

# Direct oral anticoagulants for treatment and prevention of venous thromboembolism in cancer patients

This article was published in the following Dove Press journal:  
*Vascular Health and Risk Management*

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**Abstract:** Venous thromboembolism (VTE) is a common cause of morbidity and mortality in patients with cancer. Compared with the general population, cancer patients with VTE have higher rates of both VTE recurrence and bleeding. While low molecular weight heparin (LMWH) has been the mainstay of treatment for cancer-associated VTE for over a decade, direct oral anticoagulants (DOACs) have recently emerged as a new therapeutic option due to their ease of administration and because they do not require laboratory monitoring. Several large randomized clinical trials have been performed or are ongoing at the time of writing, comparing DOACs with LMWH in this population. Three of these trials have thus far been published and suggest that DOACs are a reasonable alternative to LMWH for management of cancer-associated VTE. Despite the advantages offered by DOACs, these agents may not be appropriate for certain patient groups owing to increased risk of bleeding, organ compromise, extremes of weight, and other issues. Finally, data are emerging suggesting that DOACs may be useful for primary thromboprophylaxis in cancer patients in conjunction with validated risk assessment scores. In this evidence-based review, data for the use of DOACs to treat cancer-associated VTE will be examined, focusing on efficacy, safety, and timing of treatment. Guidance on choosing the optimal anticoagulant for a given patient is also offered.

**Keywords:** venous thromboembolism, malignancy, thrombosis, rivaroxaban, apixaban, edoxaban, DOAC

## Introduction

Venous thromboembolism (VTE) is a major cause of morbidity and mortality in cancer patients. While anticoagulation for cancer-associated VTE was limited to vitamin K antagonists (VKAs) and heparin agents for several decades, the direct oral anticoagulants (DOACs) have recently emerged as a new therapeutic option. Because no agent has demonstrated consistent superiority over the others in managing these patients, the clinician must consider issues including efficacy in preventing VTE recurrence, bleeding risk, interactions with cancer-directed treatments, route of administration, financial cost, and utility of monitoring.<sup>1</sup> As such, deciding on optimal anticoagulation is complex and patient specific. Irrespective of agent choice, anticoagulation is more challenging in cancer patients, who demonstrate greater rates of VTE occurrence as well as increased rates of bleeding complications with anticoagulation compared with non-cancer patients.

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For over a decade, low molecular weight heparin (LMWH) has been the standard of care treatment for cancer-associated VTE after pivotal clinical trials demonstrated lower rates of VTE recurrence compared with warfarin. However, LMWH therapy is associated with higher costs. Furthermore, injections frequently impact quality of life, which may reduce patient adherence. In recent years, the DOACs, which include the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors apixaban, edoxaban, and rivaroxaban, have emerged as the standard agents for treatment of VTE in the non-cancer population following several large, randomized controlled trials demonstrating non-inferiority to warfarin.<sup>2–6</sup> Consequently, these agents are an attractive alternative to LMWH to treat cancer patients.

In addition to initial anticoagulation for VTE in the cancer patient, primary prophylaxis and extended anticoagulation beyond the initial 6–12 months of treatment are important considerations. In cancer patients, DOACs have gained attention for their possible utility as primary prophylaxis for high-risk patients in conjunction with the strategic use of clinical prediction scores.

In this evidence-based review, we will discuss the challenges of anticoagulation in the cancer population, review the evolution of anticoagulation options for cancer-associated VTE, explore the most recent data for use of DOACs in cancer patients, and explore the use of DOACs for primary thromboprophylaxis and for extended anticoagulation beyond the initial treatment period.

## Thromboembolism and unique challenges in the cancer population

While rates vary depending upon several patient and malignancy-related characteristics, VTE is common in the cancer population. Malignancy accounts for 20–30% of initial VTE events<sup>7,8</sup> and VTE occurs in approximately 20% of cancer patients.<sup>8–12</sup> Cancer treatments, including cytotoxic chemotherapy, targeted therapy, hormonal therapy, radiation therapy, and surgery, may further increase VTE risk.<sup>13</sup> Altogether, this represents a four- to seven-fold increased risk of VTE relative to patients without cancer. Not only is VTE risk increased in patients with cancer but cancer patients with VTE have more hospitalizations, a higher rate of metastatic disease, and worse overall survival compared to cancer patients without VTE across multiple tumor types.<sup>14,15</sup> VTE is the second leading cause of death in cancer patients, behind only the

malignancy itself.<sup>13</sup> The thrombophilic stimulus of malignancy may be exceedingly difficult to control in some cancer patients, even with consistent, therapeutic levels of anticoagulation.<sup>16,17</sup>

Although anticoagulation is frequently effective in managing VTE in cancer patients, complications of anticoagulation are more frequent and severe in this population. Cancer patients have a three- to four-fold higher rate of VTE recurrence compared to patients without cancer.<sup>18,19</sup> Anticoagulated cancer patients also have a two- to three-fold increased rate of major bleeding compared to anticoagulated patients without cancer.<sup>18,20,21</sup> These findings may be related to drug–drug interactions with cancer-directed treatments, nausea, poor oral intake, thrombocytopenia, and metabolic derangements affecting anticoagulant levels.<sup>22,23</sup> Cost and access-related issues may present a greater burden in cancer patients as well.

