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ORIGINAL RESEARCH

Comparing Anticoagulation Strategies for Venous Thromboembolism Associated With Active Cancer

A Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND Current guidelines recommend several direct oral anticoagulant agents (DOACs) equally for managing cancer-associated venous thromboembolism (VTE).

OBJECTIVES The aim of this study was to assess the efficacy and safety of DOACs in patients with active cancer.

METHODS Literature searches were conducted in PubMed, Embase, and Cochrane Central in November 2022. Randomized controlled trials investigating anticoagulation strategies (vitamin K antagonists, parenteral anticoagulation [eg, low-molecular weight heparin], and DOACs) for VTE in patients with active cancer were identified for network meta-analysis. The outcomes included recurrent VTE, recurrent pulmonary embolism, recurrent deep venous thrombosis, major bleeding, clinically relevant nonmajor bleeding (CRNMB), and a composite outcome of major bleeding or CRNMB. Pooled HRs and 95% CIs were estimated using either the HR or relative risk provided from each study. Random-effects models were used for all the analyses.

RESULTS Seventeen randomized controlled trials involving 6,623 patients with active cancer were included. No significant differences were found among the DOACs for efficacy outcomes (recurrent VTE, pulmonary embolism, and deep venous thrombosis). In terms of major bleeding, apixaban was similarly safe compared with dabigatran and rivaroxaban but was associated with a decreased risk compared with edoxaban (HR: 0.38; 95% CI: 0.15-0.93). Regarding CRNMB, edoxaban was similarly safe compared with apixaban but was associated with a decreased risk compared with rivaroxaban (HR: 0.31; 95% CI: 0.10-0.91). Compared with parenteral anticoagulation, apixaban was associated with a reduced risk for recurrent VTE (HR: 0.60; 95% CI: 0.38-0.93) without increasing bleeding, edoxaban was associated with an increased risk for major bleeding or CRNMB (HR: 1.35; 95% CI: 1.02-1.79), and rivaroxaban was associated with an increased risk for CRNMB (HR: 3.76; 95% CI: 1.43-9.88).

CONCLUSIONS DOACs demonstrate comparable efficacy but exhibit different safety profiles. Apixaban may confer an antithrombotic benefit without an increased risk for bleeding, distinguishing it from other contemporary anticoagulation strategies in patients with active cancer and VTE. (J Am Coll Cardiol CardioOnc 2024;6:99-113) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CRNMB = clinically relevant nonmajor bleeding

DOAC = direct oral anticoagulant agent

DVT = deep venous thrombosis

LMWH = low-molecular weight heparin

PE = pulmonary embolism

RCT = randomized controlled trial

RR = relative risk

VKA = vitamin K antagonist

VTE = venous thromboembolism

Cancer-associated thrombosis represents 30% of venous thromboembolism (VTE) cases and ranks as the second leading cause of death among patients with active cancer.[1] This includes both pulmonary embolism (PE) and deep venous thrombosis (DVT), conditions for which patients with active cancer often present multiple risk factors.[2] Several randomized controlled trials (RCTs) exploring treatment for cancer-associated VTE have demonstrated that parenteral anticoagulation, such as low-molecular weight heparin (LMWH), is associated with a reduced risk for recurrent VTE without an increase in major bleeding risk compared with vitamin K antagonist (VKA) therapy.[3-6] Recent trials have shown that direct oral anticoagulant agents (DOACs) are as effective as parenteral anticoagulation in reducing recurrent VTE.[7-11] Although internationally recognized guidelines offer differing recommendations, the most recent 2022 European Society of Cardiology guidelines for cardio-oncology recommend the use of apixaban, edoxaban, rivaroxaban, and parenteral anticoagulation (Class 1, Level of Evidence: A) for treatment of patients with cancer-associated thrombosis.[12-16] However, it remains unclear whether each DOAC varies in efficacy and safety for treating VTE in patients with active cancer, thus necessitating further studies.[17,18] In this context, we conducted a systematic review and network meta-analysis to investigate the efficacy and safety of various anticoagulation strategies, with a particular focus on comparing DOACs for patients with VTE (PE or DVT) and active cancer.

METHODS

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[19] Exemption from Institutional Review Board oversight and ethics review was granted on the basis of the study's no risk or minimal risk to participants. The study protocol was registered in the International Prospective Register of Systematic Reviews (CRD42022378819).

ELIGIBILITY CRITERIA. The eligibility criteria for study inclusion were as follows. The design was an RCT or an RCT subgroup analysis of 2 different anticoagulation treatments (VKA, parenteral anticoagulation [LMWH, unfractionated heparin, fondaparinux, idraparinux, or idrabiotaparinux], dabigatran, apixaban, edoxaban, and rivaroxaban) for the treatment and recurrence prevention of cancer-associated VTE in patients with active cancer. The study reported outcomes for recurrent VTE, recurrent PE, recurrent DVT, major bleeding, clinically relevant nonmajor bleeding (CRNMB), a composite outcome of major bleeding or CRNMB, net adverse clinical outcome (a composite outcome of recurrent VTE and major bleeding), or all-cause death. The study was published in a peer-reviewed journal. We excluded outcomes from RCTs if the outcomes were derived from a population in which <90% of the patients had active cancer. Cancer was considered active if the cancer diagnosis or treatment occurred within 12 months before or after enrollment, signs of recurrence or metastasis were observed within 12 months before or after enrollment, hematologic cancer was not in complete remission, or the physicians concluded that cancer was active at the time of enrollment on the basis of their clinical judgment.

INFORMATION SOURCES AND DATA COLLECTION PROCESS. The PubMed, Embase, and Cochrane Central databases were used without language restriction to identify all studies published from database inception to November 25, 2022, that investigated the impact of various anticoagulation strategies in patients with active cancer and VTE. The retrieval strategy is shown in Supplemental Tables 1 to 3. Additional studies were identified through a manual search of secondary sources, including reviews, commentaries, and references from the initially identified papers. All references were downloaded for consolidation, duplicates were eliminated,

