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REVIEW ARTICLE

A consensus viewpoint on the role of direct factor Xa inhibitors in the management of cancer-associated venous thromboembolism in the UK

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ABSTRACT

Objective: Cancer patients are at high risk of venous thromboembolism (VTE), a significant cause of cancer-related death. Historically, low molecular weight heparins (LMWH) were the gold standard therapy for cancer-associated VTE, but recent evidence supports the use of direct factor Xa inhibitors in cancer-associated VTE and this is now reflected in many guidelines. However, uptake of direct factor Xa inhibitors varies and guidance on the use of direct factor Xa inhibitors in specific cancer subpopulations and clinical situations is lacking. This review presents consensus expert opinion alongside evaluation of evidence to support healthcare professionals in the use of direct factor Xa inhibitors in cancer-associated VTE.

Methods: Recent guidelines, meta-analyses, reviews and clinical studies on anticoagulation therapy for cancer-associated VTE were used to direct clinically relevant topics and evidence to be systematically discussed using nominal group technique. The consensus manuscript and recommendations were developed based on these discussions.

Results: Considerations when prescribing anticoagulant therapy for cancer-associated VTE include cancer site and stage, systemic anti-cancer therapy (including vascular access), drug-drug interactions, length of anticoagulation, quality of life and needs during palliative care. Treatment of patients with kidney or liver impairment, gastrointestinal disorders, extremes of bodyweight, elevated bleeding or recurrence risk, VTE recurrence and COVID-19 is discussed.

Conclusion: Anticoagulant therapy for cancer-associated VTE patients should be carefully selected with consideration given to the relative benefits of specific drugs when individualizing care. Direct factor Xa inhibitors are typically the treatment of choice for preventing VTE recurrence in non-cancer patients and should also be considered as such for cancer-associated VTE in most situations.

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Introduction

Venous thromboembolism (VTE) is associated with poor prognosis and considerable morbidity[1,2]. It is the most significant cause of thrombotic death amongst cancer patients, accounting for approximately 4,000 cancer-related deaths each year in England and Wales[3]. Compared with the general population, patients with active cancer have a 4- to 7-fold increased risk of VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE)[4,5]. While arterial thromboembolism, disseminated intravascular coagulation and thrombotic microangiopathy may present in patients with cancer[6], the most common form of cancer-associated thrombosis (CAT) is VTE, which is the focus of this article.

The pathophysiology of cancer-associated VTE is complex, several factors are known to increase the risk of VTE, including the primary tumor site, stage of cancer, surgical intervention and systemic anti-cancer treatment (SACT)[6]. A UK cohort study estimated that the incidence rates of first VTE and VTE recurrence in patients with active cancer was 5.8 (95% confidence interval [CI], 5.7–6.0) and 9.6 (95% CI, 8.8–10.4) per 100 person-years, respectively[7]. Anticoagulant treatment of VTE with low-molecular-weight heparins (LMWHs), vitamin K antagonists (VKAs) or direct factor Xa inhibitors effectively reduces thrombus progression, recurrence and associated mortality[8].

Historically, LMWHs were considered the gold standard of care for cancer-associated VTE management, but it requires

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subcutaneous injections once or twice daily - a significant burden for patients who require long-term anticoagulation[9,10]. VKAs have a high risk of drug-drug interactions (DDIs) and require frequent laboratory monitoring of international normalized ratio (INR). Direct oral anticoagulants (DOACs), specifically direct factor Xa inhibitors (apixaban, edoxaban and rivaroxaban), are an appealing alternative in cancer patients due to the oral route of administration, predictable pharmacokinetics, rapid onset of action, short half-life, minimal food and drug interactions, and the lack of need for INR monitoring[11].

Data from pivotal trials have demonstrated the efficacy and safety of direct factor Xa inhibitors in cancer-associated VTE[10,12–17], leading to the approval of direct factor Xa inhibitors for managing cancer-associated VTE in the EU[18]. In light of the expanding evidence base, direct factor Xa inhibitors have been incorporated into several treatment guidelines, some of which recognize them as a first line option[19–22]. However, in our experience, prescribing of direct factor Xa inhibitors for treatment of cancer-associated VTE is variable across the UK, despite the guidelines and supporting trial data. Reasons for this include concerns around potentially increased incidence of major bleeding events[23], lack of awareness, inadequate experience in prescribing direct factor Xa inhibitors, limited data for specific clinical situations, and uncertainty over their positioning within the anticoagulation treatment pathway.

