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Network meta-analysis of anticoagulation strategies for venous thromboembolism in patients with cancer

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Abstract

Cancer-associated thrombosis (CAT) is a common complication in patients with malignancy. Although direct oral anticoagulants (DOACs) have emerged as a treatment option for CAT, there have not been head-to-head comparisons of these agents. We searched MEDLINE and EMBASE from inception to April 2020 for studies comparing the effect of different long-term anticoagulation strategies for venous thromboembolism (VTE) in patients with cancer. We performed a network meta-analysis comparing the antithrombotic strategies in the selected studies using random-effects model. We identified a total of 20 studies [9 randomized control trials (RCTs) and 11 subgroup analyses from other unique RCTs] with total of 6699 patients for inclusion in our analysis. There was no significant difference in recurrent VTE, all-cause death, major bleeding and clinically relevant non-major bleeding among DOACs. When DOACs were combined, recurrent VTE was significantly decreased in DOACs compared to low-molecular weight heparin (LMWH) and Vitamin K antagonist (VKA) [RR (95% CI) 0.75 (0.59–0.94); RR (95% CI) 0.51 (0.39–0.66), respectively] without significant increase in major bleeding or clinically relevant non-major bleeding. In patients with CAT, there was no significant difference in recurrent thrombotic event among different DOACs. Bleeding risk was comparable among all anticoagulation strategies. When DOACs were combined, DOACs were associated with a significant decrease in recurrent VTE with comparable bleeding risk to LMWH and VKA.

Keywords Cancer associated thrombosis · Venous thromboembolism · Oral anticoagulant · Direct oral anticoagulant

Abbreviations

CAT	Cancer associated thromboembolism
CI	Confidence intervals
CRNMB	Clinically relevant non-major bleeding
DOACs	Direct oral anticoagulants
DVT	Deep vein thrombosis
LMWH	Low-molecular weight heparin
PE	Pulmonary embolism
RCT	Randomized controlled trials
RR	Risk ratio
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

Highlights

- DOACs showed significant reduction in recurrent VTE compared to LMWH and VKA.
- There was no significant difference in recurrent VTE among different DOACs.
- Bleeding risks were comparable among all anticoagulation strategies.

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Introduction

Venous thromboembolism (VTE) is a common complication in patients with malignancy, making it the second leading cause of death after cancer itself [1, 2]. Management of VTE in this population is challenging, owing to the high risk of recurrence and inherent risk of bleeding [3]. Current guidelines universally recommend subcutaneous lower molecular weight heparin (LMWH) over vitamin K antagonist(VKA) as randomized controlled trials (RCT) have shown reduced risk of VTE recurrence without significant difference in major bleeding in LMWH arm [4–7]. However, the use of LMWH can be limited due to patient intolerance to daily injection, cost, and concerns for heparin-induced thrombocytopenia [8]. As direct oral anticoagulants (DOACs) have shown promising outcomes for non-cancer VTE, they have emerged as a treatment option for cancer associated thromboembolism (CAT). The International Initiative on Thrombosis and Cancer (ITAC) and American Society of Clinical Oncology (ASCO) guidelines have already incorporated edoxaban and rivaroxaban as first line option for CAT along with already recommended LMWH [6, 7], after two RCTs showing lower rates of recurrent VTE in these agents compared to LMWH [9, 10]. A results from ADAM VTE and Caravaggio trial were published recently comparing apixaban and LMWH in CAT [8, 11]. As yet there have not been a head-to-head comparisons of DOACs, by using a network meta-analysis we sought to compare the safety and efficacy profile of different long-term anticoagulation agents including each DOAC in patients with CAT.

Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12].

Data Sources and search strategy

A comprehensive literature search of PUBMED and EMBASE database was performed from inception through April 1st 2020 to include all relevant studies investigating the safety and efficacy of different types of long-term anticoagulation for CAT. The following search terms were applied: *deep vein thrombosis or DVT or pulmonary embolism or PE or venous thromboembolism or VTE or cancer associated thromboembolism or CAT; cancer or malignancy; treatment or anticoagulation or anticoagulant or heparin or low molecular weight heparin or LMWH or vitamin K antagonist or VKA or coumadin or warfarin or novel oral anticoagulant or NOAC or direct oral anticoagulant or DOAC or apixaban or dabigatran or edoxaban or rivaroxaban; randomized controlled trial.* A detailed search strategy of each search engine is summarized in e- e-Fig. 1. We additionally conducted manual search of reviews and references of initially identified articles to include all relevant studies.