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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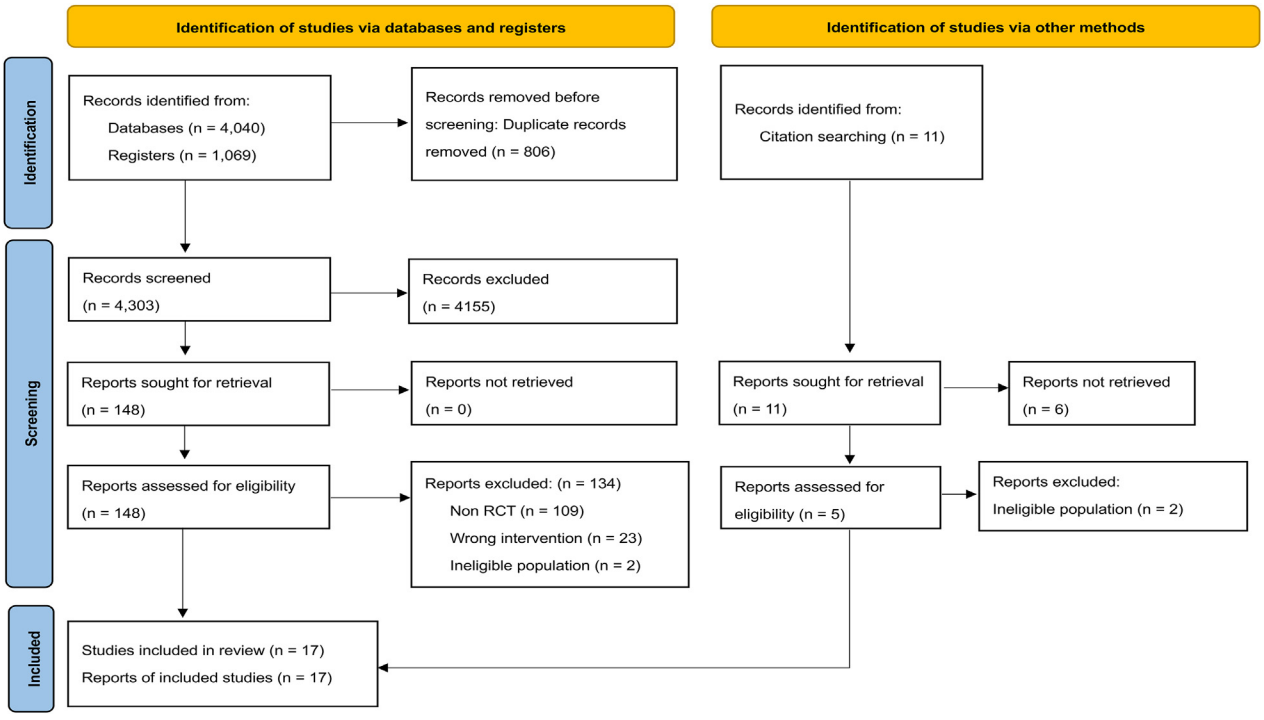
FIGURE 1 Flow Diagram of Study Selection



A total of 6,623 patients from 17 trials were included. RCT = randomized controlled trial.

and further analysis was conducted. Two independent investigators (T.F. and D.S.) reviewed the results and selected studies on the basis of the inclusion and exclusion criteria. They reviewed the studies and independently judged them for selection, comparability, and outcomes using version 2.0 of the Cochrane Collaboration tool for assessing risk of bias.[20] A third author (E.Y.) was consulted when consensus could not be reached. Disagreements were resolved by consensus.

OUTCOMES. The primary efficacy endpoint was recurrent VTE, defined as a composite outcome of objectively confirmed PE or DVT (both fatal or nonfatal). The secondary efficacy outcomes were recurrent PE only and recurrent DVT only. The primary safety outcome was major bleeding, as defined by the International Society on Thrombosis and Haemostasis as a composite of fatal bleeding, a decrease in hemoglobin level of ≥2 g/dL, transfusion of ≥2 U packed red blood cells, and bleeding that occurred at a critical site.[21] If this information was unavailable, a composite of International Society on Thrombosis and Haemostasis major bleeding (bleeding resulting in surgical intervention, bleeding requiring hospitalization, bleeding requiring surgery or decompression of a closed space, ecchymosis or hematoma >10 cm in diameter) or a composite of hemorrhage occurring at a critical site (bleeding resulting in major therapeutic interventions, bleeding causing hemodynamic compromise, bleeding requiring at least 1 U red cell concentrate, fatal bleeding) were used as alternative outcomes. The secondary safety outcomes were trial-defined CRNMB and a composite outcome of major bleeding or CRNMB. Other secondary outcomes included all-cause death and net adverse clinical outcome (a composite of major bleeding and recurrent VTE). The HRs or relative risks (RRs) were extracted from each study. If the HR or RR was not described in a study, the RR was calculated using the event and patient numbers.

STATISTICAL ANALYSIS. Pooled HRs and 95% CIs were estimated using the netmeta 3.6.2 package (R Foundation for Statistical Computing) on the basis of the HR or RR provided by each study.[22] In this meta-analysis, individual study HR results were based solely on univariable analyses. Random-effects models were used for all analyses. The I^2 value served as a measure of variation across the studies

due to heterogeneity and was interpreted as follows: <25% as low, 25% to 50% as moderate, and >50% as high. The Q statistic, a measure of heterogeneity and inconsistency, represents the treatment effect variability between the direct and indirect comparisons at the meta-analytical level and is considered statistically significant at a *P* value of <0.05.[23] Inconsistency was assessed on the basis of a full design-by-treatment interaction random-effects model.[24] The treatments were ranked using *P* scores of 0 to 1, calculated as the mean of 1-sided *P* values based on the HR and SE, measuring the likelihood that a treatment is superior to a comparison treatment. Higher scores indicate more effective therapies.[25] Publication bias was assessed using funnel plots and Egger's test.[26]

For sensitivity analyses, we first stratified parenteral anticoagulation into LMWH, unfractionated heparin, fondaparinux, idraparinux, or idrabiotaparinux and conducted the analysis. Second, we grouped apixaban, edoxaban, rivaroxaban, and dabigatran as an all-DOAC group and compared it with parenteral anticoagulation and VKA. Third, we included only RCTs in which the proportion of patients with solid malignancies was ≥90% and the proportion of patients with advanced cancer stage (stage III or IV) was ≥50% and then conducted the same analysis.

RESULTS

Our study comprised 17 RCTs, with a combined total population of 6,623 patients with active cancer from Agnelli et al (2015)[27] (AMPLIFY), Prins et al (2014)[28] (EINSTEIN DVT/PE), Schulman et al (2015)[29] (RECOVER I-II), Raskob et al (2016)[30] (HOKUSAI), Raskob et al (2018)[7] (HOKUSAI), Young et al (2018)[8] (SELECT-D), Planquette et al (2022)[9] (CASTA-DIVA), McBane et al (2020)[10] (ADAM VTE), Agnelli et al (2020)[11] (CARAVAGGIO), Mokadem et al (2021),[31] Deitcher et al (2006)[4] (ONCENOX), Lee et al (2003)[3] (CLOT), Lee et al (2015)[5] (CATCH), López-Beret et al (2001),[32] Meyer et al (2002)[6] (CANTHANOX), Amato et al (2016),[33] and van Doormaal et al (2010)[34] (Van Gogh DVT) (**Figure 1**). The mean weighted follow-up duration was 7.8 ± 2.9 months. The patient demographics for each trial are summarized in **Table 1**. Although the baseline characteristics of the patients were largely comparable among most trials, some trials did not report detailed information, as they were subgroup analyses. Furthermore, the proportion of patients with upper gastrointestinal cancer varied in trials comparing DOACs vs parenteral anticoagulation (eg, approximately 10% in the SELECT-D trial; 5% in the HOKUSAI 2018, CARAVAGGIO, and ADAM VTE trials; and 2% in the CASTA-DIVA trial). In the RECOVER I-II trial, although the results for patients with a cancer diagnosis or any treatment within 5 years before enrollment or recurrent or metastatic cancer were available, for this meta-analysis we used only outcomes from patients with cancer diagnoses during the study on the basis of the eligibility criteria.

