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REVIEW ARTICLE

Direct oral anticoagulants for venous thromboembolism in cancer patients: a systematic review and network meta-analysis

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Abstract

Background The efficacy and safety of direct oral anticoagulants (DOACs), including dabigatran, apixaban, rivaroxaban, and edoxaban, for preventing and treating venous thromboembolism (VTE) in patients with cancer is unclear.

Methods We searched the PubMed, Embase, Web of Science, and Cochrane Library databases from the establishment to November 30, 2021. In the frequency-based network meta-analysis, the odds ratio with a 95% confidence interval was reported. The relative ranking probability of each group was generated based on the surface under the cumulative ranking curve (SUCRA).

Results We included 15 randomized controlled trials involving a total of 6162 patients. Apixaban reduced the risk of VTE compared with low-molecular heparin [OR = 0.53, 95% CI (0.32, 0.89)]. The efficacy of drugs was ranked from highest to lowest as follows: apixaban (SUCRA, 81.0), rivaroxaban (73.0), edoxaban (65.9), dabigatran (51.4), warfarin (30.8), and low-molecular-weight heparin (LMWH) (27.4). Edoxaban increased the risk of major bleeding compared with LMWH [OR = 1.83, 95% CI (1.04, 3.22)]. The safety of drugs was ranked from highest to lowest as follows: major bleeding—apixaban (SUCRA, 68.5), LMWH (55.1), rivaroxaban (53.0), warfarin (35.9), dabigatran (29.2), edoxaban (16.5) and clinically relevant non-major bleeding—LMWH (73.0), apixaban (57.8), edoxaban (45.8), rivaroxaban (35.3), and warfarin (10.8).

Conclusions For preventing and treating VTE, in terms of VTE occurrence and major bleeding, apixaban had the lowest risk; in terms of clinically relevant non-major bleeding, LMWH had the lowest risk, followed by apixaban. Generally, apixaban is the most efficient and safest DOAC and presents better efficacy and relatively low bleeding risk among the VTE prevention and treatment drugs for patients with cancer.

Keywords Direct oral anticoagulant · Cancer · Venous thromboembolism · Network meta-analysis

Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in patients with cancer and has high morbidity and mortality. Patients with cancer may have 4–7 times increased VTE risk [1, 2]. Patients with cancer also have a higher risk of recurrent VTE and major bleeding (MB) events after treatment [3], so treating cancer-related thrombosis (CAT) is extremely challenging.

In earlier guidelines for treating CAT, low-molecular-weight heparins (LMWHs) were recommended as the first-line treatment for CAT, especially for treating patients with acute VTE; vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) were used for patients unable or unwilling to use long-term parenteral therapy [4–10]. However, patients requiring long-term anticoagulant treatment are required to receive LMWHs via daily subcutaneous injection. The pain and cost of the injection are prominent problems in LMWH use [11–13]. The individualized dose of the VKA warfarin varies significantly, interacts with a variety of drugs and food, and imposes a higher risk of bleeding. Therefore, frequent international normalized ratio (INR) testing is required [14]. However, DOACs can be taken orally and have less interaction

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with drugs and food, and generally do not need to be monitored. Using DOACs avoids the discomfort of injections and the frequent laboratory monitoring problems associated with LMWH and VKA use [15]. The simple application of DOACs provides more convenient treatment options for patients with cancer with VTE, with better medication compliance [16].

DOACs (e.g., dabigatran, apixaban, rivaroxaban, edoxaban) do not have inferior effectiveness compared to VKAs and are used for treating VTE in the general population [17–20]. In the National Comprehensive Cancer Network guidelines, edoxaban and rivaroxaban are also used as therapeutic drugs for patients with cancer diagnosed with VTE [21]. DOACs do not have inferior efficacy compared with LMWH monotherapy for cancer-related VTE, but the related safety results, such as the incidence of bleeding, differ [22]. Previous meta-analyses have compared the results of DOACs and LMWHs for treating cancer-related VTE. Randomized controlled trial (RCT) data show that DOACs did not significantly reduce the risk of VTE and were accompanied by an increased risk of bleeding [23–26]. The SELECT-D trial compared the oral factor Xa inhibitor rivaroxaban and dalteparin. The rivaroxaban-treated patients had a lower VTE recurrence rate, but MB events and clinically relevant non-MB (CRNMB) incidence increased [27]. Therefore, the efficacy and safety of DOACs for treating VTE in patients with cancer remains to be investigated.

A large-scale phase III non-inferiority trial confirmed that compared with VKAs, DOACs have similar or even more favorable effects in preventing VTE recurrence [28–32]. However, in preventing VTE in patients with cancer, different drug doses will yield different bleeding results. Apixaban (5 mg and 20 mg) increased the risk of MB events, while patients receiving 10 mg apixaban have reduced the risk of MB [33]. Therefore, using the appropriate doses of DOACs is particularly important for preventing VTE in patients with cancer. Although there have been many RCTs and observational studies on the efficacy and safety of DOACs for secondary prevention of CAT, their results are inconsistent [34]. Therefore, the efficacy and safety of DOACs for preventing CAT remains unclear.

Due to the limited research on the efficacy and safety of DOACs for preventing and treating VTE in patients with cancer, to better explore the efficacy and safety of DOACs in such patients and to provide a reference for selecting drugs to prevent and treat VTE in patients with cancer in the clinic, we conducted a systematic review and network meta-analysis (NMA) of the evidence from existing RCTs.

Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [35].

Data sources and searches

We searched the PubMed, Embase, Web of Science, and Cochrane Library databases for relevant research on and before November 30, 2021. To ensure a comprehensive literature search, we also searched the reference list of the literature to identify other studies. The following search terms were applied: (1) Neoplasms OR Neoplas* OR cancer OR malign* OR tumor OR tumor OR carcinoma; (2) Venous Thromboembolism OR Venous Thrombosis OR Pulmonary Embolism OR Vein Thromboembolism OR Vein Thrombosis OR venous thromboem* OR venous thrombos* OR deep vein thrombos* OR deep venous thrombos* OR phlebothrombos* OR pulmonary embolism OR pulmonary thromboembolism OR lung embolism OR VTE OR DVT OR PE; (3) dabigatran OR Pradaxa OR rivaroxaban OR Xarelto OR apixaban OR Eliquis OR edoxaban OR Savaysa OR non-vitamin K antagonist oral anticoagulant* OR non-vitamin K antagonist* OR NOAC* OR direct oral anticoagulant* OR DOAC* OR novel oral anticoagulant* OR new oral anticoagulant* OR new orally active anticoagulant* OR factor Xa inhibitor* OR factor 10a inhibitor* OR factor IIa inhibitor* OR direct thrombin inhibitor*; (4) Randomized controlled trial. Supplementary Table 1 shows the detailed search strategy for each database. Two researchers performed the literature search and screening independently.

Study selection

All studies that met the following requirements were included: (1) RCTs; (2) participants had cancer and received VTE prevention or treatment; (3) compared DOACs (dabigatran, rivaroxaban, apixaban, edoxaban) with placebo, LMWH, or warfarin; and (4) both the control and experimental groups reported at least one MB or CRNMB data. The following studies were excluded: (1) combined use of antithrombotic drugs and (2) repeated research or incomplete or unusable original research data.

Data extraction and quality assessment

Two researchers extracted the data independently. Disputes were discussed and resolved by the third researcher to reach a consensus. The following data were extracted from the included studies: study information (author, publication year), study characteristics (study population, sample size, follow-up time), participant characteristics (age, gender), intervention measures, and outcome indicators (VTE occurrence, MB, CRNMB).

The primary efficacy outcomes were the occurrence of VTE, the occurrence of acute episodes defined as

symptomatic or asymptomatic VTE (DVT and PE), and fatal pulmonary embolism [36]. The International Society of Thrombosis and Hemostasis defines MB as overt bleeding plus a hemoglobin decrease of ≥ 2 g/dL or transfusion of ≥ 2 units of packed red blood cells or intracranial, intraspinal/epidural, intraocular, retroperitoneal, pericardial, intra-articular, and intramuscular with compartment syndrome or fatal bleeding [37]. CRNMB was defined as overt bleeding not meeting the criteria for MB but that was associated with medical intervention, unscheduled contact with the health care team, or temporary anticoagulant cessation [38].

Quality assessment

Two researchers used the Cochrane risk bias assessment tool [39] to evaluate the quality of the selected literature independently. The seven evaluation items are random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. During the evaluation, disputes were resolved by having another researcher evaluate to help solve the problem.

Statistical analysis

The NMA was performed using Stata 14.0 (Stata Corporation, College Station, TX, USA) based on the frequency framework. The data were first paired and preprocessed, and the network evidence map was drawn by displaying the treatment sample size of each two intervention measure and the corresponding number of studies. The network evidence graph was drawn using the Stata 14.0 network plot command. We used 95% confidence intervals (credible intervals, CI) to evaluate the bleeding index of DOACs for VTE prevention and treatment. Inconsistency was evaluated by comparing the inconsistency factor (IF) and its 95% CI to assess the difference between direct and indirect comparison. When the *P*-value of the inconsistency test was > 0.05, it was deemed in good agreement, and the direct and indirect evidences were very consistent, and the consistency model was used for analysis; otherwise, the non-uniformity model was used. Publication bias was determined with a comparison-correction funnel chart. Using the surface under the cumulative ranking curves (SUCRA) as the evaluation index, we ranked the bleeding risk of all patients with cancer with VTE to determine the safety of the anticoagulant drugs for preventing and treating VTE in the patients. A larger area under the SUCRA curve indicated a lower risk of bleeding and greater safety.

Results

Literature search

Using the above search strategy, a total of 1882 studies were retrieved. Through screening, we included 14 RCTs [27, 40–53] in the study: five studies on preventing cancer VTE and nine studies on treating VTE. The studies involved a total of 6162 patients (treatment group, 3170 cases; control group, 2992 cases). Fig. 1 shows the literature screening process and results.

Characteristics of the studies and quality assessment

Table 1 shows the basic characteristics of the included studies. Among the 6162 patients included, a total of 397 (6.4%) had a VTE occurrence, 197 (3.2%) had MB events, and 484 (8.6%) had CRNMB. All literature included were RCTs. Each study generally had a low risk of bias, and only one study [49] reported more than one significant risk of bias. Eight studies [27, 40, 44, 47–50, 53] did not blind the participants and researchers. While the included studies were generally low risk, most did not perform participant and investigator blinding. It may be because heparin requires injection and warfarin requires blood for testing the INR indicators, so the participants and researchers could not be blinded to this. Fig. 2 shows the quality evaluation results of the included studies.

