



# Net Clinical Benefit of Direct Oral Anticoagulants in Patients With Cancer and Venous Thromboembolism: A Systematic Review and Trade-Off Analysis

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**Background:** Venous thromboembolism (VTE) is highly prevalent in cancer patients. Recent guidelines recommend considering direct oral anticoagulants (DOACs) for the treatment of cancer-associated thrombosis (CAT). However, direct head-to-head comparisons among DOACs are lacking, and almost no net clinical benefit (NCB) analysis has been performed in patients with CAT.

**Methods:** We systematically searched PubMed, EMBASE, Cochrane Library, and ClinicalTrials.gov for randomized controlled trials (RCTs) reporting on recurrent VTE, major bleeding, or clinically relevant bleeding events in patients with CAT who received DOACs and low-molecular-weight heparins. Relative risks (RRs) and 95% confidence intervals (95% CIs) were calculated using a random-effect model. Surface under the cumulative ranking curve (SUCRA) values were calculated, and a trade-off analysis was performed to estimate the NCB.

**Results:** Overall, four RCTs involving 2,894 patients were enrolled. DOACs were more effective than dalteparin in reducing the risk of recurrent VTE (RR: 0.62, 95% CI: 0.44–0.87), with a comparative risk of major bleeding (RR: 1.33, 95% CI: 0.84–2.11) and an increased risk of clinically relevant bleeding (RR: 1.45, 95% CI: 1.05–1.99). No significant difference was observed among individual anticoagulants in terms of recurrent VTE and major bleeding. With respect to the ranking of each anticoagulant for the primary outcome, edoxaban (SUCRA: 69.2) was more effective than dalteparin (SUCRA: 60.7), rivaroxaban (SUCRA: 60.7), and apixaban (SUCRA: 25.5) in reducing VTE recurrence. For major bleeding, apixaban (SUCRA: 76.3) had the highest cumulative ranking probability, followed by edoxaban (SUCRA: 66.4), dalteparin (SUCRA: 28.8), and rivaroxaban (SUCRA: 28.5). Similar results were observed for clinically relevant bleeding. In terms of both benefit and safety outcomes, DOACs, especially edoxaban, seemed to confer a better NCB profile than dalteparin.

**Conclusions:** DOACs are a safe and effective alternative therapy to dalteparin in patients with CAT. Among them, edoxaban might provide a good risk-to-benefit balance. However, because of the lack of head-to-head studies, further investigations are needed to confirm our findings.

**Keywords:** direct oral anticoagulants (DOACs), cancer, venous thromboembolism (VTE), trade-off analysis, net clinical benefit (NCB)

## INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is a well-recognized complication and a common cause of death in cancer patients, with an estimated incidence of 1–20% (1). Even in the presence of anticoagulation, cancer-associated thrombosis (CAT) has been associated with an approximate 10–20% risk of recurrent VTE and a 10% risk of bleeding annually, placing an enormous burden on global healthcare systems (2). Therefore, the optimal anticoagulation strategy that can balance the risks of VTE recurrence and bleeding has been the focus in this vulnerable population.

Most practice guidelines recommend low-molecular-weight heparins (LMWHs) for both prophylaxis and treatment in patients with CAT, and the importance of direct oral anticoagulants (DOACs) has recently been raised (3, 4). In previous randomized controlled trials (RCTs), namely SELECT-D and Hokusai VTE Cancer, rivaroxaban and edoxaban significantly reduced the risk of recurrent VTE; however, this benefit was partly offset by a higher risk of bleeding than with LMWHs, which inevitably limits the clinical application of these DOACs for CAT treatment (5, 6). Notably, two up-to-date trials (ADAM VTE and Caravaggio) comparing apixaban with dalteparin suggested the non-inferiority of apixaban in terms of recurrent VTE and bleeding in the treatment of CAT (7, 8). The net clinical benefit (NCB), which balances the risks of thromboembolism and hemorrhage, is crucial for identifying the optimal anticoagulation in CAT. Because head-to-head comparisons among DOACs are lacking, an indirect analysis could be performed to obtain the estimates of comparative results. In the present study, we conducted a systematic review and trade-off analysis of the efficacy and safety of DOACs to evaluate their NCB in patients with cancer and VTE.