Consequently, in this meta-analysis we analyzed 6 anticoagulation strategies: VKAs, parenteral anticoagulation, dabigatran, apixaban, edoxaban, and rivaroxaban (**Figure 2**). In the first sensitivity analysis, 8 anticoagulation strategies were analyzed: VKAs, LMWH, fondaparinux, idraparinux, dabigatran, apixaban, edoxaban, and rivaroxaban. In the second sensitivity analysis, the analysis focused on 3 strategies: all DOACs, parenteral anticoagulation, and VKAs. The treatment regimen networks for the sensitivity analyses are shown in Supplemental Figure 1. The definitions of the primary efficacy outcome, the primary safety outcome, CRNMB, the number of events, and HRs in each trial are summarized in Supplemental Tables 4 to 6. All the studies were generally considered to have a low risk for bias (Supplemental Figure 2), and publication bias was not observed (Supplemental Figure 3).

THE PRIMARY EFFICACY OUTCOME (RECURRENT VTE). Sixteen trials were available for the analysis of recurrent VTE (Supplemental Table 4). No significant difference was found among the DOACs for this outcome (**Figure 3**). Apixaban was associated with a reduced risk for recurrent VTE compared with parenteral anticoagulation. Apixaban, edoxaban, rivaroxaban, and parenteral anticoagulation were associated with reduced risks for this endpoint compared with VKAs. No significant heterogeneity (I^2 = 0%; P = 0.73) or inconsistency (P = 0.35) was observed. The direct and indirect comparisons for each endpoint are shown in Supplemental Figure 4. Treatments were ranked on the basis of their *P* scores, ranging from 0 to 1, with higher *P* scores indicating higher treatment efficacy. Apixaban was ranked first, followed by edoxaban, rivaroxaban, and dabigatran. Parenteral anticoagulation and VKAs received lower rankings (Supplemental Figure 5).

SECONDARY EFFICACY OUTCOMES (RECURRENT PE AND RECURRENT DVT). For recurrent PE, 9 studies were available. No significant difference was found among the 6 anticoagulation strategies for recurrent PE (Supplemental Figure 6). The analysis for PE did not indicate any significant heterogeneity (I^2 = 0%; P = 0.98), and inconsistency was not assessed, because of the limited number of included studies for this outcome.

TABLE 1 Basic Characteristics of the Patients in Each Trial

First Author (Year) (Trial)	Treatment	Dosage	Sample Size	Mean Age, y	Male	Active Cancer Definition	Primary Cancer	Cancer Stage	Follow-Up Period for Analyzed Outcomes, mo
Agnelli et al (2015) (AMPLIFY)[26]	Apixaban	10 mg BID for 7 d followed by 5 mg BID	81	65.5	(57)	Cancer that was diagnosed or treated within the past 6 mo before enrollment	Prostate (16), breast (15), colon (13), bladder (8), lung (8), others (41)	Approximately 30% of the patients had metastatic disease.	6
	VKA	LMWH followed by warfarin with target INR of 2–3	78	65.1	(61)				
Prins et al (2014) (EINSTEIN DVT/PE)[27]	Rivaroxaban	15 mg BID for 21 d, followed by 20 mg QD	354	NA (28% of patients were >75 y)	209 (59)	Diagnosis of cancer that occurred within 6 mo before enrollment, any treatment for cancer within the previous 6 mo, or recurrent or metastatic cancer, or new diagnosis of cancer or recurrence of cancer after randomization	NA	Recurrent or metastatic cancer 144 (22)	12
	VKA	LMWH followed by warfarin or acenocoumarol with target INR of 2–3	301	NA (25% of patients were >75 y)	160 (53)				
Schulman et al (2015) (RECOVER I-II)[28]	Dabigatran	LMWH or unfractionated heparin followed by dabigatran 150 mg BID	59	61 ± 14	37 (61)	A diagnosis of cancer (other than basal cell or squamous cell carcinoma of the skin) during the study	NA	NA	6
	VKA	LMWH or unfractionated heparin followed by warfarin with target INR of 2–3	55	65 ± 13	42 (76)				
Raskob et al (2016) (HOKUSAI)[29]	Edoxaban	LMWH or unfractionated heparin followed by edoxaban 60 mg QD	109	66 ± 12	54 (50)	The categorization of active cancer was made by the study physician at the time of enrollment, based on their clinical judgment, without a specific definition in the protocol.	NA	Metastatic disease 43 (21)	12
	VKA	LMWH or unfractionated heparin followed by warfarin with target INR of 2–3	99	65 ± 12	60 (61)				

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For recurrent DVT, 8 studies were available. No significant difference was found between the DOACs for recurrent DVT (Supplemental Figure 7). However, compared with parenteral anticoagulation, edoxaban was associated with a decreased risk for DVT. Similarly, apixaban, edoxaban, rivaroxaban, and parenteral anticoagulation were associated with reduced risks for DVT compared with VKAs. The analysis for this outcome did not reveal any significant heterogeneity ($I^2 = 0\%$; $P = 0.61$), and inconsistency was not assessed, because of the limited number of included studies for this outcome.

THE PRIMARY SAFETY OUTCOME (MAJOR BLEEDING). Sixteen trials were available for the analysis of this outcome (Supplemental Table 5). Apixaban was associated with a reduced risk for major bleeding compared with edoxaban (**Figure 4**). Mild heterogeneity was observed ($I^2 = 10.9\%$; $P = 0.33$), but no significant inconsistency ($P = 0.36$) was detected in this

