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REVIEW ARTICLE

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Cancer-associated venous thromboembolism: Treatment and prevention with rivaroxaban

Rupert Bauersachs MD[1,2] | Alok A. Khorana MD[3] | Agnes Y. Y. Lee MD, MSc[4] | Gerald Soff MD[5]

[1]Department of Vascular Medicine, Klinikum Darmstadt GmbH, Darmstadt, Germany

[2]Center of Thrombosis and Hemostasis, University of Mainz, Mainz, Germany

[3]Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA

[4]British Columbia Cancer Agency, University of British Columbia, Vancouver, BC, Canada

[5]Memorial Sloan Kettering Cancer Center, New York, NY, USA

Correspondence
Rupert Bauersachs, Department of Vascular Medicine, Klinikum Darmstadt GmbH, Grafenstraße 9, Darmstadt 64283, Germany.
Email: bauersachs@em.uni-frankfurt.de

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Abstract

Cancer-associated venous thromboembolism (VTE) is a frequent, potentially life-threatening event that complicates cancer management. Anticoagulants are the cornerstone of therapy for the treatment and prevention of cancer-associated thrombosis (CAT); factor Xa–inhibiting direct oral anticoagulants (DOACs; apixaban, edoxaban, and rivaroxaban), which have long been recommended for the treatment of VTE in patients without cancer, have been investigated in this setting. The first randomized comparisons of DOACs against low-molecular-weight heparin for the treatment of CAT indicated that DOACs are efficacious in this setting, with findings reflected in recent updates to published guidance on CAT treatment. However, the higher risk of bleeding events (particularly in the gastrointestinal tract) with DOACs highlights the need for appropriate patient selection. Further insights will be gained from additional studies that are ongoing or awaiting publication. The efficacy and safety of DOAC thromboprophylaxis in ambulatory patients with cancer at a high risk of VTE have also been assessed in placebo-controlled randomized controlled trials of apixaban and rivaroxaban. Both studies showed efficacy benefits with DOACs, but both studies also showed a nonsignificant increase in major bleeding events while on treatment. This review summarizes the evidence base for rivaroxaban use in CAT, the patient profile potentially most suited to DOAC use, and ongoing controversies under investigation. We also describe ongoing studies from the CALLISTO (Cancer Associated thrombosis—expLoring soLutions for patients through Treatment and Prevention with RivarOxaban) program, which comprises several randomized clinical trials and real-world evidence studies, including investigator-initiated research.

KEYWORDS

anticoagulants, cancer, neoplasms, rivaroxaban, thrombosis, venous thromboembolism

Essentials

- Cancer-associated thrombosis (CAT) is a frequent complication of cancer management.
- Direct oral anticoagulants (DOACs) have been demonstrated to be a noninferior treatment option to low-molecular-weight heparin.
- Recent studies have highlighted a potential role for DOACs in CAT prevention.

1 | INTRODUCTION

Cancer-associated thrombosis (CAT) is a frequently encountered, life-threatening event that complicates cancer management and decreases survival.[1,2] Cancer and anticancer treatments are well-established risk factors for venous thromboembolism (VTE), and cancer increases the risk of VTE 4- to 7-fold versus patients without cancer.[3] CAT makes a significant contribution to the burden of VTE, accounting for approximately 20% of all cases.[4] Anticoagulants are the cornerstone for the primary prevention and treatment of VTE but may be underused for CAT because of complications in management specific to patients with cancer.[5]

Direct oral anticoagulants (DOACs) are used for the prevention and treatment of thromboembolic events across several indications, including VTE. The direct factor Xa inhibitors apixaban, edoxaban, and rivaroxaban (and to a lesser extent the direct thrombin inhibitor dabigatran) have been investigated in studies of the prevention[6–8] and treatment[9–15] of VTE in patients with cancer; results from many of these studies are now published.[6,7,9–11] This review details the rationale, study designs, and results (where applicable) of completed and ongoing investigations of DOACs in CAT, with a focus on rivaroxaban and the studies in the CALLISTO (Cancer Associated thrombosis—expLoring soLutions for patients through Treatment and Prevention with RivarOxaban) program (Tables 1 and 2). The aim is to provide an update to a previously published review of the CALLISTO program[1].

2 | RATIONALE FOR STUDYING THE USE OF DOACS FOR CAT

2.1 | To broaden the anticoagulant options available

The availability of DOACs for the prevention and treatment of CAT broadens the anticoagulation therapy options for patients with cancer, to address issues associated with traditional options. Parenteral anticoagulants such as unfractionated heparin, and subcutaneously injectable low-molecular-weight heparin (LMWH) and fondaparinux are traditional options for the prevention of VTE in ambulatory patients with cancer at a high-risk of VTE (Table 3)[16–21] and in the treatment of CAT (Table 4).[16–20,22] Parenteral anticoagulants may not be convenient for long-term therapy, and some patients may prefer an oral drug. Until recently, vitamin K antagonists (VKAs) were the only oral alternative to parenteral drugs endorsed by international guidelines for CAT treatment, but were known to be less efficacious than LMWH in this setting[23–26]; therefore, LMWHs were preferred in guidelines. There is also no evidence to support the use of parenteral anticoagulants in patients with atrial fibrillation (AF), complicating management of patients with CAT and AF. These challenges and the rationale for DOAC use in cancer-associated VTE will be explored in more detail.

2.2 | To improve persistence with anticoagulation therapy

CAT management benefits from the availability of parenteral anticoagulants, particularly for patients experiencing nausea and vomiting or impaired gastrointestinal absorption. Long-standing experience with LMWH use, and the flexible LMWH dose adjustments, allows for easier or more flexible management of thrombocytopenia and invasive interventions than with other anticoagulants, for example, VKAs.[19,27,28] Challenges with parenteral administration (eg, inconvenience and discomfort of daily injections), alongside the high cost of LMWHs,[27,29] may be burdensome for patients needing long-term anticoagulation therapy; CAT treatment guidelines support anticoagulation therapy for at least 3 to 6 months for the prevention of recurrent VTE.[16–20,27]

Some challenges of LMWH therapy may underpin poor persistence and the high use of oral anticoagulants, as observed in large US claims database analyses of patients newly diagnosed with cancer and CAT.[30–32] In an analysis of 2941 patients from the US Humana database, many patients switched from index LMWH to warfarin or rivaroxaban therapy (12.0% and 9.9%, respectively) within the 12-month observation period.[32] In the same study, and in a similar US database analysis of 12 457 patients with CAT, patients who initiated on warfarin or rivaroxaban were significantly more likely to remain on index therapy than patients initiated on an LMWH.[31,32] One limitation of such studies is that details of anticoagulant management strategies, including switching anticoagulants for circumstances such as surgery, are easily overlooked. In contrast, persistence with therapy observed in the CLOT (Randomized Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients With Cancer) and CATCH (Comparison of Acute Treatments in Cancer Hemostasis) trials was higher with LMWH than with VKA therapy.[23,26] The DOAC CAT treatment studies were an opportunity to further explore whether an oral anticoagulant could improve treatment persistence.