## METHODS

### Literature Search

This systematic review was conducted in line with the standards in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) and Cochrane Collaboration Statements (9, 10). The PubMed, EMBASE, and Cochrane Library databases were systematically searched from inception to May 15, 2020, with language restricted to English. The full details of the search strategies are presented in **Supplementary Table 1**. Moreover, the ClinicalTrials.gov

website was searched for unpublished data. Two reviewers (Y-DY and M-MP) independently assessed the titles and abstracts to determine study eligibility, and full articles were retrieved and assessed according to the inclusion criteria. Any disagreements were resolved by the corresponding author (Z-CG).

### Study Selection

The eligibility criteria for studies were as follows: (1) RCT design, (2) inclusion of patients with cancer and VTE, (3) comparison of DOACs with LMWHs, and (4) available data of outcomes including recurrent VTE and bleeding events. Studies published only in the form of a conference abstract or letter were excluded. Studies were also excluded if they involved patients with cancer and atrial fibrillation, or any other condition requiring long-term antithrombotic therapy. To determine study eligibility, two authors (Y-DY and M-MP) independently reviewed all titles and abstracts, and all papers were assessed based on entry criteria. Discrepancies were resolved through a discussion with the corresponding author (Z-CG).

### Study Outcomes

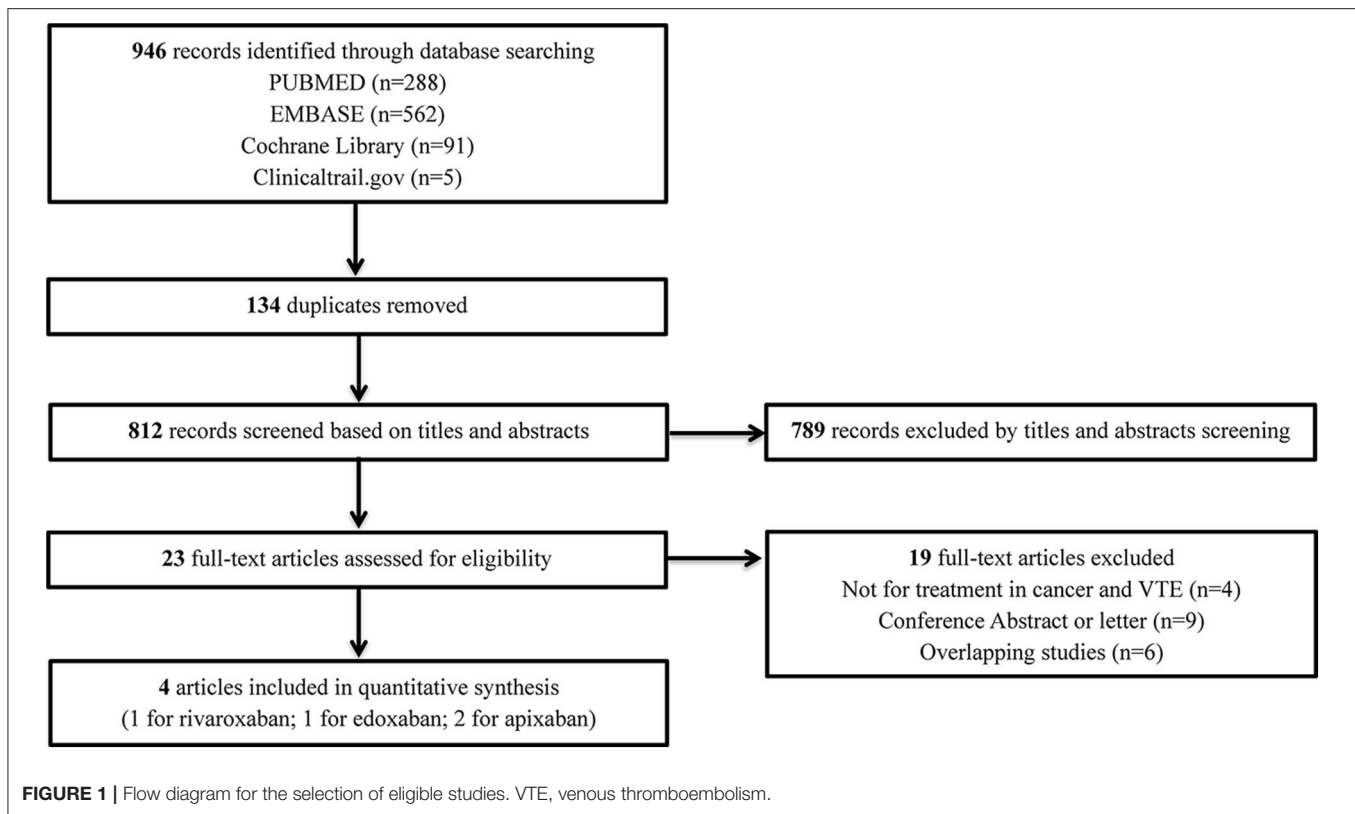
The primary efficacy outcome was the recurrence of VTE including deep vein thrombosis and pulmonary embolism. The primary safety outcomes were major bleeding and clinically relevant bleeding, as defined in each study (**Supplementary Table 2**).