TABLE 1 Continued

First Author (Year) (Trial)	Treatment	Dosage	Sample Size	Mean Age, y	Male	Active Cancer Definition	Primary Cancer	Cancer Stage	Follow-Up Period for Analyzed Outcomes, mo
Raskob et al (2018) (HOKUSAI)[7]	Edoxaban	LMWH followed by edoxaban 60 mg QD	552	64 ± 11	277 (53)	Cancer diagnosed within the previous 6 mo; recurrent, regionally advanced, or metastatic cancer; cancer for which treatment had been administered within 6 mo before randomization; or hematologic cancer that was not in complete remission	Upper GI 54 (5), pancreatic/ hepatobiliary 89 (8), colorectal 162 (15), lung 152 (14), genitourinary 136 (13), breast 124 (12), gynecological 109 (10), hematological 111 (10), others 108 (10)	Metastatic disease 554 (52)	12
	LMWH	Dalteparin 200 IU/kg QD for 1 mo followed by dalteparin 150 IU/kg QD	524	64 ± 12	263 (50)				
Young et al (2018) (SELECT-D)[8]	Rivaroxaban	15 mg BID for 21 d, followed by 20 mg QD	203	67[a]	98 (48)	A diagnosis of cancer (other than basal cell or squamous cell skin carcinoma) in the previous 6 mo, any treatment for cancer within the previous 6 mo, recurrent or metastatic cancer, or cancer not in complete remission (hematologic malignancy)	Esophageal 30 (7), gastric 11 (3), pancreatic 30 (7), colorectal 102 (25), lung 47 (12), genitourinary 42 (10), breast 40 (10), ovarian 30 (7), gynecologic 13 (3), brain 3 (1), hematological 31 (8), others 27 (7)	Early/locally advanced 160 (39) Metastatic disease 236 (58)	6
	LMWH	Dalteparin 200 IU/kg QD for 1 mo followed by dalteparin 150 IU/kg QD	203	67[a]	116 (57)				
Planquette et al (2022) (CASTA-DIVA)[9]	Rivaroxaban	15 mg BID for 21 d, followed by 20 mg QD	74	69	37 (50)	Cancer was considered active if confirmed by an imaging test or when chemotherapy, radiotherapy, or targeted therapy was ongoing or planned at inclusion.	Upper GI 3 (2), pancreatic/ hepatobiliary 11 (7), colorectal 32 (20), lung 28 (17), genitourinary 20 (13), breast 19 (12), brain 3 (2), gynecological 12 (8), hematological 13 (8), others 17 (11)	Stage I or II: 14 (9) Stage III: 22 (14) Stage IV: 115 (73)	3
	LMWH	Dalteparin 200 IU/kg QD for 1 mo followed by dalteparin 150 IU/kg QD	84	71	40 (48)				

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analysis. According to the *P* scores, apixaban was ranked first, followed by dabigatran and rivaroxaban. Parenteral anticoagulation, VKAs, and edoxaban were ranked lower (Supplemental Figure 5).

SECONDARY SAFETY OUTCOMES. For CRNMB, the analysis included 10 studies (Supplemental Table 6). Among the 5 anticoagulation strategies compared (apixaban, edoxaban, rivaroxaban, parenteral

TABLE 1 Continued

First Author (Year) (Trial)	Treatment	Dosage	Sample Size	Mean Age, y	Male	Active Cancer Definition	Primary Cancer	Cancer Stage	Follow-Up Period for Analyzed Outcomes, mo
McBane et al (2020) (ADAM VTE)[10]	Apixaban	10 mg BID for 7 d followed by 5 mg BID	150	64 ± 11	72 (48)	Any evidence of cancer on cross-sectional or positron emission tomography imaging, metastatic disease, and/or cancer-related surgery, chemotherapy, or radiation therapy within the prior 6 mo	Upper GI 11 (4), pancreatic/ hepatobiliary 47 (16), colorectal 47 (16), lung 51 (17), brain 8 (3), genitourinary 27 (9), breast 28 (9), gynecologic 29 (10), hematological 28 (9), others 19 (6)	Metastatic disease 193 (64)	6
	LMWH	Dalteparin 200 IU/kg QD for 1 mo followed by dalteparin 150 IU/kg QD	150	64 ± 11	73 (48)				
Agnelli et al (2020) (CARAVAGGIO)[11]	Apixaban	10 mg BID for 7 d followed by 5 mg BID	576	67 ± 11	292 (50)	Cancer that had been diagnosed within the past 6 mo, cancer for which anticancer treatment was being given at the time of enrollment or during 6 mo before randomization, or recurrent locally advanced or metastatic cancer	Upper GI 54 (5), pancreatic/ hepatobiliary 87 (8), colorectal 134 (12), lung 200 (17), genitourinary 139 (12), breast 155 (13), gynecological 119 (10), hematological 85 (7), others 82 (7)	Recurrent locally advanced or metastatic 785 (68)	6
	LMWH	Dalteparin 200 IU/kg QD for 1 mo followed by dalteparin 150 IU/kg QD	579	67 ± 11	276 (48)				
Mokadem et al (2021)[30]	Apixaban	10 mg BID for 7 d followed by 5 mg BID	50	61 ± 11	20 (40)	Any patient still in need for treatment with chemotherapy for malignancy was considered to have active malignancy.	Colorectal 42 (42), bladder 8 (8), prostate 11 (11), liver 6 (6), ovary 11 (11), uterus 11 (11), breast 11 (11)	Stage I: 4 (4) Stage II: 12 (12) Stage III: 0 (0) Stage IV: 84 (84)	6
	LMWH	Enoxaparin 1 mg/kg BID	50	60 ± 10	22 (44)				
Deitcher et al (2006) (ONCENOX)[4]	LMWH	Enoxaparin 1 mg/kg BID for 5 d, followed by 1 or 1.5 mg/kg QD	67	NA	NA	Active, residual malignancy determined by the presence of measurable disease, persistently elevated tumor markers, metastatic disease after tumor debulking, or histologically or cytologically confirmed cancer	NA	Metastatic disease 59 (58)	6
	VKA	LMWH followed by warfarin with target INR of 2–3	34	64 ± 12	NA				

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TABLE 1 Continued

First Author (Year) (Trial)	Treatment	Dosage	Sample Size	Mean Age, y	Male	Active Cancer Definition	Primary Cancer	Cancer Stage	Follow-Up Period for Analyzed Outcomes, mo
Lee et al (2003) (CLOT)[3]	LMWH	Dalteparin 200 IU/kg QD for 1 mo followed by dalteparin 150 IU/kg QD	338	62 ± 12	159 (47)	A diagnosis of cancer, other than basal cell or squamous cell carcinoma of the skin, within 6 mo before enrollment, any treatment for cancer within the previous 6 mo, or recurrent or metastatic cancer	Pancreas 29 (5), colorectal 108 (18), lung 90 (15), brain 27 (4), genitourinary 86 (14), breast 108 (18), gynecologic 68 (11), hematologic 70 (10), other 90 (15)	Metastatic disease 455 (67)	6
	VKA	LMWH followed by warfarin with target INR of 2–3	338	63 ± 13	169 (50)				
Lee et al (2015) (CATCH)[5]	LMWH	Tinzaparin 175 IU/kg QD	449	60 ± 13	187 (42)	Cancer diagnosis within the previous 6 mo; recurrent, regionally advanced, or metastatic disease; treatment for cancer during the previous 6 mo; or not in complete remission from a hematological malignancy	Upper GI 105 (12), colorectal 119 (13), lung 104 (12), genitourinary 94 (10), breast 84 (9), gynecologic 203 (23), hematologic 94 (10), other 97 (11)	Metastatic disease 492 (55)	6
	VKA	LMWH followed by warfarin with target INR of 2–3	451	59 ± 13	178 (40)				
López-Beret et al (2001)[31]	LMWH	Nadroparin 0.01 mL/kg BID	17	NA	NA	Cancer at an advanced stage	NA		12
	VKA	LMWH followed by acenocoumarol with target INR of 2–3	18	NA	NA				
Meyer et al (2002) (CANTHANOX)[6]	LMWH	Enoxaparin 1.5 mg/kg QD	71	65 ± 13	28 (39)	Cancer was defined as solid tumor with or without distant localization or hematologic malignancy. All malignancies were treated with ongoing antitumor treatment.	GI 22 (15), bronchial 16 (11), urologic 24 (17), breast 32 (22), genital 16 (11), hematologic 16 (11), other 20 (14)	Metastatic disease 77 (53)	6
	VKA	LMWH followed by warfarin with target INR of 2–3	75	66 ± 11	37 (49)				
Amato et al (2016)[32]	Fondaparinux	7.5 mg QD	32	NA	NA	Cancer that was treated with anticancer treatment	GI 29 (45), pancreas 13 (20), lung 8 (12), urogenital 11 (17), prostate 9 (14), breast 2 (3), hematologic 10 (15), renal 2 (3), others 2 (3)	NA	12
	VKA	Warfarin with target INR of 2–3	32	NA	NA				

