JACC: CARDIOONCOLOGY VOL. 5, NO. 4, 2023

ORIGINAL RESEARCH

Anticoagulation for the Prevention of Arterial Thrombosis in Ambulatory Cancer Patients

Systematic Review and Meta-Analysis

Yan Xu, MD,[a] Katherine Cole, MD,[b] Erin Collins, PHD,[c] Aliza Moledina, MD,[d] Caroline Mallity, BSc,[a] Marc Carrier, MD, MSc[a]

ABSTRACT

BACKGROUND The risk of arterial thrombotic events (ATEs) is high among patients on systemic anticancer therapies. Despite the efficacy of anticoagulants in the prevention of cancer-associated venous thromboembolism, it is unknown whether anticoagulation is effective to prevent ATEs.

OBJECTIVES This study sought to examine the efficacy and safety of anticoagulants in ATE prevention among ambulatory cancer patients.

METHODS We performed a systematic review using Medline, Embase, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL) from inception to May 21, 2022, and included studies comparing oral or parenteral anticoagulation with no anticoagulation among ambulatory patients receiving systemic anticancer therapy with no other indication for anticoagulation. The primary outcome was ATE (myocardial infarction, ischemic stroke, intra-abdominal arterial embolism, or peripheral artery occlusion). The secondary outcomes were major and nonmajor bleeding and all-cause mortality.

RESULTS Fourteen randomized trials involving low-molecular-weight heparins, direct oral anticoagulants, and warfarin were included. ATEs were captured as coefficacy endpoints or adverse events. Anticoagulant use was not associated with a reduction in ATEs compared with placebo or standard treatment (RR: 0.73, 95% CI: 0.50-1.04; $P = 0.08$; $I^2 = 0\%$). RRs of major and minor bleeding were 1.56 (95% CI: 1.12-2.17) and 2.25 (95% CI: 1.45-3.48) with anticoagulant use. In 13 trials that reported all-cause mortality, risk of death was not reduced with anticoagulants (RR: 0.99; 95% CI: 0.95-1.02; $P = 0.38$; $I^2 = 0\%$).

CONCLUSIONS Anticoagulants did not reduce ATE risk among ambulatory patients on systemic anticancer therapy and were associated with increased bleeding. Based on the current data, anticoagulants have a limited role in ATE prevention in this population as a whole. (J Am Coll Cardiol CardioOnc 2023;5:520–532) © 2023 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/).

From the [a]Department of Medicine, Division of Hematology, University of Ottawa, Ottawa, Ontario, Canada; [b]Department of Medicine, Division of Medical Oncology, University of Ottawa, Ottawa, Ontario, Canada; [c]School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, Canada; and the [d]Department of Medicine, Division of General Internal Medicine, University of Ottawa, Ottawa, Canada.

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.

Manuscript received December 16, 2022; revised manuscript received April 4, 2023, accepted April 11, 2023.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2023.04.003

Despite the well-established association between cancer and venous thromboembolism (VTE),[1] the link between malignancy and arterial thrombotic events (ATEs), consisting of ischemic strokes, myocardial infarctions, and peripheral arterial events, remains under-recognized.[2,3] Because of patient-, disease-, and treatment-specific factors that contribute to endothelial dysfunction and hypercoagulability, patients with cancer have a higher risk of ATE compared with matched noncancer cohorts.[4-6] A recent systematic review of observational studies demonstrated differences in ATE risks by the site of primary malignancy,[7] whereas systemic therapies such as antivascular endothelial growth factor antibodies (eg, bevacizumab) and tyrosine kinase inhibitors further increase the risk of ATE among patients with cancer.[8-11]

Although low-dose anticoagulants are efficacious, safe, and cost-effective means of VTE prophylaxis in ambulatory cancer patients,[12-14] it is unknown whether they are effective in the prevention of ATE in this patient group. Given the absence of clinical guidelines on ATE prevention among patients with cancer,[15] we undertook a systematic review and meta-analysis to examine the efficacy and safety of oral or parenteral anticoagulation compared with no anticoagulation on ATE prevention in ambulatory cancer patients receiving anticancer therapy.

METHODS

This systemic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Statement.[16] The study was reviewed and approved by the Ottawa Health Science Network Research Ethics Board (protocol ID: 20220572-01H) to enable analysis of patient-level data where required. This review was registered in the International Prospective Register of Systematic Reviews (CRD42022315125).

ELIGIBILITY CRITERIA. We included randomized trials comparing oral or parenteral anticoagulant treatment (at prophylactic, intermediate, or therapeutic dose) to standard of care (no anticoagulation) among ambulatory cancer patients with solid tumors or lymphoma who were receiving or initiating tumor-directed systemic therapy. Eligible systemic therapies included conventional chemotherapy, monoclonal antibody therapy, oral targeted therapies (eg, tyrosine kinase inhibitors or poly[adenosine diphosphate-ribose] polymerase inhibitors), checkpoint inhibitors, and hormonal therapies. Eligible studies must have collected or reported symptomatic ATEs during follow-up either as an adjudicated outcome or as an adverse event, including ischemic stroke, acute myocardial infarction (AMI), intra-abdominal arterial embolism, or peripheral artery occlusion.[17]

The exclusion criteria were as follows: 1) observational studies, reviews, abstracts, trial registries, protocols, conference proceedings, or unpublished studies; 2) <10 participants enrolled; 3) non-English abstracts; 4) more than 5% of participants with hematologic malignancies (excluding lymphoma) because these patients have an elevated risk of thromboembolism or bleeding on anticoagulants;[18] 5) patients with primary brain tumors given the increased risk of intracranial bleeding on anticoagulation (patients with brain metastases were included);[19] 6) radiation or surgery alone; 7) duration of follow-up <3 months; 8) patients on anticoagulation at enrollment; 9) more than 5% of participants with previous VTE, and 10) comparison of anticoagulants to antiplatelet agents; however, studies that included individuals on antiplatelet agents at baseline were eligible.

SEARCH STRATEGY. We conducted a systematic review of published manuscripts, meeting abstracts, and trial registrations using Medline, Embase, SCOPUS, and Cochrane Central Register of Controlled Trials (CENTRAL) from inception to May 21, 2022, with the aid of an information specialist. Before the search, key articles were identified a priori based on author expertise for use in calibrating the search. Eight candidate articles were reviewed, and the search strategy was developed by examining abstract, title, and keyword terms of these source studies. Other search terms used in the concept groups were developed through input from study authors with expertise in thrombosis and medical oncology. The Canadian Agency for Drugs and Technologies in Health database search filter was adapted to identify randomized controlled trials.[20] We did not include gray literature or "backward" searching of the included primary sources. We did not exclude the search based on date or language. The complete search strategy is included in the Supplemental Appendix.

STUDY SELECTION. Five authors (Y.X., K.C., E.C., A.M., and C.M.) conducted independent abstract screening in duplicate, with discrepancy adjudicated by initial discussion and a third author if needed. Full articles were obtained for any eligible study reporting on VTE to prevent erroneous exclusion of articles based on abstract alone, whereas ATEs were reported only in full text. Full-length articles were

ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

ATE = arterial thrombotic event

RoB 2 = Risk of Bias 2

RR = relative risk

VTE = venous thromboembolism

independently assessed by the same authors, during which the primary article and supplementary material were reviewed for eligibility. Search results including abstract and full-text publications were uploaded into Covidence (Alfred Hospital) with duplicates automatically excluded.

DATA EXTRACTION. Five authors (Y.X., K.C., E.C., A.M., and C.M.) independently extracted outcomes using a standardized extraction form in duplicates. Discrepancies in data collection were resolved through consensus. We collected participant characteristics (age, sex, cancer sites and stage, use of antiplatelets, duration of follow-up, and adherence rates), baseline risk factors for ATE (coronary artery disease, history of ischemic stroke or peripheral artery disease, and smoking status), intervention and comparator characteristics (anticoagulant type, administration route, and dose), and outcome data.