TABLE 1 Summary of key research areas for rivaroxaban in CAT under investigation as part of the CALLISTO program

Overview of key research needs	CALLISTO clinical trial name and focus area
Effectiveness and safety of DOACs versus placebo for the prevention of CAT Unclear benefit–risk profile for routine thromboprophylaxis in all patients with cancer	CASSINI: A Study to Evaluate the Efficacy and Safety of Rivaroxaban Venous Thromboembolism Prophylaxis in Ambulatory Cancer Participants Receiving Chemotherapy • Efficacy and safety of rivaroxaban prophylaxis in higher-risk ambulatory cancer patients [52] PRO-LAPSII: Rivaroxaban or Placebo for Extended Antithrombotic Prophylaxis After Laparoscopic Surgery for Colorectal Cancer • Extended rivaroxaban prophylaxis in surgical patients [8]
Effectiveness and safety of DOACs versus standard of care (LMWH) for the treatment of CAT	CASTA-DIVA: Cancer Associated Thrombosis, a Pilot Treatment Study Using Rivaroxaban • Efficacy and safety of rivaroxaban versus LMWH for VTE treatment (3 months) [14] SELECT-D: Anticoagulation Therapy in SELECTeD Cancer Patients at Risk of Recurrence of Venous Thromboembolism • Efficacy and safety of rivaroxaban for VTE treatment (6 months) versus LMWH[a] and extended VTE treatment (>6 months) versus placebo[b] [10]
Treatment satisfaction, treatment persistence and quality of life in cancer patients	CONKO-011: Rivaroxaban in the Treatment of Venous Thromboembolism in Cancer Patients – a Randomised Phase III Study • Patient reported outcomes on rivaroxaban treatment satisfaction compared with standard treatment (LMWH) [15] COSIMO: A Non-Interventional Study on Xarelto for Treatment of Venous Thromboembolism (VTE) and Prevention of Recurrent VTE in Patients With Active Cancer • Patient-reported outcomes on rivaroxaban treatment satisfaction, preference, and quality of life [92]
Dosing in patients with chemotherapy-induced side effects How to manage temporary interruptions of DOACs for invasive procedures	COSIMO • Insight into reasons for permanent cessation of treatment or any dose adjustments [92]
Practical management of thromboprophylaxis in clinical practice	FRONTLINE2: Fundamental Research in Oncology and Thrombosis • Provide insights into current strategies for thromboprophylaxis and management [93] QAI: Quality Assessment Initiative • Guideline on rivaroxaban use to improve quality of care in VTE treatment [63]

Abbreviations: CAT, cancer-associated thrombosis; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

[a]Results published.[10]

[b]A secondary objective of SELECT-D was to evaluate the feasibility of an extended VTE treatment study (>6 months) with rivaroxaban versus placebo through second-stage randomization of eligible patients. Due to slow recruitment and high mortality, this study design was concluded to be unfeasible.[10]

2.3 | To provide an oral alternative to VKAs

Difficulties with use of VKAs in CAT include high rates of VTE recurrence (~7%–30% per patient-year)[1,33]; meta-analyses indicate that this risk is about 50% lower with LMWH than with VKAs.[34,35] Major bleeding rates with VKAs are also high (~5%-16% per patient-year),[1,33] but the risk is similar to that with LMWH.[34,35]

These outcomes may be due to challenges in maintaining VKAs within the target therapeutic range for an adequate time[27]; the mean time in therapeutic range was 46% and 47% in patients treated with warfarin in the CLOT and CATCH studies, respectively.[23,26] DOACs overcome some limitations of VKAs, including having more predictable pharmacokinetic profiles. Similar to LMWHs, DOACs do not require regular laboratory monitoring or dose adjustment to maintain the desired anticoagulation effect. Drug–drug interactions (DDIs) and overlapping toxicities can affect the effectiveness and safety of anticoagulants in patients with cancer. DOACs and LMWHs have a lower potential for DDIs than VKAs.[36,37] DDIs are important because patients with cancer routinely receive numerous comedications,[36,38] but given the rapidly evolving nature of anticancer pharmacology, there is limited knowledge of DDIs between anticoagulants and anticancer therapies. More clinical experience has been gained with LMWH therapy than with DOACs, which might have exposed DDIs through adverse event reporting. This topic is further discussed later in this review.

2.4 | To provide an efficacious option for patients with CAT and AF

Patients with cancer have a high incidence of AF and stroke.[39–41] DOACs are the preferred option for stroke prevention in patients with nonvalvular AF,[42,43] whereas LMWHs are not routinely recommended in this setting due to a lack of evidence (ie, large-scale trials of LMWH in AF).[42] Use of the most effective anticoagulation therapy is particularly important in these patients because cancer further increases stroke risk in patients with AF.[44] A large Danish nationwide cohort study demonstrated that the absolute risks of thromboembolic and bleeding complications were similar in patients with AF with and

TABLE 2 An overview of the studies within the CALLISTO program

Study drug	Clinical study title	Study design	Dose and duration	Primary end point	Clinical trial status
CAT prevention (ambulatory patients)					
Rivaroxaban (vs placebo)	A Study to Evaluate the Efficacy and Safety of Rivaroxaban Venous Thromboembolism Prophylaxis in Ambulatory Cancer Participants receiving Chemotherapy (CASSINI) (NCT02555878) [6,52]	Phase III, prospective, randomized, double-blind superiority trial (N = 841)	• Rivaroxaban 10 mg once daily for 180 days • Placebo once daily for 180 days	Objectively confirmed symptomatic lower-extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic upper-extremity DVT, symptomatic nonfatal PE, incidental PE, and VTE-related death	Completed/ Published
CAT prevention (surgical patients)					
Rivaroxaban (vs placebo)	Rivaroxaban or Placebo for Extended Antithrombotic Prophylaxis After Laparoscopic Surgery for Colorectal Cancer (PROLAPSII) (NCT03055026) [8]	Phase III, randomized, double-blind, placebo-controlled trial (N = 646)	• Extended prophylaxis with rivaroxaban 10 mg once daily for 3 weeks • Extended prophylaxis with placebo once daily for 3 weeks	Composite of symptomatic objectively confirmed VTE, asymptomatic ultrasonography-confirmed DVT- or VTE-related death	Ongoing
CAT treatment					
Rivaroxaban (vs dalteparin)	Cancer Associated Thrombosis, a Pilot Treatment Study Using Rivaroxaban (CASTA-DIVA) (NCT02746185) [14]	Phase III, randomized, open-label trial (N = 200)	• Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily for 9 weeks • Dalteparin 200 IU/kg once daily for 4 weeks followed by 150 IU/kg once daily for 8 weeks	Recurrent VTE, including all symptomatic or incidental DVT/PE and worsening of pulmonary vascular obstruction or venous obstruction	Completed
Rivaroxaban	Quality Assessment Initiative (QAI) [63,64]	Investigator-Initiated Research at Memorial Sloan Kettering Cancer Center: cohort managed under guidance of a Clinical Pathway (N = 200)	• Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily • Rivaroxaban 10 mg twice daily for 3 weeks followed by 15 mg once daily for cancer patients aged ≥ 75 years	Clinical pathway guideline for patient selection and rivaroxaban use to improve quality of care in VTE treatment	Data published
CAT treatment and extended therapy					
Rivaroxaban (vs dalteparin)	Anticoagulation Therapy in SELECTeD Cancer Patients at Risk of Recurrence of Venous Thromboembolism (SELECT-D) [10]	Phase III, prospective, randomized, open-label, multicenter (N = 406)	• Initial 6 months with rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily, followed by additional 6 months with rivaroxaban or placebo • Dalteparin 200 IU/kg once daily for 1 month followed by 150 IU/kg once daily for 5 months	VTE recurrence rates (including symptomatic VTE and incidental PE)	Completed/ Published
CAT treatment satisfaction, preference and quality of life					
Rivaroxaban	A Non-Interventional Study on Xarelto for Treatment of Venous Thromboembolism (VTE) and Prevention of Recurrent VTE in Patients With Active Cancer (COSIMO) (NCT02742623) [92]	Observational cohort study (N = 500)	• Rivaroxaban as per label	Patient-reported treatment satisfaction burden score (ACTS)	Completed

(Continues)

TABLE 2 (Continued)

Study drug	Clinical study title	Study design	Dose and duration	Primary end point	Clinical trial status
Rivaroxaban (vs LMWH)	Rivaroxaban in the Treatment of Venous Thromboembolism in Cancer Patients – a Randomised Phase III Study (CONKO-011) (NCT02583191) [15]	Phase III, prospective, randomized open-label, multicenter trial (N = 450)	• Rivaroxaban 15 mg twice daily for 21 days followed by 20 mg once daily over a period of 3 months • Licensed LMWH dosage: enoxaparin 1 mg/kg twice daily, tinzaparin 175 IE/kg once daily or dalteparin 200 IE/kg once daily	Patient-reported treatment satisfaction measured using ACTS score	Ongoing
CAT management and perceptions					
N/A	Fundamental Research in Oncology and Thrombosis (FRONTLINE2) [93]	Global survey (N = 5250)	• N/A	Evaluate how clinicians perceive the risk of VTE in cancer patients and to provide insight into current strategies for thromboprophylaxis and management	Completed – pending publication