Assessment of inconsistency

Supplementary Tables 2, 3 and 4 show the consistency of the results of the included studies. The consistency testing showed that the direct and indirect comparison results of VTE occurrence, MB, and CRNMB had good consistency ($P > 0.05$), and the consistency model was used.

Network plot outcomes

VTE occurrence involved six intervention measures: warfarin, LMWH, rivaroxaban, edoxaban, apixaban, and dabigatran. MB involved six intervention measures: warfarin, LMWH, rivaroxaban, edoxaban, apixaban, and dabigatran. CRNMB involved five intervention measures: warfarin, LMWH, rivaroxaban, apixaban, and edoxaban. Both outcomes formed two closed loops. Supplementary Fig. 1 shows the detailed network relationship between the anticoagulant drugs.

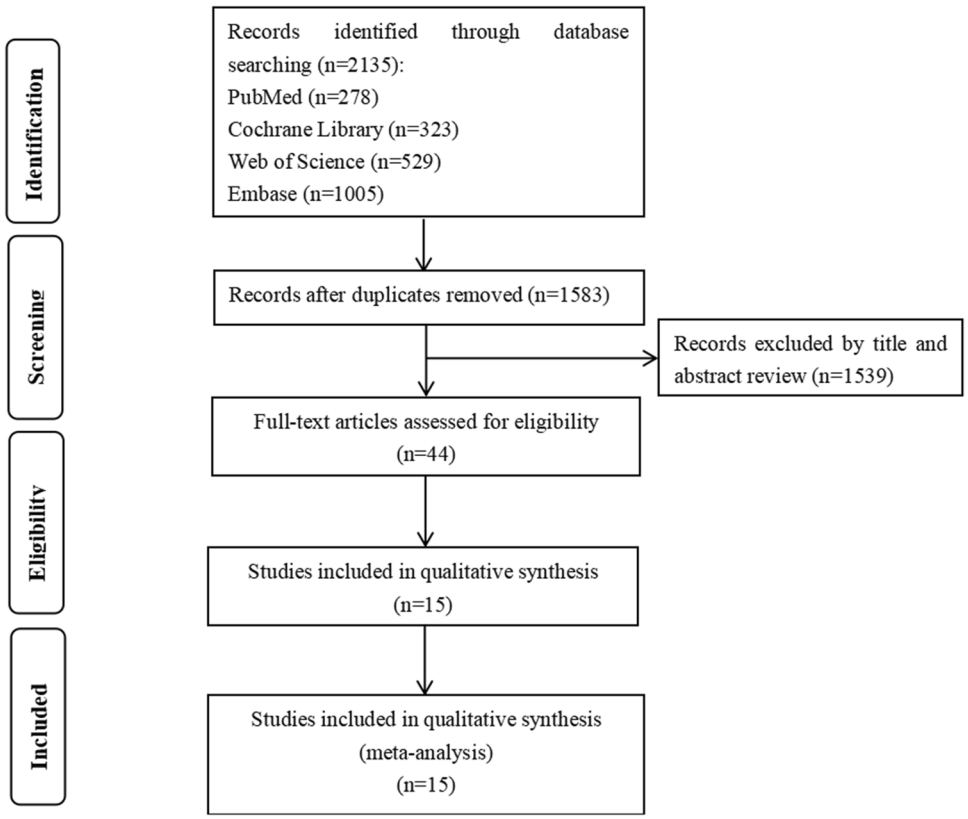

Fig. 1 Flow diagram of study selection

Network meta-analysis results

VTE recurrence

The results of the analysis of VTE occurrence are detailed in Supplementary Fig. 2. Apixaban reduced the risk of VTE compared with low-molecular heparin [OR = 0.53, 95% CI (0.32, 0.89)]. Apixaban reduced the risk of VTE compared with placebo [OR = 0.47, 95% CI (0.25, 0.89)]. Rivaroxaban reduced the risk of VTE compared with placebo [OR = 0.52, 95% CI (0.29, 0.90)]. All of the above differences were statistically significant (95% CI not including 1). The remaining DOACs (dabigatran, edoxaban) were not statistically significant (95% CI included 1) concerning the occurrence of VTE with low-molecular heparin, warfarin, and placebo.

The SUCRA results are shown in Fig. 3. The risk of VTE occurrence from lowest to highest was apixaban (SUCRA, 81.0), rivaroxaban (SUCRA, 73.0), edoxaban (SUCRA, 65.9), dabigatran (SUCRA, 51.4), warfarin (SUCRA, 30.8), and low-molecular heparin (SUCRA, 27.4).

Major bleeding

Supplementary Fig. 3 shows the NMA results for MB. Compared with placebo, edoxaban [odds ratio (OR) = 3.60, 95% CI (1.22, 10.65)] increased MB risk; the difference was statistically significant (the 95% CI did not include 1). Compared with LMWH, edoxaban [OR = 1.83, 95% CI (1.04, 3.22)] also increased MB risk, and the difference was statistically significant (the 95% CI did not include 1). The remaining DOACs (apixaban, rivaroxaban, dabigatran) and LMWH, warfarin, and placebo were not statistically significant in MB (the 95% CI included 1).