## LMWH for treatment of cancer-associated VTE

For over a decade, consensus guidelines have established LMWH as the standard of care for initial treatment of cancer-associated VTE.<sup>24–27</sup> This recommendation is based on evidence from five randomized, controlled trials that compared LMWH to VKAs, as summarized in [Table 1](#). In addition, meta-analyses of these randomized controlled trials comparing LMWH and VKA demonstrated that LMWH reduces the recurrence of VTE compared to VKAs<sup>28,29</sup> but may increase the risk of major bleeding.

The two major trials comparing LMWH with warfarin for cancer-associated VTE had disparate findings. The CLOT trial<sup>22</sup> demonstrated a statistically significant reduction in VTE recurrence rate compared with warfarin, while the CATCH trial,<sup>30</sup> the largest and most recent study to date, did not show superiority of LMWH. However, assessment of the cancer burden and pre-existing risk of VTE may help to explain the difference observed in these two trials. There were higher proportions of patients with metastatic disease, ongoing cancer treatment, and overall mortality in the CLOT trial compared to the CATCH trial, suggesting that the patient populations of the two trials were not similar. As discussed previously, cancer severity influences both VTE recurrence and bleeding rates independent of anticoagulation.<sup>18,21</sup> The CATCH patient population was less likely to develop recurrent VTE than the CLOT population and this may have decreased the power of the trial to detect a significant difference in event rates;

**Table I** Summary of major trials comparing LMWH with VKAs

Trial	VTE recurrence (%)	Major bleeding (%)	Mortality (%)
<b>CANTHANOX</b> <sup>84</sup> Warfarin vs enoxaparin (3 months)	4.0 vs 2.8 No significant difference in primary combined outcome of major bleeding or VTE recurrence. Increased rate of fatal bleeds in warfarin arm (8% vs 0%)	16.0 vs 7.0	22.7 vs 11.3
<b>CLOT</b> <sup>22</sup> VKA vs dalteparin (6 months)	17 vs 9 Significant reduction in VTE recurrence with dalteparin. No significant difference in major bleeding or mortality. The 12-month post-hoc analysis showed a probability of death of 20% in the dalteparin arm compared with 36% in the VKA arm ( $p=0.03$ ) <sup>85</sup>	4 vs 6	39 vs 41
<b>ONCENOX</b> <sup>86</sup> Warfarin vs enoxaparin (7 months)	6.5 vs 10.0 Owing to small event rates, no trends or significance could be reported	2.9 vs 9.0	32.4 vs 32.8
<b>LITE</b> <sup>87</sup> VKA vs tinzaparin (12 months)	16.0 vs 7.0 No difference in VTE recurrence or major bleeding after 3 months. After 12 months of therapy for patients meriting continuation, post-hoc analysis showed significantly lower VTE recurrence in the tinzaparin arm	7.0 vs 7.0	47.0 vs 47.0
<b>CATCH</b> <sup>30</sup> Warfarin vs tinzaparin (6 months)	10.5 vs 7.2 No statistically significant difference in rates of VTE recurrence and major bleeding. Significant reduction in rates of non-major bleeding in the tinzaparin arm	2.4 vs 2.7	32.2 vs 34.7

**Abbreviations:** LMWH, low molecular weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

in fact, the observed rate of thrombotic events in CATCH was lower than expected. The same analysis with a higher-risk population like that of CLOT may have duplicated the results of the CLOT trial.

While it is true that the more morbid CLOT patient population may have had greater difficulty achieving international normalized ratio (INR) goals owing to poor oral intake, emesis, and alterations in metabolism due to interactions with chemotherapies, the time in therapeutic range (TTR) for the warfarin groups was comparable between CLOT and CATCH (46% and 47%, respectively) as was the time above INR therapeutic range. While failure of VKA management is an important consideration in the

management of ill cancer patients, this is a less likely explanation for the discrepancy between CLOT and CATCH.

Nevertheless, despite the consensus guidelines from professional societies recommending the use of LMWH for cancer-associated thrombosis, indefinite treatment with LMWH has faced numerous real-world hurdles. A recent insurance database analysis showed that almost half of cancer patients with a primary VTE were started on warfarin as opposed to around 25% each for LMWH and rivaroxaban.<sup>31</sup> This may be due in part to lower cost and ease of oral administration, but patient and provider preference to avoid the pain, bruising, and hematomas that come with injection of LMWH has also been demonstrated in real-world data. Median treatment duration for LMWH is also less than half that of warfarin and rivaroxaban (3.3, 7.9, and 7.9 months, respectively).<sup>31</sup> These findings are particularly consequential for those patients with a limited life expectancy. Therefore, despite consensus guidelines from professional societies recommending LMWH, patient and provider adherence is suboptimal. Therefore, additional safe, effective anticoagulant choices are necessary for cancer patients.