The primary outcome was ATE, consisting of a priori–defined acute ischemic stroke, AMI, or peripheral arterial occlusion. We used standard definitions when reported by the study, such as the 2018 Joint Task Force universal definition of AMI[21] or the American Stroke Association definition of acute ischemic stroke.[22] When the definitions were not identified a priori, we used study-level definitions. The secondary outcome measures included components of the primary outcome, major and nonmajor bleeding (as defined by the study), and all-cause mortality. We contacted the study authors if additional information was required after extraction of the published data. For sources in which ATE outcome data were reported but incomplete, we extracted the remaining secondary outcomes.

All outcomes were extracted using the intention-to-treat population except for the bleeding outcome in which we used the modified intention-to-treat or per-protocol population if reported by the study.

QUALITY ASSESSMENT. We used the Cochrane Risk of Bias 2 (RoB 2) tool to complete the risk of bias assessment at the individual study level for the primary outcome.[23] Each study was independently assessed in duplicate, with disagreements resolved through consensus. The components of the RoB2 tool include 22 assessment items grouped into 5 domains, including assessments of the randomization process, assignment or adherence to intervention, handling of missing outcome data, measurement of study outcomes, and comprehensiveness of reporting study outcomes. Any study with a high risk of bias in 1 of the 5 domains was classified as a high risk of bias, in keeping with recommendations by the RoB2 tool. We assessed reporting bias through a funnel plot and Egger's test if more than 10 studies were included in the meta-analysis.

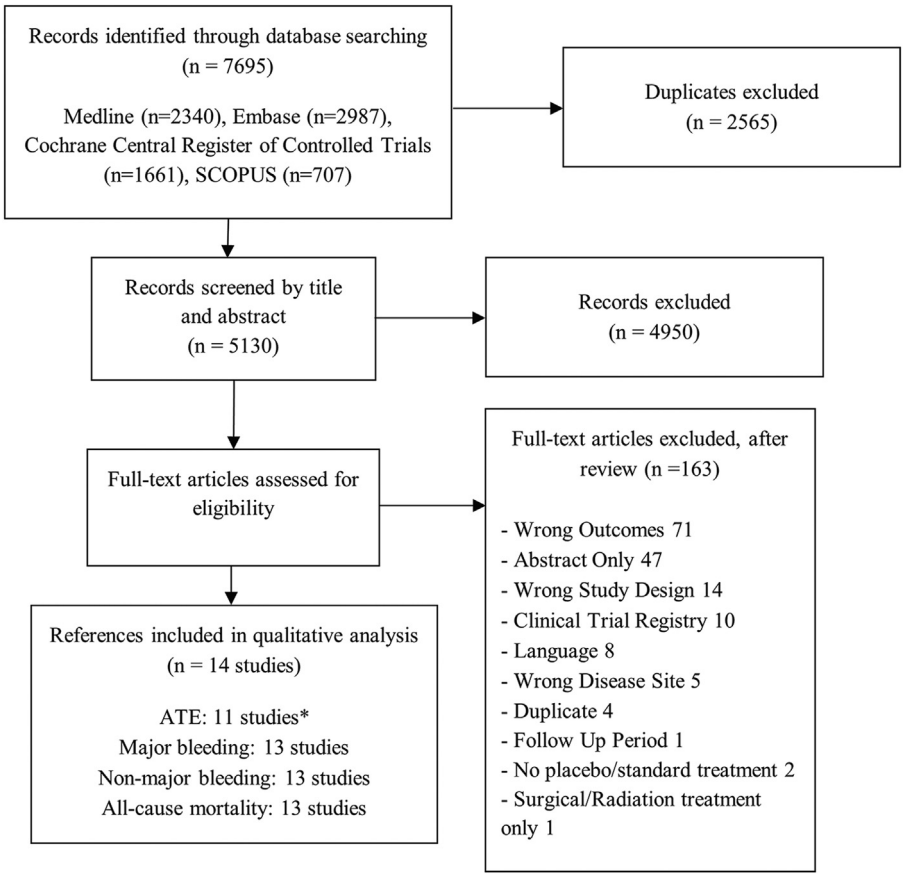
DATA SYNTHESIS AND ANALYSIS. For the primary outcome, we conducted a meta-analysis using studies that reported complete ATE data. Complete ATE data were defined as outcomes in which the classification of ATE was clearly reported (eg, total ATE, AMI, ischemic stroke, or peripheral arterial thrombosis), and the intervention arm for the reported event was indicated. Studies with vague ATE descriptions (eg, "cardiovascular insult") were not included in the primary analysis unless the study authors provided additional clarification. However, such studies were included in secondary meta-analyses of major or nonmajor bleeding and all-cause mortality if these outcomes were appropriately reported.

We generated relative risks for all outcomes. Given the clinical heterogeneity across the included studies (eg, anticoagulant type, intensity, and treatment duration), we used the DerSimonian and Laird random-effects model to determine weighted averages for measures of effect with calculation of 95% CIs. Statistical heterogeneity was assessed through visual inspection of effect size estimates and 95% CIs and via calculation of the I^2 statistic. A 2-tailed P value <0.05 was considered statistically significant. When the included trials contained more than 1 treatment group (eg, different anticoagulant dosages), these were collapsed into a single interventional arm.

We performed a priori subgroup analyses for the primary outcome, including dosing intensity, tumor site, and duration of anticoagulation treatment. We also conducted a priori sensitivity analyses focusing on studies without a high risk of bias based on the RoB2 tool and studies with a low (<30%) vs high (>30%) discontinuation rate of the study drug. To account for studies with 0 events, a treatment group continuity correction was used if 1 or both arms of a study cohort had 0 events.[24] In addition, we performed post hoc sensitivity analysis using risk differences for outcomes with studies containing 0 events in both arms, which provides an estimate without adjustment using continuity correction in the setting of rare events,[25] as well as the Peto 1-step odds ratio method using a fixed-effects model, which is reported to be the least biased and most powerful method when event rates are ≤1%.[26]

We used Review Manager (RevMan version 5.4.1, The Cochrane Collaboration) to conduct the meta-analysis, with additional use of StatsDirect version 3.3.5 for continuity correction.

FIGURE 1 Study Selection Flowchart



The figure describes the selection process of the included articles in the systematic review, including those contributing to our primary outcome (arterial thrombotic events [ATEs]) and secondary outcomes (major bleeding, minor bleeding, and mortality). *Three studies were excluded from the meta-analysis on ATEs due to incomplete outcome reporting. One study was excluded from meta-analyses on bleeding and all-cause mortality respectively, for the same reason.

RESULTS

SEARCH RESULTS. Of 7,695 records identified by the literature search, 5,130 were screened by title and abstract after the removal of duplicates. Of these, 4,960 were excluded as irrelevant based on title and abstract screening, with 177 records proceeding to full-text review. Of these, 163 records were excluded primarily because of the absence of reporting on ATEs and conference abstracts only (**Figure 1**). Therefore, 14 randomized controlled trials (published in 13 records) were eligible for inclusion in the systematic review and meta-analysis.

