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The use of direct oral anticoagulants for extended duration thromboprophylaxis in medically ill patients: a systematic review and meta-analysis

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Abstract
The extended use of thromboprophylaxis with direct oral anticoagulants (DOACs) for more than 30 days has been evaluated as an alternative for the standard duration thromboprophylaxis (7–10 days) with low molecular weight heparin in medically ill patients to reduce the risk of venous thromboembolism (VTE) after hospital discharge. EMBASE and MEDLINE were searched for studies evaluating extended duration thromboprophylaxis with DOACs versus standard thromboprophylaxis with enoxaparin in medically ill patients through October 2018. Search was limited to randomized-controlled trials. Symptomatic VTE, VTE-related death, and death from any cause, and major and clinically relevant non-major bleeding were used to assess the efficacy and safety, respectively. The Mantel–Haenszel random-effects model risk ratio (RR) and corresponding 95% CIs were calculated using the metan routine in Stata (version 14.2) to estimate the pooled treatment effects. Heterogeneity was assessed by the I^2 statistics. Four studies met the inclusion criteria. DOACs were superior to enoxaparin in preventing symptomatic VTE (RR = 0.59, 95% CI 0.44–0.79). There were no significant differences in thromboprophylactic efficacy between extended and standard thromboprophylaxis as to VTE-related death (RR = 0.81, 95% CI 0.60–1.10) and death from any cause (RR = 0.98, 95% CI 0.87–1.09). Compared to the standard duration, extended thromboprophylaxis was associated with approximately two-fold greater risk of major (RR = 1.95, 95% CI 1.25–3.04), and clinically relevant non-major (RR = 1.81, 95% CI 1.29–2.53) bleeding. The superior efficacy was diminished by the unfortunate safety profile. Therefore, we continue to support both the American Society of Hematology (ASH) and the American College of Chest Physicians (ACCP) guidelines recommendation against the extended use of thromboprophylaxis beyond the hospital stay.

Keywords Venous thromboembolism · Direct oral anticoagulants · Thromboprophylaxis · Medically ill patients

Highlights

- Hospitalized medically ill patients remain at higher risk for developing venous thromboembolism (VTE) after hospital discharge.
- Direct oral anticoagulants (DOACs) are associated with a significant reduction in symptomatic VTE events.
- The use of DOACs is associated with higher rates of major and clinically relevant non major bleeding events compared with enoxaparin.

Introduction

Venous thromboembolism (VTE), which comprises of deep vein thrombosis (DVT) and pulmonary embolism (PE), is one of the preventable vascular disease that increase morbidity and mortality among medically ill hospitalized patients [1–3]. In the United States (US), 900,000 cases of VTE events are reported annually, and 300,000 patients die from VTE events every year [3]. Advanced age, trauma, malignancy, pregnancy, and surgery are common risk factors for VTE events [2].The risk of having fatal thrombotic events among high risk patients

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who were not on prophylaxis was up to 20% [4]. Therefore, preventing VTE event is very crucial to decrease the risk of thrombotic complications, hospitalization, and death [1, 3].

Anticoagulants are used for thromboprophylaxis in high risk patients to prevent thrombosis. Both the American Society of Hematology (ASH) 2018 and the American College of Chest Physicians (ACCP) 2012 guidelines recommended the use of parenteral anticoagulants, low-molecular-weight heparin (LMWH), low-dose unfractionated heparin (LDUH) or fondaparinux, for a short duration of 7 to 10 days in hospitalized medically ill patients in order to prevent thrombotic events in this high risk population [5, 6]. Multiple studies reported that the risk of developing VTE events within 90 days of hospital discharge was between 1.9 and 3.8% [7, 8]. However, the extended use of thromboprophylaxis beyond the period of immobilization or acute hospital stay for patients who were on initial thromboprophylaxis wasn't recommended by the ASH or the ACCP guidelines [5, 6].

The EXCLAIM trial was the first trial to examine the efficacy and safety of extended duration thromboprophylaxis versus standard duration thromboprophylaxis. It evaluated the use of one of the LMWH, which was enoxaparin, for extended duration of up to 30 days [9]. The EXCLAIM trial found that the extended use of enoxaparin reduced the risk of developing VTE events as compared to placebo with similar mortality rate between the two groups in the study. However, the extended use of enoxaparin was associated with a higher risk of bleeding compared to the placebo [9].