## DOACs for treatment of cancer-associated VTE

The results of several large, pivotal, randomized controlled trials have demonstrated the non-inferiority of DOACs to warfarin for prevention of VTE recurrence as well as lower rates of bleeding in the general population.<sup>2-6,32</sup> In turn, DOACs have replaced warfarin as the standard of care for treatment of VTE in the majority of non-cancer patients. The pivotal trials establishing DOACs as standard of care for VTE treatment in the non-cancer population each contained only a small subset of cancer patients. A meta-analysis of the cancer patients from six of these phase III clinical trials found significantly lower VTE recurrence in the DOAC arm compared with the VKA arm (relative risk 0.57, 95% CI 0.36–0.91) with a similar risk of major bleeding,<sup>32</sup> while another meta-analysis examining the same cancer patient subpopulation from these six trials did not find a significant reduction in VTE recurrence. These meta-analyses may not be generalizable to the cancer population at large as several of the trials did not include patients with active cancer (for which the definition was variable), and no data on the type and stage of cancer or use of cancer-directed treatments were described. Despite these

limitations, the findings from these subgroup analyses suggest that DOACs may be appropriate for cancer patients, or at least certain groups of cancer patients.

To study the cancer population directly, several multicenter randomized controlled trials comparing direct Xa inhibitors with LMWH for initial treatment of cancer-associated VTE have been published (two as complete publications and one in abstract form, summarized in Table 2) or are currently underway at the time of writing.

## Hokusai VTE Cancer trial

This worldwide study randomized 1,050 cancer patients with proximal deep vein thrombosis (DVT), acute symptomatic pulmonary embolism (PE), or incidental PE to 5 days of LMWH followed by either oral edoxaban (60 mg once daily) or subcutaneous dalteparin (200 IU/kg once daily for 1 month, then 150 IU/kg once daily) for a period of 6–12 months.<sup>33</sup> The study utilized a composite primary outcome of recurrent VTE or major bleeding. Edoxaban was non-inferior to dalteparin (12.8% vs 13.5%,  $p=0.006$  for non-inferiority). VTE recurrence was not significantly different between edoxaban and dalteparin (7.9% vs 11.3%,  $p=0.09$ ). Major bleeding occurred more often in the edoxaban group compared with dalteparin (6.9% vs 4.0%,  $p=0.04$ ). Clinically relevant non-major bleeding (CRNMB) was also higher in the edoxaban arm (14.6%) compared with the dalteparin arm (11.1%), but this difference did not reach statistical significance. Overall survival was similar between the two groups.

## SELECT-D trial

This worldwide study compared rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg daily for a total of 6 months) with dalteparin (200 IU/kg daily for 1 month, then 150 IU/kg

daily for 5 months) in 406 patients with active cancer and PE (symptomatic or incidental) or proximal DVT.<sup>34</sup> The primary outcome was VTE recurrence. Rivaroxaban had a lower rate of VTE recurrence than dalteparin (4% vs 11%, HR 0.43, 95% CI 0.19–0.99). Rates of major bleeding were not significantly different (4% vs 6%, HR 1.83, 95% CI 0.68–4.96). However, CRNMB rates were significantly higher in the rivaroxaban arm (13% vs 4%, HR 3.74, 95% CI 1.63–8.69). Overall survival was similar between the two groups.

## ADAM VTE trial

The ADAM VTE trial is the first study comparing a DOAC to LMWH for treatment of cancer-associated VTE that had major bleeding as its primary outcome, with VTE recurrence and a composite of major bleeding plus CRNMB as secondary outcomes. This study was published in abstract form in 2018.<sup>35</sup> This phase IV randomized controlled superiority trial compared apixaban (10 mg twice daily followed by 5 mg twice daily) with dalteparin (200 IU/kg daily for 1 month followed by 150 IU/kg once daily) for 6 months in 300 patients with cancer-associated VTE.<sup>36</sup> Based on the published abstract, apixaban was associated with significantly lower VTE recurrence compared with dalteparin (3.4% vs 14.1%, HR 0.26, 95% CI 0.09–0.80,  $p=0.02$ ). Major bleeding was not significantly different between the apixaban and dalteparin arms (0.0% vs 2.1%,  $p=0.01$ ), nor was the combined major bleeding and CRNMB rate (6.2% vs 6.3%, HR 0.91, 95% CI 0.41–1.94,  $p=0.88$ ). Overall survival was similar between the two groups. Quality of life surveys as well as bruising questionnaires favored apixaban. While final results from this study are awaited, the published abstract suggests the safety and efficacy of apixaban for treatment of cancer-associated VTE.

