recommend using direct oral anticoagulants (DOACs) over warfarin for the prevention of venous thromboembolism (VTE), except in cases of morbid obesity. The use of DAOCs in patients with morbid obesity has not been thoroughly evaluated due to lack of representation in large clinical trials. To address this knowledge gap, we conducted a systematic review and meta-analysis of existing literature to determine the efficacy and safety of DOACs in patients with morbid obesity.

Materials and Methods: A systematic review of studies comparing DOACs with warfarin in patients with morbid obesity and diagnosed with acute VTE was conducted using electronic literature searches up to December 2021. Efficacy and safety were defined as the rate of recurrent VTE and major bleeding, respectively.

Results: A total of 30 822 patients were included across 13 studies. Recurrent VTE events were observed in 713 of 12 945 patients treated with DOACs, compared to 966 of 17 877 patients treated with warfarin (OR, 0.70; 95% CI, 0.50-0.99; P=0.04; I^2=69%). Major bleeding events occurred in 195 of 12 675 patients on DOACs and in 386 of 17 572 patients on warfarin (OR, 0.69; 95% CI, 0.58-0.82; P<0.0001; I^2=0%). Similar findings were noted for two specific DOACS, apixaban and rivaroxaban, when evaluated individually against warfarin.

Conclusion: Our meta-analysis indicated that DOACs are both safe and effective in preventing VTE in patients with morbid obesity. DAOCs resulted in comparable outcomes to those seen in warfarin use. This analysis consolidates extensive observational data from a large patient cohort, thereby enhancing the evidence base for the use of DOACs in patients with morbid obesity.

Keywords: Direct oral anticoagulants (DOACs); Warfarin; Morbid obesity; Venous thromboembolism (VTE)

INTRODUCTION

Traditional anticoagulants, such as warfarin and heparin, have historically served as the cornerstone of treatment for venous thromboembolism (VTE). However, the development of direct oral anticoagulants (DOACs) has introduced new options that present several advantages over conventional vitamin-K antagonists like warfarin. Such advantages include a reduced risk of drug, disease, and food interactions, quicker onset of action, the elimination of the need for routine monitoring, and fixed dosing protocols[1]. Accordingly, current guidelines endorse the use of DOACs as the preferred treatment for VTE prevention, with specific exceptions in particular clinical contexts such as morbid obesity[2].

DOI:

Obesity represents an independent risk factor for VTE, with individuals living with chronic obesity experiencing nearly a sixfold increase in risk relative to those without obesity[3]. The incidence of recurrent VTE is nearly double among these patients compared to their non-obese counterparts[4]. Furthermore, this risk increases linearly with increases in body weight. Hypothesized causes for this association include impaired fibrinolytic activity, increased levels of clotting factors—particularly factor VIII and factor IX—and a pro-inflammatory environment[4]. While multiple randomized controlled trials have demonstrated the safety and efficacy of DOACs in patients with body mass index (BMI) of less than 40 kg/m^2 or weight under 120 kg, the applicability of fixed doses of DOACs in patients with morbid obesity (BMI >40 kg/m^2 or weight > 120 kg) remains inadequately established due to the limited representation of this population in large randomized controlled trials[5]. Consequently, the International Society on Thrombosis and Hemostasis (ISTH) has issued only weak recommendations regarding the use of DOACs in patients with morbid obesity[6]. In light of this knowledge gap, we performed a systematic review and meta-analysis of the existing body of literature to evaluate the efficacy and safety of DOACs in patients with morbid obesity.

MATERIALS AND METHODS

To conduct our systematic review and meta-analysis, we followed the guidelines established by The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).[7] This systematic review has been registered with PROSPERO.

Eligibility criteria

We included studies that compared DOACs to warfarin for the treatment of VTE in patients with morbid obesity. Eligible patients included adults (age≥18 years) with morbid obesity, as defined by the presence of BMI of 40 kg/m^2 or higher, a weight of at least 120 kg, or a diagnosis of morbid obesity according to the International Classification of Diseases (ICD) codes 9 or 10 (ICD-9: 278.01, V85.4; ICD-10: E66.01, E66.2, Z68.4; ICD-9-CM: 278.01, V85.4; ICD-10-CM: E66.01, E66.2, Z68.4). Inclusion criteria required that studies reported both efficacy and safety outcomes. Patients with anticoagulation for non-valvular atrial fibrillation were excluded from this analysis. Additionally, studies that did not separately report the incidence of VTE and bleeding events were excluded. Only studies published in English were considered for inclusion.