Even though, the LMWH has reduced the risk of VTE events among hospitalized patients, the daily use of parenteral injection is considered a factor that affect patients' compliance after being discharge from hospital [10]. Furthermore, the unpredictable absorption as well as altered elimination in patients with impaired renal functions are another drawbacks for this class of anticoagulants [4]. In consideration of these concerns, the use of direct oral anticoagulants (DOACs), apixaban, rivaroxaban, and betrixaban, was considered as an alternative for extended thromboprophylaxis in medically ill patients [4]. Therefore, several randomized-controlled trials (RCTs) were conducted to assess the benefit of using DOACs for extended thromboprophylaxis compared to the current standard short-duration thromboprophylaxis with LMWH (enoxaparin) in medically ill patients [11–14]. This meta-analysis provides a summary of these phase III RCTs and presents results of the safety and efficacy outcomes regarding the use of DOACs for extended thromboprophylaxis in medically ill patients.

Methods

A systematic review was conducted using MEDLINE through October, 2018 for studies evaluating the extended use of DOACs for thromboprophylaxis in comparison to the current standard short-duration thromboprophylaxis in medically ill. Search terms included venous thromboembolism, deep-vein thrombosis, pulmonary embolism, thromboprophylaxis, enoxaparin, direct oral anticoagulants, novel oral anticoagulants, low-molecular-weight-heparin, apixaban, rivaroxaban, betrixaban, and medical patients. Search was limited to peer reviewed, phase III RCTs that were conducted in humans and published in English. Studies were excluded if they were not peer reviewed RCTs, published in non-English language or published as an abstract.

For each study, episodes of symptomatic VTE, VTE-related death, death from any cause, major bleeding and clinically relevant non-major bleeding were extracted. Data were extracted from the published papers and assessed for eligibility by two independent investigators (RAA and SMA), and verified by a third investigator (MSA). The risk of bias assessment was conducted for each study using Cochrane Collaboration risk of bias assessment tool. The metan routine in Stata (version 14.2 software, StataCorp LLC, College Station, Texas) was used to calculate the Mantel–Haenszel random-effects model risk ratio (RR) and corresponding 95% confidence interval (CI). Heterogeneity was assessed using I^2 statistics. The number needed to treat (NNT) and the number needed to harm (NNH) were calculated for significant results. This meta-analysis was conducted using the preferred reporting system for meta-analysis and systematic reviews (PRISMA).

Results

A total of 2379 articles were identified in the systematic search. Four studies, APEX, ADOPT, MAGELLAN, and MARINER, met the prespecified eligibility criteria and therefore were included in the current systematic review and meta-analysis. The flowchart in Fig. 1 illustrates the process of including and excluding articles for this systematic review. The results of the risk of bias assessment are reported in Table 1.

Summary of the trials

The ADOPT trial compared the extended use (30 days) of apixaban 2.5 mg twice daily to the standard use (6–14 days) of enoxaparin 40 mg once daily in order to assess efficacy and safety [11]. The trial found that at day 30, patients who

