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ORIGINAL ARTICLE

Efficacy and Safety of Direct Oral Anticoagulants in Pediatric Venous Thromboembolism: A Systematic Review and Meta-Analysis

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Abstract

Objectives To assess the efficacy and safety of direct oral anticoagulants (DOACs) in comparison to standard-of-care (SOC) anticoagulants in the management and prophylaxis of thromboembolic events in pediatric populations.

Methods A comprehensive search of electronic databases was conducted to identify relevant studies published between January 1, 2015, and December 18, 2022. A meta-analysis was undertaken to evaluate the effect of DOACs on clinically significant endpoints, employing trial-level data with harmonized endpoint definitions. The primary outcome was venous thromboembolism (VTE). Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. The study was registered with INPLASY (2022120065).

Results Three studies encompassing 934 subjects were included. The incidence of VTE was reduced in patients administered DOACs compared to those on SOC anticoagulants (OR 0.41 [95% CI 0.19–0.93], $I^2 = 0\%$, $P = 0.03$). No significant differences were observed between the DOAC and SOC groups in all-cause mortality (OR 0.50 [95% CI 0.07–3.59], $I^2 = 0\%$, $P = 0.35$) or serious adverse events (OR 0.75 [95% CI 0.50–1.12], $I^2 = 0\%$, $P = 0.16$). The risk of major bleeding (OR 0.50 [95% CI 0.13–1.87], $I^2 = 44\%$, $P = 0.30$) and clinically relevant non-major bleeding (OR 1.23 [95% CI 0.50–3.00], $I^2 = 0\%$, $P = 0.65$) exhibited no significant differences between the groups.

Conclusions DOACs are associated with a reduced risk of VTE in pediatric patients without increasing the risk of bleeding, all-cause mortality, or serious adverse events when compared to SOC anticoagulants. DOACs may be an alternative for the treatment and prevention of thromboembolic events in the pediatrics.

Keywords Direct oral anticoagulants · Anticoagulants · Pediatric · Venous thromboembolism

Introduction

The epidemiology, diagnosis, and management of thromboembolic events (TEs) in pediatric populations exhibit distinct characteristics in comparison to adults. Prior research has explored the incidence of TEs in children across various age groups and medical centers, revealing an escalating trend over time [1–3]. The susceptibility to TEs in children is age-dependent, with a surge in early infancy. TEs are generally uncommon in healthy neonates, albeit prevalent in those with severe congenital anomalies, such as congenital heart disease. Additionally, central venous catheterization (CVC), central arterial catheterization, mechanical ventilation, and protracted hospital stays have been identified as common risk factors for TEs in pediatric patients [4].

Direct oral anticoagulants (DOACs) have gained widespread acceptance in anticoagulant therapy among adults since their approval by the Food and Drug Administration (FDA) in 2010. DOACs, including dabigatran and rivaroxaban, offer several advantages over heparin derivatives, such as fewer dietary interactions and the obviation of intricate monitoring [5, 6]. Nonetheless, the management and prophylaxis of TEs in pediatric patients present unique challenges

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due to the ongoing development of liver and renal functions in this population, which renders the pharmacokinetics and pharmacodynamics of anticoagulants uncertain [7]. The traditional mainstays for TE management in children have been unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and vitamin K antagonists (VKAs) [5, 6]. However, apprehensions regarding subcutaneous injections, adverse effects, and the need for regular anti-Xa monitoring contribute to the complexity of their clinical utilization [3, 7]. Consequently, DOACs have emerged as a focal point of research for the management of thromboembolic disorders in children. Although preliminary studies comparing DOACs with standard-of-care (SOC) anticoagulants in pediatric thromboembolism have been promising, their interpretability is constrained by limited sample sizes, necessitating a meta-analysis [8–10].

This meta-analysis aims to critically appraise the efficacy and safety of DOACs in the treatment and prophylaxis of thromboembolic events in pediatric patients.

Material and Methods

This meta-analysis was conducted adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [11]. The protocol is registered with the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY2022120065) and is accessible in full at https://inplasy.com/inplasy-2022-12-0065. This study did not necessitate ethics approval.

An exhaustive search of electronic databases for pertinent articles published until December 18, 2022, was undertaken by three independent researchers (YG, CM, and YW). The databases encompassed PubMed, Embase, and the Cochrane database. Subsequent to the electronic search, manual selection of relevant randomized controlled trials was performed. The search strategy is delineated in the Supplementary Table S1.