Outcomes

The efficacy outcome was defined as the incidence of recurrent VTE following the initiation of anticoagulant therapy. We defined recurrent VTE as the occurrence of deep vein thrombosis or pulmonary embolism, either confirmed through imaging or diagnosed with appropriate ICD codes. The safety outcome was determined by the incidence of major bleeding events, as outlined by the ISTH guideline or Cunningham algorithm[8,9].

Information sources

A comprehensive literature review was conducted using MEDLINE, Embase, Cochrane Central, Scopus, and clinicaltrials.gov databases, with data collected up until 21st December 2021. In addition, we performed a hand search of the reference lists from the identified articles.

Search strategy

We conducted a thorough search of English-language publications focused on the broad themes of “direct oral anticoagulants”, “warfarin”, and “morbid obesity”. All possible synonyms for these three themes and their combinations were used. The search parameters were restricted to studies involving human subjects only.

Data collection process

Two reviewers, A.K. and S.N., independently screened and retrieved relevant articles pertinent to our research question, while excluding studies that did not meet the established eligibility criteria. Relevant data were extracted by the same two reviewers and subsequently verified by two additional authors, A.N. and N.N. Moreover, two other investigators, M.R.A. and V.R.B., also contributed to the review process.

Data items

Baseline characteristics and outcomes were extracted from the eligible studies, which are reported in Table 1. The data items collected included: source type, study design, comparison, indication for anticoagulation, BMI/weight threshold, total number of patients in each group (study groups), mean age, mean BMI (kg/m^2), percentage of female participants (gender), concomitant antiplatelet agents, comorbidity index, presence of malignancy, duration of study (in years), follow-up (in days), efficacy outcome of interest, incidence of efficacy outcome, safety outcome of interest, and incidence of safety outcome.

Table 1. Baseline Patient Characteristics of the Included Studies

Author, Year	Choi et al., 2017	Perales et al., 2019	Spyropoulos et al., 2019	Sa et al., 2019	Kushnir et al., 2019	Costa et al., 2020
Source type	Journal article	Journal article	Journal article	Journal article	Journal article	Journal article
Study design	Single center retrospective cohort	Retrospective cohort at 2 academic medical centers	Retrospective Cohort using two databases	Single center retrospective cohort	Single center retrospective cohort	Retrospective cohort using one database
Comparison	A vs W	R Vs W	R vs W	D vs W	A Vs R VS W	R Vs W
Indication for anticoagulation	AF and VTE	AF and VTE	VTE	VTE	AF and VTE	VTE
BMI/Weight threshold	BMI ≥40	BMI>40, Weight >120kg	ICD 9/ICD 10 diagnosis code for morbid obesity	Weight ≥120	BMI ≥40	BMI ≥40
Study groups (Total no. of patients in each group)	T=146 D=58 W=88	T=146 D=58 W=89	T=5780 D=2890 W=2890	T=133 D=71 W=62	T=366 D=199 W=167	T=3394 D=1697 W=1697
Mean Age (years)	D=61.7[£] W=61.7[£]	D=56[£] W=55[£]	D=53.3 W=53.1	N	D=52.6 W=58.1	N
Mean BMI (kg/m2)	D=45.8[£] W=46.6[£]	D=45[£] W=44[£]	N	N	D=43.7 W=45.3	N
Gender (Female %)	D=59.66[£] W=66.5[£]	N	D=60.51 W=60.20	N	D=67.83 W=70.65	N
Concomitant antiplatelets	N	D=47[£] W=46[£]	N	N	N	N
Comorbidity index	N	D=3 W=3	D=1.22 W=1.23	N	D=1 W=2	N
Malignancy	N	D=3[£] W=7[£]	D=211 W=199	D=0 W=0	N	N
Duration of study (years)	4	~4	5	5	~4	~7
Follow-up (Days)	N	365	365	365	196[€]	365
Primary Outcome of interest	VTE events confirmed by imaging	VTE recurrence,	recurrent VTE (ICD code)	VTE recurrence (according to ISTH)	VTE events confirmed by imaging	Recurrent VTE (ICD code)
Primary Outcome Incidence	D=1 W=1	D=2 W=4	D=485 W=459	D=2 W=0	D=4 W=2	D=66 W=118
Primary outcome in BMI≥50	D=0/11 W=0/16	N	N	N	D=0/40 W=2/52	N
Secondary Outcome of interest	Bleeding events (according to ISTH)	Bleeding events (according to ISTH)	Recurrent bleeding according to validated Cunningham algorithm	Bleeding events	Bleeding events (according to ISTH)	Recurrent bleeding according to validated Cunningham algorithm
Secondary Outcome Incidence	D=1[£] W=9 [£]	D=3 W=2	D=52 W=73	D=1 W=1	D=3 W=4	D=21 W=30