### Data Extraction and Quality Evaluation

Data were extracted into a pre-specified form: including study characteristics (study name, number of patients, intervention, and follow-up duration); patient demographics (age, sex, renal function, proportion of cancer types); and information (recurrent VTE, major bleeding, and clinically relevant bleeding). The methodological quality of the included RCTs was evaluated using the Cochrane Collaboration Risk of Bias Tool (11).

### Statistical Analysis

Results were reported as relative risks (RRs) with 95% confidence intervals (95% CIs) using a random-effect model. Statistical heterogeneity was assessed using the  $I^2$ -test, with a value of >50% representing considerable heterogeneity (12). In the indirect comparison among DOACs, LMWHs were used as the reference comparator. Surface under the cumulative ranking curves (SUCRA) values were calculated to rank treatments with respect to different outcomes based on cumulative probability plots, with a larger SUCRA value indicating better ranking of the treatment (13). For the NCB, clustered ranking plots of treatments were



depicted according to the SUCRA probabilities for both efficacy and safety. Narrow NCB weighted both recurrent VTE and major bleeding, and broad NCB balanced recurrent VTE and clinically relevant bleeding. Publication bias was qualitatively evaluated using funnel plots when >10 studies were available in a single analysis (9). All statistical analyses were performed using the STATA software (version 13.0, STATA Corporation), with a *P*-value of <0.05 indicating statistical significance.

## RESULTS

### Study Selection and Characteristics of the Included Studies

The flow diagram of the study selection process is shown in **Figure 1**. The initial search yielded 946 records, among which 23 full-text articles were obtained for further assessment for eligibility. Finally, four eligible RCTs (5–8) involving 2,894 patients with CAT were enrolled, with 1,446 patients using DOACs and 1,448 patients using dalteparin. The characteristics of the included studies are presented in **Table 1**. The mean or median age of the patients ranged from 64 to 67 years, and the proportion of women ranged from 47 to 52%. The tumor types were comparable across the four trials, with the exception of gastric (2.5–5.2%), gynecologic (3.0–10.5%), and hematologic (2.5–10.6%) cancers. An evidence network map comparing DOACs and dalteparin is outlined in **Figure 2**. The overall quality of the four RCTs was relatively high (**Table 1**).

### Efficacy and Safety of DOACs in Patients With CAT

Both direct and indirect comparisons were conducted for efficacy (recurrent VTE) and safety (major bleeding and clinically relevant bleeding). In the direct comparison, DOACs were more effective than dalteparin in reducing the risk of recurrent VTE (RR: 0.62, 95% CI: 0.44–0.87), with a comparative risk of major bleeding (RR: 1.33, 95% CI: 0.84–2.11) and an increased risk of clinically relevant bleeding (RR: 1.45, 95% CI: 1.05–1.99) in patients with CAT (**Table 2**). In the indirect comparison, no significant difference was observed among individual anticoagulants (dalteparin, edoxaban, rivaroxaban, and apixaban) in terms of recurrent VTE and major bleeding. With respect to clinically relevant bleeding, edoxaban (RR: 1.33, 95% CI: 1.01–1.76) and rivaroxaban (RR: 2.77, 95% CI: 1.51–5.06) significantly increased the risk compared with dalteparin, and rivaroxaban showed a higher risk than apixaban (RR: 2.27, 95% CI: 1.15–4.48) (**Table 3**).