Figure 4 shows the SUCRA results. The probabilistic ranking of MB risk from superior to inferior were apixaban (SUCRA, 68.5), LMWH (SUCRA, 55.1), rivaroxaban (SUCRA, 53.0), warfarin (SUCRA, 35.9), dabigatran (SUCRA, 29.2), and edoxaban (SUCRA, 16.5).

Clinically relevant non-major bleeding

Supplementary Fig. 4 shows the NMA results for CRNMB. DOACs (apixaban, rivaroxaban, edoxaban) and LMWH, warfarin, and placebo were not statistically significant in CRNMB (the 95% CI included 1).

Figure 5 shows the SUCRA results. The effect of CRNMB risk from superior to inferior order of probability was LMWH (SUCRA, 73.0), apixaban (SUCRA, 57.8), edoxaban (SUCRA, 45.8), rivaroxaban (SUCRA, 35.3), and warfarin (SUCRA, 10.8).

Table 1 Main characteristics of included trials

Study	Indication	DOACs	Control	Number		Age (mean or median)		Sex (female, %)		Major bleeding/*n*		Clinically relevant non-major bleeding/*n*		Recurrent VTE/*n*		Follow-up
				DOACs	Control	DOACs	Control	DOACs	Control	DOACs	Control	DOACs	Control	DOACs	Control	
Khorana et al., 2019	Solid tumor and lymphoma	Rivaroxaban 10 mg once daily for 180 days	Placebo	405	404	63 (23–87)	62 (28–88)	47.1	51.1	8	4	11	8	25	37	6 months
Young et al., 2018	VTE and solid and hematologic malignancies	Rivaroxaban 15 mg twice daily for 3 weeks and then 20 mg once daily for a total of 6 months	Dalteparin 200 IU/kg during month 1 and then 150 IU/kg once daily for months 2–6	203	203	67 (22–87)	67 (34–87)	43	52	11	6	25	7	8	18	24 months
Agnelli et al., 2015	VTE and active cancer	Apixaban 10 mg twice daily for 7 days then 5 mg twice daily	Enoxaparin 1 mg/kg twice daily for at least 5 days then dose-adjusted warfarin (target (INR) of 2–3)	87	80	65.5	65.1	43.2	39.5	2	4	11	18	3/81	4/78	6 months
Raskob et al., 2016	VTE and active cancer	Edoxaban 60 mg once daily or 30 mg once daily under special clinical conditions	Warfarin ((INR) between 2·0 and 3·0) or placebos	109	99	67·0 (61·0–74·0)	66·0 (59·0–73·0)	50	39	5	3	16	23	4	7	12 months

Table 1 (continued)

Study	Indication	DOACs	Control	Number		Age (mean or median)		Sex (female, %)		Major bleeding/*n*		Clinically relevant non-major bleeding/*n*		Recurrent VTE/*n*		Follow-up
				DOACs	Control	DOACs	Control	DOACs	Control	DOACs	Control	DOACs	Control	DOACs	Control	
Raskob et al., 2018	VTE and active cancer	Edoxaban 60 mg once daily or 30 mg once daily under special clinical conditions	Dalteparin 200 IU/kg once daily for 30 days, a maximum daily dose of 18,000 IU then 150 IU/kg once daily	522	524	64.3 (11.0)	63.7 (11.7)	46.9	49.8	36	21	76	58	41	59	12 months
Levine et al., 2012	VTE and metastatic cancer	Apixaban 5 mg, 10 mg, 20 mg daily	Placebo	32, 29, 32	29	57 (41–67), 60 (39–76), 64 (25–86)	59 (20–82)	53.1, 56.7, 39.4	50	0, 0, 2	1	1, 1, 2	0	0, 0, 0	3	12 weeks
Carrier et al., 2019	VTE and cancer	Apixaban 2.5 mg twice daily	Placebo	288	275	61.2 (12.4)	61.7 (11.3)	58.4	58	10	5	21	15	12	28	210 days
Prins et al., 2014	VTE and active cancer	Rivaroxaban 15 mg twice daily for 21 days, followed by 20 mg once daily	Enoxaparin 1·0 mg/kg twice daily and warfarin INR 2·0–3·0	258	204	_	_	41	47	5	8	30	27	6	8	12 months

Table 1 (continued)

Study	Indication	DOACs	Control	Number		Age (mean or median)		Sex (female, %)		Major bleeding/*n*		Clinically relevant non-major bleeding/*n*		Recurrent VTE/*n*		Follow-up
				DOACs	Control	DOACs	Control	DOACs	Control	DOACs	Control	DOACs	Control	DOACs	Control	
Mokadem et al., 2020	Acute deep venous thrombosis and active malignancy	Apixaban 10 mg twice daily for 7 days followed by apixaban 5 mg twice daily (2.5 mg twice daily under special clinical conditions)	LMWH, enoxaparin (1 mg/kg/SC every 12 h) in 1:1 ratio	50	50	61.26 (11.23)	59.94 (9.71)	60	56	2	4	/	/	3	5	6 months
McBane II et al., 2020	VTE and active cancer/solid tumor	Apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months	Dalteparin (200 IU/kg for 1 month, followed by 150 IU/kg once daily)	145	142	64.4 (11.3)	64.0 (10.8)	52	51.3	0	2	9	7	1	9	6 months
Guntupalli et al., 2020	Postoperative patients with gynecologic malignant neoplasm	Apixaban 2.5 mg twice daily	Enoxaparin 40 mg daily	204	196	58.0 (21.0–87.0)	58.5 (18.0–89.0)	100	100	1	1	12	19	2	3	90 days
Schulman et al., 2015	VTE and cancer	Dabigatran	Warfarin	105	100	63.5 (12.1)	65.3 (12.0)	49	45	4	3	/	/	4/114	5/107	6 months