CHARACTERISTICS OF INCLUDED STUDIES. Of the 13 references identified,[27-39] 1 publication contained 2 distinct trials[35] and was analyzed separately (**Table 1**). One trial did not mention the number of ATEs in the intervention and comparator arms,[36] and 3 reported venous and arterial thrombotic events as a composite outcome.[35] Of the 11 trials that reported ATEs amenable to meta-analysis, 6 collected this outcome in a passive fashion (eg, as an adverse event) rather than as primary or secondary outcomes.[29-32,38,39] Six of the trials were open-label in design.[28,30,34,37,39,40] Prior ATEs were captured in 1 study[31] at 0.7% and 1.3% among the interventional and control arms, respectively. Similarly, 1 study reported baseline use of antiplatelet agents at 23.0% in the interventional group and 22.6% in the placebo group.[29]

Five of the 11 trials that reported complete ATE outcome had a high risk of bias (**Table 1**), primarily driven by passive reporting of ATEs rather than as part of an outcome measure. Distribution of the primary tumor sites is listed in **Table 2**, definitions of

TABLE 1 Characteristics of the Included Studies

First Author (Year)	Study Design	N	Women (%)	Age (y)	CVC (%)	Prior VTE (%)	Follow-Up Duration (mo)	Anticoagulant Type (Duration)	Risk of Bias for Primary Outcome
Levine et al[31] (1994)	Double-blind, 1:1 RCT	311						Warfarin with target INR 1.3-1.9 (median 181 days)	High
Intervention		152	NR	57.1 (10.2)	2.6	0	6.6		
Control		159	NR	56.1 (10.9)	4.4	1.3	6.3		
Agnelli et al[27] (2009)	Double-blind, 2:1 RCT	1,166						Nadroparin 3800 IU daily (duration of chemotherapy or up to 120 days)	Some concerns
Intervention		779	51.6	62.1 (10.3)	41.9	1.6	3.7		
Control		387	52.0	63.7 (9.2)	38.6	1.6	3.8		
Young et al[36] (2009)	Open-label, 1:1:1 RCT	812					NR (45 months for mortality)	Warfarin 1mg daily, or INR 1.5-2.0 (median 90-119 days between 2 warfarin regimens)	Not applicable (incomplete ATE data)
Intervention		408	37.5	60 (53-68)	100	NR			
Control		404	38.9	61 (53-68)	100	NR			
Van Doormaal et al[37] (2011)	Open-label, 1:1 RCT	503						First cycle: therapeutic nadroparin[a] for 2 weeks, then half-therapeutic for 4 weeks Subsequent cycles: therapeutic nadroparin for 2 weeks then 4-week washout (mean 12.6 ± 5.3 weeks)	Some concerns
Intervention		244	19.3	65 (10)	NR	NR	10.5		
Control		259	20.5	65 (9.8)	NR	NR	10.4		
Agnelli et al[32] (2012)	Double-blind, 1:1 RCT	3212						Semuloparin 20 mg daily (median 3.5 months)	High
Intervention		1,608	39.4	59.8 (10.6)	19.7	2.0	3.5		
Control		1,604	40.4	59.4 (10.6)	18.8	2.3			
Maraveyas et al[34] (2012)	Open-label, 1:1 RCT	123						Dalteparin 200 IU/kg daily (4 weeks), then 175 IU/kg daily (8 additional weeks)	Some concerns
Intervention		60	40.0	62 (40-79)	NR	NR	3.3		
Control		63	42.9	66 (43-82)	NR	NR			
Haas et al[35] (2012)	Double-blind, 1:1 RCT	353						Certoparin 3,000 IU daily (6 months)	Not applicable (incomplete ATE data)
Intervention		174	NR	54.6 (10.3)	NR	NR	6		
Control		179	NR	56.6 (11.0)	NR	NR			
Haas et al[35] (2012)	Double-blind, 1:1 RCT	547						Certoparin 3,000 IU daily (6 months)	Not applicable (incomplete ATE data)
Intervention		273	16.8	60.8 (9.5)	NR	NR	6		
Control		274	16.8	60.3 (10.0)	NR	NR			
Lavau-Denes et al[39] (2013)	Open-label, 1:1:1 RCT	413						Intervention 1: LMWH at recommended prophylactic dosing (90 days) Intervention 2: warfarin 1 mg daily (90 days)	High
Intervention 1		141	42.6	61 (10.6)	100	NR	3		
Intervention 2		135	39.3	59 (10.9)	100	NR			
Control		137	37.2	60 (11.8)	100	NR			
Macbeth et al[28] (2016)	Open-label, 1:1 RCT	2,202						Dalteparin 5,000 IU daily (planned 24 weeks; median 106 days)	Some concerns
Intervention		1,101	40.0	65 (59-71)	NR	NR	23.1		
Control		1,101	40.4	64 (58-71)	NR	NR			
Ek et al[30] (2018)	Open-label, 1:1 RCT	390						Enoxaparin 1 mg/kg daily (days 1-21 per chemotherapy cycle)	High
Intervention		186	58.0	67 (7.9)	NR	NR	41		
Control		191	57.1	68 (8.5)	NR	NR			
Meyer et al[40] (2002)	Open-label, 1:1 RCT							Tinzaparin 100 IU/kg daily (12 weeks)	High
Intervention		272	37.9	61.6 (9.0)	NR	NR	68		
Control		281	32.5	61.6 (8.8)	NR	NR			
Carrier et al[29] (2019)	Double-blind, 1:1 RCT	574						Apixaban 2.5 mg twice daily (157 days)	High
Intervention		291	58.4	61.2 (12.4)	43.2	3.1	6.1		
Control		283	58.0	61.7 (11.3)	32.1	2.8	6.1		
Khorana et al[33] (2019)	Double-blind, 1:1 RCT	841						Rivaroxaban 10 mg daily (4.3 months)	Low
Intervention		420	47.1	63 (23-87)	NR	3.1	6		
Control		421	51.1	62 (28-88)	NR	0.5			

[a]Age column is mean ± or median (Q1-Q3 range). Weight <50 kg: 3,800 IU twice daily; weight 50-70 kg: 11,400 IU daily; and weight >70 kg: 15,200 IU daily.

ATE = arterial thrombotic event; CVC = central venous catheter; INR = international normalized ratio; IU = international units; LMWH = low-molecular-weight heparin; NR = not reported; RCT = randomized controlled trial; VTE = venous thromboembolism.

TABLE 2 Cancer Type Distribution Among Included Studies

First Author (Year)	Primary Cancer Site								Metastatic Disease
	Lung	Gastric	Colorectal	Pancreatic	Breast	Ovarian	Lymphoma	Other/Unknown	
Levine et al[31] (1994)									
Intervention	0	0	0	0	100	0	0	0	NR
Control	0	0	0	0	100	0	0	0	NR
Agnelli et al[27] (2009)									
Intervention	25.9	7.5	27.8	4.7	14.3	12.5	NR	4.8	30.2
Control	21.0	10.5	28.3	4.5	14.4	12.3	NR	4.5	27.8
Young et al[36] (2009)									
Intervention	25.9	22.5[a]	53.2	NR	7.8	NR	NR	16.4	NR
Control	21.0	27.0[a]	49.8	NR	7.9	NR	NR	15.3	NR
Van Doormaal et al[37] (2011)								Prostate	
Intervention	33.2	0	0	25.8	0	0	0	41.0	NR
Control	33.2	0	0	27.8	0	0	0.8‖	37.5	NR
Agnelli et al[32] (2012)								Bladder	
Intervention	36.8	12.7	28.9	7.8	0	11.9	0	2.0	68.2
Control	36.6	12.9	28.7	8.0	0	11.7	0	1.9	68.1
Maraveyas et al[34] (2012)									
Intervention	0	0	0	100	0	0	0	0	48.3
Control	0	0	0	100	0	0	0	0	58.7
Haas et al[35] (2012)									
Intervention	0	0	0	0	100	0	0	0	100
Control	0	0	0	0	100	0	0	0	100
Haas et al[35] (2012)									
Intervention	100	0	0	0	0	0	0	0	53.8
Control	100	0	0	0	0	0	0	0	52.0
Lavau-Denes et al[39] (2013)									
Intervention 1	9.2	17.0[a]	14.9	4.3	7.8	7.1	NR	12.7	46.2% across 3 arms
Intervention 2	11.3	14.2[a]	14.2	5.7	11.3	2.1	NR	11.3	
Control	11.3	14.2[a]	13.5	4.3	11.3	4.3	NR	10.7	
Macbeth et al[28] (2016)									
Intervention	100	0	0	0	0	0	0	0	60.9
Control	100	0	0	0	0	0	0	0	60.5
Ek et al[30] (2018)									
Intervention	100	0	0	0	0	0	0	0	61.2[b]
Control	100	0	0	0	0	0	0	0	59.2[b]
Meyer et al[40] (2002)									
Intervention	100	0	0	0	0	0	0	0	8.9
Control	100	0	0	0	0	0	0	0	11.1
Carrier et al[29] (2019)									
Intervention	10.7	8.6	1.0	12.7	NR	NR	26.1	Gynecologic: 25.4 Other: 14.8	40.5[c]
Control	9.9	6.7	2.8	14.5	NR	NR	24.4	Gynecologic: 26.1 Other: 15.6	35.1[c]
Khorana et al[33] (2019)									
Intervention	14.8	21.2	NR	32.4	2.1	5.7	7.9	16.0	54.8
Control	17.1	20.7	NR	32.8	2.1	7.1	6.2	14.0	54.2