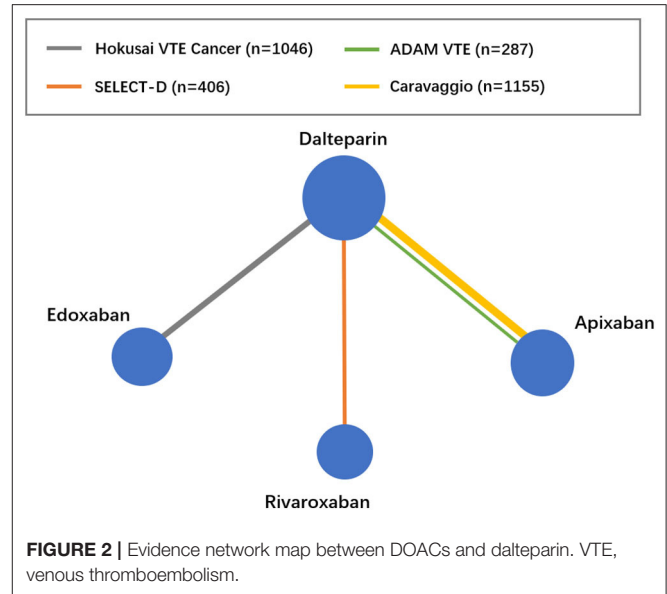
### Efficacy and Safety of DOACs Based on Ranking

The ranking of each anticoagulant is shown in **Table 4**. In terms of recurrent VTE, edoxaban (SUCRA: 69.2) was more effective than dalteparin (SUCRA: 60.7), rivaroxaban (SUCRA: 60.7), and apixaban (SUCRA: 25.5). With respect to major bleeding, apixaban (SUCRA: 76.3) had the highest cumulative ranking probability, followed by edoxaban (SUCRA: 66.4), dalteparin

**TABLE 1** | Details of studies included in the analysis.

Study	Number	Interventions	Follow-up	Age, yr (mean/median)	Female (%)	Ccr of 30-50 ml/min (%)	Metastatic cancer (%)	Hematologic cancer (%)	Colorectal cancer (%)	Lung cancer (%)	Breast cancer (%)	Gynecologic cancer (%)	Gastric cancer (%)	Risk of bias
Hokusai VTE Cancer (2018)	1,046	Edoxaban 60 mg once Dalteparin	12 m	64.3	47.7	6.9	53	10.6	15.5	14.6	11.9	10.5	5.2	Low
SELECT-D (2018)	406	Rivaroxaban 15 mg twice and then 20 mg once Dalteparin	6 m	67	47	NR	58	2.5	25	11.5	10	3	2.5	Low
ADAM VTE (2019)	287	Apixaban 10 mg twice and then 5 mg twice Dalteparin	6 m	64.4	51.7	9.3	65.7	9.3	15.9	17.3	9	9.8	3.8	Low
Caravaggio (2020)	1,155	Apixaban 10 mg twice and then 5 mg twice Dalteparin	6 m	67.2	50.8	9.7	NR	7.4	20.3	17.3	13.4	10.3	4.7	Low

VTE, venous thromboembolism; yr, year; m, month; Ccr, creatinine clearance rate; NR, not reported.



**FIGURE 2** | Evidence network map between DOACs and dalteparin. VTE, venous thromboembolism.

(SUCRA: 28.8), and rivaroxaban (SUCRA: 28.5). Similar results were observed for clinically relevant bleeding.

### Trade-Off Analysis Balancing Efficacy and Safety

The clustered ranking plot according to SUCRA values indicated that DOACs in general seemed to confer a better NCB profile than dalteparin, irrespective of narrow and broad NCB. Edoxaban occupied the most favorable position with respect to efficacy and safety. Apixaban formed a cluster of “relatively low effectiveness but the highest safety level,” whereas rivaroxaban presented a cluster of “moderate effectiveness and the highest bleeding risk” (Figure 3).

### DISCUSSION

The present analysis, based on four RCTs involving 2,894 patients, demonstrated that DOACs are a safe and effective alternative therapy to dalteparin in patients with CAT. No significant difference in VTE recurrence and major bleeding was observed among individual anticoagulants in the treatment of CAT. In terms of both benefit and safety outcomes, DOACs, especially edoxaban, seemed to confer a better NCB profile than dalteparin.