Study selection

Studies meeting the following criteria were included in our network meta-analysis: (1) the study was published in a peer-reviewed journals; (2) the design was RCT or subgroup analysis of RCT; (3) the study was comparing the effect of different types of long-term (≥ 3 months) anticoagulation in patients with CAT; (4) the study reported at least one of the prespecified endpoints. There was no restriction on publication language.

Outcomes

The primary efficacy outcome of this network meta-analysis was recurrent VTE. Secondary efficacy outcomes were recurrent deep vein thrombosis (DVT), and recurrent pulmonary embolism (PE) and all-cause mortality. The safety endpoints were trial defined endpoints of major bleeding and clinically relevant non-major bleeding (CRNMB).

Data extraction and quality assessment

Two investigators (HU and HM) had independently performed a literature search using a prespecified search term. The search was initially screened for eligibility through the titles and abstracts. When there was any potential correlation, full texts of articles were retrieved for further assessment. Any divergence in the study selection and data extraction process was solved by consulting with the third author (TK).

The study characteristics (publication year, trial design, comparison regimen, maximum reported follow-up period, and studied outcomes), baseline patient characteristics (number of patients, age, cancer status, and cancer type), and outcome measures were extracted from each included trial.

The risk of bias in regard to random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting were assessed by using the Cochrane Collaboration's tool [13]. Two investigators (HU and HM) reviewed the studies and judged selection, comparability and, outcomes independently with any uncertainties resolved by discussion.

Data synthesis and statistical analysis

For each study, event numbers in relation to the main outcomes were collected. The pooled results are presented as risk ratios (RR) and 95% confidence interval (CI). Seven anticoagulation strategies were to be compared. We included LMWH and VKA as strategies while each of the DOACs; apixaban, rivaroxaban, edoxaban [Factor Xa inhibitors], and dabigatran [direct thrombin inhibitor]) were individually analyzed. In different analysis, we analyzed outcomes comparing combined DOACs versus LMWH versus VKA.

A network meta-analysis was performed using the "netmeta" 3.6.1 package (R Foundation for Statistical Computing, Vienna, Austria) [14]. The random-effects model was used for the analysis. A p-value of less than 0.05 was considered significant. $I^2$and the Q statistics were used to quantify heterogeneity. An I^2 value < 25% suggests low heterogeneity whereas a value > 50% suggests high heterogeneity [15].

Results

Literature search and study characteristics

Our search identified 20 studies (9 RCTs and subgroup analysis taken from 11 separate RCTs) with total of 6699 patients eligible to be included in our network meta-analysis (Fig. 1). Ten studies compared LMWH versus VKA [4, 5, 16–23], 6 studies compared DOACs versus VKA [24–29], and 4 studies compared DOACs versus LMWH [8–11]. The details of study design of the included trials and patient characteristics are summarized in Table 1 and e-Table 1, respectively. The mean age of the studied population ranged from 59.2 to 67.2. The summary of studied outcomes and definition of major bleeding and CRNMB are summarized in e-Table 2 and e-Table 3, respectively. The risk of bias of the studies included in our analysis is summarized in e-e-Fig. 2. The diagram of network meta-analysis comparing recurrent VTE and other outcomes are provided in Fig. 2 and e- e-Fig. 3 and e- e-Fig. 4, respectively.