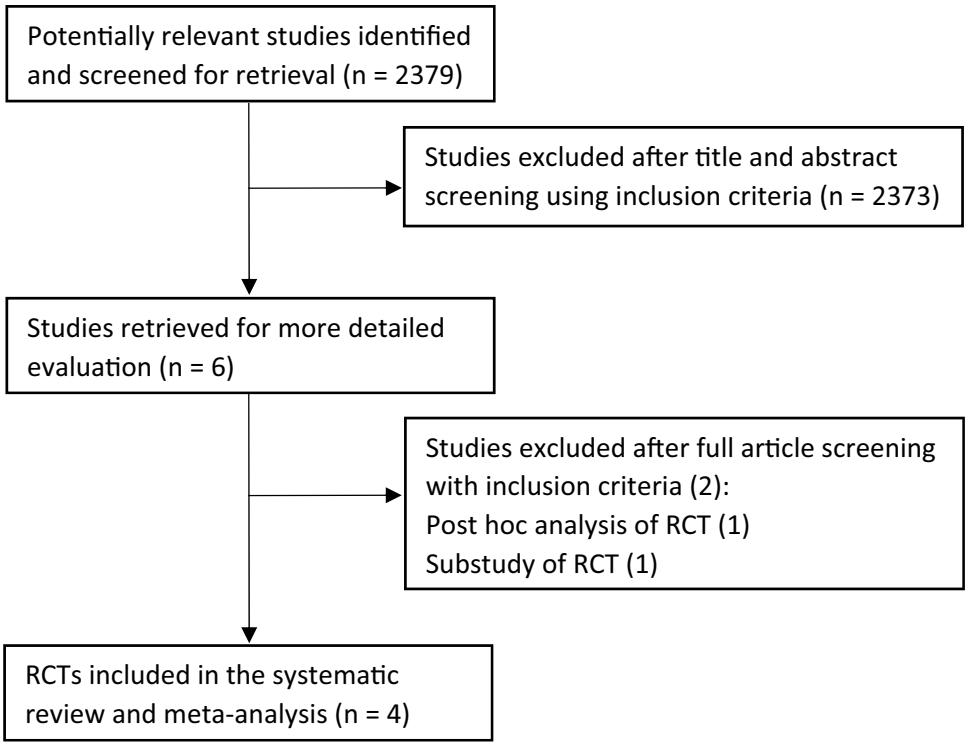

Fig. 1 Flow diagram for study selection

Table 1 Risk of bias assessments for studies assessing the use of direct oral anticoagulants for extended duration thromboprophylaxis in medically ill patients

Trial name	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcomes	Incomplete outcome data	Selective reporting	Other bias
ADOPT	Low	Low	Low	Low	Low	Low	Low
MAGELLAN	Low	Low	Low	Low	Low	Low	Low
APEX	Low	Low	Low	Low	Low	Low	Low
MARINER	Low	Low	Low	Low	Low	Low	Low

were on apixaban had a lower rate of VTE events compared to patients who were on the standard enoxaparin regimen (2.71% vs. 3.06%; RR = 0.87, 95% CI 0.62–1.23; P = 0.44), but this outcome didn't reach the level of statistical significance, which indicates similar efficacy between the two regimens. Moreover, the extended use of apixaban compared to the standard use of enoxaparin was associated with a significant increase in the risk of major bleeding events (0.47% vs. 0.19%; RR = 2.58, 95% CI 1.02–7.24; P = 0.04). All-bleeding and clinically relevant bleeding events were similar for both groups (for all-bleeding: RR = 1.13, 95% CI 0.95–1.34; P = 0.18; and for clinically relevant bleeding: RR = 1.28, 95% CI 0.93–1.76; P = 0.12). The rate of death and adverse events, such as myocardial infarction, stroke, and thrombocytopenia, didn't show any statistical significance [11].

Likewise, the MAGELLAN trial evaluated the extended use (35 ± 4 days) of oral rivaroxaban 10 mg once daily in comparison to the standard therapy with enoxaparin 40 mg once daily for (10 ± 4 days) [12]. The study found that at day 35, patients who were on rivaroxaban had a significantly lower rate of VTE events compared to patients who were on the standard enoxaparin regimen (4.4% vs. 5.7%; RR = 0.77, 95% CI 0.62–0.96; P = 0.02). However, the extended use of rivaroxaban compared to the standard use of enoxaparin was associated with a significant increase in the risk of major bleeding events (1.1% vs. 0.4%; RR = 2.9, 95% CI 1.60–5.15; P < 0.001), and clinically relevant (major and non-major) bleeding events (4.1% vs. 1.7%; RR = 2.5, 95% CI 1.85 to 3.25; P < 0.001). There was no significant difference between the two regimens for the death from any cause outcome (5.1% vs. 4.8%) [12].

The APEX trial compared the extended use (35–42 days) of betrixaban 80 mg once daily, with a loading dose of 160 mg, to the standard use (6–14 days) of enoxaparin 40 mg once daily [13]. The trial distributed the patients into

three different cohorts based on their D-dimer level and age, but the results from the overall cohort only are reported in here as it fit the scope of this systematic review. The study found that at day 42, patients who were on betrixaban for an extended duration had a significantly lower rate of VTE events compared to patients who were on the standard enoxaparin regimen (5.3% vs. 7.0%; RR = 0.76, 95% CI 0.63–0.92; P = 0.006). Moreover, the rate of major bleeding events was comparable between the betrixaban group and the enoxaparin group (0.7% and 0.6%, respectively; RR = 1.19, 95% CI 0.67–2.12; P = 0.55). However, the rate of clinically relevant (major and non-major) bleeding events was significantly higher for the betrixaban group compared to the enoxaparin group (3.1% vs. 1.6%; RR = 1.97, 95% CI 1.44–2.68; P < 0.001), and no significant difference was found between the two regimens in term of death from any cause (5.7% and 5.8%, respectively) [13].