Abbreviations: ACTS, Anti-Clot Treatment Scale; CAT, cancer-associated thrombosis; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; N/A, not available; PE, pulmonary embolism; VTE, venous thromboembolism.

without cancer, irrespective of VKA or DOAC prescription.[45] Guidance from the Scientific and Standardization Committee of the ISTH on anticoagulation of patients with cancer with nonvalvular AF receiving chemotherapy has recently been published.[46]

3 | EVIDENCE BASE FOR THE USE OF RIVAROXABAN IN CAT

In some clinical circumstances, DOACs are used in VTE prophylaxis in patients without cancer.[47,48] Studies specific to VTE prevention in patients with cancer were warranted, given the benefits observed with LMWH for the prevention of CAT in ambulatory patients receiving systemic anticancer therapy in the SAVE-ONCO (Evaluation of AVE5026 in the Prevention of VTE in Cancer Patients Undergoing Chemotherapy) and PROTECHT (PROphylaxis of ThromboEmbolism during CHemoTherapy) trials.[49,50] Data from the AVERT (Apixaban for the Prevention of Venous Thromboembolism in High-Risk Ambulatory Cancer Patients: A Randomized Placebo-Controlled, Double-Blind Clinical Trial)[7] and CASSINI (Efficacy and Safety of Rivaroxaban Prophylaxis Compared With Placebo in Ambulatory Cancer Patients Initiating Systemic Cancer Therapy and at High Risk for Venous Thromboembolism)[6] trials provide valuable insights into apixaban and rivaroxaban, respectively, for CAT prevention in high-risk patients in the ambulatory setting (Table 5).

3.1 | AVERT

In the AVERT study of thromboprophylaxis with apixaban 2.5 mg twice daily, patients with cancer at high risk of VTE (based on a Khorana score cutoff of ≥ 2 and initiating systemic chemotherapy) were enrolled.[7,51] The primary efficacy outcome in AVERT was objectively documented VTE over a 180-day follow-up period and the main safety outcome was major bleeding.

Of 574 randomized patients, 563 were included in a modified intention-to-treat analysis. VTE occurred in 12 of 288 patients (4.2%) in the apixaban group and 28 of 275 patients (10.2%) in the placebo group (hazard ratio [HR], 0.41; 95% confidence interval [CI], 0.26-0.65; $P < .001$). In an on-treatment analysis, VTE occurred in 3 of 288 patients (1.0%) in the apixaban group and in 20 of 275 patients (7.3%) in the placebo group (HR, 0.14; 95% CI, 0.05-0.42). In the modified intention-to-treat analysis, 10 patients (3.5%) in the apixaban group and 5 patients (1.8%) in the placebo group experienced major bleeding (HR, 2.00; 95% CI, 1.01-3.95; $P = .046$). Major bleeding occurred during the treatment period in 6 patients (2.1%) in the apixaban group and 3 patients (1.1%) in the placebo group (HR, 1.89; 95% CI, 0.39-9.24).

3.2 | CASSINI

CASSINI was a multicenter trial, with a similar study design to AVERT, which assessed rivaroxaban versus placebo for thromboprophylaxis in ambulatory patients with cancer who initiated systemic therapy and had a Khorana risk score ≥ 2.[6,52] A major difference in the design of CASSINI versus AVERT is that CASSINI mandated lower-extremity ultrasonography at baseline (thus excluding any inapparent deep vein thrombosis [DVT] at baseline) and serial time points during the study, and accepted on-study screen-detected VTE as an end point, whereas AVERT focused on symptomatic VTE only.[51,52] In CASSINI, advanced pancreatic cancer status was used for stratification, as prior to the study, approximately 25% of enrolled patients were expected to have the disease (the actual proportion was 32.6% of randomized

TABLE 3 Summary of guidelines and recommendations on the management of anticoagulation for the prevention of CAT[a]

	Guidelines or guidance published before/without reference to CASSINI and AVERT		Guidelines or guidance published after/with reference to CASSINI and AVERT		
	European Society for Medical Oncology (2011) [18]	National Comprehensive Cancer Network (2019) [17]	American Society of Clinical Oncology (2019) [16]	International Initiative on Thrombosis and Cancer (2019) [19]	International Society on Thrombosis and Hemostasis: primary thromboprophylaxis in ambulatory patients with cancer [21]
Hospitalized patients	Inpatient: UFH, LMWH, or fondaparinux in hospitalized patients confined to bed Surgery: LMWH, UFH, or fondaparinux	Inpatient: LMWH, fondaparinux, UFH, or warfarin[b] Surgery: LMWH, fondaparinux, UFH, or warfarin; perioperative dosing with UFH or LMWH for high-risk surgery (eg, abdominal or pelvic)[b]	Inpatient: Pharmacological thromboprophylaxis recommended in the absence of bleeding or other contraindications Perioperative: UFH or LMWH unless contraindicated because of active bleeding or high bleeding risk	Inpatient: LMWH or fondaparinux when CrCl ≥ 30 mL/min, or UFH in hospitalized patients with reduced mobility Surgery: LMWH (when CrCl ≥ 30 mL/min) or low-dose UFH	N/A
Ambulatory patients	Routine: Thromboprophylaxis is not recommended in patients receiving chemotherapy, but may be considered in high-risk patients (Khorana score recommended to identify patients at high risk of VTE) Chemotherapy: For patients with myeloma, LMWH, ASA, or warfarin in patients receiving thalidomide plus dexamethasone or thalidomide plus chemotherapy	Routine: VTE prophylaxis not recommended outside of clinical trial settings Chemotherapy: For patients with myeloma receiving thalidomide, lenalidomide, or pomalidomide, ASA (low-risk patients) and LMWH or warfarin (high-risk patients) (Khorana score recommended to identify patients at high risk of VTE)	Routine: Routine thromboprophylaxis should not be offered to all outpatients with cancer Chemotherapy: High-risk outpatients with cancer (Khorana score ≥ 2 prior to starting a new systemic chemotherapy regimen) may be offered thromboprophylaxis with apixaban, rivaroxaban, or LMWH provided there are no significant risk factors for bleeding and no drug interactions. Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should be offered pharmacologic thromboprophylaxis with either ASA or LMWH for lower-risk patients and LMWH for higher-risk patients	Routine: Primary prophylaxis is not recommended routinely in patients receiving systemic anticancer therapy. Anti-cancer therapy: Primary pharmacological prophylaxis of VTE with LMWH is indicated in ambulatory patients with locally advanced or metastatic pancreatic cancer Primary prophylaxis with a DOAC (rivaroxaban or apixaban) is recommended in patients at intermediate-to-high risk of VTE not actively bleeding or not at a high risk of bleeding	Chemotherapy: DOACs are recommended as primary thromboprophylaxis in ambulatory cancer patients starting chemotherapy with Khorana score ≥ 2 in patients with no drug–drug interactions and not at high risk of bleeding. Currently, apixaban and rivaroxaban are the only DOACs with evidence from randomized clinical trials. In high-risk ambulatory cancer patients where primary thromboprophylaxis is planned but with concerns for safety of DOACs, LMWHs are suggested

Abbreviations: ASA, acetylsalicylic acid; CAT, cancer-associated thrombosis; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; N/A, not available; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

[a]Summary of key recommendations shown; further details and caveats apply. See reference for full details.[16-19,21]

[b]Category 1 options shown with agent selection based on: renal failure (CrCl < 30 mL/min), US Food and Drug Administration approval, cost, ease of administration, monitoring, and ability to reverse anticoagulation.