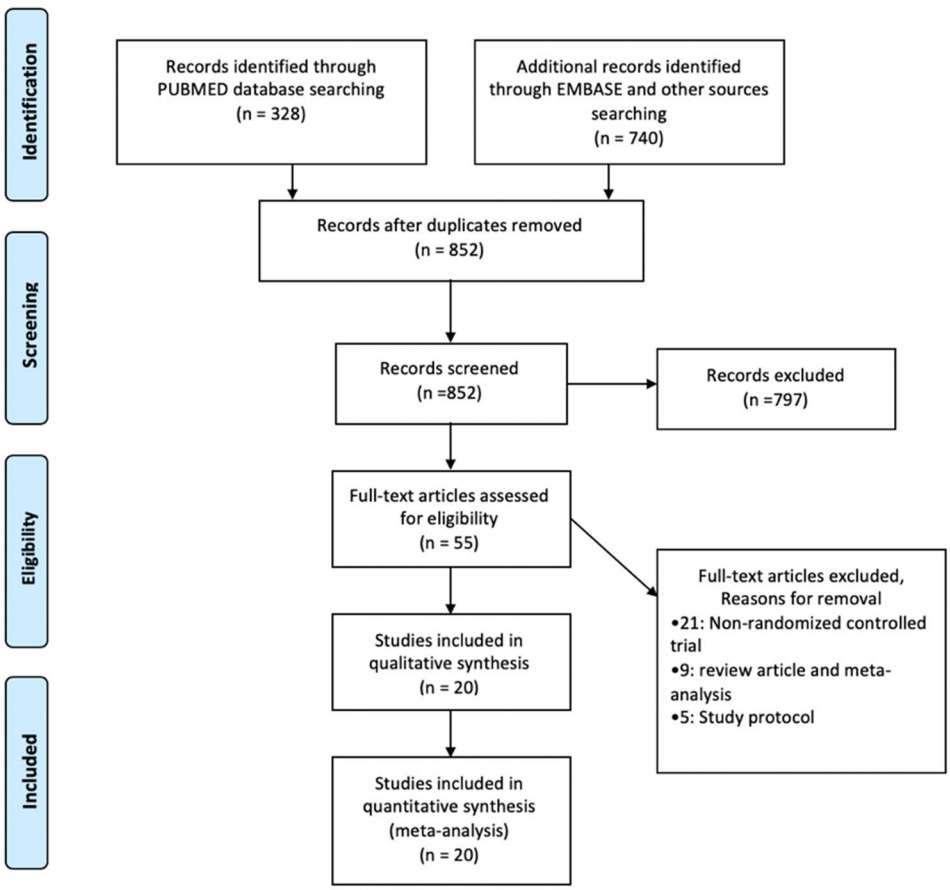


Fig. 1 The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram of study selection

Table 1 Study characteristics

Study	Year	Study design	Comparison			Follow up (Months)	Diagnosis	Studied outcome
LMWH versus. VKA			Drug	Dosage	Duration (Months)			
CANTHANOX [16]	2002	RCT	Enoxaparin	1.5 mg/kg subcutaneously QD	3	6	PE/VTE (No definition of symptomatic or asymptomatic)	Recurrent VTE, All-cause death, Major bleeding, CRNMB
			Warfarin	Enoxaparin bridge to warfarin INR goal 2–3				
CATCH [4]	2015	RCT	Tinzaparin	175 IU/kg subcutaneously QD	6	6	Symptomatic PE/proximal DVT	Recurrent VTE, Recurrent DVT, Recurrent PE, All-cause death, Major bleeding, CRNMB
			Warfarin	Tinzaparin bridge to warfarin INR goal 2–3				
CLOT [5]	2003	RCT	Dalteparin	200 IU/kg subcutaneously QD × 1 month followed by 150 IU/kg subcutaneously QD	6	6	Symptomatic PE/ proximal DVT	Recurrent VTE, Recurrent DVT, Recurrent PE, All-cause death, Major bleeding
			VKA	Dalteparin bridge to warfarin or acenocoumarol INR goa 2–3				
Daskalopoulos [17]	2005	RCT subgroup	Tinzaparin	175 IU/kg subcutaneously QD	6	12	Symptomatic proximal DVT	Recurrent VTE, Recurrent DVT, All-cause death, Major bleeding, CRNMB
			Acenocoumarol	UFH bridge to acenocoumarol INR goal 2–3				
Gonzalez-Fajardo [18]	1999	RCT subgroup	Enoxaparin	40 mg subcutaneously BID × 7 days followed by 40 mg subcutaneously QD	3	12	Symptomatic DVT without PE	Recurrent VTE, All-cause death
			Coumarin	UFH bridge to coumarin INR goal 2–3				
LITE [19]	2006	RCT	Tinzaparin	175 IU/kg subcutaneously QD	3	12	Symptomatic proximal DVT with or without PE	Recurrent VTE, Recurrent DVT, Recurrent PE, All-cause death, Major bleeding, CRNMB
			Warfarin	UFH bridge to warfarin INR goal 2–3				
Lopez-Beret [20]	2001	RCT subgroup	Nadroparin	0.1025 IU/kg subcutaneously BID	3–6	12	Symptomatic DVT	Recurrent VTE, Recurrent DVT, All-cause death, Major bleeding, CRNMB
			Acenocoumarol	Nadroparin bridge to acenocoumarol INR goal 2–3				
ONCENOX [21]	2006	RCT	Enoxaparin	1.0 mg/kg subcutaneously BID × 5 days followed by 1.0 or 1.5 mg/kg subcutaneously	6	7	Symptomatic VTE	Recurrent VTE, All-cause death, Major bleeding, CRNMB
			Warfarin	Enoxaparin bridge to warfarin INR goal 2–3				
Romera [22]	2008	RCT subgroup	Tinzaparin	175 IU/kg subcutaneously QD	6	12	Symptomatic proximal DVT	Recurrent VTE
			Acenocoumarol	Tinzaparin bridge to acenocoumarol INR goal 2–3				