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TABLE 1 Continued

First Author (Year) (Trial)	Treatment	Dosage	Sample Size	Mean Age, y	Male	Active Cancer Definition	Primary Cancer	Cancer Stage	Follow-Up Period for Analyzed Outcomes, mo
van Doormaal et al (2010) (Van Gogh DVT)[33]	Idraparinux	2.5 mg weekly	140	NA	NA	Cancer diagnosis or receiving anticancer treatment within 6 mo before randomization	NA	NA	6
	VKA	LMWH or IV heparin followed by warfarin or acenocoumarol with target INR of 2-3	130	NA	NA				

Values are n (%) or mean ± SD. [a]Median.

BID = twice a day; DVT = deep venous thrombosis; GI = gastrointestinal; INR = international normalized ratio; IV = intravenous; LMWH = low-molecular weight heparin; NA = not available; PE = pulmonary embolism; QD = once a day; VKA = vitamin K antagonist.

anticoagulation, and VKAs, except dabigatran), rivaroxaban was associated with increased risks for CRNMB compared with edoxaban and parenteral anticoagulation (Supplemental Figure 8). Moderate heterogeneity was observed ($I^2 = 37.1\%$; $P = 0.19$), but no significant inconsistency ($P = 0.15$) was detected in this analysis.

For a composite outcome of CRNMB or major bleeding, 9 studies were included in the analysis. No significant difference was found among the DOACs (Supplemental Figure 9). Apixaban was associated with a reduced risk for this outcome compared with VKAs, whereas edoxaban and VKAs were associated with an increased risk for this outcome compared with parenteral anticoagulation. No significant heterogeneity ($I^2 = 0\%$; $P = 0.62$) or inconsistency ($P = 0.81$) was observed.

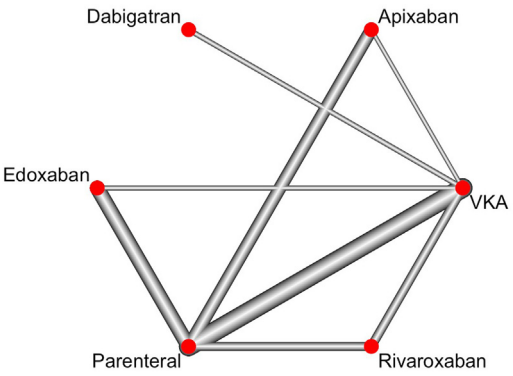
NET ADVERSE CLINICAL OUTCOME (VTE AND MAJOR BLEEDING). Four studies were included, and 5 anticoagulation strategies, except dabigatran, were compared in this analysis. There was no significant difference among the DOACs (Supplemental Figure 10). Apixaban and rivaroxaban were associated with reduced risks for net adverse clinical outcome compared with VKAs. Given the limited number of studies included in this analysis, neither heterogeneity nor inconsistency could be assessed.

ALL-CAUSE DEATH. Fifteen studies were included in this analysis. There was no significant difference among the 6 anticoagulation strategies for this outcome (Supplemental Figure 11). No significant heterogeneity ($I^2 = 0\%$; $P = 0.55$) or inconsistency ($P = 0.79$) was observed.

SENSITIVITY ANALYSES. The parenteral anticoagulation strategy was divided into LMWH, fondaparinux, and idraparinux in the first sensitivity analysis, and 4 types of DOACs were grouped together as an all-DOAC group in the second sensitivity analysis (Supplemental Figure 1). Furthermore, we performed a third sensitivity analysis by including RCTs in which the proportion of patients with solid malignancies was ≥90% (or hematologic malignancies ≤10%), as well as the proportion of patients with advanced cancer stage (stage III or IV), was ≥50%.

The first sensitivity analysis showed consistent results with those of the primary analysis (Supplemental Figures 12 to 19). Mild to moderate heterogeneity was observed for major bleeding ($I^2 = 21.6\%$; $P = 0.24$) and CRNMB ($I^2 = 47.5\%$; $P = 0.12$). The second sensitivity analysis showed that the all-DOAC group was associated with a decreased risk for VTE and DVT compared with parenteral anticoagulation and VKAs, and the all-DOAC group was associated with reduced risks for net adverse clinical outcome and a composite outcome of major bleeding or CRNMB compared with VKA (**Figures 3 and 4**, Supplemental Figures 6 to 11). There was moderate heterogeneity in the secondary sensitivity analysis for major bleeding ($I^2 = 28.8\%$; $P = 0.24$) and CRNMB ($I^2 = 48.8\%$; $P = 0.08$). The third sensitivity analysis included eight RCTs (HOKUSAI,[7] SELECT-D,[8] CASTA-DIVA,[9] ADAM VTE,[10] CARAVAGGIO,[11] Mokadem et al,[31] CLOT,[3] and CATCH[5]) and showed consistent results with those of the primary analysis (Supplemental Figures 20 to 27). Of note, rivaroxaban was associated with increased risks for CRNMB compared with apixaban, edoxaban, and parenteral

FIGURE 2 Treatment Regimen Network for this Network Meta-Analysis



The thickness of the lines between strategies corresponds to the number of patients in that comparison. VKA = vitamin K antagonist.

anticoagulation. The third sensitivity analysis showed mild heterogeneity for all-cause death ($I^2 = 23.1\%$; $P = 0.28$).