Table 1 (continued)

Study	Indication	DOACs	Control	Number		Age (mean or median)		Sex (female, %)		Major bleeding/*n*		Clinically relevant non-major bleeding/*n*		Recurrent VTE/*n*		Follow-up
				DOACs	Control	DOACs	Control	DOACs	Control	DOACs	Control	DOACs	Control	DOACs	Control	
Ageno et al., 2020	VTE and active cancer	Apixaban 10 mg twice daily for 7 days, followed by 5 mg twice daily	Dalteparin 200 IU/kg once daily for 1 month followed by 150 IU/kg (maximum daily dose allowed for dalteparin was 18,000 IU)	576	579	67.2 (11.3)	67.2 (10.9)	49.3	52.3	22	23	52	35	32	46	6 months
Wang et al., 2019	VTE and advanced or metastatic solid tumors	Rivaroxaban10 mg/days; 20 mg/days	Dalteparin 0.4 ml/day	26, 25	23	56 (27–76), 55 (20–72)	56 (24–79)	62, 44	70	0, 0	0	/	/	1	4	1 month
Planquette et al., 2021	VTE and solid cancer	Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily	Dalteparin once daily subcutaneous injections of 200 IU per kilogram of body weight for 1 month, then 150 IU per kilogram for 2 months	74	84	68.6 (62.9–77.8)	70.7 (62.7–78.7)	63	60	1	3	/	/	4	6	3 months

Abbreviations: *DOAC* direct oral anticoagulants, *INR* international normalized ratio, *LMWH* low-molecular-weight heparin, *VTE* venous thromboembolism