Table 1 (continued)

Study	Year	Study design	Comparison			Follow up (Months)	Diagnosis	Studied outcome
LMWH versus. VKA			Drug	Dosage	Duration (Months)			
Veiga [23]	2000	RCT subgroup	Enoxaparin	UFH bridge to enoxaparin 40 mg subcutaneously QD	3–6	12	Symptomatic proximal DVT without PE	Recurrent VTE, Recurrent DVT, Recurrent PE, Major bleeding, CRNMB
			Acenocoumarol	UFH bridge to acenocoumarol INR goal 2–3				
DOAC versus VKA								
AMPLIFY [24]	2015	RCT subgroup	Apixaban	10 mg BID × 7 days followed by 5 mg BID	6	6	Symptomatic PE/ proximal DVT	Recurrent VTE, Major bleeding, CRNMB
			Warfarin	Enoxaparin bridge to warfarin INR goal 2–3				
EINSTEIN-DVT [25] EINSTEIN-PE [26, 37]	2010 2012	RCT subgroup	Rivaroxaban	15 mg BID × 21 days followed by 20 mg QD	3/6/12	12	Symptomatic PE/DVT	Recurrent VTE, All-cause death, Major bleeding, CRNMB
			VKA	Enoxaparin bridge to warfarin or acenocoumarol INR goal 2–3				
HOKUSAI-VTE [27]	2016	RCT subgroup	Edoxaban	Enoxaparin or UFH bridge to edoxaban 60 mg QD[a]	3–12	12	Symptomatic PE/ proximal DVT	Recurrent VTE, Major bleeding, CRNMB
			Warfarin	Enoxaparin or UFH bridge to warfarin INR goal 2–3				
RE-COVER I [28] RECOVER II [29, 38]	2009 2014	RCT subgroup	Dabigatran	UFH/LMWH/fondaparinux bridge to dabigatran 150 mg BID	6	6	VTE (No definition of symptomatic or asymptomatic)	Recurrent VTE, Recurrent DVT, Recurrent PE, All-cause death, Major bleeding, CRNMB
			Warfarin	UFH/LMWH/fondaparinux bridge to warfarin INR goal 2–3				
DOAC versus LMWH								
ADAM VTE [8]	2019	RCT	Apixaban	10 mg BID × 7 days followed by 5 mg BID	6	6	DVT/PE/Splanchnic VT/ cerebral VT	Recurrent VTE, Recurrent DVT, Recurrent PE, All-cause death, Major bleeding, CRNMB
			Dalteparin	200 IU/kg subcutaneously QD × 1 month followed by 150 IU/kg subcutaneously QD				
Caravaggio [11]	2020	RCT	Apixaban	10 mg BID × 7 days followed by 5 mg BID	6	7	Symptomatic or incidental proximal DVT/PE	Recurrent VTE, Recurrent DVT, Recurrent PE, All-cause death, Major bleeding, CRNMB
			Dalteparin	200 IU/kg subcutaneously QD × 1 month followed by 150 IU/kg subcutaneously QD				

Table 1 (continued)