DISCUSSION

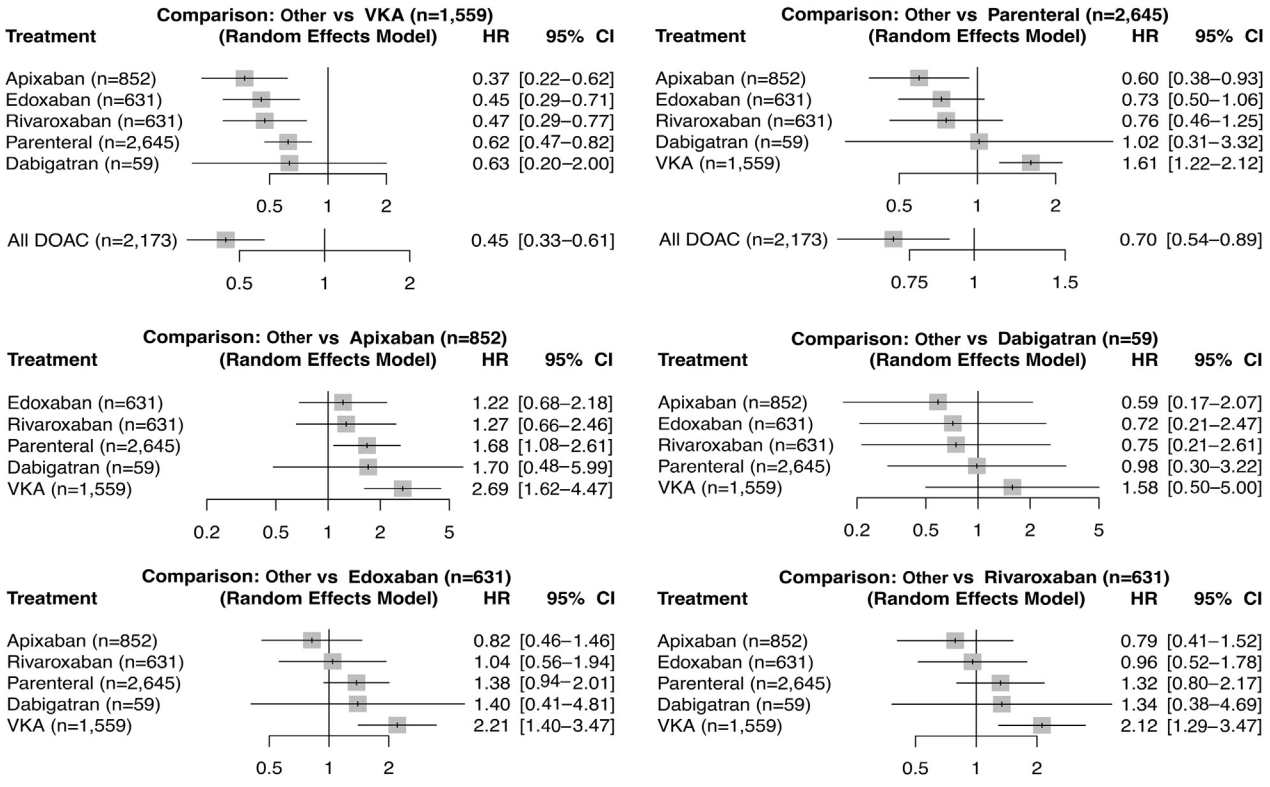
The principal findings of this network meta-analysis of 6,623 patients with active cancer and VTE indicated that each DOAC had comparable efficacy for the treatment and recurrence prevention of VTE. However, each DOAC had a significantly distinct safety profile for bleeding outcomes, with apixaban associated with a reduced risk for major bleeding compared with edoxaban, and edoxaban associated with a decreased risk of CRNMB compared with rivaroxaban. Additionally, compared with parenteral anticoagulation, apixaban was associated with a reduced risk for recurrent VTE without an increased risk for bleeding, whereas edoxaban and rivaroxaban were associated with increased bleeding risks.

In patients with active cancer, various malignancy-related factors (eg, cancer type, primary site, advanced stage), patient-related factors (eg, aging, performance status, comorbidities, low body weight), and treatment-related factors (eg, bone marrow suppression, hormonal therapy, surgery, hospitalization) can contribute to a complex interplay between thrombotic and hemorrhagic events.[12,35,36] The ensuing risks for recurrent thrombosis and bleeding in patients with active cancer and VTE underscore the critical and challenging nature of therapeutic anticoagulation. Minimizing the risk for these adverse events is vital not only for optimizing patient quality of life but also for avoiding any interruption or delay of cancer therapy.

Our study's findings largely align with and validate those of previous meta-analyses. However, our present research differed significantly because we specifically excluded patients with nonactive cancer and differentiated among the DOACs, with the aim of performing a robust and meticulous network meta-analysis. We conducted a thorough head-to-head comparison of each DOAC, revealing the novel and noteworthy finding that each DOAC may have a distinct safety profile for bleeding outcomes. Previous meta-analyses investigating anticoagulation strategies in patients with active cancer demonstrated that DOACs were associated with a reduced risk for recurrent VTE and an increased risk for nonmajor bleeding compared with LMWH.[9,18] However, these previous analyses were significantly limited in methodology because they grouped apixaban, edoxaban, rivaroxaban, and dabigatran together without conducting any head-to-head comparisons. Furthermore, the inclusion of patient populations with both active and nonactive cancer led to significant heterogeneity.[37,38] Consequently, these limited studies failed to identify any significant differences in safety outcomes among DOACs.

The management of bleeding events is a crucial consideration when determining appropriate anticoagulation strategies for treating VTE in patients with cancer, particularly in those with luminal gastrointestinal or urologic cancers.[8,18,39] The SELECT-D trial, which compared rivaroxaban and LMWH, showed no significant difference in major bleeding, but it did show numerically worse results for major bleeding and a significantly higher risk for CRNMB. The higher risk for bleeding may be attributed to the high proportion (10%) of patients with upper gastrointestinal cancer in the SELECT-D trial.[8] In the HOKUSAI trial, which compared edoxaban and LMWH, the rate of major bleeding was significantly higher in the edoxaban arm, mainly because of the higher rate of upper gastrointestinal bleeding.[7] In contrast, the CARAVAGGIO trial, which compared apixaban with LMWH, found no signs of an increased risk for gastrointestinal major bleeding in the apixaban group, with only nonmajor bleeding in the genitourinary and upper airway systems displaying a numerical increase in the apixaban group.[11,40] Similarly, the ADAM VTE trial, which compared apixaban and LMWH, revealed no significant difference in bleeding outcomes.[10] Some evidence suggests that the observed higher bleeding rate in upper gastrointestinal cancer in the SELECT-D trial may have led to a selection bias in subsequent trials, resulting in a

FIGURE 3 Results for the Primary Efficacy Outcome (Recurrent Venous Thromboembolism)