Values are %. [a]Upper gastrointestinal cancer. [b]Extensive disease based on small cell lung cancer staging. [c]Subgroup analysis of trial participants with data on metastatic disease status.
NR = not reported.

ATE and major bleeding used by included studies are outlined in **Table 3**, and component RoB2 domains are included in Supplemental Figure 1.

ARTERIAL THROMBOTIC EVENTS. Eleven studies, including a total of 10,248 patients, reported ATEs. The pooled risk of ATE was 0.98% (95% CI: 0.57%-1.49%) in the anticoagulation group and 1.48% (95% CI: 0.93%-2.17%) in the control group. Anticoagulant use was not associated with risk reduction in ATE (RR: 0.73; 95% CI: 0.50-1.04; $P = 0.084$; **Figure 2A**) when compared with the administration of placebo or standard treatment. Statistical heterogeneity of effect estimate was low among the included studies ($I^2 = 0\%$; $P = 0.74$).

JACC: CARDIOONCOLOGY, VOL. 5, NO. 4, 2023
AUGUST 2023:520–532

TABLE 3 Definitions Used for Arterial Thromboembolism and Major Bleeding

Study First Author, Year	Arterial Thromboembolism	Major Bleeding	Central Adjudication
Levine et al,[31] 1994	Myocardial infarction, ischemic stroke, or peripheral-artery thrombosis	Hemoglobin decrease of ≥20 g/L, a need for transfusion of ≥2 U of whole blood or red cells, or retroperitoneal or intracranial bleeds	ATE and major bleeding
PROTECHT Agnelli et al,[27] 2009	Acute myocardial infarction, ischemic stroke, and acute peripheral arterial thromboembolism occurring during the study treatment plus 10 days	ISTH definition	ATE and major bleeding
WARP Young et al,[36] 2009	Non-catheter-related thrombotic events in the arterial system	Intracranial, retroperitoneal, requiring transfusion or hospital admission, or directly leading to death (British Committee for Standards in Haematology 1998 recommendation)	Not reported
INPACT Van Doormaal et al,[37] 2011	Myocardial infarction, ischemic stroke, and systemic embolism according to conventional criteria	Fatal, hemoglobin decrease of ≥20 g/L; a need for transfusion of ≥2 U of whole blood or red cells; retroperitoneal, pericardial, intracranial bleeding; bleeding located in a critical organ	ATE and major bleeding
SAVE-ONCO Agnelli et al,[32] 2012	Adverse event	ISTH definition	Major bleeding only
FRAGEM Maraveyas et al,[34] 2012	All arterial events (eg, cerebrovascular accident/ myocardial infarction) based on clinical symptomatology, postmortem or incidentally	ISTH definition	Major bleeding only
TOPIC-1 Haas et al,[35] 2012	Composite outcome with VTE	Fatal, retroperitoneal, intracranial, transfusion of ≥2 U of packed red cells or drop in hemoglobin of ≥20 g/dL	ATE and major bleeding
TOPIC-2 Haas et al,[35] 2012	Composite outcome with VTE	Fatal, retroperitoneal, intracranial, transfusion of ≥2 U of packed red cells or drop in hemoglobin of ≥20 g/dL	ATE and major bleeding
Lavau-Denes et al,[39] 2013	Adverse event	Not defined	Not reported
FRAGMATIC Macbeth et al,[28] 2016	Efficacy endpoint; not defined	ISTH definition	Not reported
RASTEN Ek et al,[30] 2018	Adverse event	Hemoglobin decrease of ≥20 g/L, transfusion of ≥2 U of blood, any intracranial hemorrhage	Not reported
TILT Meyer et al,[40] 2018	Adverse event	Fatal, necessitating blood transfusion, hospital admission, or interventional treatment; intracranial or intraocular bleeding; hemoglobin decrease of ≥20 g/L	ATEs (fatal events only) and major bleeding adjudicated
AVERT Carrier et al,[29] 2019	Adverse event	ISTH definition	Major bleeding only
CASSINI Khorana et al,[33] 2019	Confirmed myocardial infarction, ischemic stroke, and systemic arterial embolism	ISTH definition	ATE and major bleeding

ATE = arterial thrombotic event; ISTH = International Society on Thrombosis and Haemostasis.

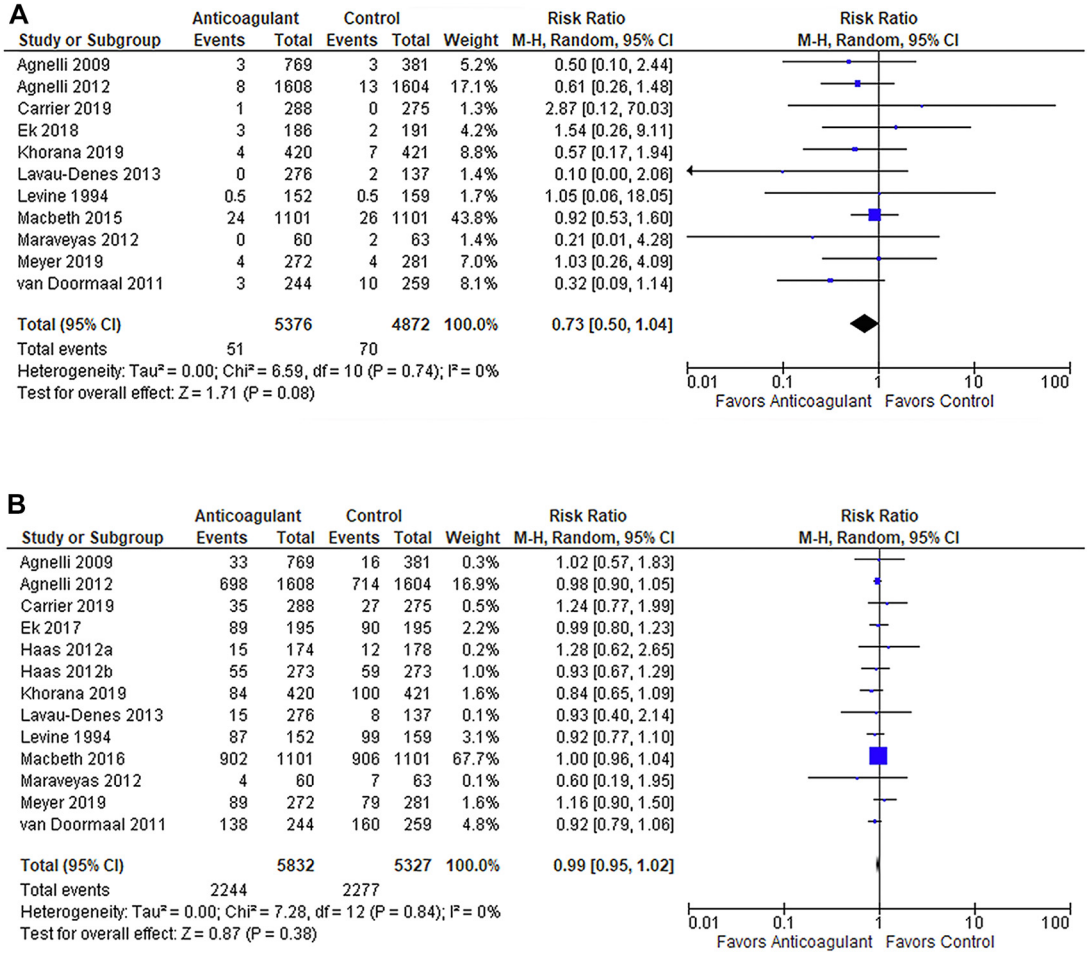
ALL-CAUSE MORTALITY. All-cause mortality was reported by 13 trials including 11,159 patients. Approximately 38% (n = 2,244) of patients receiving anticoagulant therapy and 42.7% (n = 2,277) of patients not receiving anticoagulant therapy died before the end of the study (RR: 0.99; 95% CI: 0.95-1.02; P = 0.38; I^2 = 0%) (**Figure 2B**).