Guidance on the role of direct factor Xa inhibitors for managing cancer-associated VTE may be helpful to UK prescribers. Therefore, in this article we discuss our view on the positioning of direct factor Xa inhibitors in the cancer-associated VTE treatment pathway, and endeavor to provide clarity on the appropriate prescription of anticoagulants in several subpopulations with complex clinical considerations. Our guidance incorporates available evidence supplemented by our consensus opinion as experienced practitioners in this field. This correlates with recently published European Society of Cardiology guidance on cardio-oncology[24].

Methods

Relevant guidelines and recent clinical studies, meta-analyses and literature reviews on anticoagulation treatment for cancer-associated VTE were identified by pragmatic, non-structured hand searching of available literature relating to direct factor Xa inhibitor use for cancer-associated VTE. Searches were conducted on PubMed, Google Scholar and Ovid online using key word terms, which included cancer-associated thrombosis, venous thromboembolism, cancer, DOAC, apixaban, rivaroxaban, edoxaban, LMWH; supplementary evidence was also provided by the lead authors. The authors attended a virtual roundtable meeting in which direct factor Xa inhibitor clinical trial data were examined and the risk-benefit profile of direct factor Xa inhibitor use in different cancer subpopulations was discussed. Using a nominal group technique approach, each topic was discussed systematically by all clinical expert authors, who provided their input in turn. Based on these discussions the manuscript outline was drafted and consensus viewpoints were formulated. The meeting was facilitated by HEOR Ltd and chaired by ATC and RA. Follow-up discussions and revisions were conducted via email correspondence facilitated by ARM and PDG. All authors participated in revisions and approved the final article. Review and incorporation of comments from the clinical authors were conducted by ARM and PDG independently of Bristol Myers Squibb (BMS) and Pfizer.

Current treatment options for patients with cancer-associated VTE

Direct factor Xa inhibitors vs LMWH in initial treatment (up to 6 months)

Table 1 summarizes the key phase III randomized controlled trials evaluating the safety and efficacy of direct factor Xa inhibitors for managing patients with cancer-associated VTE versus LMWH (dalteparin). The Caravaggio and ADAM VTE trials demonstrated non-inferior VTE recurrence rates with comparable bleeding risk for apixaban vs. dalteparin, a LMWH[10,12]. For edoxaban, the Hokusai VTE Cancer study found that most cancer patients could expect the same outcomes as with dalteparin, as shown by non-inferiority for edoxaban in the composite primary outcome of VTE recurrence and major bleeding[13]. Edoxaban was considered by the investigators to have an acceptable risk-benefit profile in most cancer types, according to subgroup analysis of the Hokusai VTE Cancer trial[14]. However, gastrointestinal (GI) cancers had a greater risk of bleeding, and special consideration is required before prescribing edoxaban in this group[14]. SELECT-D and CASTA DIVA (a non-inferiority trial) evaluated rivaroxaban versus dalteparin[15,17]. The SELECT-D trial demonstrated a significant reduction in VTE recurrences with rivaroxaban compared with dalteparin, while the CASTA DIVA trial had insufficient patient data to reach the non-inferiority criteria. Both found increases in clinically relevant non-major bleeding (CRNMB) versus LMWH that were comparable to other direct factor Xa inhibitors. Following review from the data and safety monitoring committee, the SELECT-D protocol was amended to exclude patients with GI cancers due to a safety signal of bleeding events with rivaroxaban in this subgroup[15].