Study	Year	Study design	Comparison			Follow up (Months)	Diagnosis	Studied outcome
LMWH versus. VKA			Drug	Dosage	Duration (Months)			
HOKUSAI VTE cancer [9]	2018	RCT	Edoxaban	LMWH bridge to edoxaban 60 mg QD[a]	6–12	12	Symptomatic or asymptomatic proximal DVT/PE	Recurrent VTE, Recurrent DVT, Recurrent PE, All-cause death, Major bleeding, CRNMB
			Dalteparin	200 IU/kg subcutaneously QD × 30 days followed by 150 IU/kg QD				
SELECT-D [10]	2018	RCT	Rivaroxaban	15 mg BID × 21 days followed by 20 mg QD	6	24	Symptomatic and incidental PE, symptomatic proximal DVT	Recurrent VTE, Recurrent DVT, Recurrent PE, All-cause death, Major bleeding, CRNMB
			Dalteparin	200 IU/kg subcutaneously QD × 1 month followed by 150 IU/kg subcutaneously QD				

BID twice daily, *CRNMB* clinically relevant non-major bleeding, *DVT* deep vein thrombosis, *DOAC* direct oral anticoagulant, *INR* International normalized ratio, *LMWH* low-molecular weight heparin, *PE* pulmonary embolism, *QD* once daily, *RCT* randomized control trial, *UFH* unfractionated heparin, *VKA* vitamin K antagonist, *VT* venous thrombosis, *VTE* venous thromboembolism

[a]30 mg QD for patients with: Creatinine Clearance of 30–50 ml/min, bodyweight of 60 kg or less, or receiving concomitant treatment with the P-glycoprotein inhibitors quinidine or verapamil

Each DOAC vs. LMWH vs. VKA

Among DOACs, the Factor Xa inhibitors, rivaroxaban, edoxaban, and apixaban were associated with a decreased risk of recurrent VTE compared to VKA [RR (95% CI) 0.49 (0.29–0.83), P = 0.01; 0.53 (0.36–0.77), P = 0.001; 0.44 (0.27–0.72), P = 0.001, respectively] but the direct thrombin inhibitor, dabigatran was not. Similarly, LMWH was associated with a decreased risk of recurrent VTE compared to VKA [RR (95% CI) 0.67 (0.53–0.85), P < 0.001] (Fig. 3). LMWH and edoxaban were associated with a decreased risk of recurrent DVT compared to VKA [RR (95% CI) 0.53 (0.33–0.85), P = 0.01; 0.29 (0.12–0.71), P = 0.01, respectively] (e-Fig. 5). There was no significant difference in recurrent PE among studied antithrombotic strategies (e-Fig. 6). Overall, there was no significant difference in recurrent VTE, DVT, and PE among DOACs (Fig. 3, e-Fig. 4, and e-Fig. 5, respectively). There was no significant heterogeneity or inconsistency on recurrent VTE ($I^2 = 4.4\%$, P = 0.53; P = 0.21, respectively). There was no significant heterogeneity on recurrent DVT ($I^2 = 19.5\%$, P = 0.28), and PE ($I^2 = 20.2\%$, P = 0.29).

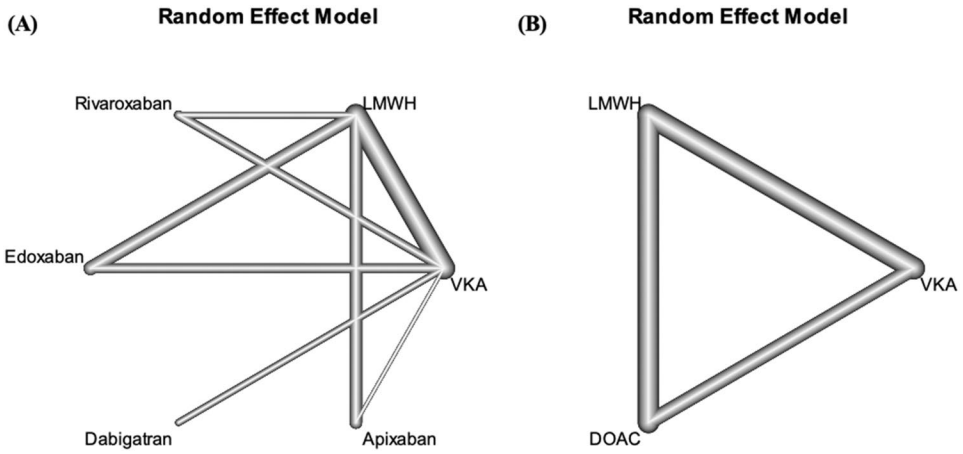
There was no significant difference in all-cause mortality among studied antithrombotic strategies (e-Fig. 7) with no significant heterogeneity or inconsistency ($I^2 = 0\%$, P = 0.44; P = 0.75, respectively).