The EndNote (X9 version) software was selected for document management, two investigators independently evaluated the eligibility of the identified items. The title and summary were filtered for the first time, and qualified articles were reserved for a full-text review. Inclusion criteria for studies included: (1) Pediatric patients with DOACs for the treatment and prevention of venous thromboembolism (VTE). (2) Outcomes indicators: VTE, major bleeding, major or clinically relevant non-major bleeding, all-cause death, or any severe event. The primary effective endpoint was VTE. The primary safety outcomes were major bleeding or clinically relevant non-major bleeding, all-cause death, or any severe event. The exclusion criteria were as follows: (1) Adult patients with DOACs. (2) Studies without enough data to extract, such as the summary of meetings; literature materials, such as reviews and pharmacological introduction.

The two researchers independently evaluated, preliminarily selected and checked the literature data according to the unified and standardized method, and included them in accordance with the admission and exclusion criteria strictly, and then collected the information. The authors evaluated the quality of the selected articles according to the quality evaluation standards in the Cochrane Reviewer Handbook 6.3 [12].

Revman 5.3 and R Studio were used for the meta-analysis. Data which met the homogeneity ($P > 0.10$ and $I^2 \leq 50\%$) through heterogeneity test were meta-analyzed using fixed effect model. If the homogeneity ($P \leq 0.10$ or $I^2 > 50\%$) was not met, and heterogeneity couldnot be ruled out, random effect model was used to combine effects. Notably, the sensitivity analysis should be considered for this type of analysis data. The results from all relevant studies were merged to estimate the pooled odds ratio (OR) and the associated 95% confidence intervals (CIs) for dichotomous outcomes. A P value <0.05 was considered statistically significant.

Results

The flow chart (Fig. 1) summarizes the process of the study search and selection. A total of 231 studies were identified through the electronic searches, of which 45 were excluded due to duplication, then 141 were excluded after reading the titles and abstracts, and the remaining 45 studies were assessed by reading the full texts. Finally, data from 3 trials evaluating the efficacy and safety of DOACs for the treatment and prevention in pediatric VTE were included.

The main features of included trials are presented in Table 1 [8–10]. A total of 934 patients allocated to DOACs ($n = 621$) or SOC ($n = 313$) were included in the analyses. All included studies were randomized controlled trials, and the follow-up time was 3 mo. Among the three studies, EINSTEIN-Jr [9] and DIVERSITY [8] compared the efficacy and safety of DOACs with SOC anticoagulants for the treatment of children VTE, and ENNOBLE-ATE [10], focused on the prevention of VTE. No differences were observed in terms of the proportion of patients lost to follow up across trials between DOACs and SOC anticoagulants.

The safety and efficacy outcomes are summarized in Fig. 2. The risk of VTE was lower among the patients who received DOACs than among those who received SOC anticoagulants (OR 0.41 [95% CI 0.19–0.93], $I^2 = 0\%$, $P = 0.03$) for VTE treatment and prevention. No differences were observed between those who received DOACs and those who received SOC anticoagulants in terms of all-cause death (OR 0.50 [95% CI 0.07–3.59], $I^2 = 0\%$, $P = 0.35$) and any severe event (OR 0.75 [95% CI 0.50–1.12], $I^2 = 0\%$, $P = 0.16$). The risk of major