Author, Year	Patil et al., 2020	Falk et al., 2020	Cohen et al., 2021	Cook et al., 2021	Lachant et al., 2021	Samaranayake et al., 2021	Crouch et al., 2021
Source type	Journal article	Journal article	Journal article	Journal article	Journal article	Journal: Letter to the editor	Journal article
Study design	Single center retrospective cohort	Single center retrospective cohort	Retrospective cohort using five databases	Retrospective cohort at 2 medical centers	initially single center retrospective later prospective	Multisite case control study	multicenter retrospective cohort
Comparison	D Vs W	D Vs W	A Vs W	D (A +R) Vs W	D Vs W	Ds Vs W	A vs W
Indication for anticoagulation	AF and VTE	AF and VTE	VTE	VTE	PE	PE	VTE
BMI/Weight threshold	BMI>40, Weight >120kg	BMI>40, Weight >120kg	ICD 9/ICD 10 diagnosis code for morbid obesity.	BMI ≥40, Weight ≥120	BMI ≥40	BMI>40, Weight >120kg	BMI ≥40, Weight ≥120
Study groups (Total no. of patients in each group)	T=152 D=79 W=73	T=141 D=42 W=99	T=19751 D=7411 W=12340	T=77 D=31 W=46	T=29 D=19 W=10	T=150 D=104 W=46	T=594 D=297 W=297
Mean Age (years)	D=67.02 W=67.55	D=55[£] W=52[£]	D=62.3 W=62.1	D=55[€] W=42.5[€]	N	N	D=59.1 W=59.1
Mean BMI (kg/m2)	D=44.35 W=41.6	D=44.9[£] W=50[£]	N	D=43.2 W=45.5[€]	N	N	D=44.3 W=44.2
Gender (Female %)	D=6.32 W=4.1	**N**	D=63.5 W=63	D=58.06 W=50	N	N	D=49.8 W=48.5
Concomitant antiplatelets	D=58 W=49	**N**	D=548 W=917	N	N	N	D=139 W=130
Comorbidity index	N	**N**	D=2.9 W=2.9	N	N	N	N
Malignancy	D=3 W=4	D=7 W=7	N	N	N	N	D=22 W=23
Duration of study (years)	~3	3	~5	~7	~3	5	7
Follow-up (Days)	N	N	180	730	180	180	365
Primary Outcome of interest	Recurrent VTE	Recurrent VTE	Recurrent VTE (ICD code)	Recurrent VTE (Imaging confirmed)	Recurrent VTE (Imaging confirmed)	Recurrent VTE (Imaging confirmed)	Recurrent VTE (ICD code)
Primary Outcome Incidence	D=1 W=6	D=2 W=3	D=130 W=337	D=2 W=10	D=0 W=0	D=6 W=3	D=12 W=23
Primary outcome in BMI≥50	N	D=1/24[£] W=1/64[£]	N	N	N	N	D=3/93[£] W=33/335[£] (Pre-match)
Secondary Outcome of interest	Bleeding events (according to ISTH)	Bleeding events (according to ISTH)	Major bleeding	Bleeding events (according to ISTH)	N	N	Bleeding events (according to ISTH)
Secondary Outcome Incidence	D=1 W=1	D=21[£] W=15[£]	D=107 W=268	D=0 W=1	N	N	D=10 W=8

A: Apixaban; W: Warfarin; R: Rivaroxaban; D: Direct oral anticoagulants; AF: Atrial fibrillation; VTE: Venous thromboembolism; PE: Pulmonary embolism; BMI: Body Mass Index; ICD: International Classification of Diseases; T: Total patients; N: Not available; ISTH: International Society on Thrombosis and Hemostasis; [£]Composite data for Atrial fibrillation and Venous thromboembolism
[€] Median value

Risk of bias assessment

Two authors (N.N. and A.N.) individually assessed each study for the risk of bias using the Newcastle-Ottawa Scale for assessing the quality of non-randomized studies in meta-analyses[10]. Star template for the risk of bias assessment is given in the supplementary Table 1.