A meta-analysis of five major trials (ADAM VTE[10], Caravaggio[12], Hokusai VTE Cancer[13], SELECT-D[15], and CASTA DIVA[17]) found direct factor Xa inhibitors were associated with significantly lower risk of VTE recurrence compared with LMWH (hazard ratio, HR: 0.63; 95% CI, 0.47–0.86) but also a non-significantly higher risk of major bleeding (HR: 1.26; 95% CI, 0.84−1.90) and a significantly higher risk of CRNMB (HR: 1.48; 95% CI, 1.18−1.85)[17]. Other meta-analyses, which did not incorporate CASTA DIVA, had broadly similar findings but variations in confidence intervals led to differing conclusions on statistical significance[25–27]. Nevertheless, the outcomes from these analyses indicate that treatment with direct factor Xa inhibitors confer a similar improvement in risk of VTE recurrence to the improvement conferred by LMWH in comparison to VKAs (relative risk, RR = 0.60, 95% CI: 0.45−0.79)[28].

Table 1. Trials evaluating direct factor Xa inhibitors versus LMWH in cancer-associated VTE populations.

Trial	Intervention/ Comparator	Population	Cancer types	Primary outcome(s)	VTE recurrence HR (95% CI)	MB HR (95% CI)	CRNMB HR (95% CI)	Summary of outcomes
Apixaban								
Caravaggio NCT03045406[12]	Apixaban vs. dalteparin	Cancer pts with symptomatic or incidental acute proximal DVT/PE	Cancers exc. BCC or SCC of the skin, primary brain tumor, intracerebral metastases or acute leukemia	Recurrent VTE (<6 months)	0.63 (0.37, 1.07); p <.001*	0.82 (0.40, 1.69). p = .60	1.16 (0.77, 1.75)	Apixaban (oral) was noninferior to dalteparin (SC) for the treatment of cancer associated VTE without an increased risk of MB.
ADAM VTE NCT02585713[10]	Apixaban vs. dalteparin	Cancer pts with acute DVT/PE/splanchnic or CVT	Solid and hematologic malignancies	Major bleeding (<6 months)	0.099 (0.013, 0.780); p = .0281	Not estimable†	NR	Apixaban (oral) was associated with low MB and VTE recurrence rates for the treatment of VTE in cancer patients.
Rivaroxaban								
SELECT-D NCT02583191[15]	Rivaroxaban vs. dalteparin	Cancer pts with symptomatic or incidental PE/symptomatic lower extremity proximal DVT	Solid and hematologic malignancies exc. BCC or SCC of the skin	Recurrent VTE (<6 months)	0.43 (0.19, 0.99)	1.83 (0.68, 4.96)	3.76 (1.63, 8.69)	Rivaroxaban was associated with significantly lower VTE recurrence but higher MB and significantly higher CRNMB compared with dalteparin.
CASTA DIVA NCT02746185[17]	Rivaroxaban vs. dalteparin	Cancer pts with symptomatic or incidental proximal lower limb DVT/iliac or inferior vena cava thrombosis and/or PE	Solid active cancer, high grade lymphoma or myeloma	Recurrent VTE (<3 months)	SHR: 0.75 (0.21, 2.66); p = .13	SHR: 0.36 (0.04, 3.43)	1.48 (1.18, 1.85)	The number of patients was insufficient to reach the predefined criteria for noninferiority, but efficacy and safety results were consistent with those previously reported with DOACs
Edoxaban								
Hokusai VTE Cancer NCT02073682[13,14]	Edoxaban vs. dalteparin	Cancer pts with acute symptomatic or incidental proximal DVT and/or PE	GI, lung, urogenital, breast, hematological, gynecological	Recurrent VTE or major bleeding over 12 months	0.97 (0.70, 1.36) p = .006*	1.77 (1.03, 3.04) p = .04	1.38 (0.98, 1.94)	Edoxaban was noninferior to dalteparin for the composite outcome of recurrent VTE or major bleeding. The rate of recurrence was lower but the rate of major bleeding was higher with edoxaban. Edoxaban has a similar risk-benefit ratio to dalteparin in most cancer groups.

*p-value for non-inferiority; †0 bleeding events in apixaban group.
BCC, basal cell carcinoma; CRNMB, clinically relevant non-major bleeding; CVT, cerebral vein thrombosis DVT, deep vein thrombosis; GI, gastrointestinal; HR, hazard ratio; MB, major bleeding; NR, not reported; PE, pulmonary embolism SCC, squamous cell carcinoma; SHR, subdistribution hazard ratio; VTE, venous thromboembolism.