**Table 2** Summary of major trials comparing DOACs with LMWH

Trial	VTE recurrence (%)	Major bleeding (%)	Clinically relevant non-major bleeding (%)	Mortality (%)
<b>Hokusai VTE Cancer</b> <sup>33</sup> Dalteparin vs edoxaban	8.8 vs 6.5	3.2 vs 5.6	8.2 vs 12.3	24.2 vs 24.8
	Edoxaban was non-inferior to LMWH in combined outcome of VTE recurrence or major bleeding. Major bleeding occurred more often in the edoxaban group. Rates of non-major bleeding were not significantly different, nor was mortality			
<b>SELECT-D</b> <sup>34</sup> Dalteparin vs rivaroxaban	11 vs 4	4 vs 6	4 vs 13	30 vs 25
	Rivaroxaban had a significantly lower rate of VTE recurrence. Rates of major bleeding were not significantly different, although rates of non-major bleeding were significantly higher in the rivaroxaban arm. No difference in mortality			
<b>ADAM VTE</b> <sup>35</sup> Dalteparin vs apixaban	14.1 vs 3.4	2.1 vs 0.0	4.2 vs 6.2	10.6 vs 15.9
	Significant reduction in VTE recurrence with apixaban. No significant difference in bleeding rates or mortality			

**Note:** Six-month study outcomes are reported for all trials.

**Abbreviations:** DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; VTE, venous thromboembolism.

Unlike the pivotal trials comparing DOACs to VKAs in the general population, these trials had strict inclusion criteria for patients with active cancer. The patient populations of all three trials had rates of mortality, active cancer-directed treatment, and metastatic disease comparable to those of the aforementioned LMWH vs VKA trials, signifying a representative cancer population. The results of these three studies suggest that DOACs are at least non-inferior to LMWH for preventing VTE recurrence in the cancer population. This conclusion has been corroborated by six recent meta-analyses<sup>28,29,37–40</sup> as well as several cohort analyses describing the efficacy of DOACs in clinical practice.

However, both Hokusai VTE Cancer and SELECT-D, as well as the meta-analyses, observed increased bleeding events, including numerous gastrointestinal (GI) bleeds, in the DOAC arms. These findings are consistent with prior trials examining DOACs for treatment of VTE,<sup>32</sup> as well as trials examining DOACs for stroke prevention in patients with atrial fibrillation.<sup>41–43</sup> Many of the bleeding events occurred in patients with esophageal and gastric cancers. A safety analysis of the first 220 patients in the SELECT-D trial observed a non-significant difference in major bleeding (especially upper GI bleeding) between the rivaroxaban and dalteparin arms in patients with cancers of the esophagus or gastroesophageal junction; patients with these cancers were subsequently excluded for the remainder of the trial. Similarly, subgroup analysis of the Hokusai VTE Cancer trial demonstrated that in patients with GI cancer, there was a higher risk of major bleeding events in the edoxaban arm than in the dalteparin arm (12.7 vs 3.6%, HR 4.0, 95% CI 1.5–10.6,  $p=0.005$ ), most of which were GI bleeds.<sup>44</sup> A recent claims database analysis of 26,894 patients with cancer-associated VTE<sup>45</sup> corroborated these results by showing heterogeneity in bleeding risk with DOACs by cancer type, with upper GI cancers having the highest rate (8.6% per patient-year). Lower rates were observed in lung cancer (6.0%), colorectal cancer (4.5%), prostate cancer (4.0%), hematological cancer (3.5%), and breast cancer (2.9%). Of note, when stratified by cancer type, there was a borderline but non-significant increased bleeding risk for DOACs vs LMWH in patients with upper GI cancers. A recent study examining longer-term rivaroxaban treatment of cancer-associated VTE echoes these findings: over a 3-year observation period, a considerably lower rate of bleeding relative to those of the DOAC arms in Hokusai VTE Cancer and SELECT-D was achieved by excluding patients with GI or genitourinary malignancies.<sup>46</sup> Overall, the results from

many of these studies raise questions about the appropriateness of DOAC use in patients with GI cancers, or at least the appropriateness of rivaroxaban or edoxaban use. In addition, the somewhat provocative findings of superiority of apixaban without increased bleeding in the ADAM VTE trial suggest that the specific direct factor Xa inhibitor employed may matter and that results of each study examining a specific agent may not be generalizable across the class of direct factor Xa inhibitors. The possible difference in bleeding events with apixaban versus edoxaban or rivaroxaban in the cancer patient population will be addressed by the Caravaggio study.<sup>47</sup>

Notably, each of these trials excluded certain subpopulations of cancer patients: those with Eastern Cooperative Oncology Group (ECOG) performance status of 3 or 4, those with brain metastases, and those with thrombocytopenia (platelet count of  $<50 \times 10^9/L$ ) are some notable examples. A retrospective study published in 2019 found no increase in bleeding rates in patients with primary brain tumors or brain metastases in patients receiving DOACs compared with those receiving LMWH,<sup>48</sup> but many of the subpopulations excluded from the aforementioned trials remain unstudied. It remains unclear whether DOACs are safe and of similar efficacy in these patient subpopulations.