MAJOR AND NONMAJOR BLEEDING. Thirteen trials assessed major bleeding complications for a total of 11,060 patients in the safety population. Anticoagulant use was associated with a 1.6-fold increased risk of major bleeding (RR: 1.56; 95% CI: 1.12-2.17; P = 0.009; I^2 = 0%) (**Figure 3A**) when compared with the administration of placebo or standard treatment. Minor bleeding was found to be 2.3-fold more likely in patients receiving anticoagulant therapy than in patients receiving placebo or standard treatment among the 13 trials (n = 11,060) reporting this outcome (RR: 2.25; 95% CI: 1.45-3.48; P < 0.001, I^2 = 68%) (**Figure 3B**).

SUBGROUP AND SENSITIVITY ANALYSES. We did not detect heterogeneity in effect estimates among studies using prophylactic (RR: 0.78; 95% CI: 0.52-1.18) compared with intermediate or therapeutic anticoagulant doses (RR: 0.63; 95% CI: 0.28-1.43; P = 0.65 for interaction) (Supplemental Figure 2).

Subgroup analysis based on the primary site of cancer was limited to 3 studies involving 3,128 patients with lung cancer (RR: 0.97, 95% CI 0.60-1.59), 1 study of 122 patients with pancreatic cancer (RR: 0.21; 95% CI: 0.41-4.22), and 1 study of 311 patients with breast cancer (RR: 1.09; 95% CI: 0.06-18.89), demonstrating no heterogeneity in the impact of anticoagulation on ATE by the primary site of malignancy (P = 0.61 for interaction). Effect estimates were consistent across ATE subtypes (P = 0.37 for

FIGURE 2 Measures of Efficacy



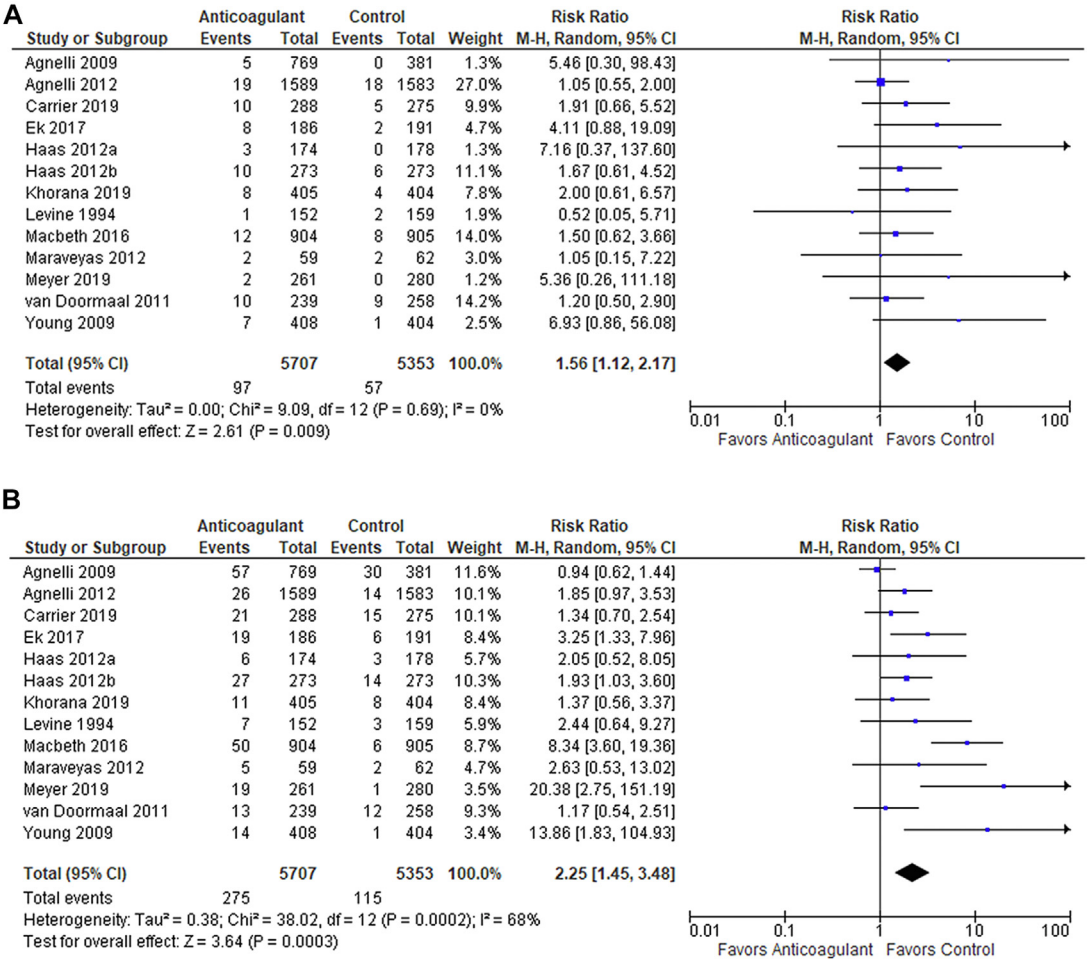
Forest plots illustrating results of meta-analysis evaluating comparative effects between anticoagulation and no anticoagulation among ambulatory cancer patients starting systemic therapy **(A)** on arterial thrombotic events and **(B)** mortality.

interaction) (Supplemental Figure 3) and durations of anticoagulant treatment (P = 0.65 for interaction) (Supplemental Figure 4).

Sensitivity analysis using risk difference for the primary outcome to account for 0 cells showed consistent estimate of the effect size, indicating no difference in ATE between anticoagulation and control arms (risk difference −0.27%; 95% CI: −0.63% to 0.09%; P = 0.14) (Supplemental Figure 5). Similarly, the Peto 1-step odds ratio for rare events using a fixed-effects model showed consisted findings (OR: 0.70; 95% CI: 0.48-1.00; P = 0.050) (Supplemental Figure 6).