Direct factor Xa inhibitors vs LMWH for secondary prevention of VTE (beyond 6 months)

The SELECT-D extension study of rivaroxaban vs placebo evaluated patients after six months of trial anticoagulation, but the study was insufficiently powered to detect statistically significant differences in the primary endpoints[16]. While there was an indication of long-term reduction of VTE recurrence, along with increased risk of bleeding, the population was at low risk of recurrence. A *post hoc* analysis of the Hokusai VTE Cancer trial, which examined extended therapy with edoxaban, demonstrated that it was as effective and had a similar rate of VTE recurrence and bleeding risk as seen with dalteparin[29]. The results of the API-CAT (NCT03692065) and EVE (NCT03080883) trials are eagerly awaited: they examine reduced dose vs standard dose apixaban after six months of anticoagulation and will provide evidence on the incremental value of dose reduction to reduce the risk of bleeding versus the risk of VTE recurrence[30,31].

A systematic literature review of clinical studies assessing long-term anticoagulation reinforced current treatment guidelines, demonstrating that VTE recurrence is still a significant risk in those discontinuing anticoagulation after 6 months[1]. Furthermore, a US retrospective database study found that although adherence (the extent to which a patient complies with their prescribed anticoagulant regimen) was similar between LMWH and DOACs, treatment persistence was greater for DOACs; i.e. patients remained on DOACs for longer on average than on LMWH[32]. This suggests that, while LMWH is a reliable choice of anticoagulation therapy, it is perhaps less favourable than DOACs for longer-term treatment, as DOACs are more convenient for patients and LMWH may involve increased overall cost and treatment administration burden[9,32,33].

The role of direct factor Xa inhibitors in managing cancer-associated VTE

Current treatment guidelines for the management of cancer-associated VTE

Current treatment guidelines for the management of cancer-associated VTE are summarized in Table 2, in order of publication date. Due to the protracted writing process and the ever-evolving landscape, they do not necessarily incorporate the most up-to-date evidence. All guidelines recommend a minimum of 3 months of anticoagulation, with most recommending at least 6 months. Extended phases of therapy beyond 6 months may be considered on an individual basis, dependent on an appropriate risk to benefit assessment. Direct factor Xa inhibitors and LMWH are consistently recommended over unfractionated heparin (UFH), fondaparinux and VKAs, such as warfarin, in most patient subgroups. VKAs are not recommended as the primary choice but as an option if direct factor Xa inhibitors or LMWH are contraindicated, inappropriate or unavailable.

In the acute period of treatment for cancer-associated VTE, typically defined as the first 1–3 weeks, guidelines are split between recommending direct factor Xa inhibitors[19,20,22] or LMWH[34–36]. It should be noted that, for patients treated with edoxaban, LMWH is required for the initial 5 days following the incident cancer-associated VTE, unlike apixaban or rivaroxaban which can be initiated immediately[38]. Over the standard treatment period, typically up to 6 months, guidelines state a preference for direct factor Xa inhibitors over LMWH[19,20,22], or recommend both[35,36], with the exception of the National Comprehensive Cancer Network (NCCN) guidelines, which recommends LMWH[34].

Despite the availability of treatment guidelines, there remains variation in how cancer-associated VTE is managed in the UK, with direct factor Xa inhibitors having not been fully embraced as a viable alternative to LMWH yet. This is in part due to a lack of experience of when and how to use direct factor Xa inhibitors, but also the result of insufficient guidance for specific and complex clinical situations that are often encountered during cancer-associated VTE management. We discuss some of these topics below and a synopsis is provided in Figure 1.

Considering cancer site when prescribing anticoagulation therapy

The site of the primary cancer is a risk factor for VTE, VTE recurrence and bleeding. Hence, the site of origin is an important consideration when prescribing anticoagulants for cancer-associated VTE. In patients with cancer-associated VTE treated with a direct factor Xa inhibitor, a higher rate of overall bleeding events has been observed in those with pancreatic, colorectal, gastroesophageal, and genitourinary (GU) cancers[13–15,39]. Increased bleeding with direct factor Xa inhibitors may be due to mucosal bleeding which is influenced by malignancy type and the prescribed direct factor Xa inhibitor, with higher risk of bleeding in upper gastrointestinal (GI) malignancies versus LMWH, particularly with edoxaban or rivaroxaban[40,41].