Ongoing randomized controlled open-label trials examining DOACs for cancer-associated thrombosis will help to clarify many outstanding questions. These trials include the Caravaggio study (NCT03045406), comparing apixaban with dalteparin; the CANVAS trial (NCT02744092), comparing DOAC therapy (rivaroxaban, apixaban, edoxaban, or dabigatran, by investigator's choice) with LMWH with or without a transition to warfarin; the CONKO-0211 (NCT02583191) and CASTA-DIVA (NCT02746185) studies, comparing rivaroxaban with LMWH; and the single-arm CAP study (NCT02581176), investigating the use of apixaban as treatment for cancer-associated thrombosis. Information gathered from these trials will further inform clinicians regarding the efficacy and safety profile of DOACs as anticoagulation for cancer-associated VTE.

## Choosing between DOACs and other anticoagulants for VTE management

As new data are published, management strategies for cancer-associated VTE are evolving quickly. DOACs represent an attractive alternative to the well-established LMWH, expanding the armamentarium of anticoagulants studied in cancer



patients. At the time of writing, most consensus guidelines still favor LMWH, but this is beginning to change. In 2018, the International Society for Thrombosis and Haemostasis (ISTH) became the first major body to suggest the use of DOACs for cancer patients with an acute diagnosis of VTE, a low risk of bleeding, and no drug–drug interactions with current systemic therapy.<sup>49</sup> National Comprehensive Cancer Network (NCCN) guidelines now recommend rivaroxaban as a monotherapy option, apixaban “for patients who refuse or have compelling reasons to avoid LMWH”, as well as edoxaban following a lead-in with heparin agents (category 1 evidence).<sup>50</sup> New guidelines from the American Society of Hematology (ASH) are expected in late 2019. It is important to note that while DOACs are favorable in many ways (fixed-dose regimens without laboratory monitoring, fewer interactions with cancer therapies,<sup>51</sup> oral route of administration), this does not mean that they will be universally preferred for all cancer patients.

The major aspect of DOACs that makes them attractive relative to LMWH is oral administration. In the SELECT-D trial, the median duration of assigned treatment was shorter with dalteparin primarily owing to the inconvenience of injections. An interview analysis of patients, also from the SELECT-D trial, however, showed that most patients found injections straightforward and acceptable as an element of holistic cancer care, contrary to these findings.<sup>52</sup> In addition, a choice-based conjoint exercise showed that preference for oral administration over injection was relatively mild; minimal interference with cancer treatment, low thrombosis recurrence rate, and low risk of major bleed were most valued by the patients.<sup>53</sup> An international survey of over 500 physicians and 800 patients showed that clinicians greatly overestimate their patients’ expected perceived burden of daily subcutaneous injections.<sup>54</sup> Just as cancer patients being treated for VTE strongly value effectiveness and safety in addition to comfort, so too must clinicians in discussing with patients their individual preferences.<sup>55</sup>

In addition, while there is high awareness of drug interactions with VKAs, there is a relative lack of data regarding DOACs’ interactions with anticancer medications. Dabigatran is metabolized via P-glycoprotein pathways, while rivaroxaban and apixaban are also metabolized by the CYP3A4 and CYP2J2 pathways; none of the currently approved DOACs are known to affect the activity of these metabolic pathways themselves. To date, the clinical significance of DOAC interactions with other medications in general is relatively unknown and there are few published clinical data on interactions with anticancer medications.<sup>56,57</sup> It is important to recognize that although there are several drugs that may modulate

plasma levels of DOACs, there is a lack of pharmacokinetic data regarding specific drug interactions. On a theoretical basis, clinicians should be cautious when utilizing chemotherapies or other medications (e.g., antifungals) which may influence DOAC metabolism. In addition, chemotherapies may influence the bioavailability of DOACs because of side effects. For instance, the increased risk of GI bleeds observed with DOACs may make these medications less favorable in patients taking anticancer agents that disrupt the GI mucosa, potentially increasing absorption.