Recently, the MARINER trial assessed the efficacy and safety of the extended use of rivaroxaban 10 mg once daily for thromboprophylaxis and compared it to placebo, both given to medically ill patients for 45 days after discharge from hospital [14]. The study found that at day 45, patients who were on rivaroxaban had a lower rate of VTE events compared to patients who were on placebo (0.83% vs. 1.1%; Hazard Ratio [HR] = 0.76, 95% CI 0.52–1.09; P = 0.14), but this outcome didn't reach the level of statistical significance, which indicates similar efficacy between the two regimens. Likewise, the rate of major bleeding events was comparable between the rivaroxaban group and the placebo group (0.28% and 0.15%, respectively; HR = 1.88, 95% CI 0.84–4.23). However, the rate of clinically relevant non-major bleeding events was significantly higher for the rivaroxaban group compared to the placebo group (1.42% vs. 0.85%; HR = 1.66, 95% CI 1.17–2.35), and no significant difference was found between the two regimens in term of death from any cause (1.18% and 1.48%, respectively) [14].

Results from the meta-analysis

Demographic characteristics

More than 30,000 patients were included in this analysis. The main reasons for admission varied among the studies. Heart failure was the main reason for admission in the APEX trial followed by infectious diseases. In ADOPT trial, respiratory failure was the predominant cause for admission. Correspondingly, most of the patients in MAGELLAN trial were mainly admitted because of infectious diseases and ischemic stroke. Patient demographics and their clinical status from the four trials were summarized in Table 2 In terms of risk factors, the MARINER trial included more patients with a history of VTE compared to the other studies. Whereas, history of cancer was the major risk factor in patients included in MAGELLAN trial.

Efficacy outcomes

The extended use of DOACs for thromboprophylaxis was associated with a 41% reduction in the risk of symptomatic VTE events compared to the standard short-duration regimen with no observed heterogeneity (RR = 0.59, 95% CI 0.44–0.79; $I^2 = 0\%$, NNT = 314). Though, the extended use of DOACs for thromboprophylaxis was not associated with any additional significant benefit in term of preventing VTE-related death events compared to the standard short-duration regimen with enoxaparin (RR = 0.81, 95% CI 0.60–1.10; $I^2 = 0\%$). Similarly, the extended use of DOACs for thromboprophylaxis did not show any statistically significant reduction in terms of death from any cause outcome (RR = 0.98, 95% CI 0.87–1.09; $I^2 = 0\%$). The forest plots for the efficacy outcomes are demonstrated in Fig. 2.

Safety outcomes

The extended use of DOACs for thromboprophylaxis was associated with an approximately twofolds increase in the risk of major bleeding events compared to the standard short-duration regimen (RR = 1.95, 95% CI 1.25–3.04; $I^2 = 37.1\%$, NNH: 343). Likewise, the extended use of DOACs was associated with an approximately two-folds increase in the risk of clinically relevant non-major bleeding events with a high level of heterogeneity (RR = 1.81, 95% CI 1.29–2.53; $I^2 = 73.5\%$, NNH:102). The forest plots for the safety outcomes are demonstrated in Fig. 3.

Discussion

The aim of this systematic review and meta-analysis was to assess the efficacy and safety of the extended use of DOACs for VTE thromboprophylaxis in patients hospitalized for an acute medical illness. So far, four clinical trials have been conducted to investigate the potential benefits or harm from using DOACs in this patient population and all of them were included in this meta-analysis. The primary finding of this meta-analysis showed that the extended use of thromboprophylaxis with DOACs for more than 30 days was superior over the standard short-duration regimen with enoxaparin in reducing VTE events. However, this superiority in the main efficacy outcome was offset with a significant increase in the risk of both safety outcomes, major and clinically relevant non-major bleeding events.