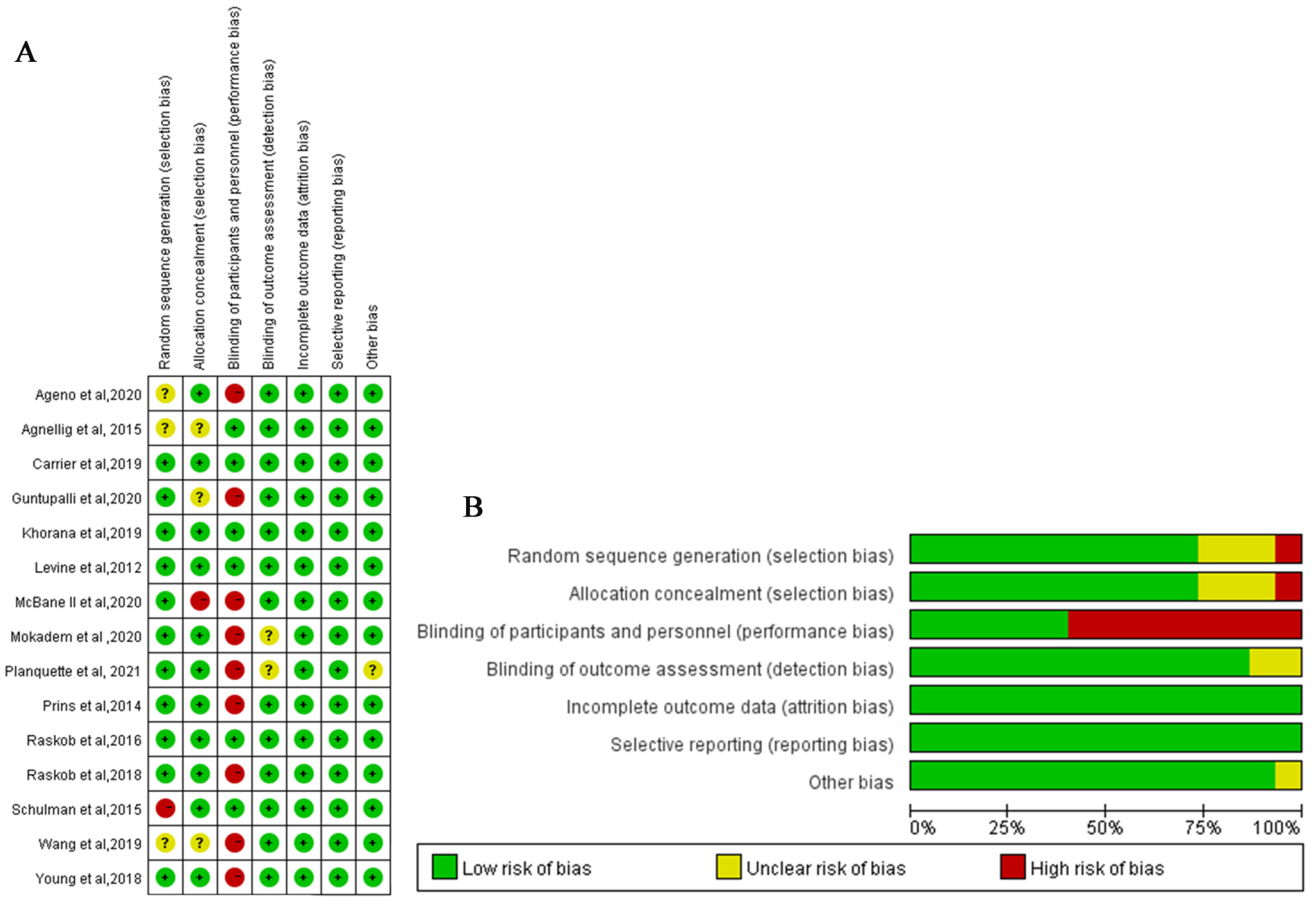

Fig. 2 Risk of bias in each study (**A**) and overall risk of each type of bias (**B**). Green, low risk of bias; yellow, unclear risk of bias; and red, high risk of bias

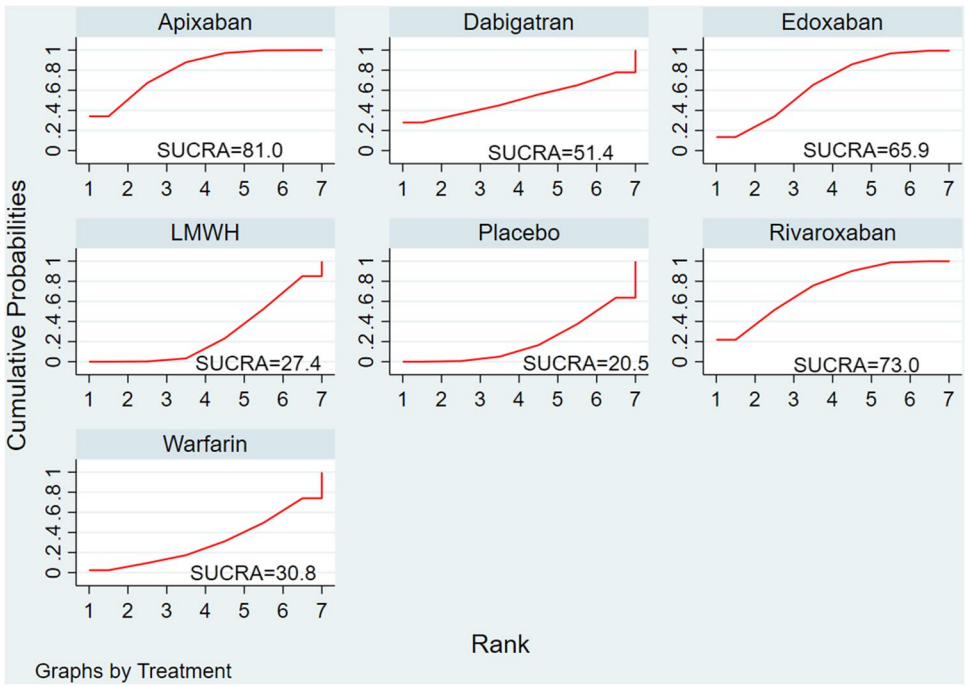

Fig. 3 The ranking for the cumulative probability of VTE occurrence. Higher scores are better

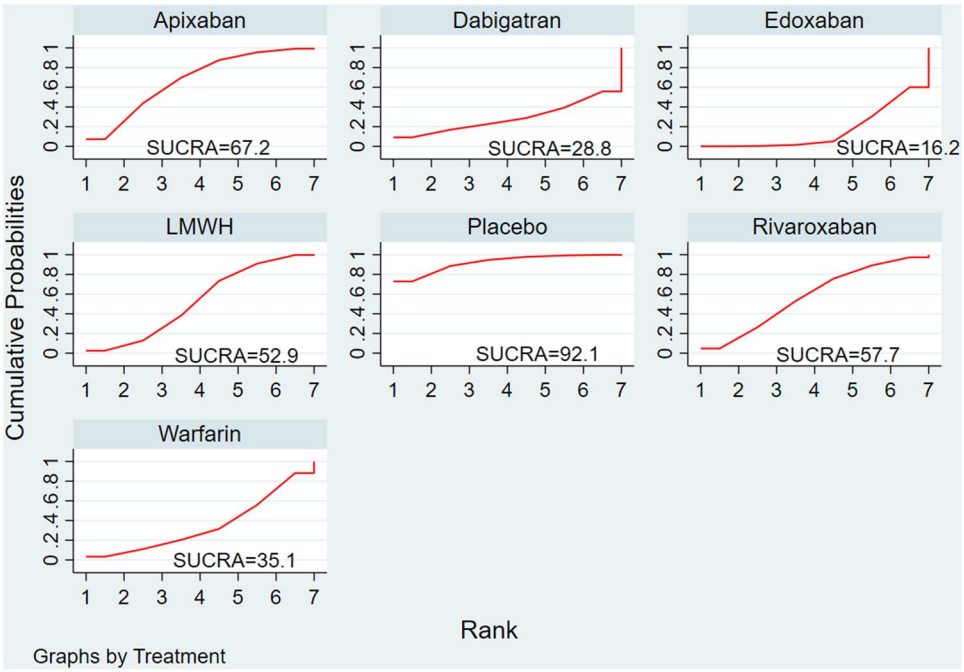

Fig. 4 The ranking for the cumulative probability of major bleeding. Higher scores are better