In the case of elderly or more frail patients for whom significant bleeds can be highly morbid, reversibility of anticoagulation is another important consideration. Reversal agents are available for DOACs. Idarucizumab is an Fab antibody fragment approved to rapidly reverse the effects of dabigatran.<sup>58</sup> Andexanet alfa is a recombinant modified human FXa protein which acts as a decoy to bind factor Xa inhibitors, thereby dramatically reducing anti-Xa activity.<sup>59</sup> Currently, andexanet is not readily available in many US hospitals and is extremely expensive. Ciraparantag (PER977, Perosphere) is a small, synthetic, water-soluble, cationic molecule currently under development. It was originally designed to reverse the effects of unfractionated heparin and LMWH but has also been shown to reverse the effects of DOACs.<sup>60</sup> Importantly, many of these DOAC reversal agents have associated thrombosis and mortality risks, as demonstrated in clinical trials evaluating their use, but an in-depth discussion of anticoagulation reversal is beyond the scope of this article.

Poor renal function associated with age or chemotherapy-associated renal toxicity may preclude the use of both LMWH and DOACs. Currently, dabigatran is not recommended for patients with low creatinine clearance while apixaban and rivaroxaban can be used with significant caution.<sup>61</sup> LMWH, unlike unfractionated heparin, is primarily renally excreted and is therefore also used with significant caution in patients with poor renal function.<sup>23</sup> In select cancer patients with poor renal function, LMWH can be administered in reduced doses with close monitoring of anticoagulation with anti-Xa levels. Notably, the degree of renal dysfunction correlates with the risk of major bleeding in cancer patients,<sup>62</sup> making the optimal choice of anticoagulant and its associated safety profile an important consideration. For some of these patients, warfarin may be the best choice as it is the only agent that can be readily monitored.

Optimal selection of anticoagulation for treatment of cancer-associated thrombosis may take into account several of the above clinical considerations, which are summarized in Table 3. This list is not exhaustive and treatment

decisions should be individualized treatment considering both provider recommendations and patient values.

## DOAC utility for primary prophylaxis of VTE

Although current clinical guidelines from the American Society of Clinical Oncology<sup>63</sup> recommend primary thromboprophylaxis (i.e., before any VTE event) in

hospitalized patients with active cancers, it is not recommended in the routine outpatient setting owing a higher number needed to treat of 40 to 50 (with the exception of myeloma patients receiving treatment with immunomodulatory agents).<sup>64</sup> However, these guidelines do indicate that thromboprophylaxis may be considered for select high-risk patients. Several characteristics may inform which patients are high risk. In particular, tumor site of origin is associated with different risks of VTE, with pancreatic ductal adenocarcinoma and gastric adenocarcinoma carrying the highest risk.<sup>65–67</sup> Stage also informs the risk of VTE; patients with metastatic disease have a 20-fold increased risk of VTE compared to those without cancer.<sup>9</sup> Molecular biomarkers such as tissue factor,<sup>68</sup> D-dimer,<sup>69</sup> and P-selectin<sup>70</sup> have also been shown to predict an increased risk of cancer-associated VTE. Ongoing use of regression analyses and forward selection of candidate variables will continue to best identify other clinical criteria that may be useful in predicting the risk of cancer-associated VTE.<sup>71</sup>

Numerous clinical prediction scores have been created to best identify those patients who may merit primary prophylaxis given their individual risk profiles. The Khorana score was the first clinical prediction score to predict VTE risk specifically in cancer patients and is the most widely utilized. Advantages of the Khorana score include its relative simplicity, successful validation in multiple studies,<sup>67,72,73</sup> and high negative predictive value, allowing clinicians to effectively exclude low-risk patients from thromboprophylaxis and associated bleeding risks.<sup>12</sup> Relative limitations include a low positive predictive value, a need for further risk stratification (most patients are classified as intermediate risk), and lack of consistent validity in single sites of cancers. Other clinical prediction scores that modify the original Khorana score include the ProtecT score<sup>74</sup> and the Vienna score.<sup>75</sup> The clinical characteristics of interest for each of these scores are summarized in Table 4.

Recent clinical trials (summarized in Table 5) have examined the utility of DOACs, in conjunction with clinical prediction scores, for primary thromboprophylaxis in high-risk cancer patients. The AVERT trial<sup>76</sup> is a randomized, placebo-controlled, double-blind clinical trial comparing 6 months of apixaban (2.5 mg twice daily) with placebo in 574 patients with a Khorana score  $\geq 2$ . Patients with conditions predicting an increased risk of significant bleeding, hepatic dysfunction, renal insufficiency, and thrombocytopenia were excluded. The primary efficacy outcome of VTE occurrence rate was lower in the