TABLE 4 Summary of guidelines and recommendations on management of anticoagulation for acute and long-term treatment of CAT[a]

	Guidelines published before publication of Hokusai-VTE-Cancer and SELECT-D			Guidelines published post publication of Hokusai-VTE-Cancer and SELECT-D		
	European Society for Medical Oncology (2011)[18]	American College of Chest Physicians (2016)[27]	International Society on Thrombosis and Haemostasis (2018)[22]	American Society of Clinical Oncology (2019)[16]	International Initiative on Thrombosis and Cancer (2019)[19]	National Comprehensive Cancer Network (2019)[17]
Acute treatment	LMWH	LMWH is preferred over VKA or DOACs In patients not treated with LMWH: no preference is stated for VKAs or DOACs, and one DOAC is not preferred over the others	Recommend individualized treatment regimen after shared decision-making with patients DOACs (currently edoxaban and rivaroxaban) are suggested for patients with a low risk of bleeding and no DDIs with current systemic therapy (LMWHs are an acceptable alternative) LMWHs are suggested for patients with a high risk of bleeding (DOACs are an acceptable alternative in the absence of DDIs) No recommendations on duration of therapy are provided	Initial anticoagulation may involve LMWH, UFH, fondaparinux, or rivaroxaban	LMWHs are preferred over VKAs for the treatment of VTE in patients with cancer with CrCl ≥ 30 mL/min (grade 1A); DOACs are recommended for patients with cancer with CrCl ≥ 30 mL/min in the absence of strong drug–drug interactions or gastrointestinal absorption impairment (grade 1A). LMWH or DOACs should be used for a minimum of 6 months to treat established VTE in patients with cancer (grade 1A)	Dalteparin monotherapy[b] and with edoxaban (edoxaban following ≥ 5 days of dalteparin) are preferred (category 1); enoxaparin monotherapy, rivaroxaban monotherapy, fondaparinux monotherapy, UFH with edoxaban (edoxaban following ≥ 5 days of UFH therapy) and combinations of warfarin with parenteral agents are category 2A options; UFH monotherapy is a category 2B option Apixaban monotherapy or dabigatran (following ≥ 5 days of parenteral therapy) are listed as potential options (pending further data) in patients who refuse or have compelling reasons to avoid LMWH (painful, inconvenient, or expensive), which may contribute to poor compliance
Long-term treatment	LMWH at 75%-80% of initial dose for 6 months	Extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy; continued use of treatment should be reassessed at periodic intervals		For long-term anticoagulation, LMWH, edoxaban, or rivaroxaban for at least 6 months are preferred because of improved efficacy over VKAs	After 6 months, termination or continuation of anticoagulation (LMWH, DOACs, or VKAs) should be based on individual evaluation of the benefit-risk ratio, tolerability, drug availability, patient preference, and cancer activity (guidance in the absence of data).	Treatment should be continued for at least 3 months

(Continues)

TABLE 4 (Continued)

	Guidelines published before publication of Hokusai-VTE-Cancer and SELECT-D		Guidelines published post publication of Hokusai-VTE-Cancer and SELECT-D		
Duration of extended treatment	For as long as there is clinical evidence of active malignancy	Extended anticoagulation therapy (no scheduled stop date) for patients with active cancer (regardless of bleeding risk)	LMWH or VKA in select patients with active cancer can continue beyond 6 months	After 3-6 months, termination or continuation of anticoagulation should be based on individual assessment of the benefit-to-risk ratio, tolerability, drug availability, patient preference, and cancer activity	Continue for as long as there is active cancer or persistent risk factors

Abbreviations: CAT, cancer-associated thrombosis; DDI, drug-drug interaction; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; RCT, randomized controlled trial; UFH, unfractionated heparin; VKA, vitamin K antagonist.

[a]Summary of key recommendations shown, further details and caveats apply. See reference for full details.[16-19,22,27]

[b]Although several LMWHs have been studied in RCTs in cancer patients, the efficacy of dalteparin in this population is supported by the highest-quality evidence and is the only LMWH approved by the US Food and Drug Administration for this indication.

patients). The primary efficacy end point was the incidence of the composite of objectively confirmed symptomatic or asymptomatic VTE or VTE-related death during the 6-month treatment period. The primary safety end point was ISTH major bleeding events.[6]

Overall, 841 patients were randomized; rivaroxaban did not significantly reduce VTE or VTE-related death in the primary analysis period, largely due to a high rate of treatment discontinuation and/or early mortality. The primary end point occurred in 25 of 420 patients (6.0%) in the rivaroxaban group and 37 of 421 patients (8.8%) in the placebo group.

(HR, 0.66; 95% CI, 0.40-1.09; P = .10) in the intention-to-treat population up-to-day-180 observation period, with the majority of events (24/62; 39%) in the rivaroxaban arm occurring after drug discontinuation. In a prespecified analysis of the intention-to-treat population for the on-treatment period, primary end point events were significantly reduced with rivaroxaban versus placebo. In total, 11 of 420 patients (2.6%) in the rivaroxaban group versus 27 of 421 (6.4%) in the placebo group experienced a primary end point event (HR, 0.40; 95% CI, 0.20-0.80). Major bleeding occurred in 8 of 405 patients (2.0%) and 4 of 404 patients (1.0%) in the rivaroxaban and placebo groups, respectively (HR, 1.96; 95% CI, 0.59-6.49; P = .26).[6]

Table 5 summarizes the key characteristics and data from AVERT and CASSINI. AVERT and CASSINI were the first phase III randomized trials assessing the efficacy and safety of DOAC thromboprophylaxis in higher-risk outpatients with cancer, and provide the first data on the use of long-term oral anticoagulation for the primary prevention of VTE in this setting.[1,6,7,52]

3.3 | Hokusai-VTE-Cancer

The Hokusai-VTE-Cancer study (A Phase IIIb, Prospective, Randomized, Open-Label, Blind Evaluator Study Evaluating the Efficacy and Safety of LMWH/Edoxaban Versus Dalteparin in VTE Associated With Cancer) was a large, open-label, noninferiority trial evaluating edoxaban (60 mg once daily, administered after ≥ 5 days of LMWH) versus dalteparin (200 IU/kg once daily for 1 month [capped at a maximum daily dose of 18 000 IU] followed by 150 IU/kg once daily thereafter) for the treatment of CAT. Of the 1050 patients enrolled, 98% had active cancer, 53% had metastatic cancer, 72% were receiving anticancer therapy, and 24% had an Eastern Cooperative Oncology Group (ECOG) status of 2[9] (whereas an ECOG status of 3 or 4 is a criterion for exclusion across CAT treatment trials).[9,10,23,26]

The composite outcome of the first recurrent VTE or major bleeding event at 12 months occurred in 12.8% of patients treated with edoxaban compared with 13.5% of patients treated with dalteparin, demonstrating statistically significant noninferiority (HR, 0.97; 95% CI, 0.7-1.36; P = .0056). Although the median duration of therapy was significantly longer with edoxaban than with dalteparin (211 days vs 184 days, respectively; P = .01), a sensitivity analysis of events that occurred in the per-protocol population during treatment or ≤ 3 days of discontinuation confirmed noninferiority of the primary outcome. A total of 15% of patients who had permanently discontinued LMWH therapy did so because of the inconvenience of dosing (compared with 4% of patients on oral edoxaban therapy). Recurrent VTE risk was initially similar between treatment arms, but the Kaplan–Meier curves separated from approximately day 100 in favor of edoxaban. This led to a numerically but not significantly lower risk of recurrent VTE with edoxaban compared with dalteparin treatment (7.9% vs 11.3%; HR, 0.71; 95% CI, 0.48-1.06; P = .09), driven by a reduction in the rate of recurrent DVT (3.6% vs 6.7%; HR, 0.56; 95% CI, 0.32-0.97). The rate of recurrent pulmonary embolism was similar between treatment arms (5.2% vs 5.3%; HR, 1.00; 95% CI, 0.59-1.69).[9] Reassuringly, the risk of recurrent VTE at 6 months with dalteparin therapy (8.8%)[9] was similar to that observed in previous trials of dalteparin for CAT.[23,53]