Supplementary Table 1. Newcastle Ottawa scale for the included studies

Included studies	Selection	Comparability	Outcome
Choi et al.	★★★★	★	★
Perales et al.	★★★★	★★	★★
Spyropoulos et al.	★★★★	★★	★★
Sa et al.	★★★★		★★
Kushnir et al.	★★★★	★★	★★
Costa et al.	★★★★	★★	★★
Patil et al.	★★★	★★	★★
Falk et al.	★★★★		★★
Cohen et al.	★★★★	★★	★★
Cook et al.	★★★★		★★★
Lachant et al.	★★★★		★★
Smaranayake et al.	★★★★	★★	★★
Crouch et al.	★★★★	★★	★★

Effect measures and synthesis methods

Outcomes from the individual studies were aggregated with RevMan (version 5.3, Cochrane Collaboration, Oxford, United Kingdom) applying the Mantel-Haenszel test. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using a random-effects method to account for the presence of variability among the studies. The I^2 statistic was used to assess heterogeneity. Two-tailed p- values <.05 were considered to have statistical significance. We estimated ORs for safety and efficacy of DOACs compared to warfarin. Since rivaroxaban and apixaban were the most commonly used DOACs, we also did a subgroup analysis to check for the safety and efficacy of apixaban and rivaroxaban compared to warfarin

RESULTS

We identified 154 references after the comprehensive literature search. Thirteen retrospective studies were included after the full-text review of 39 articles. The PRISMA flowchart showing the study selection process is displayed in Figure 1.

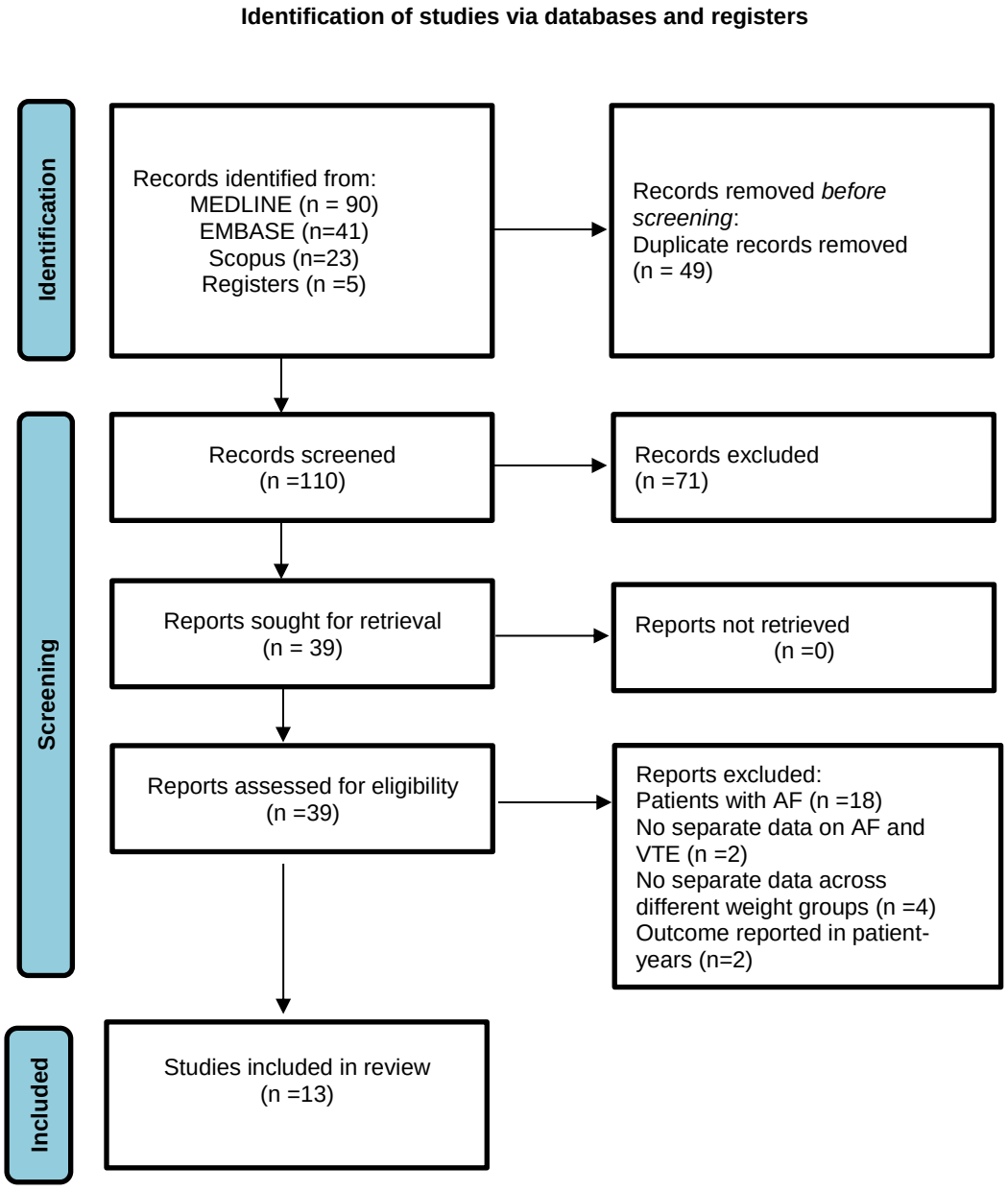

Figure 1. PRISMA Flow diagram describing the systematic search and study selection process