The latest ASH and ACCP guidelines recommended the use of the parenteral anticoagulants in hospitalized medically ill patients for a short 7 to 10 days, and recommended

Table 2 Patient demographics and clinical status

	ADOPT		MAGELLAN		APEX		MARINER	
	Apixaban (N = 3255)	Enoxaparin (N = 3273)	Rivaroxaban (N = 4050)	Enoxaparin (N = 4051)	Betrixaban (N = 3759)	Enoxaparin (N = 3754)	Rivaroxaban (N = 6007)	Placebo (N = 6012)
Age, mean (SD) years	66.8 (12.0)	66.7 (12.0)	71[a]	71[a]	76.6 (8.46)	76.2 (8.31)	69.7	69.7
Women (%)	50.0	51.80	44.40	47.30	54.60	54.20	47.9	47.5
Main disease on admission								
Heart failure (%)	39.0	38.10	32.30	32.40	44.60	44.50	40.6	39.9
Respiratory failure (%)	37.10	37.10	27.30	28.70	11.90	12.60	26.2	26.8
Infection (%)	21.50	22.80	45.80	45.10	29.60	28.20	17.5	17.4
Ischemic stroke (%)	NA	NA	17.30	17.30	10.90	11.50	14.3	14.4
Risk factors for VTE								
History of cancer (%)	9.60	9.80	17.30	16.70	12.40	11.80	8.1	8.9
History of VTE (%)	4.30	3.80	5.0	4.40	8.30	7.90	12.7	12.4
Age ≥ 75 years (%)	29.60	29.90	38.30	38.60	68.50	67.0	35.9	35.6
Hormonal replacement therapy (%)	1.50	0.80	1.20	1.20	1.10	0.80	NR	NR

DOAC direct oral anticoagulant, *NA* not available, *NR* not reported, *VTE* venous thromboembolism

[a]Median reported only

against the extended use of anticoagulants for thromboprophylaxis beyond the recommended 10 days period [5, 6]. These recommendations were based on the results of the previously discussed trials in which extended duration thromboprophylaxis showed a significant reduction in VTE events compared with the standard duration thromboprophylaxis but increased the incidence of major bleeding events [9, 12]. Since the beneficial effect from the extended use of DOACs for thromboprophylaxis was offset by the increased risk of bleeding, the findings from this meta-analysis continue to support the guidelines recommendation.

To our knowledge, this is the largest meta-analysis so far comparing the extended use of DOACs for thromboprophylaxis against the current standard short-duration thromboprophylaxis with enoxaparin. Several meta-analyses were conducted on the use of anticoagulants for extended duration thromboprophylaxis. In those meta-analyses, the extended use of DOACs for thromboprophylaxis showed a consistent superiority in preventing VTE-events but at the cost of increasing the bleeding events. Two meta-analyses analyzed data of patients from the ADOPT, MAGELLAN and APEX trials; Tao and colleagues found that extended DOACs thromboprophylaxis showed a statistically significant reduction in both symptomatic VTE and total VTE events but with an incremental risk in both total and major bleeding events [15]. The second meta-analysis showed also a statistically significant reduction in both symptomatic VTE and total VTE events, but with a significant increase in the risk of major bleeding events and no significant benefit in term of death from any cause [4]. In addition to the previously mentioned meta-analyses, Liew et al. pooled the data from ADOPT, MAGELLAN, APEX and EXCLAIM trials. They found a statistically significant reduction in the risk for symptomatic DVT (proximal or distal) and non-fatal pulmonary embolism, but these benefits were associated with a two-fold increase in the risk of major bleeding [16].

There are some limitations in this meta-analysis which might influence the interpretation of our findings. The included studies vary in the inclusion criteria, risk of VTE assessment, and setting which might affect our results. Additionally, the average duration of thromboprophylaxis in the control arms of these RCTs (6–14 days) is longer than the typical duration in real practice, where thromboprophylaxis is usually given during hospitalization and discontinue at discharge. This may underestimate the true benefit from the extended use of the DOACs for thromboprophylaxis. We have combined studies that used different anticoagulants, which might have different effect on the safety and efficacy