The incidence of major bleeding was significantly higher in patients treated with edoxaban compared with dalteparin (6.9% vs

TABLE 5 Results from the phase III AVERT and CASSINI studies, which evaluated DOACs versus placebo for the prevention of CAT in high-risk ambulatory patients with cancer who were receiving systemic cancer therapy

	AVERT[7] (apixaban vs placebo)	CASSINI[6] (rivaroxaban vs placebo)
N	574 randomized (mITT analysis: 288 apixaban, 275 placebo)	841 randomized (ITT up-to-day-180 analysis: 420 rivaroxaban, 421 placebo)
Design	Randomized, placebo-controlled, double-blind trial in 7 Canadian centers	Randomized, placebo-controlled, double-blind multinational trial
Study duration	180 days with a minimum intention to treat with systemic cancer therapy for 3 months	6 months with a plan to initiate a new systemic regimen within 1 week of initiating study drug
Treatment arms	Apixaban 2.5 mg twice daily or placebo twice daily	Rivaroxaban 10 mg once daily or placebo once daily
Metastatic disease	25.1% vs 23.7%	54.5% overall
ECOG performance status ≥ 2	14.7% vs 13.4%	8.8% vs 9.3%
Median duration of assigned therapy	157 days vs 155 days	4.3 months for overall population
VTE or VTE-related death	Primary analysis: 4.2% vs 10.2% HR, 0.41; 95% CI, 0.26-0.65; *P* < .001 mITT on-treatment analysis: 1.0% vs 7.3% HR, 0.14; 95% CI, 0.05-0.42	Primary analysis: 6.0% vs 8.8% HR, 0.66; 95% CI, 0.40-1.09; *P* = .10 ITT on-treatment analysis: 2.6% vs 6.4% HR, 0.40; 95% CI, 0.20-0.80
Major bleeding	3.5% vs 1.8% HR, 2.00; 95% CI, 1.01-3.95; *P* = .046	1.98% vs 0.99% HR, 1.96; 95% CI, 0.59-6.49; *P* = .26
Major bleeding severity category 3 or 4	10.0% vs 40.0% of all major bleeding events per arm	N/A
Fatal bleeding	0% vs 0%	0.25% vs 0%
ICH	N/A	2 of 809 patients (0.25%)
GI bleeding	N/A	8 of 809 patients (0.99%)
Clinically relevant nonmajor bleeding	7.3% vs 5.5% HR, 1.28; 95% CI, 0.89-1.84	2.72% vs 1.98% HR, 1.34; 95% CI, 0.54-3.32; *P* = .53
Mortality	12.2% vs 9.8%	20% vs 23.8%

Abbreviations: CAT, cancer-associated thrombosis; CI, confidence interval; DOAC, direct oral anticoagulant; ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; HR, hazard ratio; ICH, intracranial hemorrhage; mITT, modified intention-to-treat; N/A, not available; VTE, venous thromboembolism.

4.0%; HR, 1.77; 95% CI, 1.03-3.04; *P* = .04). Subclassification of the clinical presentation of major bleeding events was performed according to prespecified criteria.[54] Severe bleeding at presentation, that is, events considered a medical emergency (category 3; eg, bleeding with hemodynamic instability or intracranial bleeding with neurologic symptoms) or resulting in fatality (category 4), was similar between the treatment arms (2.3% vs 2.5%, respectively). Two fatal bleeding events occurred during the study (both in the dalteparin group) and 6 intracranial hemorrhages (2 in the edoxaban group and 4 in the dalteparin group). A higher rate of gastrointestinal bleeding events (nonemergency; category 2) was observed with edoxaban versus dalteparin therapy (3.8% vs 1.1%, respectively), which occurred primarily in patients with gastrointestinal cancer. However, severe major bleeding (categories 3 and 4) within this subgroup occurred in 3.0% of patients in the edoxaban group and 2.1% of patients within the dalteparin group.[9,55] All-cause mortality at 6 months was 26%, lower than in CATCH (32%) and CLOT (39%), as were the number of patients classed as severely ill (eg, metastatic disease, high ECOG status), and such differences should be kept in mind when interpreting data. It is difficult to compare the outcomes of these studies because they were conducted 15 years apart, and progress made in cancer treatment and supportive care since then may be a confounding factor.[56]

3.4 | SELECT-D

SELECT-D (Anticoagulation Therapy in SELECTeD Cancer Patients at Risk of Recurrence of Venous Thromboembolism), the first published randomized trial from the CALLISTO program, was a randomized, open-label, pilot trial designed to obtain estimates of recurrent VTE in patients with CAT, treated with rivaroxaban or dalteparin therapy, to gauge feasibility of recruitment to a phase III study. Patients with active cancer and objectively confirmed VTE received rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg once daily thereafter) or dalteparin (200 IU/kg once daily for 1 month, 150 IU/kg once daily thereafter [capped at a maximum daily dose of 18 000 IU]). Approximately 80% of patients were treated with a parenteral anticoagulant for the qualifying venous thromboembolic

event before randomization to a study drug, with a median treatment duration of 48 hours.[10] Results were similar to those from Hokusai-VTE-Cancer, although the difference in statistical power between the 2 studies should be considered when interpreting results: SELECT-D was much smaller (N = 406) and underpowered for efficacy and safety hypotheses testing.

In SELECT-D, rivaroxaban demonstrated a reduced risk of VTE recurrence (cumulative rate at 6 months: 4% vs 11%, respectively; HR, 0.43; 95% CI, 0.19-0.99) compared with dalteparin. The difference in the effect of rivaroxaban compared with dalteparin on VTE recurrence became evident at approximately 2 months after treatment initiation, after the acute treatment phase. Rivaroxaban had a similar risk of major bleeding events, as demonstrated for edoxaban in the Hokusai-VTE-Cancer study (cumulative rate at 6 months: 6% vs 4%, for rivaroxaban vs dalteparin, respectively; HR, 1.83; 95% CI, 0.68-4.96), and the incidence of fatal bleeding events was similar between treatment arms (0.5% vs 0.5%, respectively). No instances of bleeding events in the central nervous system were observed. Most major bleeding events (12/17 [70.6%]) were in the gastrointestinal tract; two-thirds of these major gastrointestinal bleeds were attributable to rivaroxaban therapy (8/12 [66.7%] with rivaroxaban vs 4/12 [33.3%] with dalteparin). The risk of clinically relevant nonmajor bleeding was also higher with rivaroxaban versus dalteparin therapy (cumulative rate at 6 months: 13% vs 4%, respectively; HR, 3.76; 95% CI, 1.63-8.69). Of note, patients with esophageal or gastroesophageal cancer were excluded from enrollment partway through the study as a precautionary measure because an interim safety analysis of the first 220 patients noted a nonsignificant excess in the risk of bleeding in these patients. More patients with esophageal or gastroesophageal cancer experienced major bleeding with rivaroxaban (36%) versus dalteparin (5%) therapy.[10]

Together, Hokusai-VTE-Cancer and SELECT-D provide evidence that DOACs are effective for CAT treatment, although the higher risk of bleeding with DOACs than with LMWH suggests that careful risk assessment and patient selection are needed. Following these studies, the ISTH has released guidance suggesting edoxaban or rivaroxaban for patients with CAT and a low risk of bleeding and no DDIs with current systemic therapy (LMWHs are an acceptable alternative).[22] LMWH is suggested for patients at high risk of bleeding, including patients with luminal gastrointestinal cancers with an intact primary; cancers at risk of bleeding from genitourinary tract, bladder, or nephrostomy tubes; or patients with active gastrointestinal mucosal abnormalities such as duodenal ulcers, gastritis, esophagitis, or colitis (edoxaban or rivaroxaban are acceptable alternatives if no DDIs with systemic therapies in use).[22] The guidance further states that "a final treatment recommendation should be made after shared decision-making with patients regarding reduced potential recurrence but greater bleeding rates with specific DOACs, incorporating patient preferences and values."[22]