There were no significant differences in major bleeding and CRNMB among studied antithrombotic strategies (e-Fig. 8 and e-Fig. 9). Major bleeding was not accompanied by significant heterogeneity or inconsistency ($I^2 = 19.1\%$, P = 0.33; P = 0.22, respectively). CRNMB was accompanied with high heterogeneity and significant inconsistency ($I^2 = 54.7\%$, P = 0.35; P = 0.004, respectively).

Combined DOACs vs. LMWH vs. VKA

When DOACs were combined, recurrent VTE was significantly decreased in DOACs compared to LMWH and VKA [RR (95% CI) 0.75 (0.59–0.94), P = 0.02; 0.51 (0.39–0.66), P < 0.001, respectively], and in LWMH compared to VKA [RR (95% CI) 0.68 (0.55–0.85), P < 0.001] (Fig. 4). There was no significant heterogeneity but significant inconsistency ($I^2 = 0\%$, P = 0.81; P = 0.03, respectively).

Major bleeding and CRNMB were comparable among DOACs, LMWH and VKA (e-Fig. 10). Major bleeding was not accompanied by significant heterogeneity or inconsistency ($I^2 = 22\%$, P = 0.33; P = 0.07, respectively). CRNMB was accompanied with moderate heterogeneity and significant inconsistency ($I^2 = 42\%$, P = 0.06; P = 0.01, respectively).