Finally, the effect size estimates were consistent when we restricted the meta-analysis of the primary outcome to 5 studies at low or moderate risk of bias (Supplemental Figure 7) as well as studies with ≥30% drug discontinuation (n = 9) compared with studies with <30% discontinuation (n = 2) (Supplemental Figure 8). We did not observe evidence of publication bias for the primary outcome based on the funnel plot (Supplemental Figure 9) supported by the Egger's test for publication bias (P = 0.41). Results were also consistent when we excluded 2 trials that sequentially contributed more than 30% weighting to the overall random-effects model (RR: 0.60; 95% CI: 0.34-1.07; P = 0.085) (Supplemental Figure 10) and across types of anticoagulants (RR: 0.73 [95% CI: 0.49-1.07] vs 0.70 [95% CI: 0.22-2.20]; P = 0.96 for interaction) (Supplemental Figure 11).

FIGURE 3 Measures of Safety



Forest plots illustrating results of meta-analysis evaluating comparative effects between anticoagulation and no anticoagulation among ambulatory cancer patients starting systemic therapy on **(A)** major bleeding and **(B)** minor bleeding.

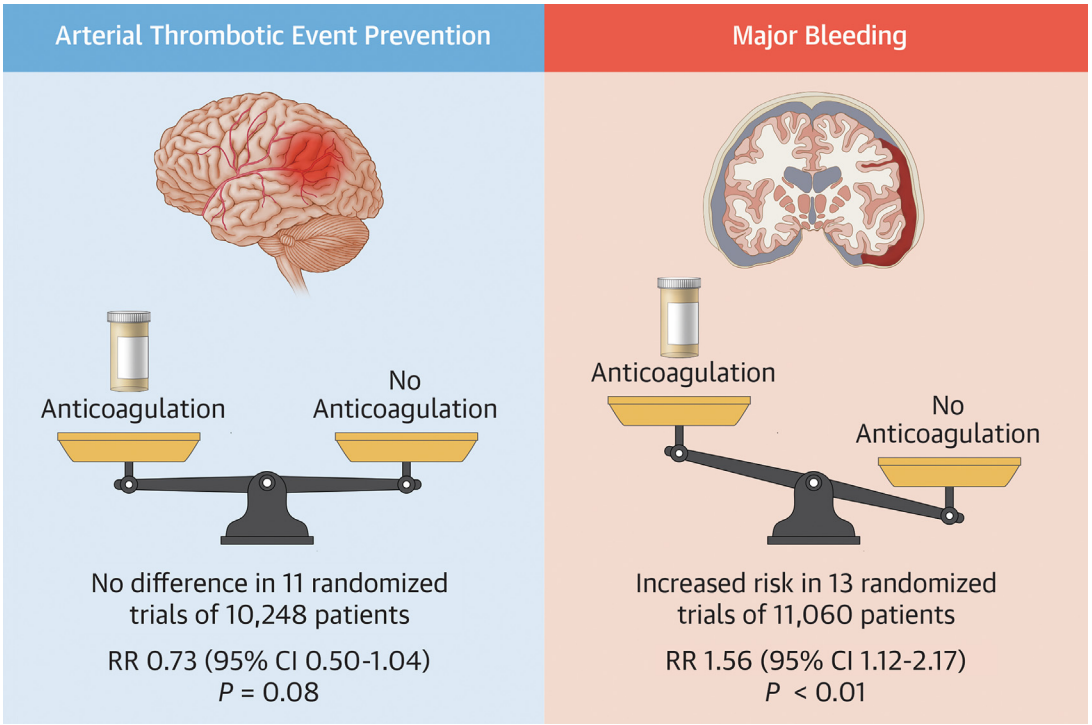
DISCUSSION

In our systematic review and meta-analysis of 14 randomized controlled trials with over 10,000 participants, we did not detect a difference in ATE with the use of anticoagulation among ambulatory cancer patients undergoing anticancer therapy (**Central Illustration**). On the other hand, the risks of major and nonmajor bleeding were increased with anticoagulant use. All-cause mortality was similar between the anticoagulation and control groups.

The effectiveness of oral or parenteral anticoagulants to prevent ATE in cancer remains a contentious topic of debate. Although international guidelines recommend the use of low-dose anticoagulants among outpatients receiving systemic anticancer therapy at high risk of VTE,[41,42] there is paucity of systematic data synthesis on the prevention of cancer-associated arterial thrombotic events. Importantly, although the risks of ATE in malignancy are elevated compared with noncancer populations,[7,43] their absolute incidence appears to be 5-fold lower than those of VTE among patients with cancer.[44] Therefore, understanding the impact of anticoagulants on ATE among ambulatory cancer patients is crucial to optimize primary prevention strategies for cancer-associated thrombosis.

We found a 1.48% overall risk of ATE among patients starting systemic anticancer therapy who were assigned to no anticoagulation. This is consistent with

CENTRAL ILLUSTRATION **Anticoagulation and Risk of Arterial Thrombosis and Bleeding in Ambulatory Cancer Patients**



Xu Y, et al. J Am Coll Cardiol CardioOnc. 2023;5(4):520–532.

The figure describes the overall results of the study by illustrating the comparative effects of anticoagulation and no anticoagulation among ambulatory cancer patients starting systemic therapy on arterial thrombotic events and major bleeding.

recent meta-analyses that reported rates of ATE in this population; a systematic review and meta-analysis by Proverbs-Singh et al[9] reported a 0.67% incidence of ATE among cisplatin-treated patients, whereas a 2011 meta-analysis of randomized controlled trials in mesothelioma, renal cell, colorectal, breast, pancreatic, and lung cancers reported an incident ATE rate of 1.3% with combination chemotherapy alone, which increased to 2.6% with the addition of bevacizumab, an antivascular endothelial growth factor.[10]

Despite the increased risk of ATE in the ambulatory cancer population, our systematic review and meta-analysis did not demonstrate ATE risk reduction with anticoagulant use. There are several potential reasons for this null finding; first, anticoagulants alone have not been shown to be superior to antiplatelet agents for ATE prevention outside of atrial tachyarrhythmia, mechanical heart valves, and antiphospholipid antibody syndrome.[45-50] For example, a clinical trial involving 7,213 patients did not demonstrate a reduction in stroke recurrence among patients randomized to rivaroxaban 15 mg daily compared with aspirin after an embolic stroke of an undetermined source (5.1% vs 4.8%; HR: 1.07; $P = 0.52$),[48] with similar findings in the subgroup analysis of cancer patients.[47] Another clinical trial of over 27,000 patients with stable cardiovascular disease showed a reduction in cardiovascular death, stroke, or myocardial infarction with a combination of rivaroxaban 2.5 mg twice daily and aspirin compared with aspirin alone.[49] However, there was no significant difference in this outcome among patients randomized to rivaroxaban 5 mg twice daily alone compared with aspirin. Second, dosing studied in primary ATE prevention may be insufficient. Although most studies used low-dose anticoagulants known to be effective in VTE prevention, anticoagulant dosing in ATE prevention in atrial tachyarrhythmias and mechanical heart valves correspond to VTE treatment dosing.[45,51] Third, therapy discontinuation rates were more than 30% in many included studies, which may have attenuated the true effect of anticoagulants on ATE

JACC: CARDIOONCOLOGY, VOL. 5, NO. 4, 2023
AUGUST 2023:520–532

prevention. Nonetheless, this is reflective of challenges associated with primary prevention of cancer-associated thrombosis in ambulatory patients. Incorporating patient values and preferences into decision making can increase confidence in and adherence to treatments;[52] this is a crucial step in future evaluations of antithrombotic therapy in ATE prevention. Finally, risk factors for ATE among patients with cancer undergoing chemotherapy may be different compared with those for VTE. Therefore, new predictive tools for cancer-associated ATE are needed to identify high-risk ambulatory cancer populations who are most likely to benefit from anticoagulation for the prevention of ATE.