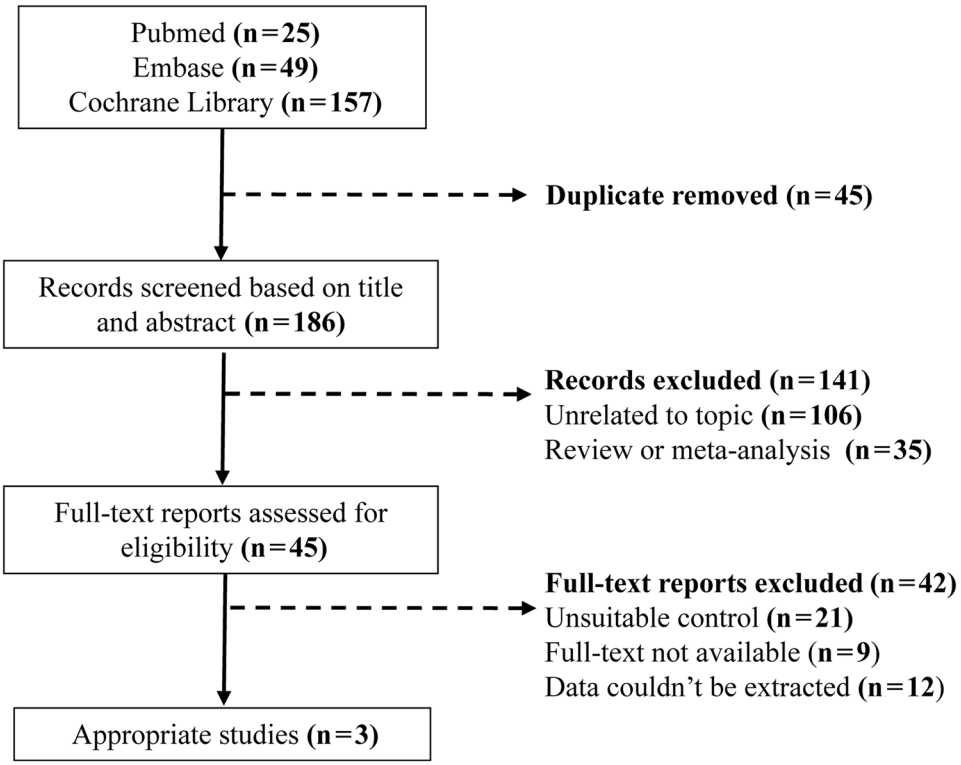

Fig. 1 Flow diagram of the study selection process

bleeding (OR 0.50 [95% CI 0.13–1.87], $I^2 = 44\%$, P=0.30) and major or clinically relevant non-major bleeding (OR 1.23 [95% CI 0.50–3.00], $I^2 = 0\%$, P=0.65) was similar among those who received DOACs and those who received SOC anticoagulants.

The authors used Revman and R software to investigate the influence of a single study on the overall pooled estimate of each predefined outcome, and found that the removal of any one study would not affect the following results (Fig. 3). The traffic light plot summarizing the Risk of bias (ROB) in individual randomized control trials are summarized in the Supplementary Fig. S1. Three studies were considered at low risk for the overall risk of bias.

Discussion

This meta-analysis investigated the efficacy and safety of DOACs compared to SOC anticoagulants in pediatric patients for the treatment and prevention of thromboembolism. The salient findings include a reduced risk of venous thromboembolism in patients treated with DOACs compared to SOC anticoagulants, without a significant difference in all-cause mortality, serious adverse events, or major bleeding.

Table 1 Key study features

	Year	Region	Number of pediatric patients			DOAC	Indications	Age	Follow-up
			Overall	DOAC	SOC				
EINSTEIN-Jr [9]	2019	Austria	500	335	165	Rivaroxaban	VTE treatment	Birth to 17 y	3 mo
DIVERSITY [8]	2021	Canada	267	177	90	Dabigatran	VTE treatment	Birth to 18 y	3 mo
ENNOBLE-ATE [10]	2022	USA	167	109	58	Edoxaban	VTE prevention	Birth to 18 y	3 mo

DOAC Direct oral anticoagulant, *SOC* Standard-of-care, *VTE* Venous thromboembolism