**Table 3** Clinical considerations for selection of anticoagulation

DOAC	Optimal	<ul style="list-style-type: none"> <li>• Patient without GI malignancy<sup>33,34</sup></li> <li>• Low risk of major bleeding<sup>a</sup></li> <li>• Ease of treatment for patient is a priority<sup>31</sup></li> <li>• No strong drug–drug interactions</li> </ul>
	Avoid	<ul style="list-style-type: none"> <li>• Active GI malignancy<sup>33,34</sup></li> <li>• History of GI bleeding<sup>33,34</sup></li> <li>• Extremes of weight (&lt;50 kg or &gt;150 kg)<sup>b</sup></li> <li>• Renal insufficiency/fluctuating renal status<sup>61</sup></li> </ul>
LMWH	Optimal	<ul style="list-style-type: none"> <li>• Frequent emetogenic chemotherapy, nausea and vomiting, difficulty with oral intake</li> <li>• Concerns for GI absorption (feeding tubes, gastric or bowel resections)</li> <li>• Drug–drug interactions with DOAC or VKA</li> <li>• Motivated patient willing to use for extended durations<sup>31</sup></li> <li>• Known increased bleeding risk</li> <li>• Recurrent cancer-associated VTE while on anticoagulants<sup>c88–90</sup></li> </ul>
	Avoid	<ul style="list-style-type: none"> <li>• Strong aversion to injectable therapy<sup>31</sup></li> <li>• Renal insufficiency/fluctuating renal status<sup>23</sup></li> <li>• Extremes of weight (&lt;50 kg or &gt;150 kg)<sup>b</sup></li> </ul>
VKA	Optimal	<ul style="list-style-type: none"> <li>• Any situation in which close anticoagulant monitoring is necessary (eg, multiple prior bleeds) or concern about absorption and metabolism</li> <li>• Advanced chronic kidney disease</li> <li>• Extremes of weight (&lt;50 kg or &gt;150 kg)<sup>b</sup></li> </ul>
	Avoid	<ul style="list-style-type: none"> <li>• Lack of access to dedicated anticoagulation monitoring service with experience caring for cancer patients<sup>91</sup></li> </ul>

**Notes:** <sup>a</sup>If a DOAC reversal agent is not readily available, LMWH may be preferred for patients with increased risk of bleeding at baseline. <sup>b</sup>Prescribing information for factor Xa inhibitors and LMWH recommend against use in extremes of weight, although a 2018 study suggests that DOACs may be appropriate for obese patients.<sup>92</sup> <sup>c</sup>Using twice-daily dosing of enoxaparin, given at 120–125% of standard twice-daily dosing. No data for DOACs in this setting are available, and how to increase the DOAC dose with limited pill strengths is not known. Please note: This is not an exhaustive list. Anticoagulant choices may be appropriate in some patients not meeting “optimal” criteria. Reproduced from Al-Samkari H, Connors JM. The role of direct oral anticoagulants in treatment of cancer-associated thrombosis. *Cancers (Basel)*. 2018;10 (8). Creative Commons license and disclaimer available from: <http://creativecommons.org/licenses/by/4.0/legalcode>.<sup>1</sup>

**Abbreviations:** GI, gastrointestinal; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist; VTE, venous thromboembolism; LMWH, low molecular weight heparin.

**Table 4** Clinical prediction scoring tools for venous thromboembolism risk in cancer patients

Score	Characteristics of interest
<b>Khorana</b> <sup>12</sup>	Site of cancer: Very high risk: stomach, pancreas High risk: lung, lymphoma, gynecological, bladder, testicular Prechemotherapy platelet count $\geq 350 \times 10^9/L$ Hemoglobin level $< 10$ g/dL or use of red cell growth factors Prechemotherapy leukocyte count $> 11 \times 10^9/L$ Body mass index $\geq 35$ kg/m <sup>2</sup>
<b>Vienna</b> <sup>75</sup>	Khorana score plus the following: Soluble P-selectin, D-dimer
<b>Protecht</b> <sup>74</sup>	Khorana score plus the following: Use of platinum-based therapy Use of gemcitabine

apixaban group compared with the placebo group (4.2% vs 10.2%, HR 0.41, 95% CI 0.26–0.65,  $p < 0.001$ , number needed to treat of 17). Major bleeding was higher in the apixaban group compared with the placebo group (3.5% vs 1.8%, HR 2.00, 95% CI 1.01–3.95,  $p = 0.046$ ) in the intention-to-treat analysis, although analysis limited to the treatment period (median duration 157 days vs 155 days) showed that the bleeding rate was not significantly higher (2.1% vs 1.1%, HR 1.89, 95% CI 0.39 to 9.24, number needed to harm of 100). There was no difference in non-major bleeding or mortality. No fatal bleeds or bleeds into critical organs occurred.

The CASSINI trial<sup>77</sup> is a double-blind, randomized, placebo-controlled, parallel-group, multicenter study comparing 6 months of rivaroxaban (10 mg once daily) with placebo in 841 adult ambulatory patients also with a Khorana score  $\geq 2$ . Notably, during the screening period of this trial, compression limb ultrasound was performed and patients with evidence of DVT on ultrasound

examination were excluded. During the on-treatment period (prior to any treatment discontinuation such as voluntary termination or secondary to side-effects), rivaroxaban significantly reduced the primary endpoint of VTE or VTE-related death compared with placebo (2.62% vs 6.41%, HR 0.40, 95% CI 0.20 to 0.80,  $p = 0.007$ , number needed to treat of 26). However, there was no significant difference in the primary endpoint between the groups in analysis of the full observation period (180 days). Rates of major bleeding were low (1.98% vs 0.99%, HR 1.96, 95% CI 0.59 to 6.49,  $p = 0.265$ , number needed to harm of 101), as were rates of CRNMB (2.72 vs 1.98%, HR 1.34, 95% CI 0.54 to 3.32,  $p = 0.53$ , number needed to harm of 135).