Owing to hypercoagulability, patients with cancer have a high risk for both recurrent VTE, even in the presence of anticoagulation, and bleeding complications (14). Therefore, the balance between efficacy and safety is often neglected in the treatment of patients with CAT. Most guidelines recommend LMWHs as the first-line treatment for CAT, mainly based on the landmark CLOT trial (15). Two RCTs, namely Hokusai VTE Cancer and SELECT-D, provided new evidence and supported the recommendation of DOACs as an alternative to LMWHs for the treatment of CAT (5, 6). Notably, both the contemporary ADAM VTE trial and Caravaggio trial revealed that apixaban

**TABLE 2 |** Direct comparisons of treatments for the risk of clinical outcomes.

Treatment comparison	No. of studies	With DOAC therapy	With dalteparin therapy	Total	RR	95% CI	I <sup>2</sup>
<b>RECURRENT VTE</b>							
Edoxaban vs. dalteparin	1	41/522 (7.85%)	59/524 (11.26%)	100/1,046 (9.56%)	0.70	0.48–1.02	–
Rivaroxaban vs. dalteparin	1	8/203 (3.94%)	18/203 (8.87%)	26/406 (6.40%)	0.44	0.20–1.00	–
Apixaban vs. dalteparin	2	33/721 (4.58%)	55/721 (7.63%)	88/1,442 (6.10%)	0.37	0.06–2.08	66.9%
DOACs vs. dalteparin	4	82/1,446 (5.67%)	132/1,448 (9.12%)	214/2,894 (7.39%)	0.62	0.44–0.87	24.9%
<b>MAJOR BLEEDING</b>							
Edoxaban vs. dalteparin	1	36/522 (6.90%)	21/524 (4.01%)	57/1,046 (5.45%)	1.72	1.02–2.91	–
Rivaroxaban vs. dalteparin	1	11/203 (5.42%)	6/203 (2.96%)	17/406 (4.19%)	1.83	0.69–4.86	–
Apixaban vs. dalteparin	2	22/721 (3.05%)	25/721 (3.47%)	47/1,442 (3.26%)	0.89	0.47–1.71	2.3%
DOACs vs. dalteparin	4	69/1,446 (4.77%)	52/1,448 (3.59%)	121/2,894 (4.18%)	1.33	0.84–2.11	27.0%
<b>CLINICALLY RELEVANT BLEEDING</b>							
Edoxaban vs. dalteparin	1	97/522 (18.58%)	73/524 (13.93%)	170/1,046 (16.25%)	1.33	1.01–1.76	–
Rivaroxaban vs. dalteparin	1	36/203 (17.73%)	13/203 (6.40%)	49/406 (12.07%)	2.77	1.51–5.06	–
Apixaban vs. dalteparin	2	79/721 (10.96%)	65/721 (9.02%)	144/1,442 (9.99%)	1.22	0.89–1.66	0%
DOACs vs. dalteparin	4	212/1,446 (14.66%)	151/1,448 (10.43%)	363/2,894 (12.54%)	1.45	1.05–1.99	50.3%

DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; VTE, venous thromboembolism.

**TABLE 3 |** Network meta-analysis for the risk of clinical outcomes.

Treatment comparison	Recurrent VTE	Major bleeding	Clinically relative bleeding
Edoxaban vs. dalteparin	0.70 (0.08, 5.94)	1.72 (0.92, 3.21)	1.33 (1.01, 1.76)
Rivaroxaban vs. dalteparin	0.44 (0.05, 4.25)	1.83 (0.65, 5.15)	2.77 (1.51, 5.06)
Apixaban vs. dalteparin	0.37 (0.05, 2.46)	0.89 (0.11, 7.35)	1.22 (0.89, 1.66)
Edoxaban vs. rivaroxaban	1.57 (0.07, 35.30)	0.94 (0.28, 3.14)	0.48 (0.25, 0.94)
Edoxaban vs. apixaban	1.91 (0.11, 33.55)	1.92 (0.21, 17.31)	1.09 (0.72, 1.66)
Rivaroxaban vs. apixaban	1.22 (0.06, 23.34)	2.05 (0.20, 21.40)	2.27 (1.15, 4.48)

VTE, venous thromboembolism.

was non-inferior to dalteparin in the treatment of CAT, without increasing the risk of bleeding (7, 8), which prompted systematic reassessments of the benefits and harms associated with DOACs.