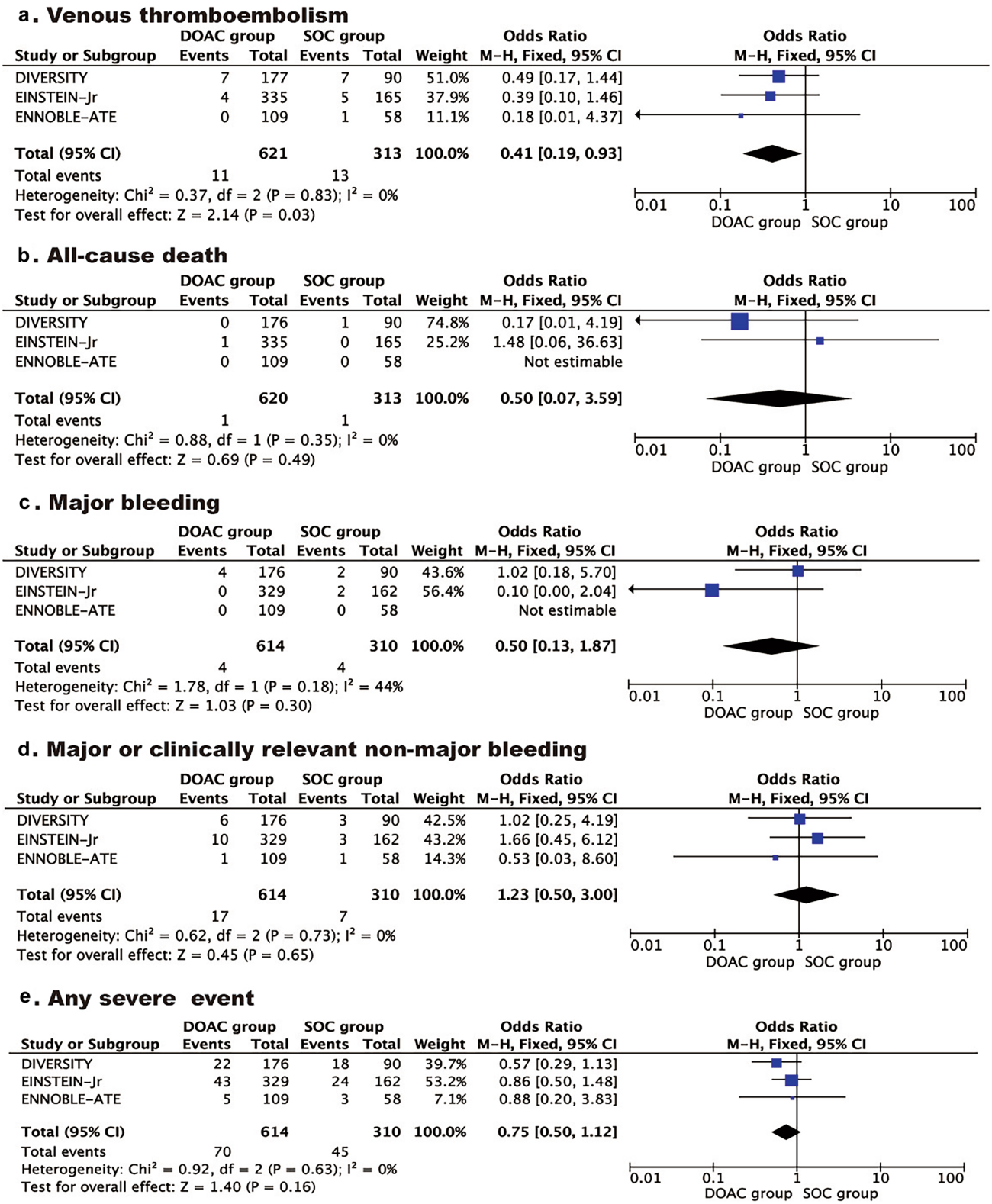

Fig. 2 Forest plot for the effect of direct oral anticoagulants (DOAC) vs. standard-of-care (SOC) anticoagulants for a main treatment in pediatric thromboembolism treatment and prevention **a** venous thromboembolism; **b** all-cause death; **c** major bleeding; **d** major or clinically relevant non-major bleeding; **e** any severe event