Our consensus viewpoint is that patients with luminal GI/GU cancer with an unresected primary tumor and tumors at risk of bleeding should not be prescribed edoxaban or rivaroxaban as first-line therapy; LMWH or apixaban are more suitable treatment strategies, provided no contraindications exist[42,43]. We advise that patients with resected lower GI tumors are treated with a direct factor Xa inhibitor as first-line therapy; apixaban may be preferred since no increased risk of bleeding is apparent in patients with GI cancer receiving apixaban versus dalteparin[10,12]. We do not generally recommend direct factor Xa inhibitors in patients with upper GI cancer. However, apixaban or LMWH may be used with caution in this group, based on the limited trial data available[44]; risks (bleeding vs recurrence) and treatment preference should be discussed with the patient.

Data in certain cancer subtypes are insufficient, including brain metastases and hematological malignancies, often due to the exclusion criteria of clinical trials. As such, the transition to direct factor Xa inhibitors in these groups has been challenging. Nevertheless, real-world evidence suggests similar safety of direct factor Xa inhibitors and LMWH in patients

Table 2. Summary of cancer-associated VTE clinical guidelines.

Guideline	Initial treatment	<6 Months	>6 Months
NCCN[34] (2022), USA	First 5–10 days • LMWH, UFH, fondaparinux, rivaroxaban or apixaban are recommended for the first 5–10 days.	• LMWH is preferred in pts with proximal DVT or PE and for prevention of recurrent VTE in pts with advanced metastatic cancer. • For patients who refuse/contraindicated to LMWH, direct factor Xa inhibitors should be considered	• Warfarin, edoxaban, or dabigatran
	Patients with gastric or gastroesophageal tumors treated with direct factor Xa inhibitors are at greater risk of hemorrhage. Apixaban may be safer than edoxaban/rivaroxaban for patients with gastric or gastric esophageal lesions (category 2B)		
CHEST[20] (2021), USA	First 5–21 days • Apixaban, edoxaban, rivaroxaban preferred over LMWH for 3 months	<3 Months • Apixaban, edoxaban, rivaroxaban preferred over LMWH for 3 months	>3 Months • Direct factor Xa inhibitors recommended, with reduced-dose apixaban or rivaroxaban preferred • VKAs are recommended in those who cannot receive direct factor Xa inhibitors. • Aspirin is recommended over no therapy at all.
	Edoxaban and rivaroxaban appear to be associated with a higher risk of GI major bleeding than LMWH in patients with CAT and a luminal GI malignancy, while apixaban does not. Apixaban or LMWH may be the preferred option in patients with luminal GI malignancies.		
ASH[19] (2021), USA	Week 1 • Apixaban, rivaroxaban or LMWH. • LMWH preferred over UFH and fondaparinux.	For patients with active cancer, apixaban, edoxaban, or rivaroxaban preferred over LMWH, with both preferred over VKAs.	Recommended to continue indefinitely on direct factor Xa inhibitors or LMWH for patients with active cancer and VTE
	Note: DOACs should be used carefully in patients with GI cancers, considering specific clinical setting to minimise risk, after careful consideration of potential DDIs, bleeding risk, patient preference and availability of treatment options including cost considerations		
NICE[22] (2020), UK	Offer anticoagulation for 3–6 months. DOAC recommended. If not suitable, consider one of: • LMWH • LMWH and a VKA for at least 5 days or until INR ≥2.0 on 2 consecutive readings, then a VKA alone Take into account tumor site, drug interactions including cancer drugs, and bleeding risk (HAS-BLED score)		• Consider stopping after provoked DVT/PE if uncomplicated and the provoking factor is not present. • Consider continuing after an unprovoked DVT/PE if well tolerated. In this who decline to continue, consider aspirin
ASCO[35] (2020), USA	First 5–10 days • LMWH recommended (if CrCl ≥30 mL/min) • LMWH, UFH, fondaparinux or rivaroxaban	• LMWH, edoxaban, or rivaroxaban preferred for at least 6 months • VKAs should be considered only if LMWH or direct factor Xa inhibitors are inaccessible	• Selective continuation beyond 6 months (e.g. unprovoked DVT/PE; metastatic disease; receiving SACT) • Reassess intermittently to ensure an appropriate risk-benefit profile
ITAC[36] (2019), international	First 5–10 days • LMWH recommended (if CrCl ≥30 mL/min) • Rivaroxaban (0–10 days) or edoxaban (>5 days after parenteral anticoagulation) are alternatives • UFH/fondaparinux may be used if LMWH/direct factor Xa inhibitors are contraindicated	Minimum treatment period of 6 months LMWH and direct factor Xa inhibitors (edoxaban/rivaroxaban) preferred over VKAs	Any continuation should be evaluated based on appropriate risk-benefit profile
ISTH[37] (2018), international	Low-risk of bleeding: • Edoxaban and rivaroxaban preferred based on available evidence • LMWH is also an acceptable option • Individualized decision making including patient consultation High risk of bleeding (e.g. GI/genitourinary malignancy or mucosal abnormalities): • LMWH are recommended • Edoxaban and rivaroxaban are acceptable alternatives, if no DDI with current therapy		