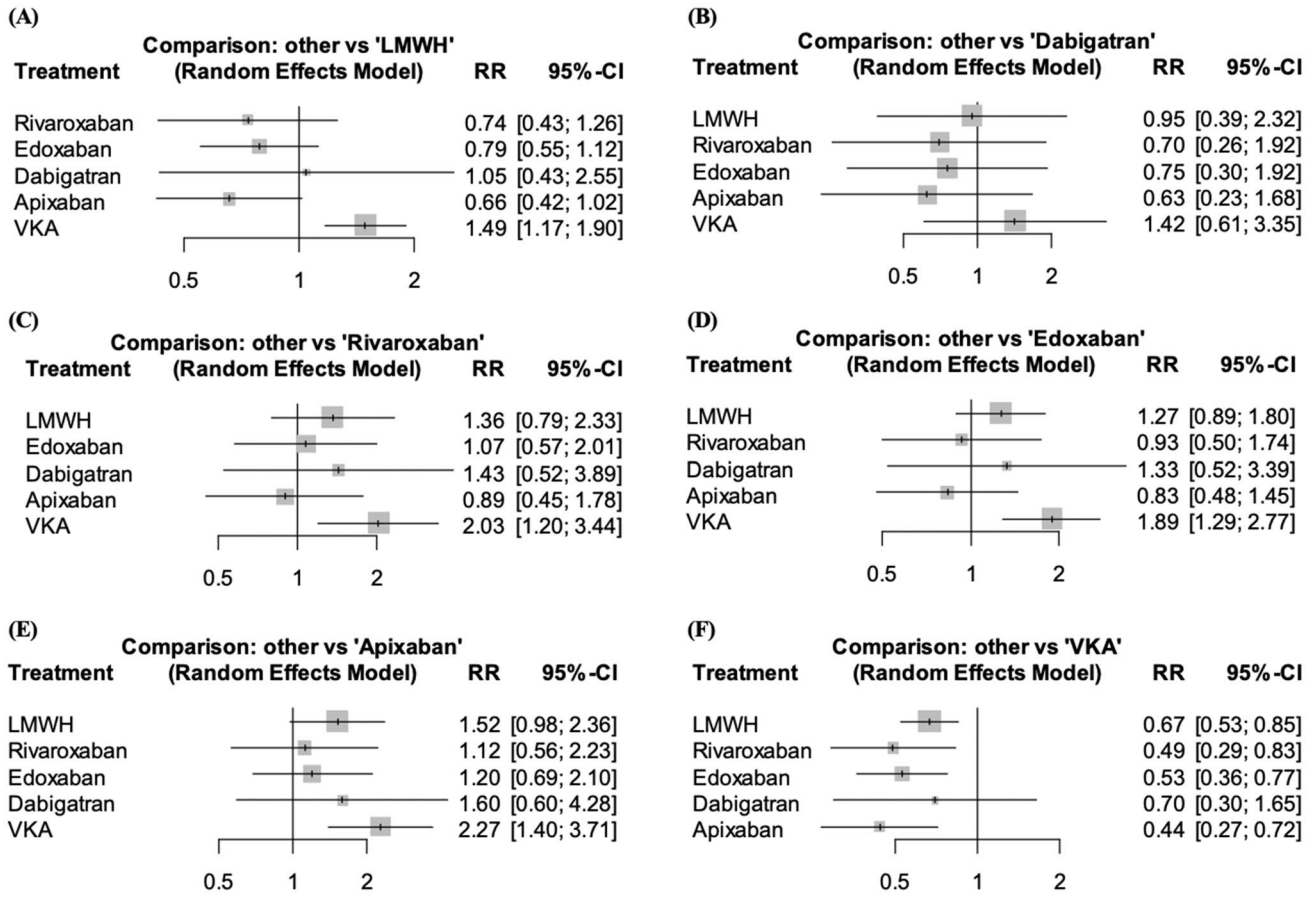


Fig. 2 Diagram of network meta-analysis comparing recurrent venous thromboembolism. **a** each DOAC versus LMWH versus VKA, **b** combined DOAC versus LMWH versus VKA. *DOAC* direct oral anticoagulant, *LMWH* low-molecular weight heparin, *VKA* vitamin K antagonist

Fig. 3 Effect of antithrombotic strategies on recurrent venous thromboembolism (Each DOAC vs. LWMH vs. VKA) (random effect model). The figure presents risk ratio (RR) and 95% confidence interval (CI) for each treatment arm. **a** others versus LMWH, **b** others versus Dabigatran, **c** others versus Rivaroxaban, **d** others versus Edoxaban, **e** others versus Apixaban, **f** others versus VKA. *LMWH* low molecular weight heparin, *VKA* vitamin K antagonist

Discussion

The main findings of this network meta-analysis comparing different anticoagulation strategies for patients with CAT are as follows: (1) There was no significant difference in recurrent VTE, DVT, and PE among DOACs. (2) There was no significant difference in major bleeding and non-major bleeding among all anticoagulation strategies. (3) LMWH and Xa inhibitors were associated with a decreased risk of

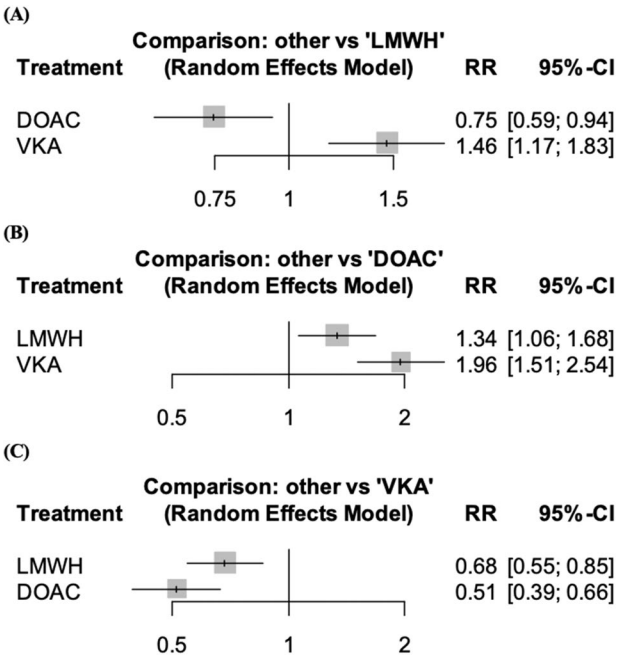


Fig. 4 Effect of antithrombotic strategies on recurrent venous thromboembolism (Combined DOACs vs. LWMH vs. VKA) (random effect model). The figure presents risk ratio (RR) and 95% confidence interval (CI) for each treatment arm. **a** others versus LMWH, **b** others versus DOACs, **c** others versus VKA. *DOAC* direct oral anticoagulant, *LMWH* low-molecular weight heparin, *VKA* vitamin K antagonist

recurrent VTE compared to VKA but dabigatran was not. (4) When DOACs were pooled together, DOACs were associated with a significant decrease in recurrent VTE with comparable bleeding risk compared to LMWH and VKA.