We retrieved information from the VTE subgroup only if both VTE and AF patients were included in the study[11–15]. We retrieved information from a subgroup of patients with morbid obesity only if weight for other patients were included in the study[11,16–18]. Studies that did not report bleeding outcomes or reported bleeding outcomes separately from efficacy results were not used for safety analysis[11,13,19,20]. We only included post-matching data for study by Cohen et al. and Crouch et al. to reduce confounding[18,21]. The study by Quan et al. was excluded because DOACs were compared with traditional therapies using composite data for both warfarin and low molecular weight heparin[22]. All the articles were retrospective and published in peer-reviewed journals. The study by Lachant et al.[19] was retrospective initially but subsequently converted to a prospective cohort.

A total of 30,822 patients were included from thirteen studies for this meta-analysis[11–21,23,24]. The study[18] by Cohen et al. alone included 19,751 patients across the DOAC and warfarin arms. A total of 12,945 patients were treated with DOACs and 17,877 patients were treated with warfarin. Apixaban and rivaroxaban were the most commonly utilized DOACs. Among 12,860 patients, who were on a known DOAC, apixaban was prescribed to 61% (n=7883) and rivaroxaban to 39% (n=4977). A majority of the studies had similar proportions of male and female patients with slight predominance of females except in the study by Patil et al.[12] where more than 90% of patients were male veterans. From four studies (N=20,643) that reported the concomitant use of antiplatelet medications, we found 792 patients (3.83%) in the DOAC arm and 1142 patients (5.53%) in the warfarin arm were concomitantly taking antiplatelet medications[12,15,18,21]. The number of patients with malignancy was reported in six studies(N=6946), and included 246 patients (3.54%) in the DOAC arm and 240 patients (3.45%) in the warfarin arm[12,13,15,17,21,24].

Efficacy and safety outcomes with DOACs and warfarin

A majority of the studies had a follow- up period of one year. Recurrent VTE events occurred in 713 out of 12945 patients (5.5%) treated with DOACs and in 966 out of 17877 (5.4%) patients treated with warfarin (OR: 0.70; 95% CI: 0.50 to 0.99, p= 0.04, I^2=69%) (Figure 2).

Major bleeding occurred in 195 out of 12675 patients (1.53%) on DOACs and 386 out of 17572 (2.19%) patients on warfarin (OR: 0.69; 95% CI: 0.58 to 0.82, p<0.0001, I^2=0%)(Figure 2).

Efficacy and safety outcomes with apixaban and warfarin

A total of 20,705 patients from four studies were included in a subgroup analysis comparing outcomes of apixaban versus warfarin[11,14,18,21]. Recurrent VTE events occurred in 144 out of 7813 patients (1.84%) on apixaban and in 363 out of 12892 (2.8%) patients on warfarin (OR: 0.63; 95% CI: 0.52 to 0.77, p<0.00001, I^2=0%) (Figure3). Major bleeding occurred in 118 out of 7755 (1.52%) patients on apixaban and 280 out of 12804 (2.18%) patients on warfarin (OR: 0.69; 95% CI: 0.55 to 0.85, p=0.0007, I^2=0%)(Figure 3).

Efficacy and safety outcomes with rivaroxaban and warfarin

A total of 9,602 patients from four studies were included in a subgroup comparing rivaroxaban and warfarin[14–16,24]. Recurrent VTE events occurred in 556 out of 4786 patients (11.61%) on rivaroxaban and in 583 out of 4816 (12.10%) patients on warfarin (OR: 0.81; 95% CI: 0.46 to 1.42, p= 0.46, I^2=81%) (Figure 4). Major bleeding occurred in 77 out of 4786 patients (1.60%) on rivaroxaban and 111 out of 4816 (2.30%) patients on warfarin (OR: 0.70; 95% CI: 0.52 to 0.93, p=0.02, I^2=0%) (Figure 4).