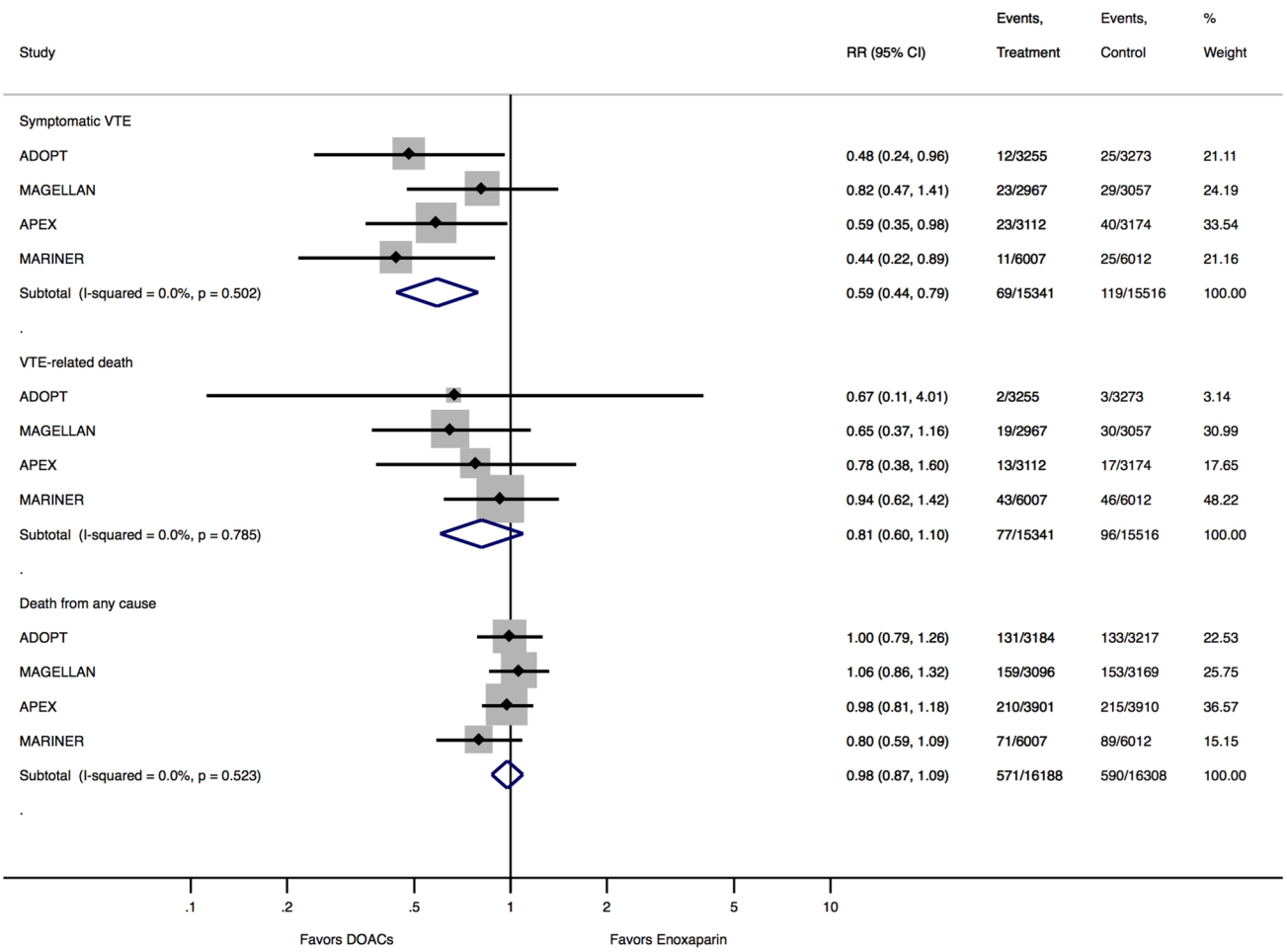

Fig. 2 Efficacy outcomes

outcomes, and that became apparent with the high level of heterogeneity in the safety outcomes. Lastly, in contrast to the ADOPT, MAGELLAN, and APEX trials, the MARINER trial randomized the patients at the hospital discharge stage, which is a significant difference in the design of the study compared to the other studies. However, it is the more accurate way to assess the true impact for the extended use of thromboprophylaxis in the short duration after hospitalization and this design should be utilized later on to assess the true impact for the extended use of anticoagulants.