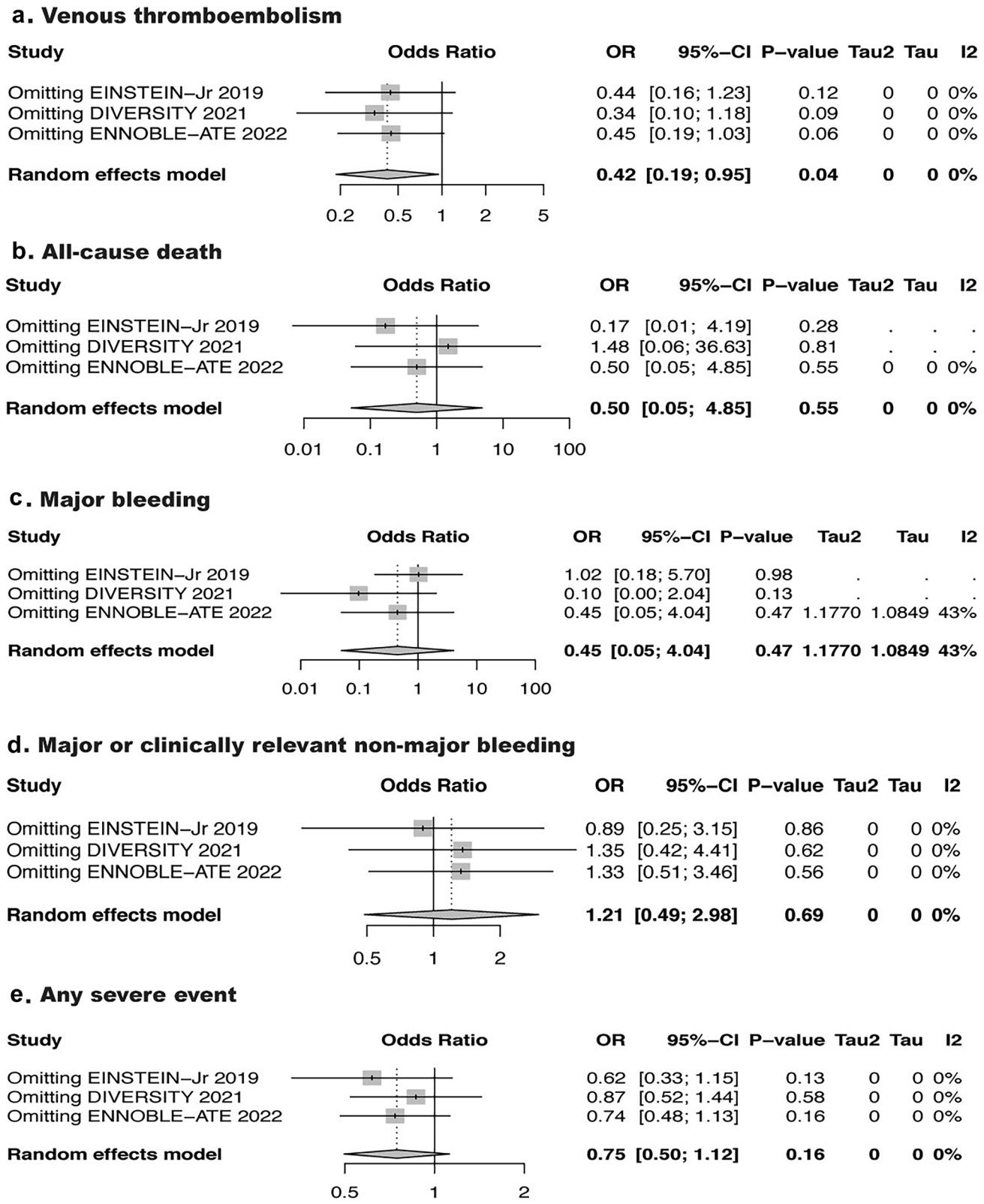

Fig. 3 Sensitivity analyses of pooled odds ratios for outcomes **a** venous thromboembolism; **b** all-cause death; **c** major bleeding; **d** major or clinically relevant non-major bleeding; **e** any severe event

Thromboembolisms (TEs) in children can lead to significant increase in morbidity and mortality [13–15]. Conventional treatment options for pediatric TEs have been limited to unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or vitamin K antagonists (VKAs) [5, 6]. Oral VKAs have notable drug-food interactions, require frequent dose adjustments, and necessitate regular blood tests [16]. DOACs, on the other hand, have garnered interest due to their ease of administration, favorable pharmacokinetic and pharmacodynamic profiles, fewer food interactions, and reduced need for therapeutic drug monitoring [17–19]. Therefore, the challenge of the traditional treatment has led to interest in DOACs as a potential treatment option among the pediatric patients.