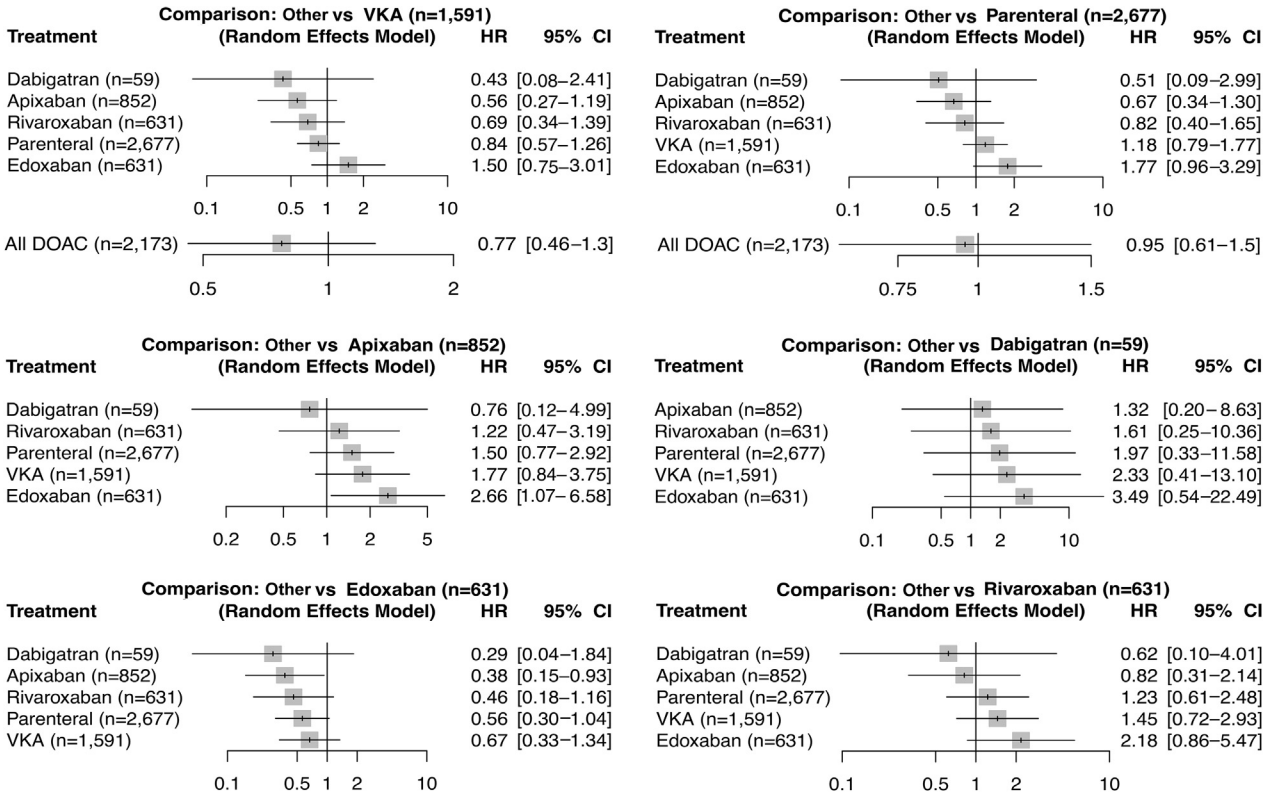


The figure shows the HR and 95% CI for each treatment arm. DOAC = direct oral anticoagulant agent; VKA = vitamin K antagonist.

reduced proportion of patients with upper gastrointestinal cancer (approximately 5% in the CARAVAGGIO and ADAM VTE trials) and ultimately improved safety outcomes. However, despite the proportion of patients with upper gastrointestinal cancer also at approximately 5% in the HOKUSAI trial, edoxaban was associated with increased bleeding risks compared with LMWH. Furthermore, the rate of major bleeding was approximately 4% in the parenteral anticoagulation arm in the CARAVAGGIO, HOKUSAI, and SELECT-D trials. In addition, although the CARAVAGGIO trial was an open-label design, patients meeting the inclusion and exclusion criteria were consecutively enrolled and randomly assigned in a 1:1 ratio to receive monotherapy with either apixaban or LMWH. Because neither the inclusion nor exclusion criteria referred to gastrointestinal malignancy, it is unlikely that the proportion of patients with gastrointestinal malignancy in this consecutively enrolled cohort was affected by selection bias. Therefore, selection bias is unlikely to explain the reduced proportion of patients with gastrointestinal malignancies in this trial. However, it remains plausible that this reduction may have contributed to the improved safety outcomes for apixaban. Our network meta-analysis included these studies and presents a comprehensive summary of currently available evidence, suggesting that the antithrombotic benefit of apixaban does not seem to come at the cost of increased bleeding events in patients with active cancer and VTE compared with other DOACs or parenteral anticoagulation.

The findings of the present study on cancer-associated VTE harmonize with those of previous studies indicating the favorable safety profile of apixaban in patients with both cancer and atrial fibrillation. For instance, retrospective studies with large contemporary cohorts with cancer and atrial fibrillation, such as those conducted by Deitelzweig et al[41] and Shah et al,[42] have reported that apixaban is associated with a lower risk for major bleeding, whereas dabigatran and rivaroxaban demonstrate comparable risks for major bleeding compared with

FIGURE 4 Results for the Primary Safety Outcome (Major Bleeding)