DOACs have rapidly expanded their role in treatment for CAT, after RCTs showing edoxaban and rivaroxaban to be associated with relatively decreased risk of recurrent VTE but with higher risk of bleeding compared to LMWH [9, 10]. The ITAC and ASCO guidelines now include these two DOACs as first line option for CAT along with LMWH [6, 7]. Recently, two RCTs were published comparing apixaban versus LMWH for CAT, adding another evidence of DOACs use in CAT. The ADAM VTE trial demonstrated apixaban to be associated with low risk of VTE recurrence and major bleeding compared to LMWH [8]. The Caravaggio trial has shown apixaban to be non-inferior to LMWH in terms of recurrent VTE without an increased risk of major-bleeding [11]. By using a network meta-analysis, our study demonstrated robust evidence of comparable efficacy and safety of DOACs, LMWH and VKA in the treatment of CAT.

Currently, there is no head-to-head RCT comparing DOACs in patients with CAT. A large propensity score-matched cohort analysis of apixaban versus rivaroxaban in patients with VTE demonstrated apixaban to be associated with a decreased risk of VTE and major bleeding events compared to rivaroxaban. However, this effect was not demonstrated in the subgroup analysis in patients with active cancer [30]. A Network meta-analysis comparing only Xa inhibitors in CAT has shown apixaban to be associated with lower risk of VTE recurrence compared to rivaroxaban and edoxaban in ranking probability analysis, however there was no significant statistical difference among the studied Xa inhibitors [31]. In our study, we were able to compare all available DOACs including dabigatran, and showed comparable rates of recurrent VTE, DVT and PE. Moreover, when DOACs were pooled together, they were associated with decreased risk of VTE compared to LMWH and VKA. DOACs appears to have a class effect of reduction of VTE in CAT, and it may be plausible to use any available DOAC in these patients.

RCTs have shown conflicting results about the bleeding risk of DOACs compared to LMWH in CAT; compared to LMWH, rivaroxaban and edoxaban have increased risk of CRNMB and major bleeding, respectively whereas, apixaban was associated with similar if not decreased major bleeding [8–11]. Although the reason for lower bleeding rates with apixaban is unclear, it has been hypothesized that lower peak-to-trough ratio of DOACs dosed twice daily (apixaban and dabigatran) compared to DOACs dosed once daily (rivaroxaban and edoxaban) may be contributing to the decreased incidence of bleeding [32–36]. Nonetheless, when each DOACs were compared using network meta-analysis, our analysis revealed no significant difference in bleeding rate. Moreover, when DOACs were pooled together, DOACs, LMWH, and VKA showed comparable bleeding rate.

The major strength of this study is that this study is the first study to investigate the difference of all existing DOACs for treatment of VTE in patients with cancer. In the context of lacking RCTs directly comparing each DOACs, by demonstrating no significant difference in thrombotic and bleeding outcomes, our study result provides evidence that it may be plausible to use any existing DOACs in these population.

The present analysis has several limitations. First, the lack of individual patient level data limits our ability to adjust for patient characteristics. Second, as bleeding risk of using DOACs are known to be different in between cancer types [9, 10], it may have been ideal if adjusting with or subgroup analysis among different cancer type was available to perform. However, this was unavailable due to lack of reporting of the individual trial included. Third, we included sub-analysis for CAT of trials performed for all-comer VTE. Nonetheless, this is a largest meta-analysis comparing anticoagulation regimen in CAT with reassuring result of DOACs use in this population.

Conclusions

In patients with CAT, there was no significant difference in recurrent VTE, DVT and PE among each DOACs. Bleeding risk was comparable among all anticoagulation strategies. When DOACs were combined, they were associated with significant reduction in recurrent VTE with comparable bleeding risk compared to LMWH and VKA.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts to report.

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