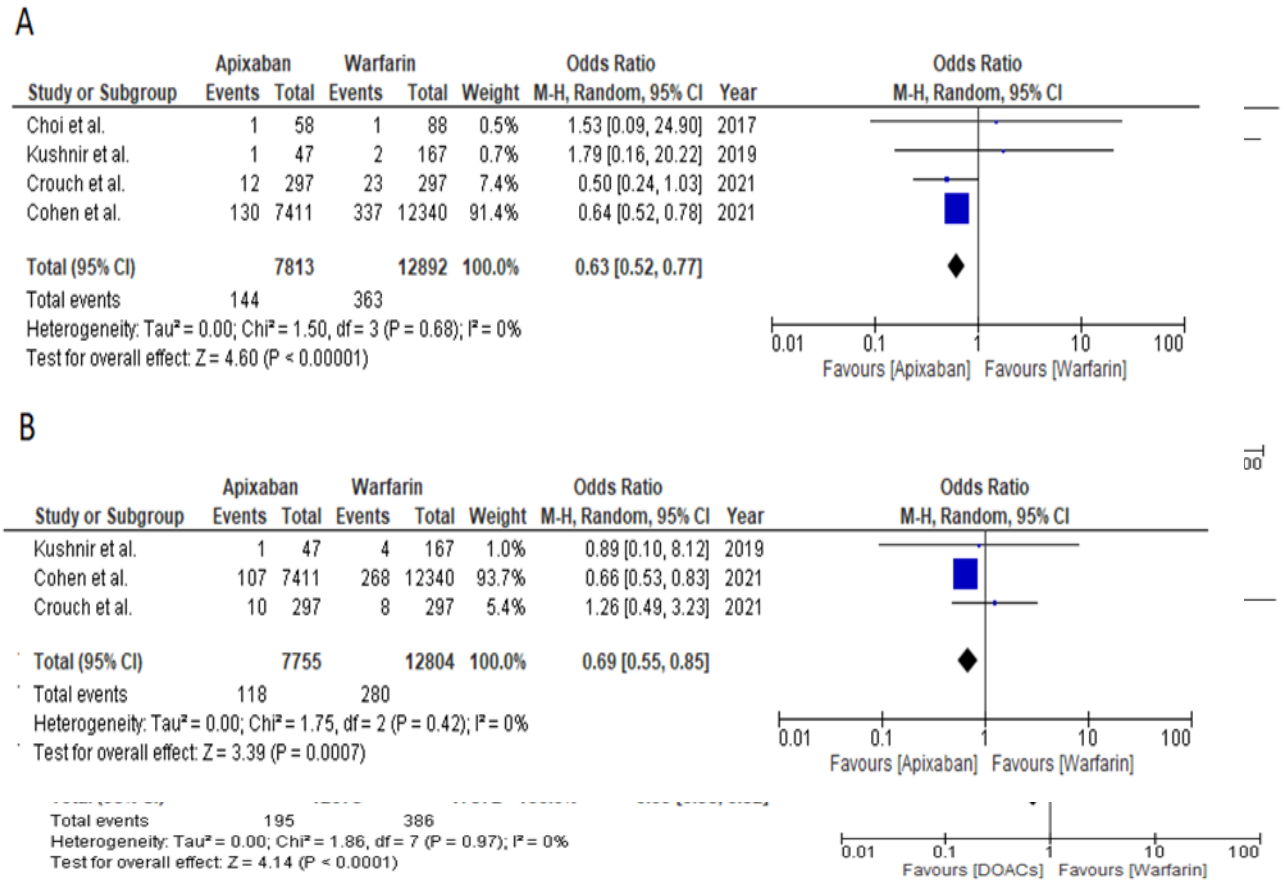

Figure 2. Efficacy and safety of DOACs compared to warfarin in morbidly obese patients, Outcome A: Recurrence of VTE; Outcome B: Major bleeding