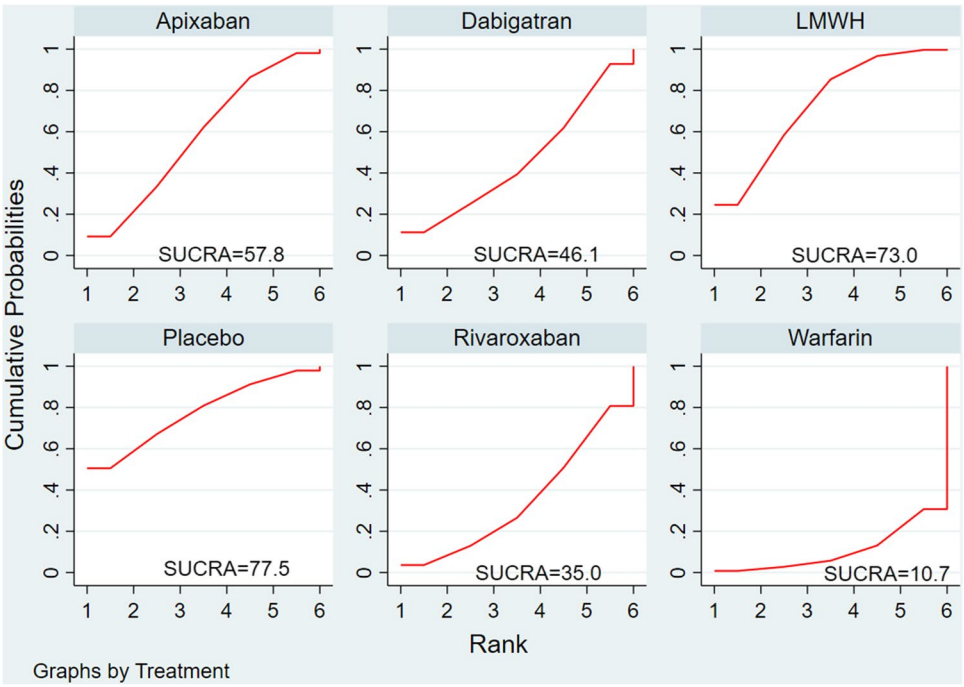

Fig. 5 The ranking for the cumulative probability of clinical non-major bleeding. Higher scores are better

Publication bias

Comparative-corrected funnel plots of VTE occurrence, MB, and CRNMB are shown in Supplementary Figs. 5, 6, and 7. The symmetry of the corrected funnel plot of the three indicators as seen in the figure is average, and there are individual scattered points, indicating that there may be small sample events in this study.

Discussion

In this systematic review and meta-analysis, we have compiled data from 15 RCTs comparing DOACs with LMWH, warfarin, and placebo for preventing and treating cancer-related VTE and provide comparative evidence for the efficacy and safety of apixaban, edoxaban, rivaroxaban, dabigatran, LMWH, and warfarin in CAT. The main findings

are that (1) apixaban reduces the risk of VTE in patients compared with LMWH. The results of the SUCRA ranking chart showed that apixaban was the most likely to reduce the risk of VTE occurrence, followed by rivaroxaban, edoxaban, dabigatran, and warfarin, respectively, and low-molecular heparin was the least likely to reduce the risk of VTE occurrence. (2) Edoxaban may increase the risk of MB in cancer patients with VTE. The results of the SUCRA ranking chart showed that apixaban was the most likely to reduce the risk of MB in cancer patients, followed by LMWH, rivaroxaban, warfarin, and dabigatran, respectively, and edoxaban was the least likely to reduce the risk of MB. (3) LMWH had the highest potential to reduce the risk of CRNMB, followed by apixaban, edoxaban, and rivaroxaban, respectively, and warfarin had the lowest.

In terms of VTE occurrence, apixaban had the highest efficacy, and LMWH had the lowest efficacy. DOACs reduced the risk of VTE more than warfarin and LMWH. This is partially consistent with the results of the meta-analysis by Dong et al. [15] and Song et al. [54]. Our SUCRA results showed that among DOACs, apixaban had the best efficacy against VTE in cancer patients, followed by rivaroxaban, edoxaban, and dabigatran, respectively. The results are consistent with the results of the NMA by Fuentes et al. [36]. Since Fuentes et al. included only three trials, SELECT-D [27], Hokusai VTE Cancer [44], and ADAM VTE [49], in their meta-analysis, and lacked information about the trials related to dabigatran, the results of this study can complement them and improve the comparison of the efficacy of different DOACs in preventing and treating of VTE in cancer patients.