A prior meta-analysis of three RCTs (Hokusai VTE Cancer, SELECT-D, and ADAM VTE) assessed the efficacy and safety of DOACs in patients with CAT, and revealed borderline significant results for DOACs vs. dalteparin in terms of recurrent VTE (RR: 0.51, 95% CI: 0.25–1.03) and major bleeding (RR: 1.64, 95% CI: 1.00–2.69) (16). The latest Caravaggio trial (7), with a large sample size of 1,155 patients with CAT, emphasized that the use of apixaban for up to 6 months was non-inferior to subcutaneous dalteparin in terms of recurrent VTE and major bleeding. Similar to the Caravaggio trial, our results revealed that the DOACs were overall more effective than dalteparin in reducing the risk of recurrent VTE, without increasing the risk of major bleeding. However, confusion remains with respect to the

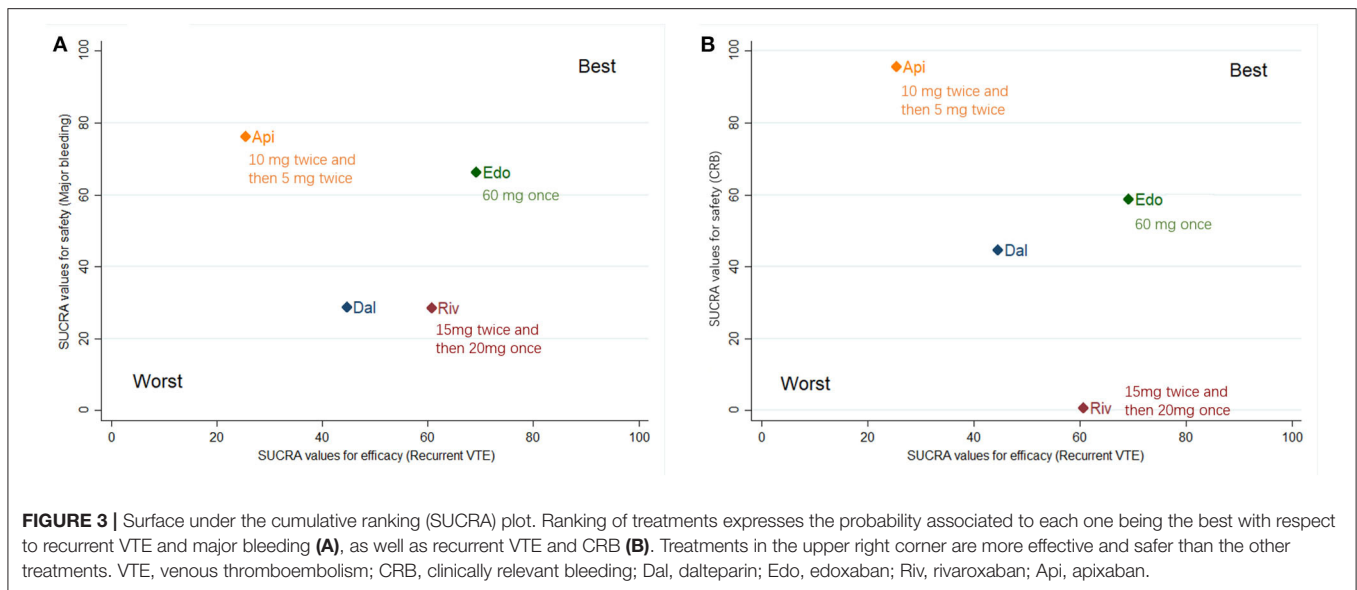
**TABLE 4 |** SUCRA ranking of anticoagulants for clinical outcomes.

Treatment	Recurrent VTE		Major bleeding		Clinically relevant bleeding	
	SUCRA	Mean rank	SUCRA	Mean rank	SUCRA	Mean rank
Edoxaban	69.2	1.9	66.4	2.0	58.9	2.2
Rivaroxaban	60.7	2.2	28.5	3.1	0.8	4.0
Apixaban	25.5	3.2	76.3	1.7	95.7	1.1
Dalteparin	60.7	2.2	28.8	3.1	44.6	2.7

SUCRA, the surface under the cumulative ranking curve; VTE, venous thromboembolism.

optimal selection of individual DOACs because of the absence of head-to-head comparisons.