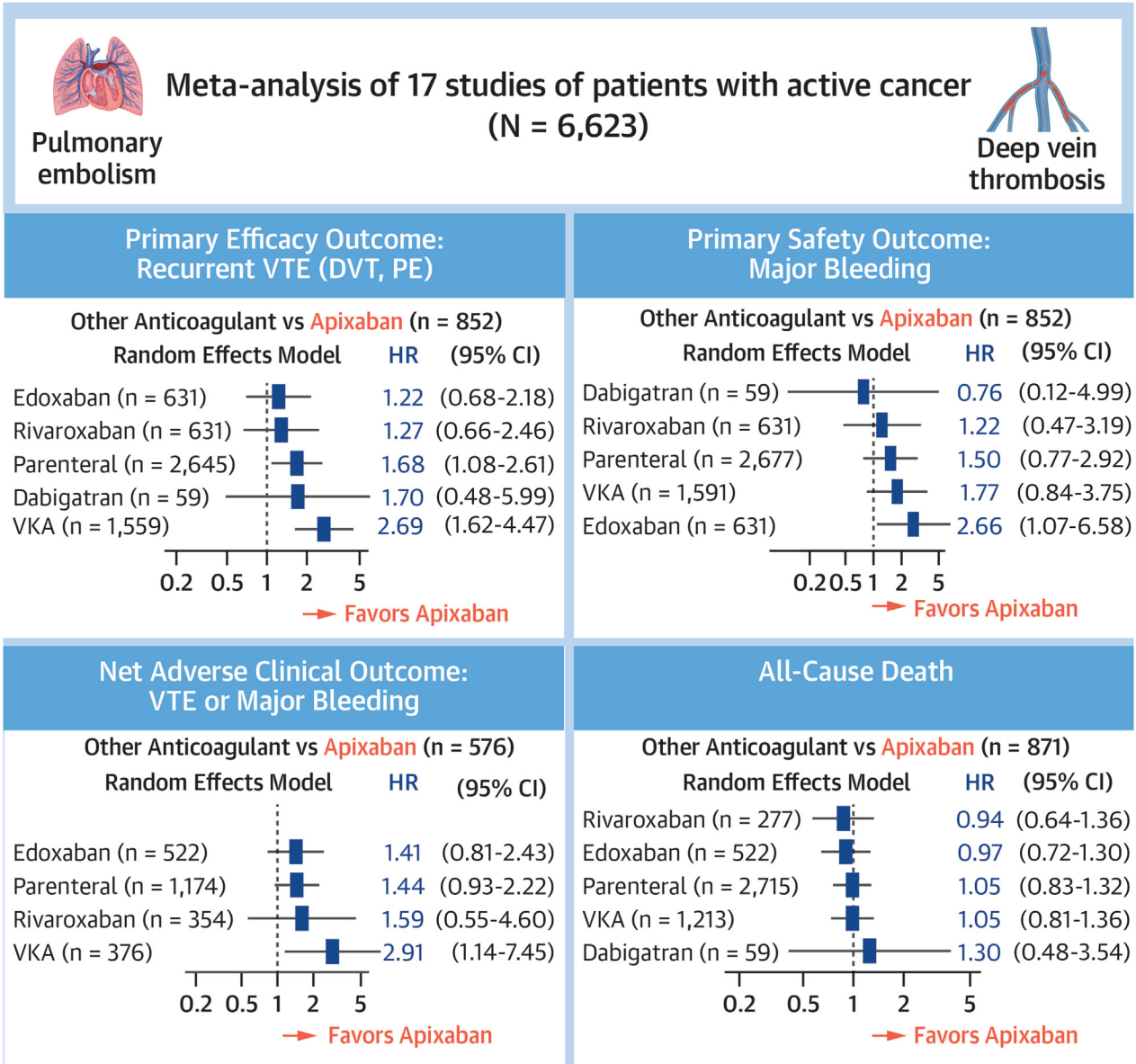
The figure displays the HR and 95% CI for each treatment arm. Abbreviations as in Figure 3.

VKA across different major cancer types. Furthermore, Deitelzweig et al[41] reported that apixaban was associated with a reduced risk for gastrointestinal major bleeding compared with rivaroxaban. Similarly, Shah et al[42] reported that the rate of severe bleeding was significantly lower among apixaban users than rivaroxaban users. These real-world studies provide support for the findings of our study and contribute to the body of evidence supporting the safety profile of apixaban in patients with active cancer and VTE.

Our novel findings provide evidence for the potential preferential use of apixaban over edoxaban or rivaroxaban in patients with active cancer and VTE. This distinction is important because these 3 agents are equally recommended for cancer-associated VTE in the recent guidelines, including the 2022 European Society of Cardiology cardio-oncology guidelines.[12-16] Furthermore, our findings are important given the emphasis in the updated European Society for Medical Oncology clinical practice guideline published in 2023, highlighting the lack of head-to-head comparisons in the literature that hinder definitive conclusions on the comparative performance of different DOACs.[43] By addressing this evidence gap, our findings enable patients and clinicians to make well-informed decisions, taking into account the careful balance among thrombotic risk, bleeding risk, and patient preference on a case-by-case basis. Furthermore, our finding that apixaban is more effective and has a similar safety profile compared with parenteral anticoagulation could offer reassurance to physicians, considering the convenience of oral therapy in contrast to the inconvenience of long-term self-injected parenteral anticoagulation. Therefore, our findings may have significant implications for clinicians and policy makers.

STUDY LIMITATIONS. First, this study relied on a meta-analysis of trial-level data, which may not fully account for differences in the trial design, treatment regimen, and individual data differences. Second, variations in endpoint definitions across studies could have introduced some degree of bias. However, we selected the most appropriate outcomes in line with the study protocol registered in the International Prospective Register of Systematic Reviews. Third, mild to moderate heterogeneity was observed

CENTRAL ILLUSTRATION **Selection of Venous Thromboembolism Anticoagulation Outcomes in Patients With Active Cancer**



Fujisaki T, et al. J Am Coll Cardiol CardioOnc. 2024;6(1):99-113.

The figure illustrates the HR and 95% CI for each treatment arm. DVT = deep venous thrombosis; PE = pulmonary embolism; VKA = vitamin K antagonist; VTE = venous thromboembolism.

in certain analyses, although our inclusion criteria focused on patients with active cancer and used a more robust and conservative assessment of the pooled effect size through the use of random-effects models. Fourth, the exclusion of patients with remote histories of cancer and specific medical conditions, such as life expectancy of <6 months, end-stage renal disease, hepatic disease with coagulopathy, thrombocytopenia, metastatic brain cancer, or acute leukemia, may limit the generalizability of our findings. Fifth, our evaluation assessed only DVT and PE as VTE events, and other types of thrombosis were not assessed. Finally, evidence suggests that the primary tumor site, cancer stage or progression, or

anticancer treatment could affect the risk for thrombosis and bleeding, consequently affecting the efficacy and safety of anticoagulation.[44-46] Although several studies included in this meta-analysis did not provide these critical data or only reported them within subgroup analyses, conducting more detailed sensitivity analyses on the basis of these characteristics was not feasible. However, our third additional sensitivity analysis, focusing on data representative of patients with advanced solid malignancies, provided robust and reliable results for this population. Notably, the results of the third sensitivity analysis were concordant with the main analysis, with a higher proportion of patients with solid malignancies included in the main analysis. Consequently, it seems plausible to presume that the results of the main analysis could be applicable to patients with solid malignancies (as opposed to hematological malignancies) until further evidence is produced by future studies.

CONCLUSIONS

DOACs appear to demonstrate comparable efficacy in treating and preventing recurrent VTE. Nonetheless, our findings highlight that the use of apixaban might offer a more favorable safety profile compared with other contemporary anticoagulation strategies in patients with active cancer and VTE (**Central Illustration**). Further large-scale randomized controlled studies are needed to directly compare various DOACs in patients with VTE and active cancer.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Current guidelines propose several DOACs as comparable options for VTE treatment in patients with cancer. This network meta-analysis compared DOACs and demonstrated that the antithrombotic benefit of apixaban may not result in an increased risk for bleeding events, distinguishing it from other contemporary anticoagulation strategies in patients with active cancer.

TRANSLATIONAL OUTLOOK: Further large-scale randomized controlled studies are needed to directly compare DOACs in patients with active cancer.

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KEY WORDS **bleeding, cancer-associated thrombosis, deep venous thrombosis, direct oral anticoagulant agents, pulmonary embolism, venous thromboembolism**

APPENDIX **For supplemental tables and figures, please see the online version of this paper.**