In terms of MB, edoxaban increases the risk of MB in patients with cancer VTE compared to LMWH. There is no statistically significant difference between the other DOACs and LMWH and warfarin. This indicates that apixaban, rivaroxaban, and dabigatran are not inferior to LMWH and warfarin for MB. However, Samaranyake et al. [55] showed that there was no difference between DOACs (apixaban, rivaroxaban, edoxaban, dabigatran) and LMWH and warfarin. This may be because the RCTs they included did not include a comparison experiment with placebo, resulting in slightly different results from our study. Although the meta-analysis results show that the differences between the drugs are not large, there were significant differences between individual trials. In the SELECT-D [27] study, rivaroxaban presented a higher risk of MB in patients with gastrointestinal malignancies. Subgroup analysis of the Hokusai-VTE study [44] suggested that edoxaban may have a direct effect on the gastrointestinal tract. In the Caravaggio study [52], 33% of patients had gastrointestinal tumors, but the overall risk of hemorrhage in apixaban-treated patients did not increase. It is not clear whether these conflicting findings are related to the pharmacodynamics of specific DOACs (apixaban and other drugs). Therefore, if patients with a high risk of bleeding (e.g., patients with gastrointestinal tumors) choose DOACs for preventing and treating thrombosis, the bleeding-related laboratory indicators and clinical manifestations should be closely monitored. In terms of safety ranking, apixaban is the safest, followed by LMWH. In the results of Samaranyake et al. [55], the safety of LMWH in MB was higher than that of apixaban, which is inconsistent with our results. It may be because the RCTs that Samaranyake et al. included involved anticoagulant therapy for at least 6 months, while the anticoagulation treatment durations of the RCTs included in the present study were 3–12 months. The length of treatment may affect the bleeding results.

What is more, idarucizumab has been licensed by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) as a dabigatran-specific reversal drug for emergency surgery/urgent procedures and life-threatening or uncontrolled bleeding and has become the standard of care for dabigatran reversal [56–59]. Andexanet alfa is approved for reversing apixaban and rivaroxaban if the patient has life-threatening or excessive blood loss. Meanwhile, the EMA noted that there was insufficient evidence for the use of andexanet alfa to reverse the effects of edoxaban, another FXA inhibitor [60, 61].

In addition, in terms of CRNMB, there were no statistically significant differences between DOACs (apixaban, rivaroxaban, edoxaban) and LMWH and warfarin, which is the same as the results of Li et al. [24] and Rossel et al. [62], indicating that apixaban, rivaroxaban, and edoxaban are not inferior to LMWH and warfarin in terms of CRNMB. LMWH was the safest for CRNMB, followed by apixaban, which is consistent with the results of Fuentes et al. [36] and Samaranyake et al. [55]. In general, apixaban is comparable to LMWH in the safety ranking for MB and CRNMB, but because LMWHs are administered by injection, LMWH compliance is not as good as that of apixaban. Therefore, apixaban may be a safer drug for preventing and treating VTE in patients with cancer.

Our meta-analysis has several advantages. First, most of the patients included in the meta-analysis had active cancers and were receiving active treatment, which makes the research results more applicable to real-world clinical practice. By providing the comparative efficacy and safety results of six anticoagulant drugs, our NMA provides clinicians with new insights, which may aid anticoagulant drug choices selection. Apixaban may be preferred when considering MB that endangers the life and health of the patient and has the highest effectiveness and safety. Second, we conducted a comprehensive literature search to provide a detailed summary of the current best evidence and investigated the differences of all existing DOACs for preventing and treating VTE in patients with cancer. In the absence of RCTs that directly compare each DOAC, we used NMA

to indirectly compare the outcome data of all treatments, including edoxaban, rivaroxaban, apixaban, dabigatran, warfarin, and LMWH. Our findings provide evidence that the use of existing DOACs in patients with cancer with VTE is feasible.

At the same time, our research has several limitations. Firstly, our NMA was aimed at comparing the safety of DOACs, LMWH, and warfarin in the treatment of cancer-related VTE. However, as the number of included studies was insufficient, it was not possible to conduct a subgroup analysis of anticoagulation time. Therefore, we could not evaluate the optimal anticoagulation treatment duration for the patients. Consequently, it is not clear whether the relative risks and benefits of the assessed anticoagulant drugs will be different if a longer (or shorter) treatment time is used. Secondly, only the age and gender of the patients were extracted from this paper, and other basic characteristics of the patients were not described in this study because they were described differently in the included literature. Also, the oncological treatment adopted by the patients was not described in detail in the included literature, and therefore, it was not described in this study. In addition, due to the lack of detailed descriptions of patient's cancer subtype in many of the studies, we could not assess the results according to the cancer subtype. Cancers affecting different systems, such as gastrointestinal cancer, genitourinary system cancer, or hematological cancer, can also have differing bleeding risks. Therefore, it would be worthwhile to include more studies for further analysis in the future.

Conclusion

DOACs reduce the risk of developing or recurring VTE in cancer patients compared to LMWH and warfarin. Among the DOACs, apixaban had the highest efficacy, followed by rivaroxaban. For MB, apixaban had the highest safety profile, followed by LMWH, while for CRNMB, LMWH had the highest safety profile, followed by apixaban. Generally speaking, apixaban is the most effective and safest DOAC and presents better efficacy and relatively low bleeding risk among the VTE prevention and treatment drugs for patients with cancer.

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Author contribution JZ initiated the study. SW and ML performed data extraction and analyses. SW drafted the first version of the manuscript. JZ, SW, JC, and ML critically reviewed the manuscript and revised it. WX and SJ contributed to the analysis of data and provided critical revisions. ZZ, ZF, JQ, CG, and MC contributed to the conception and design, and they provided critical revisions of the paper for crucial intellectual content. All authors read and approved the final manuscript.

Data availability All data relevant to the study are included in the article or uploaded as supplementary information.

Code availability Not applicable.

Declarations

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate Not applicable.

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Conflict of interest The authors declare no competing interests.

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