The NCB, which comprehensively considers the balance of recurrent VTE risk and bleeding risk, provides a more quantitatively informed basis for decision making. The results of our trade-off analysis indicated that DOACs may generally confer a better NCB profile than dalteparin in patients with CAT. Edoxaban was the most favorable DOAC in terms of benefit and safety. Accordingly, we speculated that edoxaban may provide a good risk-to-benefit balance. Interestingly, the Hokusai VTE Cancer trial, the only RCT that compared edoxaban with dalteparin, revealed a significantly increased risk of major bleeding with edoxaban, which was mainly due to a higher risk of upper gastrointestinal bleeding in gastric cancer patients (5). Inconsistent results between direct and indirect comparisons were observed, as in other studies (17). Unlike direct comparison, indirect analysis included both direct evidence and indirect effects from the other three studies. The smaller proportion of gastric cancer patients in the other three trials (6–8) (SELECT-D: 2.5%, ADAM VTE: 3.8%, and Caravaggio: 4.7%) than



in the Hokusai VTE Cancer trial (5.2%) might explain the relatively lower bleeding risk. Such integrated results possibly underestimated the overall rate of bleeding with edoxaban compared with dalteparin and failed to demonstrate an increased risk of major bleeding. As no head-to-head RCT of DOACs exists, further studies are needed to confirm that edoxaban confers a better NCB profile in patients with CAT.

With respect to VTE prophylaxis, two emerging clinical trials (AVERT and CASSINI) compared DOACs with placebo among high-risk ambulatory cancer patients with a Khorana score of >2 (score range: 0–6, with higher scores indicating a higher risk of VTE) (18, 19). The AVERT trial revealed that apixaban therapy resulted in a significantly lower rate of VTE than placebo (HR: 0.41; 95% CI: 0.26–0.65) at the cost of an increased risk of major bleeding (HR: 2.00; 95% CI, 1.01–3.95). In contrast, the CASSINI trial indicated that rivaroxaban led to a substantially lower incidence of VTE (HR: 0.40; 95% CI: 0.20–0.80) with a low incidence of major bleeding (HR, 1.96; 95% CI: 0.59–6.49). On the basis of the above evidence, DOACs might represent an alternative choice for thromboprophylaxis in cancer patients. However, all results should be cautiously interpreted because of the absence of a direct comparison among anticoagulants.

In the clinical setting, despite fewer interactions with DOACs than with vitamin K antagonists, pharmacokinetic interactions between DOACs and anticancer drugs should be considered. Certain chemotherapeutic and targeted agents that interfere with P-glycoprotein or CYP3A4, such as vinblastine, doxorubicin, crizotinib, and sunitinib, may affect the plasma levels of DOACs and subsequently influence the anticoagulation effect (20). However, the clinical significance of drug-drug interactions between NOACs and anticancer agents is still largely unknown. Undeniably, interactions between anticancer drugs and DOACs might exist in the included studies; however, detailed information was not provided. Therefore, we did not have get access to data related to the co-administered anticancer drugs, which precluded a powerful subgroup analysis.

This study had several noteworthy limitations. First, minor differences in baseline characteristics existed across the included RCTs, especially with respect to tumor types. The overall heterogeneity among the four RCTs was moderate, as revealed by the  $I^2$ -values. Accordingly, a random-effect model was used in the statistical analysis. Second, no statistical significance of recurrent VTE and major bleeding among the three DOACs was observed owing to an insufficient sample size in each arm of the DOACs. Further studies with direct head-to-head comparisons among DOACs are necessary. Third, we did not have access to patient-level data related to the type, stage, or location of cancer, as well as detailed information related to combination chemotherapy, which precluded a powerful subgroup analysis. In addition, publication bias could not be assessed owing to the limited number of included studies.

## CONCLUSIONS

The results of this study suggest that DOACs are a safe and effective alternative therapy to dalteparin in patients with CAT. Among the DOACs, edoxaban may provide a good risk-to-benefit balance. However, further studies with head-to-head comparisons among DOACs are needed to confirm our findings.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

## AUTHOR CONTRIBUTIONS

Z-CG and CZ are the guarantors of the entire manuscript. Z-CG and Y-DY contributed to the study conception and design, the critical revision of the manuscript for important intellectual

content, and the final approval of the version to be published. ZD, M-MP, QX, J-JC, and L-WW contributed to the data acquisition, analysis, and interpretation. All authors contributed to the article and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fcvm.2020.586020/full#supplementary-material>

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

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