National Comprehensive Cancer Network guidelines recommend dalteparin monotherapy or LMWH plus edoxaban as category 1 options, with rivaroxaban monotherapy also listed as a category 2A option.[17] They state that "patients may refuse or be poor candidates for LMWH injections because they are painful, inconvenient, and expensive. These factors may contribute to poor compliance with long-term LMWH treatment."[17]

Whether results from Hokusai-VTE-Cancer and SELECT-D represent a class effect of factor Xa inhibitors will require further evidence. Recently, the randomized, open-label ADAM VTE (apixaban or dalteparin in reducing blood clots in patients with cancer-related VTE) safety study (N = 287) reported on the use of apixaban compared with dalteparin for the 6-month treatment of VTE in patients with active cancer.[11,57] The study did not meet its primary end point for major bleeding due to the lower than anticipated number of major bleeding events in both treatment arms (0 of 145 patients receiving apixaban and 1.4% of 142 patients receiving dalteparin). The incidence of recurrent VTE was 0.7% with apixaban and 6.3% with dalteparin (HR, 0.099; 95% CI, 0.013-0.780; P = .0281).[11] The CARAVAGGIO (apixaban for the treatment of venous thromboembolism in patients with cancer) trial, an investigator-led, multinational, prospective, randomized trial that is currently ongoing, should provide further insight into the role of apixaban in the treatment of CAT.[13] Table 6 summarizes the key characteristics and data from Hokusai-VTE-Cancer, SELECT-D, and ADAM VTE studies. Additional studies include the single-arm phase IV CAP (apixaban as treatment of venous thrombosis in patients with cancer) study[58] and others that include dabigatran.[59,60]

3.5 | Real-world evidence for DOACs in the treatment of CAT

Real-world evidence for DOACs in the treatment of CAT provides additional insights into their use and management, as well as effectiveness, safety, and patient-reported outcomes associated with use. To date, most of the evidence has been limited to studies of rivaroxaban,[61–67] whereas real-world evidence for apixaban in CAT is limited[68] and for dabigatran and edoxaban is currently lacking. When interpreting such data, it is important to note that observational studies are often limited to highly selected and/or small populations of patients with CAT, and that database analyses are limited by retrospective data collection with the possibility of incomplete/missing data.

A Quality Assessment Initiative (QAI) cohort study conducted at Memorial Sloan Kettering Cancer Center (MSKCC) is a prospective real-world evidence study evaluating rivaroxaban within the CALLISTO program. Following the approval of rivaroxaban for VTE treatment, MSKCC implemented a clinical pathway for rivaroxaban use in CAT. The pathway included patient selection criteria, recommending against rivaroxaban use in patients with known gastrointestinal or urinary tract lesions, untreated primary or metastatic brain cancer, or severe renal impairment.[63] As of October 2016, the QAI study had examined 1072 patients with CAT managed with rivaroxaban in the MSKCC clinical pathway. However, being an observational study, patients were included regardless

TABLE 6 Results from the randomized Hokusai-VTE-Cancer study, SELECT-D pilot study, and the ADAM VTE study, which evaluated DOAC versus LMWH therapy for the treatment of CAT

	Hokusai-VTE-Cancer[9] (edoxaban vs dalteparin)	SELECT-D[10] (rivaroxaban vs dalteparin)	ADAM VTE[11] (apixaban vs dalteparin)
N	1050 mITT population: 522 vs 524	406 (203 vs 203)	300 (150 vs 150)
Design	Open-label, multinational, noninferiority, randomized phase III trial	Open-label, multicenter (UK-based), randomized pilot study	Open-label, multicenter (North America-based), investigator-initiated, randomized superiority trial
Study duration	12 months (with an intended treatment period of ≥ 6 months)	6 months	6 months
Treatment arms	Edoxaban 60 mg once daily following ≥ 5 days of LMWH (or 30 mg once daily in patients with CrCl 30-50 mL/min, a body weight of ≤ 60 kg or receiving concomitant potent P-glycoprotein inhibitors) vs dalteparin 200 IU/kg once daily for 30 days (max daily dose of 18 000 IU) and 150 IU/kg once daily thereafter	Rivaroxaban 15 mg bid for 21 days followed by 20 mg once daily thereafter (discontinued if platelet counts < 50 000/mm^3 until recovery; dose reduction or discontinuation was specified for different levels of renal impairment) vs dalteparin 200 IU/kg once daily for 30 days and 150 IU/kg once daily thereafter (maximum daily dose of 18 000 IU; dose reduction or discontinuation was specified for low platelet count or significant renal failure until recovery)	Apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months vs weight-based subcutaneous dalteparin (200 IU/kg once daily for 1 month followed by 150 IU/kg once daily for months 2 through 6); dosing was based on actual body weight with no upper dose limit
Receiving cancer treatment at baseline	757 (72.4)	282 (69.5)	218 (72.7)
Chemotherapy	N/A	233 (57.4)	N/A
Metastatic disease	554 (53.0)	236 (58.1)	193 (64.3)
ECOG performance status = 2	247 (23.6)	95 (23.4)	32 (10.7)
Thrombocytopenia	55 (5.3)[a]	336 (82.8)[b]	N/A
Median duration of assigned therapy	211 days vs 184 days; *P = .01*	5.9 months vs 5.8 months	5.78 months vs 5.65 months
Recurrent VTE or major bleeding	12.8% vs 13.5%; HR, 0.97; 95% CI, 0.70-1.36; *P = .006 for noninferiority*[a]	N/A	N/A
Recurrent VTE	7.9% vs 11.3%; HR, 0.71; 95% CI, 0.48-1.06; *P = .09* (At 6 months: 6.5% vs 8.8%)	3.9% vs 8.9%	0.7% vs 6.3% HR, 0.099; 95% CI, 0.013-0.780; *P = .0281*
Major bleeding	6.9% vs 4.0%; HR, 1.77; 95% CI, 1.03-3.04; *P = .04* (At 6 months: 5.6% vs 3.2%)	5.4% vs 3.0%	0% vs 1.4% *P = .138* (HR not estimable due to zero bleeding events in the apixaban group)
Major bleeding severity category 3 or 4	33.3% vs 61.9% of all major bleeding events per arm	N/A	N/A
Fatal bleeding	0.0% vs 0.4%	0.5% vs 0.5%	0%
ICH	0.4% vs 0.8%	0.0% vs 0.0%	N/A
GI bleeding	3.8% vs 1.1%	3.9% vs 2.0%	N/A
Clinically relevant nonmajor bleeding	14.6% vs 11.1%; HR, 1.38; 95% CI, 0.98-1.94 (At 6 months: 12.3% vs 8.2%)	12.3% vs 3.4%	6.2% vs 4.2%

(Continues)

TABLE 6 (Continued)

	Hokusai-VTE-Cancer[9] (edoxaban vs dalteparin)	SELECT-D[10] (rivaroxaban vs dalteparin)	ADAM VTE[11] (apixaban vs dalteparin)
Mortality	39.5% vs 36.6%; HR, 1.12; 95% CI, 0.92-1.37 (At 6 months: 26.8% vs 24.2%)	23.6% vs 27.6%	16% vs 11% HR, 1.40; 95% CI, 0.82-2.43; *P = .3078)*

Abbreviations: CAT, cancer-associated thrombosis; CI, confidence interval; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; HR, hazard ratio; ICH, intracranial hemorrhage; LMWH, low-molecular-weight heparin; max, maximum; mITT, modified intention-to-treat; N/A, not available; VTE, venous thromboembolism.

[a]Platelet count 50 000-100 000/μL.

[b]Platelet count ≤ 350 000/μL.

of compliance with the clinical pathway.[63,64] The 6-month cumulative incidence rate of recurrent VTE was 4.2% (95% CI, 2.7%-5.7%) and the 6-month cumulative incidence rate of major bleeding was 2.2% (95% CI, 1.1%-3.2%); although the recurrent VTE rate was similar to that observed in SELECT-D, major bleeding was less frequent.[10,64] The lower incidence of bleeding in the QAI cohort is likely due to the suggested avoidance/caution with rivaroxaban in patients with known gastrointestinal and genitourinary lesions. SELECT-D only excluded patients with esophageal and gastroesophageal cancers partway through the study, again highlighting that DOACs are suitable for some but not all patients with cancer.