Our analysis encompassed two randomized controlled trials (RCTs) on the treatment of TEs and one on their prevention. The findings suggest that DOACs are associated with a lower risk of TEs without an increase in bleeding events when compared to standard anticoagulants. This is consistent with prior studies, which also demonstrated a similarly low recurrence risk and reduced thrombotic burden without increased bleeding events compared to standard anticoagulants [9]. A previous meta-analysis reported that compared with standard anticoagulation, patients receiving DOACs presented a lower rate of recurrent VTE [20]. The results of their meta-analysis were shown basing on different categories of DOACs' effects on recurrent VTE but prevention of VTE was not evaluated. Notably, authors included different literatures according to different criteria with their study. Meanwhile, several clinical studies of different DOACs are underway (Supplementary Table S2). Of note, repeat imaging showed an improved effect of rivaroxaban on thrombotic burden as compared with standard anticoagulants in EINSTEIN-Jr phase 3 trial [9]. In DIVERSITY, dabigatran was similar to the standard of care in terms of major bleeding events and clinically relevant non-major bleeding events, resulting in a smaller number of minor bleeding events [8]. In a systematic review of therapeutic LMWH in children, the incidence of major bleeding was 1.8% [21]. Meanwhile, the DIVERSITY study also shows subtle therapeutic differences between children born to under 2 y of age and children at least 2 y of age [8]. Overall, the observed clinically relevant non-major bleeding rate has been low in all of the pediatric DOACs trials, among both the intervention and SOC comparator groups, affecting the ability to evaluate superiority or non-inferiority [8–10]. In context, the clinically relevant non-major bleeding rate was 0.9% in the ENNOBLE-ATE trial, 3% in EINSTEIN-Jr, and 1% in DIVERSITY for drug treatment groups during similar 3-mo main treatment periods. Treating patients with anticoagulation to resolve venous thromboembolism and preventing recurrent venous thromboembolism always requires a balance of bleeding risk.

Unlike adults, anticoagulation in children is influenced by several unique factors related to thromboembolism (TEs) [7, 22]. The coagulation system undergoes significant developmental changes during childhood, particularly in the fetal stage and early infancy. These developmental changes, along with age-dependent differences in drug absorption, metabolism, and elimination, contribute to distinct pharmacokinetic and pharmacodynamic profiles of anticoagulants in children. Consequently, pediatric patients require age-specific dosing regimens. Moreover, the risk of bleeding associated with anticoagulation may fluctuate based on underlying medical conditions such as thrombocytopenia or liver disease and the risk of trauma in physically active children. Upcoming trials, slated for completion in the near future, promise to shed light on thromboembolism prevention in specific pediatric subgroups and diverse clinical settings.

This study has certain limitations that warrant discussion. First, the meta-analysis relied exclusively on data from published literature, and certain outcomes were not reported. It is noteworthy that only one study focused on thromboprophylaxis. Further research is needed to ascertain the efficacy and safety of DOACs in the pediatric population. Second, the meta-analysis used study-level data rather than individual patient-level data, which is an inherent limitation of this type of analysis. Ongoing studies addressing various clinical conditions are nearing completion and are expected to inform the authorization of DOACs for children with different disorders. Third, the three studies included in the meta-analysis were open-label in design. This may be considered a potential weakness; however, the ethical and practical considerations render long-term administration of placebo injections and sham laboratory monitoring infeasible in children randomized to rivaroxaban. Additionally, there is considerable clinical heterogeneity among the included studies. The limited availability of randomized controlled trials (RCTs) that directly compare DOACs and standard anticoagulants, and the consequently limited statistical power, strengthen the rationale for this meta-analysis. Nevertheless, a sensitivity analysis was performed, and the results remained consistent.

This study heralds a paradigm shift in clinical strategy. It is anticipated that clinicians will have the flexibility to prescribe DOACs in tablet or suspension form for pediatric patients, tailored to their weight, obviating the need for regular laboratory monitoring and dose adjustments. This anticoagulant regimen has been validated in the pediatric population with venous thromboembolism, avoiding the utilization of adult dosage forms and substantially reducing the number of injections and blood samples required by standard anticoagulation therapies.

Conclusions

In conclusion, DOACs are associated with a lower risk of venous thromboembolism in pediatric patients without an increase in bleeding, all-cause mortality, or severe adverse events compared to standard of care anticoagulants. Hence, DOACs may present an attractive alternative for both the treatment and prevention of thromboembolism in children.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12098-023-04952-8.

Authors' Contributions YG, TG and CM searched the scientific literature and drafted the manuscript. LB and SL helped to collect the data and performed statistical analysis. YW and PZ contributed to the conception, design, data interpretation, manuscript revision for critical intellectual content, and supervision of the study. All authors read and approved the manuscript. YW and PZ will act as guarantors for this manuscript.

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Declarations

Conflict of Interest None.

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