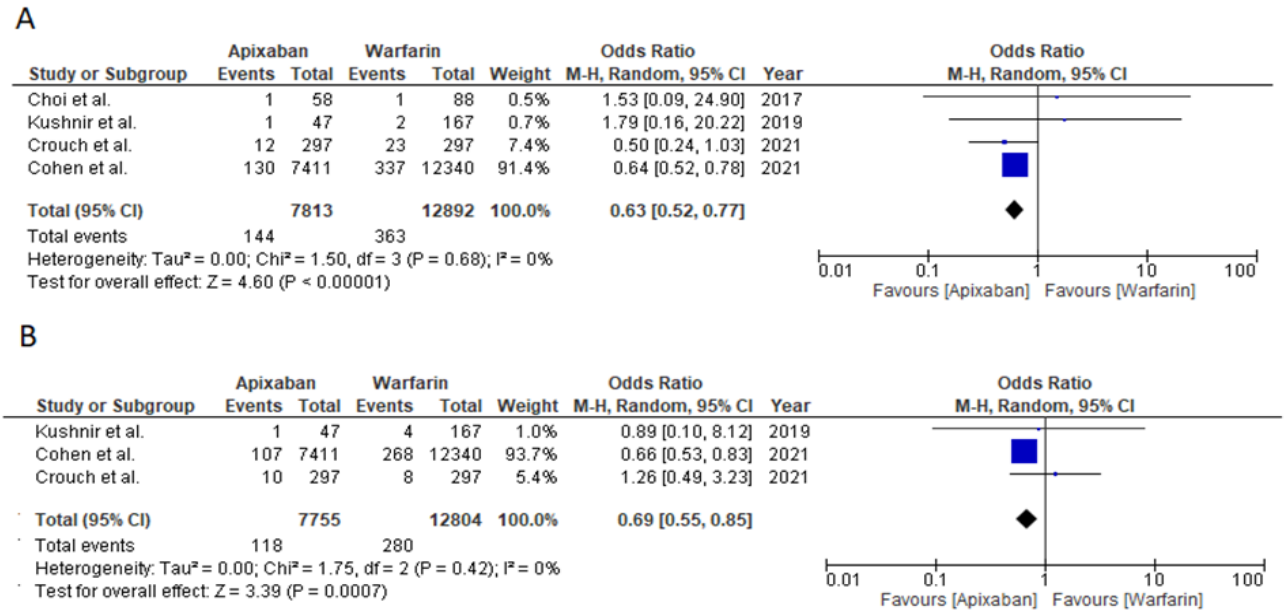

Figure 3. Efficacy and safety of Apixaban compared to warfarin in morbid obesity, Outcome A: Recurrent VTE; Outcome B: Major bleeding

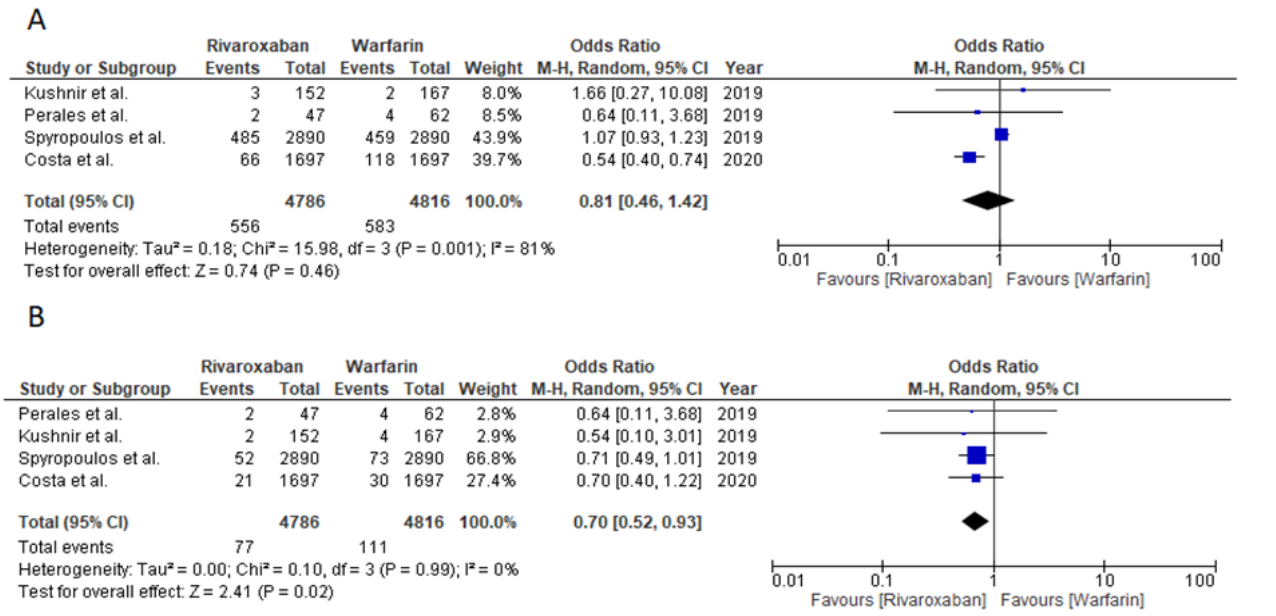

Figure 4. Efficacy and safety of Rivaroxaban compared to warfarin in morbid obesity, Outcome A: Recurrent VTE; Outcome B: Major bleeding

DISCUSSION

Our large meta-analysis of over 30,000 patients highlighted that the use of DOACs in patients with morbid obesity is safe and effective with outcomes comparable to or possibly slightly better than warfarin. These results were consistent in subgroup analyses comparing apixaban and rivaroxaban to warfarin. Prior reviews by Elshafei et al. and Katel et al. on the same topic showed similar incidence of recurrent VTE and bleeding events in both arms. However, they included fewer studies and therefore had smaller sample size (about 4.5 times smaller) and power compared to ours[25,26]. Systematic review and meta-analysis by Mhanna et al. in morbidly obese patients with AF showed DOACs were superior to warfarin[27]. Our study is in line with their study where we showed DOACs were superior compared to warfarin. Another meta-analysis of six randomized controlled trials for the comparison of DOACs with warfarin across high, normal and low body weights showed comparable efficacy and safety in the high body weight group.[28] However, the cut-off for high body weight was 90kg in two trials and 100 kg in four trials[28].