Conclusion

Extended duration thromboprophylaxis is superior to the standard duration thromboprophylaxis with enoxaparin in terms of preventing symptomatic VTE events. However, this superiority in efficacy was mitigated by an incremental risk in bleeding events. The clinical characteristics of medically ill patients who can benefit from the extended use of DOACs for thromboprophylaxis remain unclear. Therefore, our findings continue to support the current clinical practice guidelines recommendation.

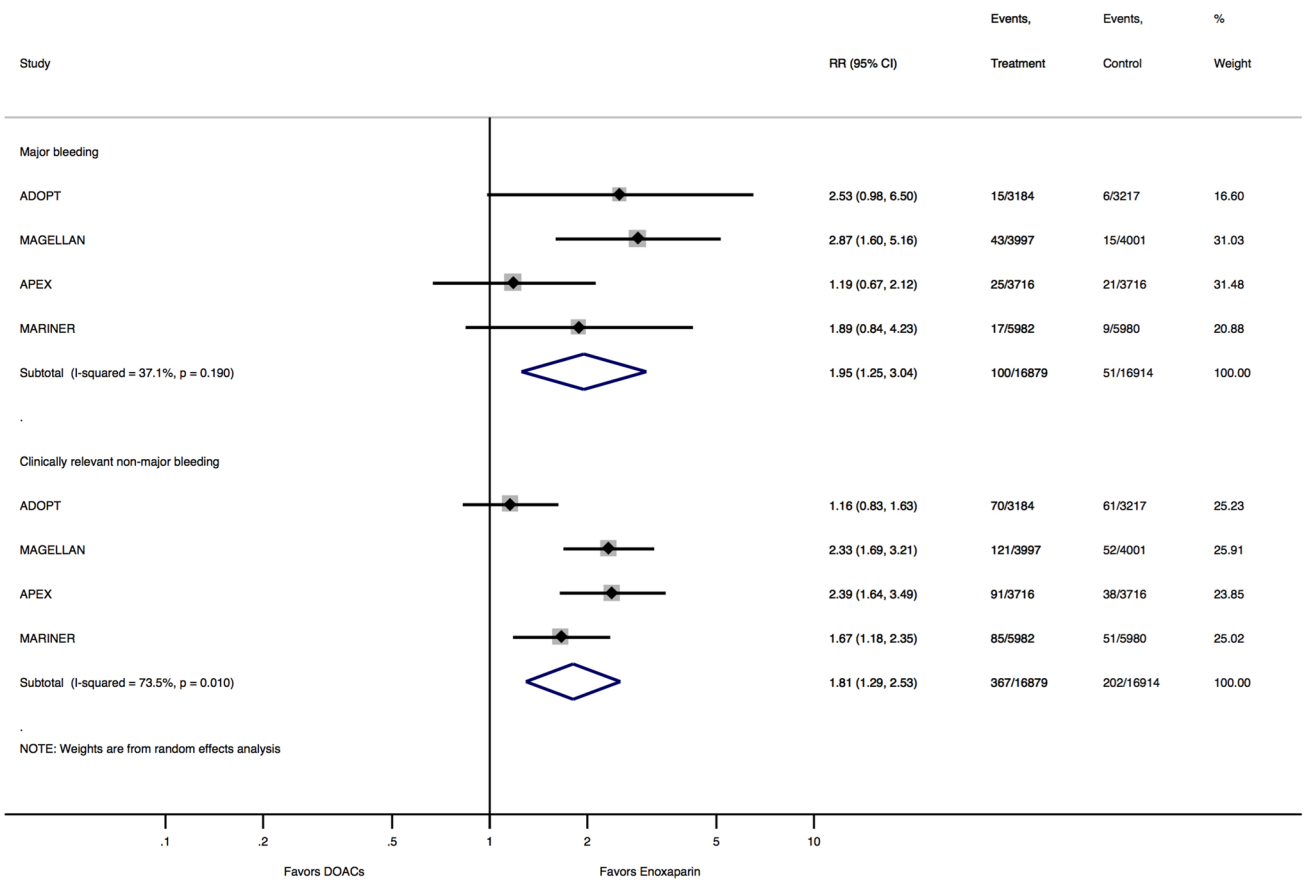

Fig. 3 Safety outcomes

Author contributions All authors had access to the data and a role in writing this manuscript

Compliance with ethical standards

Conflicts of interests All authors declare no conflicts of interest.

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