Results were presented recently on patient-reported treatment satisfaction from the single-arm, noninterventional COSIMO (Cancer-associated thrOmboSIs—patient-reported outcoMes with rivarOxaban) study, which enrolled patients with cancer and VTE who were changing from LMWH, fondaparinux, or VKA to rivaroxaban therapy for the treatment of CAT. Treatment satisfaction was evaluated through the Anti-Clot Treatment Scale (ACTS), a 17-item measure of the negative and positive aspects of anticoagulation treatment, on subscales for ACTS Burdens and ACTS Benefits, respectively. The primary outcome was a change in the ACTS Burdens score at week 4 compared with baseline. Patients with CAT reported a durable improvement in anticoagulation-associated treatment satisfaction, specifically a reduction in the perceived burdens of therapy, following the change to rivaroxaban.[12] As part of this study, a discrete choice experiment was presented to patients, who were asked to decide between completely hypothetical treatment options based on a combination of different attributes (route of administration [injection/tablet], frequency of intake [once daily/twice daily], need for regular assessment of international normalized ratio at least every 3-4 weeks [yes/no], and interactions with food/alcohol [yes/no]), regardless of efficacy or safety. Data were collected using semistructured telephone interviews, performed between week 4 and week 12 after enrollment of patients in the study and the start of rivaroxaban administration. This study showed that patients with CAT who changed from standard of care to rivaroxaban primarily preferred to take an orally administered anticoagulant. This is of importance because, so far, little is known about the specific preferences of patients with CAT with respect to anticoagulation therapy. Therefore, individual preferences should be considered for the initiation and long-term treatment of VTE in patients with CAT because this may result in improved treatment adherence and consequently better effectiveness and safety in routine clinical practice.[69]

4 | CURRENT CONTROVERSIES IN CAT

4.1 | Patient selection strategies for outpatient primary prophylaxis are not well defined

CAT occurs primarily in the outpatient setting,[52] and VTE is a significant cause of death in ambulatory patients with cancer.[70] The benefit–risk profile of antithrombotic prophylaxis among ambulatory patients with cancer is hard to establish because the risk of CAT is highly variable (2%-20%) and depends on the cancer type, stage, and treatment.[71,72] Studies evaluating anticoagulants in this setting have focused on outpatients receiving systemic anticancer therapies but have differed in their approach to patient selection according to VTE risk.

In the SAVE-ONCO and PROTECHT trials, a significant reduction in the relative risk of VTE with LMWH compared with placebo was demonstrated in mixed cancer-type populations with no selection for VTE risk. The absolute benefit was modest, meaning that many patients required prophylaxis to prevent a single venous thromboembolic event; therefore, more rigorous selection criteria would be required to identify high-risk patients who would derive a clinically meaningful benefit from prophylaxis.[49,50] In addition, the durations of therapy in these studies were relatively short (~3-4 months), limiting the ability to adequately assess the value of prophylactic anticoagulation.[49,50] Consequently, guidelines do not recommend routine thromboprophylaxis for ambulatory patients with cancer.[16–19,21]

Other studies have focused specifically on high-risk cancer types such as pancreatic cancer and multiple myeloma,[73–75] and based on their outcomes, guidelines suggest consideration of anticoagulant prophylaxis in such patients receiving systemic anticancer therapies.[16–19,21]

A third approach has been to enroll a mixed cancer-type study population limited to patients with a high or intermediate-to-high risk of VTE using the Khorana score.[6,7,76] This widely validated risk-assessment tool categorizes ambulatory patients with cancer receiving systemic anticancer therapy as being at a low (score 0), medium (score

2), or high (score ≥ 3) risk of VTE.[16–18,33,77] In a recent retrospective database analysis of over 6000 patients with newly diagnosed cancer who had initiated cancer therapy, patients with a Khorana score ≥ 2 (25% of the study cohort) were 2 to 3 times more likely to develop VTE than those with a score < 2.[78] The AVERT and CASSINI studies limited enrollment to patients with a Khorana score of ≥ 2 and demonstrated that risk-adapted prophylaxis enables a clinically meaningful absolute risk reduction of VTE.[6,7] Based on such evidence, recently published guidelines and guidance endorse the use of the Khorana score to identify patients who may benefit from thromboprophylaxis.[16,19,21] However, the Khorana score is less informative for assessing the risk of VTE when evaluating patients with lung cancer, as shown in a recent systematic review and meta-analysis of CAT.[79]

Since the validation of the Khorana score, multiple new scores or modifications have been proposed.[80] Pabinger et al[81] proposed a simplified score retaining the original categorization of primary cancer sites but substituted the other variables with only D-dimer. Comparison of different risk tools is challenging; a prospective comparison of the validated Khorana, Vienna CATS, and PROTECHT prediction scores showed that they were poor at predicting VTE in patients with cancer.[82] However, this study enrolled patients up to several months after starting systemic cancer therapy (instead of obtaining baseline information before chemotherapy initiation), which can affect many variables included in most risk tools (eg, platelet counts). The study results are perhaps unsurprising given this.[82]

4.2 | Duration of anticoagulant therapy for the treatment of CAT remains unclear

Decisions regarding the duration of anticoagulation therapy are central to the secondary prevention of VTE, which involves periodic reassessment of the risk of recurrence if anticoagulation is stopped and the risk of bleeding if it is continued.[20,27] The optimal duration of anticoagulation for CAT treatment is particularly challenging.[83] Most guidelines for CAT support extended anticoagulation therapy (≥6 months) for the secondary prevention of VTE, or the continuation of therapy for as long the patient harbors active malignancy (with no scheduled stop date).[16–19,27] The shortcoming of this expert consensus is a paucity of clinical trial data on benefit–risk profile beyond the acute treatment period (3-6 months).[83] Such data gathering is complicated by the recruitment and retention of patients in extended treatment trials (ie, because of high mortality and a general reluctance to continue treatment beyond 6 months).[10,84]

The DALTECAN (Evaluation of Dalteparin for Long-Term [One Year] Treatment of Blood Clots in Subjects With Cancer), TiCAT (Tinzaparin in Cancer-Associated Thrombosis), and Hokusai-VTE-Cancer studies have had some success in evaluating the extended use of anticoagulation for CAT. The primary outcome of the DALTECAN study was the rate of major bleeding between 6 and 12 months of treatment with dalteparin. A total of 334 patients with active cancer and acute VTE were enrolled, with 109 patients (33%) completing 12 months of therapy (the overall mean duration of treatment was 210 days). In total, 116 patients (33.8%) died during the 12-month study plus 2-month follow-up period. The incidence of major bleeding was 3.6% in the first month of treatment, and 1.1% and 0.7% per patient-month during months 2 through 6 and months 7 through 12, respectively. Similarly, the risk of a recurrent event was highest in the first month, at 5.7%, reducing to 3.4% during months 2-6 and 4.1% during months 7 through 12.[53] In the TiCAT study, 247 patients were enrolled, with 136 patients (55.1%) completing 12 months of therapy (the overall mean duration of treatment was 15.6 months). Thirty-nine patients (15.8%) died during the first 6 months and 30 (12.1%) died during the subsequent 12 months. In TiCAT, rates of clinically relevant bleeding (0.6%) and VTE recurrence (1.1%) during months 7 through 12 following the diagnosis of VTE were low; the event rates during months 1-6 were 0.9% for clinically relevant bleeding and 4.5% for VTE recurrence.[85] In the Hokusai-VTE-Cancer study, a total of 1050 patients were enrolled, with 354 (33.8%) of the 1046 patients included in the intention-to-treat analysis completing treatment for 12 months or until study closure (the overall median duration of treatment was 211 days for edoxaban and 184 days for dalteparin). A total of 398 patients (38.0%) died over the trial period. As outlined previously, this trial achieved its noninferiority end point for recurrent VTE and major bleeding with edoxaban versus dalteparin.[9] In a post hoc analysis focused on the follow-up period of 6 to 12 months, rates of recurrent VTE and major bleeding were demonstrated to be low. Recurrent VTE occurred in 2 (0.7%) of 294 patients in the edoxaban group and in 3 (1.1%) of 273 patients in the dalteparin group; major bleeding events occurred in 5 and 3 patients, respectively.[86]