Similarly, our study is the first study to assess the safety and efficacy of rivaroxaban and apixaban with warfarin in morbid obesity separately.

Although guidelines suggest cautious use of DOACs in morbid obesity, DOACs are increasingly used in patients with morbid obesity[13]. Given their ease of use, dosing and lack of monitoring and lack of drug interactions, the increase in prescribing is not surprising. Study by Upreti et al. and Kubitza et al. on pharmacokinetics and pharmacodynamics of apixaban and rivaroxaban respectively across patients with different body weights showed the medications were effective across patients with different body weights and dosage adjustments were not required[29,30]. This suggests body weight may have little effect on the pharmacology of these agents. The majority of the patients in our study (>97%) were prescribed one of these two drugs, which is similar to the real-world prescribing patterns of DOACs[13]. Therefore, our study has the clinical implication of using fixed dose DOACs for patients with different body weights. Although study on the effect of body weight in the pharmacological parameters of dabigatran and edoxaban were lacking, we could find use of other DOACs in a minority of the patients in our cohort. Given the absence of large -scale randomized controlled trials on efficacy and safety in this population and increasing trend in the use of DOACs, prior pharmacologic studies and the results of our study serve to provide clinically useful data to inform recommendations on their use in morbidly obese patients.

In our study we found the rates of recurrent VTE to be around 5% in both arms. This rate is very high compared to prior studies. Two major randomized controlled trials, AMPLIFY and EINSTEIN that compared the effectiveness of apixaban and rivaroxaban respectively with warfarin, showed almost half of the rates of recurrent VTE.[31,32] Although this finding could have been due to the adverse effects of obesity, diagnostic inaccuracies with diagnostic coding which was used in few studies could have also played in a role in this overestimation[16,18,24].

Because of high heterogeneity we conducted subgroup analyses of apixaban and rivaroxaban. Subgroup analysis with rivaroxaban and apixaban showed comparable effects. Our finding is similar to a study by Buck et al. who showed similar results of rivaroxaban and apixaban in patients with increased body mass (BMI≥25) without morbid obesity[33]. Our findings also align with recommendations for use of rivaroxaban on morbidly obese patients with AF as well[34].

LIMITATIONS

The majority of the individual studies in our analysis were retrospective observational studies done in one or two centers. Without randomization, we are unable to control for the effects of patient selection and differences between groups. This model of study leads to selection bias as well as decreased generalizability. For the diagnosis of morbid obesity and outcome events, few studies have included the use of ICD codes which could have caused over- or under-estimation of weight as well as outcome events.

Fat distribution is a confounding factor which has not been reported in any studies. Also, most of the

studies have not stratified the effect of anticoagulants in different BMI groups within the morbidly obese population because of which we can only speculate that our result applies in similar way to patients with a BMI of 45 and that with a BMI of 65. Many studies did not report INR levels at recurrent VTE events in the warfarin arm. We therefore are unable to assess compliance and efficacy in the warfarin arm. Another major limitation of our study was in the grouping many drugs of similar class but with different pharmacological properties into one group of DOACs. This could have potentially led to difficulties in assessing the individual effect and could have contributed to high degree of heterogeneity that we observed. These unaccounted confounders could have led to high clinical and statistical heterogeneity in our study.

CONCLUSION

Our meta-analysis determined that DOACs, mainly apixaban and rivaroxaban, are safe and effective in preventing VTE with outcomes comparable to those seen among patients treated with warfarin. These results provide cumulative observational evidence from a large cohort of patients to inform the use of DOACs in patients with morbid obesity. These results also support conducting well-designed randomized controlled trials that can provide confirmatory evidence.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

ACKNOWLEDGEMENTS

We thank Anthony Donato for the review of our manuscript.

STATEMENTS AND DECLARATIONS

Funding: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics approval: Not applicable

Consent to participate: Not applicable

Consent to publish: Not applicable

Availability of data: The data that support the findings of this study are available in MEDLINE, Embase, Cochrane CENTRAL, Scopus, and clinicaltrials.gov.

Code availability: RevMan (version 5.3, Cochrane Collaboration, Oxford, United Kingdom) was used for the data analysis.

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