In our study, we did not observe a difference in all-cause mortality with the use of anticoagulation. The association between anticoagulation and overall survival in patients with cancer had been observed previously,[53] although more recent study-level meta-analyses and an individual patient meta-analysis did not corroborate this finding.[54-56] This finding from our meta-analysis is further supported by a recently published randomized controlled trial enrolling 614 adults with colorectal cancer comparing extended (8 weeks) to inpatient-only tinzaparin administration after surgical resection, which was halted for futility with no difference in 3-year disease-free survival or 5-year overall survival.[57]

STUDY LIMITATIONS. To our knowledge, this is the first systematic review and meta-analysis to evaluate the impact of anticoagulants on ATE prevention among ambulatory cancer patients receiving systemic anticancer therapy. By restricting our search and synthesis to randomized controlled trials, we aimed to reduce the risk of confounding.[58] However, our study is subject to several limitations. First, 3 studies meeting our inclusion criteria could not be included in our meta-analysis of the primary outcome[35,36] because they did not specify the arm in which the ATE had occurred or reported a composite endpoint consisting of ATE and VTE. However, these studies reported low numbers of events overall and are therefore unlikely to have biased our conclusion. Second, several studies involved passive capture of ATE (often as adverse events) rather than an active surveillance for this outcome at each study visit. This is relevant because prior studies show discordant rates of thrombotic complications between those actively captured as an efficacy outcome compared with an adverse event.[59] However, this was accounted for in the risk of bias tool, and a sensitivity analysis removing studies with a high risk of bias demonstrated comparable results. Third, rates of concomitant cardiovascular disease or frequency of antiplatelet use at enrollment were not reported in the majority of the included studies. Nonetheless, these baseline characteristics would likely have been equally distributed between anticoagulation and control groups through randomization, and studies that reported these measures did not demonstrate a skewed distribution of risks. Finally, although the 95% CI for ATE reduction crosses null, its lower bound includes the possibility of a 0.69% absolute risk reduction in ATE with anticoagulant use. However, whether a reduction at this threshold meets the minimal clinically important difference is unclear; in atrial fibrillation, an absolute risk reduction of 1.8 ischemic strokes per 100 person-years was deemed by patients as an appropriate threshold to accept anticoagulation and its associated bleeding risks,[60] whereas a similar risk difference of 2% for ATEs was established for sample size calculation among patients undergoing periprocedural warfarin interruptions in the setting of atrial fibrillation or mechanical heart valves.[61]

CONCLUSIONS

In summary, our systematic review and meta-analysis of randomized trials involving over 10,000 participants did not detect a statistically significant reduction in ATE with anticoagulant use among ambulatory cancer patients starting systemic anticancer therapy, whereas major and nonmajor bleeding were increased with anticoagulant use. Our data do not support the routine use of anticoagulation for ATE prevention in ambulatory cancer patients.

ACKNOWLEDGMENT The authors thank Risa Shorr, MLIS, for her expertise and input on our search strategy.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Xu is a trainee of the CanVECTOR Network; the Network receives grant funding from the Canadian Institutes of Health Research (funding reference: CDT-142654). Dr Carrier has received research funding from BMS, Pfizer, and Leo Pharma; and has received honoraria from Bayer, Pfizer, BMS, Servier, and Leo Pharma. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Marc Carrier, Division of Hematology, The Ottawa Hospital, Box 201a, 501 Smyth Road, Ottawa, Ontario K1H 8L6, Canada. E-mail: mcarrier@toh.ca.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with cancer receiving chemotherapy, the use of anticoagulants did not prevent arterial thrombotic events. Although anticoagulants are effective to prevent venous thromboembolism among patients with cancer starting chemotherapy, these data do not support their use for the prevention of arterial events such as myocardial infarction, stroke, or peripheral arterial disease.

TRANSLATIONAL OUTLOOK: Future studies on optimal risk stratification of arterial thrombotic events among patients with cancer are needed in order to focus interventional studies on patients at highest risk of developing arterial vascular complications.

REFERENCES

1. Horsted F, West J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. *PLoS Med*. 2012;9(7):e1001275.

2. Mosarla RC, Vaduganathan M, Qamar A, Moslehi J, Piazza G, Giugliano RP. Anticoagulation strategies in patients with cancer: JACC review topic of the week. *J Am Coll Cardiol*. 2019;73(11):1336–1349.

3. De Stefano V. Arterial thrombosis and cancer: the neglected side of the coin of Trousseau syndrome. *Haematologica*. 2018;103(9):1419–1421.

4. Navi BB, Reiner AS, Kamel H, et al. Risk of arterial thromboembolism in patients with cancer. *J Am Coll Cardiol*. 2017;70(8):926–938.

5. Bai Y, Li JY, Li J, et al. Risk of venous and arterial thromboembolic events associated with tyrosine kinase inhibitors in advanced thyroid cancer: a meta-analysis and systematic review. *Oncotarget*. 2019;10(41):4205–4212.

6. Bolzacchini E, Pomero F, Fazio M, et al. Risk of venous and arterial thromboembolic events in women with advanced breast cancer treated with CDK 4/6 inhibitors: a systematic review and meta-analysis. *Thromb Res*. 2021;208:190–197.

7. Yu J, Li A, Laureano M, Crowther M. Frequency of arterial thromboembolism in populations with malignancies: a systematic review. *Thromb Res*. 2019;184:16–23.

8. Vallerio P, Orenti A, Tosi F, et al. Major adverse cardiovascular events associated with VEGF-targeted anticancer tyrosine kinase inhibitors: a real-life study and proposed algorithm for proactive management. *ESMO Open*. 2022;7(1):100338.

9. Proverbs-Singh T, Chiu SK, Liu Z, et al. Arterial thromboembolism in cancer patients treated with cisplatin: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2012;104(23):1837–1840.

10. Schutz FAB, Je Y, Azzi GR, Nguyen PL, Choueiri TK. Bevacizumab increases the risk of arterial ischemia: a large study in cancer patients with a focus on different subgroup outcomes. *Ann Oncol*. 2011;22(6):1404–1412.

11. Wall JG, Weiss RB, Norton L, et al. Arterial thrombosis associated with adjuvant chemotherapy for breast carcinoma: a Cancer and Leukemia Group B Study. *Am J Med*. 1989;87(5):501–504.

12. Rutjes AW, Porreca E, Candeloro M, Valeriani E, Di Nisio M. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. *Cochrane Database Syst Rev*. 2020;12:CD008500.

13. Kimpton M, Kumar S, Wells PS, Coyle D, Carrier M, Thavorn K. Cost-utility analysis of apixaban compared with usual care for primary thromboprophylaxis in ambulatory patients with cancer. *CMAJ*. 2021;193(40):E1551–E1560.

14. Li A, Kuderer NM, Garcia DA, et al. Direct oral anticoagulant for the prevention of thrombosis in ambulatory patients with cancer: a systematic review and meta-analysis. *J Thromb Haemost*. 2019;17(12):2141–2151.

15. Streiff MB, Abutalib SA, Farge D, Murphy M, Connors JM, Piazza G. Update on guidelines for the management of cancer-associated thrombosis. *Oncologist*. 2021;26(1):e24–e40.

16. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;372:n160.

17. Khorana AA, McNamara MG, Kakkar AK, et al. Assessing full benefit of rivaroxaban prophylaxis in high-risk ambulatory patients with cancer: thromboembolic events in the randomized CASSINI trial. *TH Open*. 2020;4(2):e107–e112.