Abbreviations. ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; CHEST, the American College of Chest Physicians; CrCl, creatinine clearance; DOAC, direct oral anticoagulants; DVT, deep vein thrombosis; FDA, Food & Drug Administration; ISTH, International Society on Thrombosis and Haemostasis; ITAC, International Initiative on Thrombosis and Cancer; LMWH, low molecular weight heparin; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; PE, pulmonary embolism; UFH, unfractionated heparin; VKA, vitamin-K antagonists; VTE, venous thromboembolism.

Disease characteristics

We recommend direct factor Xa inhibitors as first-line anticoagulation therapy for most cancers, with the following considerations:

- We advise that patients with resected lower GI tumours are treated with a direct factor Xa inhibitor as first-line therapy
- We do not recommend edoxaban or rivaroxaban as first line in patients with unresected primary luminal GI/GU tumours, upper GI cancers or with tumours at risk of bleeding: LWMH or apixaban are more suitable. In upper GI cancers LMWH or apixaban may be used with caution
- We suggest LMWH as first-line in acutely unwell/unstable inpatients; in stable patients we prefer direct factor Xa inhibitors, subject to the other considerations
- Direct factor Xa inhibitors may be used in advanced cancer after individual risk assessment

Cancer treatment considerations

- In vascular access thrombosis, consider chemotherapy and anticoagulants together in the context of VTE and bleed risk. Guidelines typically recommend LMWH; use caution if prescribing direct factor Xa inhibitors. If treating beyond 3 months, re-assess risks regularly
- Check for major drug interactions, particularly with cytochrome P450 3A4 or P-glycoprotein. Check SmPCs of both anticoagulant and SACT for interactions before prescribing
- Discuss any potential DDIs with patients when initiating direct factor Xa inhibitors and re-evaluate on regimen change

Kidney/liver impairment

- We recommend regular monitoring of kidney function to ensure optimal treatment
- Direct factor Xa inhibitors can be used in patients with CrCl > 30 mL/min; apixaban, edoxaban or rivaroxaban use in kidney-impaired patients with CrCl > 15 mL/min can be considered case-by-case
- Reduced dose LMWH can be used if CrCl < 15 mL/min; consider switching to a direct factor Xa inhibitor if kidney function improves
- Direct factor Xa inhibitors can be used in patients with liver impairment unless it is severe and otherwise contraindicated

GI disorders and bodyweight

- Direct factor Xa inhibitors should be used with caution in patients with impaired absorption or GI resection
- Direct factor Xa inhibitors (particularly apixaban and rivaroxaban) can be used in patients without restrictions for high bodyweight, the greatest experience is in those up to 150 kg
- Direct factor Xa inhibitors should be used with caution in patients with low body weight (< 50 kg)

Quality of life considerations

- If the patient prefers oral administration, we recommend direct factor Xa inhibitors unless contraindicated
- Anticoagulants may be discontinued where there is limited benefit in patients approaching end of life