However, patients with cancer in the palliative care setting are underrepresented in these clinical trials. Recent data from a multicenter observational study (N = 1199) found a low incidence of VTE (0.5% symptomatic DVT) but a high incidence (9.8%) of clinically relevant bleeding associated with thromboprophylaxis, suggesting that the bleeding risk of VTE prophylaxis might outweigh the benefits in this population.[46,87]

Further studies regarding extended-duration CAT treatment would be beneficial but will likely continue to be challenging to obtain. The upcoming DOAC studies for the treatment of CAT—CARAVAGGIO and CONKO-011 (Rivaroxaban in the Treatment of VTE in Cancer Patients)—are assessing durations of therapy of ≤ 6 months.[13,15]

4.3 | There is limited knowledge of drug interactions between anticoagulants and anticancer therapies

Patients with cancer routinely receive numerous co-medications, including antimitotic agents, tyrosine kinase inhibitors, and immune-modulating agents, some of which induce or inhibit the activity of cytochrome P450 3A4 enzymes and/or P-glycoprotein transporters involved in the physiological processing of rivaroxaban and other DOACs. Some patients may even receive combinations of inhibitors and inducers of cytochrome P450 3A4 enzymes and P-glycoprotein transporters, which

further complicates matters. Concomitant medications may increase the risk of bleeding or thrombotic complications with DOAC therapy, depending on the magnitude of the effect on P450 3A4 enzymes and/or P-glycoproteins. Currently, DOACs have not been shown to have a clinically significant impact on the performance of any antiangiogenic therapies. Frequently used platinum-based and anticancer hormonal agents do not appear to induce or inhibit cytochrome P450 3A4 or P-glycoprotein activity[36]; however, there is limited knowledge of drug interactions between anticoagulants and anticancer therapies because of the ever-evolving nature of the field. Therefore, careful consideration of potential DDIs and overlapping toxicities using the resources available, along with regular monitoring and reviews of drug combinations on a case-by-case basis, is essential.

5 | ONGOING STUDIES IN THE CALLISTO PROGRAM

The CALLISTO international clinical research program, involving more than 3000 patients globally, is investigating the effectiveness and safety of rivaroxaban for prevention and treatment of CAT. Further aims include evaluation of treatment satisfaction and adherence with rivaroxaban and insight into real-world management and patterns of anticoagulation use. CALLISTO involves several randomized controlled trials (RCTs) and noninterventional studies, as well as expert guidance on DDIs and surveys. Details of ongoing and planned CALLISTO initiatives can be found in Tables 1 and 2.

5.1 | CAT prevention

In addition to CASSINI, the CALLISTO program includes another ongoing phase III CAT prevention trial, PRO-LAPSII (Rivaroxaban or Placebo for Extended Antithrombotic Prophylaxis After Laparoscopic Surgery for Colorectal Cancer).[8] PRO-LAPSII will assess the rate of CAT with rivaroxaban versus placebo for extended prophylaxis (~3 weeks) after laparoscopic surgery for colorectal cancer.[8] This study will be similar to the PRO-LAPSI phase III study, which demonstrated reduced rates of CAT and similar rates of major bleeding with extended LMWH prophylaxis (4 weeks) compared with short prophylaxis (1 week).[88]

5.2 | CAT treatment

5.2.1 | Efficacy and safety

The CALLISTO program includes several investigator-led studies assessing the effectiveness and safety of rivaroxaban in CAT treatment. As discussed previously, results from the QAI study[63] and SELECT-D[10] have been published. A second phase III RCT, CASTA-DIVA (Cancer Associated Thrombosis, a Pilot Treatment Study Using Rivaroxaban), has recently been completed (pending publication)[14]; similar to SELECT-D, this study compared the safety and effectiveness of rivaroxaban and dalteparin for the treatment of CAT. CASTA-DIVA focused on patients at high risk of recurrent VTE and with high-grade lymphoma or myeloma treated with immunomodulatory drugs (thalidomide or lenalidomide).[14] The CONKO-011 study (discussed in more detail below) will also assess the efficacy and safety of rivaroxaban versus LMWH, but as secondary objectives.[15] Other DOAC treatment studies, including CARAVAGGIO[13] for apixaban, are ongoing.

5.2.2 | Treatment satisfaction

Several studies have demonstrated patient satisfaction and acceptability of long-term treatment with LMWH for the treatment of CAT.[89–91] However, real-world evidence on patient satisfaction with, or preferences for, DOACs in patients with CAT were lacking. The CALLISTO program was developed with an RCT (COSIMO) and a real-world study (CONKO-011) to collect data on patient-reported treatment satisfaction as a primary objective.[15,92] The recent results from COSIMO were mentioned in section 3. The phase III clinical trial CONKO-011 will compare patient-reported treatment satisfaction in patients after randomization to rivaroxaban or LMWH therapy.[15,92] Quality of life will be measured using the Spitzer index, ACTS, and the treatment satisfaction questionnaire for medication.

5.3 | CAT management and perceptions

Secondary objectives of COSIMO included comprehensive data on cancer type and stage, treatment patterns, and clinical management, including planned treatment duration, switching rates, and reasons for switching or discontinuing therapy. Validated tools for measuring patient fatigue (the Functional Assessment of Chronic Illness Therapy Fatigue score) and for defining the ideal anticoagulant treatment for CAT from the patient perspective have also been used to further inform perceptions of anticoagulants for CAT.

An additional study is the FRONTLINE2 (fundamental research in oncology and thrombosis 2) global survey.[93] It was designed to evaluate how clinicians perceive the risk of VTE in patients with cancer and to provide insights into current strategies for thromboprophylaxis and disease management. Views from oncologists, hematologists, surgeons, radiation oncologists, and members of the palliative care team responsible for treating CAT were collected. A questionnaire (available in 9 languages) was distributed, and the results are currently being analyzed.

6 | CONCLUSIONS

Results from Hokusai-VTE-Cancer and SELECT-D support DOACs (specifically edoxaban and rivaroxaban at present) for treatment of

CAT. The results from AVERT and CASSINI demonstrate the potential benefits of thromboprophylaxis with DOACs in the outpatient setting for patients with cancer at higher risk of VTE.[16,17,19–21] The CALLISTO program, comprising numerous studies, will provide further information on the use of rivaroxaban to simplify the complex management of patients with CAT. It will also evaluate VTE prevention in medically managed patients and surgical patients with active cancer and offer recent data on patient-reported treatment satisfaction. With many of the CALLISTO studies and other DOAC studies scheduled to be completed over the next couple of years, it is anticipated that the management of CAT will evolve quickly.

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CONFLICT OF INTEREST

RB has received personal fees from Bayer AG, Bristol-Myers Squibb, Pfizer Inc, Daiichi Sankyo, Boehringer Ingelheim, and Leo Pharma. AAK has received personal fees from Janssen Pharmaceuticals, Bayer AG, Pfizer Inc, Sanofi SA, Halozyme Inc, and AngioDynamics Inc. AYYL has received consultancy honoraria from Bayer AG, Pfizer Inc and Leo Pharma, received lecture honoraria from Servier Laboratories and an investigator-initiated study grant from Bristol-Myers Squibb. GAS has received consultancy honoraria from Bayer AG and Janssen Pharmaceuticals and has received an investigator-initiated study grant from Janssen Pharmaceuticals.

ORCID

Rupert Bauersachs https://orcid.org/0000-0001-6192-1741
Gerald Soff https://orcid.org/0000-0002-8781-903X

TWITTER

Alok A. Khorana @aakonc
Agnes Y. Y. Lee @AggieLeeMD

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