The results of these studies (summarized in Table 4) suggest that apixaban and rivaroxaban as primary thromboprophylaxis in high-risk patients may reduce the rate of VTE with largely favorable safety profiles, although these studies excluded patients with baseline organ dysfunction, which is common in real-world cancer patients.

## DOAC utility for extended anticoagulation

To date, there is a paucity of studies investigating the efficacy and safety of continuing anticoagulation for cancer-associated VTE beyond the first 3–6 months (whether at full or reduced dose). Trials such as EINSTEIN CHOICE<sup>78</sup> and AMPLIFY-EXT<sup>79</sup> have demonstrated the efficacy and safety of DOACs in extended anticoagulation for patients with VTE in the general population but these trials did not include large numbers of cancer patients. Most current guidelines recommend continuing therapy if the cancer is still present or if the patient is still receiving cancer-directed treatment.<sup>27,80</sup> The DALTECAN<sup>81</sup> and TiCAT<sup>82</sup> studies were both single-arm cohort analyses in which patients with cancer-associated VTE were treated with dalteparin or tinzaparin for 12 months. The results of these studies support the recommendation to

**Table 5** Summary of published trials for primary thromboprophylaxis in high-risk patients

Trial	VTE occurrence (%)	Major bleeding (%)	Clinically relevant non-major bleeding (%)	Mortality (%)
<b>AVERT</b> <sup>76</sup> Apixaban vs placebo	4.2 vs 10.2	3.5 vs 1.8	7.3 vs 5.5	12.2 vs 9.8
	Apixaban significantly reduced the rate of VTE compared to placebo. Major bleeding was higher in the intention-to-treat analysis. There was no difference in non-major bleeding			
<b>CASSINI</b> <sup>77</sup> Rivaroxaban vs placebo	2.60 vs 6.41	1.98 vs 0.99	2.72 vs 1.98	20.0 vs 23.8
	Rivaroxaban significantly reduced the rate of VTE compared to placebo during the on-treatment period. There was no difference in the rate of major or non-major bleeding			

**Abbreviation:** VTE, venous thromboembolism.



continue anticoagulation beyond 6 months. They demonstrated that the risk of VTE recurrence or bleeding was highest in the first 3–6 months and that risk of VTE recurrence persisted beyond 6 months, indicating a need for ongoing anticoagulation.

The most robust evidence for treatment of cancer-associated VTE with DOACs beyond the initial 6-month period comes from the previously discussed Hokusai VTE Cancer trial, which followed patients for up to 12 months. The results of this study support extended anticoagulation beyond an initial 6-month treatment period. In addition, a recent cohort study also demonstrated a reduced risk of VTE recurrence at 12 months for patients treated with rivaroxaban compared with LMWH and warfarin.<sup>83</sup> Although the SELECT-D trial was initially intended to study patients beyond 6 months, this phase was terminated owing to slow recruitment.

## Conclusion

To optimize treatment of VTE in cancer patients, clinicians must consider both the unique challenges of anticoagulation in this population as well as the risks and benefits of the various anticoagulant agents. Cancer patients have increased risks of bleeding and VTE recurrence relative to other patients with VTE. While DOACs have emerged as an attractive alternative to LMWH, there may be an excessive bleeding risk in certain patient groups, particularly those with GI malignancies. DOACs may vary in VTE prevention efficacy and bleeding risk. Recent studies have demonstrated that DOACs may be effective as primary thromboprophylaxis in high-risk cancer patients. Ongoing studies will further elucidate the optimal role of DOACs in diverse subpopulations of cancer patients and further inform best practices for anticoagulation in this patient population.

## Acknowledgments

H Al-Samkari is the recipient of the National Hemophilia Foundation-Shire Clinical Fellowship Award, which provides partial salary support.

## Author contributions

AB Song wrote the first draft of the manuscript and contributed to concept and design, critical writing and revision of the intellectual content; RP Rosovsky contributed to critical revision of the intellectual content; JM Connors contributed to critical revision of the intellectual content; and H Al-Samkari contributed to concept and design, critical writing and revising the intellectual content. All authors contributed to data

analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

RP Rosovsky reports grants from BMS, Janssen, and Portola, outside the submitted work; JM Connors reports personal fees from Bristol-Myers Squibb and Portola, during the conduct of the study; H Al-Samkari reports personal fees from Agios, outside the submitted work. The authors report no other conflicts of interest in this work.

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