18. Bradbury CA, Craig Z, Cook G, et al. Thrombosis in patients with myeloma treated in the Myeloma IX and Myeloma XI phase 3 randomized controlled trials. *Blood*. 2020;136(9):1091–1104.

19. Zwicker JI, Karp Leaf R, Carrier M. A meta-analysis of intracranial hemorrhage in patients with brain tumors receiving therapeutic anticoagulation. *J Thromb Haemost*. 2016;14(9):1736–1740.

20. CADTH. Strings attached: CADTH's database search filters. 2021. https://www.cadth.ca/cadth-search-filters-database

21. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. *Circulation*. 2018;138(20):e618–e651.

22. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for health care professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(7):2064–2089.

23. RoB 2 and ROBINS-I. 2021. Accessed May 19, 2022. https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2?authuser=0

24. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med*. 2004;23(9):1351–1375.

25. Xu C, Furuya-Kanamori L, Zorzela L, Lin L, Vohra S. A proposed framework to guide evidence synthesis practice for meta-analysis with zero-events studies. *J Clin Epidemiol*. 2021;135:70–78.

26. Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med*. 2007;26(1):53–77.

27. Agnelli G, Gussoni G, Bianchini C, et al. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. *Lancet Oncol*. 2009;10(10):943–949.

28. Macbeth F, Noble S, Evans J, et al. Randomized phase III Trial of standard therapy plus low molecular weight heparin in patients with lung cancer: FRAGMATIC trial. *J Clin Oncol*. 2016;34(5):488–494.

29. Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent venous thromboembolism in patients with cancer. *N Engl J Med*. 2019;380(8):711–719.

30. Ek L, Gezelius E, Bergman B, et al. Randomized phase III trial of low-molecular-weight heparin enoxaparin in addition to standard treatment in small-cell lung cancer: the RASTEN trial. *Ann Oncol*. 2018;29(2):398–404.

31. Levine M, Hirsh J, Gent M, et al. Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. *Lancet*. 1994;343(8902):886–889.

32. Agnelli G, George DJ, Kakkar AK, et al. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. *N Engl J Med*. 2012;366(7):601–609.

33. Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. *N Engl J Med*. 2019;380(8):720–728.

34. Maraveyas A, Waters J, Roy R, et al. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. *Eur J Cancer*. 2012;48(9):1283–1292.

35. Haas SK, Freund M, Heigener D, et al. Low-molecular-weight heparin versus placebo for the prevention of venous thromboembolism in metastatic breast cancer or stage III/IV lung cancer. *Clin Appl Thromb Hemost*. 2012;18(2):159–165.

36. Young AM, Billingham LJ, Begum G, et al. Warfarin thromboprophylaxis in cancer patients with central venous catheters (WARP): an open-label randomised trial. *Lancet*. 2009;373(9663):567–574.

37. van Doormaal FF, Di Nisio M, Otten H-M, Richel DJ, Prins M, Buller HR. Randomized trial of the effect of the low molecular weight heparin nadroparin on survival in patients with cancer. *J Clin Oncol*. 2011;29(15):2071–2076.

38. Meyer G, Besse B, Doubre H, et al. Anti-tumour effect of low molecular weight heparin in localised lung cancer: a phase III clinical trial. *Eur Respir J*. 2018;52(4):1801220.

39. Lavau-Denes S, Lacroix P, Maubon A, et al. Prophylaxis of catheter-related deep vein thrombosis in cancer patients with low-dose warfarin, low molecular weight heparin, or control: a randomized, controlled, phase III study. *Cancer Chemother Pharmacol*. 2013;72(1):65–73.

40. Meyer G, Marjanovic Z, Valcke J, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. *Arch Intern Med*. 2002;162(15):1729–1735.

41. Farge D, Frere C, Connors JM, et al. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol*. 2019;20(10):e566–e581.

42. Wang TF, Zwicker JI, Ay C, et al. The use of direct oral anticoagulants for primary thromboprophylaxis in ambulatory cancer patients: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2019;17(10):1772–1778.

43. Lun R, Roy DC, Hao Y, et al. Incidence of stroke in the first year after diagnosis of cancer-a systematic review and meta-analysis. *Front Neurol*. 2022;13:966190.

44. Van Es N, Di Nisio M, Cesarman G, et al. Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study. *Haematologica*. 2017;102(9):1494–1501.

45. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146(12):857–867.

46. Massel DR, Little SH. Antiplatelet and anticoagulation for patients with prosthetic heart valves. *Cochrane Database Syst Rev*. 2013;7:CD003464.

47. Martinez-Majander N, Ntaios G, Liu YY, et al. Rivaroxaban versus aspirin for secondary prevention of ischaemic stroke in patients with cancer: a subgroup analysis of the NAVIGATE ESUS randomized trial. *Eur J Neurol*. 2020;27(5):841–848.

48. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med*. 2018;378(23):2191–2201.

49. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017;377(14):1319–1330.

50. Tektonidou MG, Andreoli L, Limper M, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. *Ann Rheum Dis*. 2019;78(10):1296–1304.

51. Van Es N, Coppens M, Schulman S, Middeldorp S, Büller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. *Blood*. 2014;124(12):1968–1975.

52. Zhang Y, Coello PA, Brozek J, et al. Using patient values and preferences to inform the importance of health outcomes in practice guideline development following the GRADE approach. *Health Qual Life Outcomes*. 2017;15(1):52.

53. Akl EA, Schunemann HJ. Routine heparin for patients with cancer? One answer, more questions. *N Engl J Med*. 2012;366(7):661–662.

54. Schünemann HJ, Ventresca M, Crowther M, et al. Evaluating prophylactic heparin in ambulatory patients with solid tumours: a systematic review and individual participant data meta-analysis. *Lancet Haematol*. 2020;7(10):e746–e755.

55. Montroy J, Lalu MM, Auer RC, et al. The efficacy and safety of low molecular weight heparin administration to improve survival of cancer patients: a systematic review and meta-analysis. *Thromb Haemost*. 2020;120(5):832–846.

56. Sanford D, Lazo-Langner A. The effect of low molecular weight heparin on survival in cancer patients: an updated systematic review and meta-analysis of randomized trials: reply. *J Thromb Haemost*. 2014;12(9):1574–1575.

57. Auer RC, Ott M, Karanicolas P, et al. Efficacy and safety of extended duration to perioperative thromboprophylaxis with low molecular weight heparin on disease-free survival after surgical resection of colorectal cancer (PERIOP-01): multicentre, open label, randomised controlled trial. *BMJ*. 2022;378:e071375.

58. Di Liello R, Arenare L, Raspagliesi F, et al. Thromboembolic events and antithrombotic prophylaxis in advanced ovarian cancer patients treated with bevacizumab: secondary analysis of the phase IV MITO-16A/MaNGO-OV2A trial. *Int J Gynecol Cancer*. 2021;31(10):1348–1355.

59. Chiasakul T, Patell R, Maraveyas A, Carrier M, Zwicker JI. Discordant reporting of VTE in pancreatic cancer: a systematic review and meta-analysis of thromboprophylaxis versus chemotherapeutic trials. *J Thromb Haemost*. 2021;19(2):489–501.

60. Devereaux PJ, Anderson DR, Gardner MJ, et al. Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study. *BMJ*. 2001;323(7323):1218–1222.

61. Kovacs MJ, Wells PS, Anderson DR, et al. Postoperative low molecular weight heparin bridging treatment for patients at high risk of arterial thromboembolism (PERIOP2): double blind randomised controlled trial. *BMJ*. 2021;373:n1205.

KEY WORDS coronary artery disease, epidemiology, peripheral vascular disease, prevention, thrombosis

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

Go to http://www.acc.org/jacc-journals-cme to take the CME/MOC/ECME quiz for this article.