COVID-19

- Patients receiving anticoagulation before COVID-19 infection should normally continue current therapy
- Consider switching to LMWH during hospitalization if patient is unstable, critically unwell, unable to have oral treatment or there is concern over DDIs (e.g. with ritonavir); revert to direct factor Xa inhibitors at discharge where possible

Long-term anticoagulation in patients at high recurrence risk

- We recommend extended anticoagulation, preferably with direct factor Xa inhibitors, if risk factors for VTE recurrence are present
- Reduced-dose apixaban (2.5 mg BD) or rivaroxaban (10 mg OD) can be considered if recurrence risk diminishes or bleeding risk is high
- Upon recurrence, check prior dosage and adherence then re-assess risk factors for recurrence, e.g. DDIs, cancer progression
- We recommend continued direct factor Xa inhibitor use after recurrence; consider increasing dosage or switching, including to LMWH at full therapeutic dose

Long-term anticoagulation in patients at high risk of bleeding

- For most patients we recommend anticoagulation for at least 3 months after VTE; assess risk individually after this point
- We recommend direct factor Xa inhibitors in patients with platelet counts down to > $50x10^9$/L
- Consider reduced dose LMWH at platelet counts down to > $25x10^9$/L; below this, consider not using anticoagulation
- Avoid IVC filters where possible in patients at high risk of bleeding

BD: twice daily; CrCl: creatinine clearance; DDI: drug-drug interactions; GI: gastrointestinal; GU: genitourinary; IVC: inferior vena cava; LMWH: low molecular-weight heparin; OD: once daily; SACT: systemic anti-cancer treatment; SmPC: summaries of products characteristics; VTE: venous thromboembolism

Figure 1. Synopsis.

with primary brain tumors and brain metastases, though further robust data are required to warrant a recommendation for direct factor Xa inhibitors in these populations[45]. We consider observational data to be useful for informing clinical practice where randomized trial data in sub-populations are scarce or non-existent, but such data should be used with caution.

Considering cancer stage when prescribing anticoagulant therapy

The risk of VTE recurrence and major bleeding increases with advancing cancer stage[6]. Accordingly, our consensus view is to consider whether the cancer is localized, locally spread or metastatic when prescribing anticoagulation therapy. Cancer

patients may also exhibit highly dynamic characteristics, including fluctuating platelet count and organ function, requiring regular modifications to treatment regimens. It is therefore necessary to individualize patient assessment and review therapy in response to patients' evolving needs along their cancer pathway[46].

Direct factor Xa inhibitors can be prescribed to patients at any stage of cancer, though locally spread and metastatic cancers are at a greater risk of recurrent VTE and of major bleeding events with anticoagulation treatment[47]. We suggest advanced stage cancer patients may be treated with direct factor Xa inhibitors according to an individualized risk-benefit profile of recurrence and bleeding risk. We also consider LMWH to be the preferred first-line option in acutely unwell and/or unstable hospitalized patients, as LMWH have fewer DDIs than direct factor Xa inhibitors[43]. They also have a shorter half-life and can be administered in patients with organ dysfunction, thrombocytopenia, or in need of an invasive procedure, with easier dose management if necessary. For more stable outpatients, we consider direct factor Xa inhibitors to be a more suitable long-term option.

Anticoagulation therapy in patients with vascular access thrombosis

Upper limb and catheter-associated VTE is prevalent in cancer patients[48], but there is insufficient guidance on how to manage it. In addition, patients often have vascular access devices for delivery of SACT, which are an additional potential risk factor for bleeding and thrombosis. For these reasons, SACT and anticoagulant regimens should be considered together in the context of the associated risk. Guidelines typically recommend LMWH for the treatment of cancer-associated VTE in patients with line-associated thrombosis[49,50], though direct factor Xa inhibitors are used in clinical practice at some centres. More trials are required to verify observational findings that direct factor Xa inhibitors preserved line function and reduced recurrence after catheter-associated thrombosis[51], and there was no observed difference in VTE recurrence and bleeding risk versus LMWH[52]. Nevertheless, we suggest both LMWH and direct factor Xa inhibitors are appropriate treatment options for line-associated thrombosis and advise a treatment duration of three months. Should the line remain in place beyond a 3-month treatment period, we suggest the benefit of continuing anticoagulation, in relation to risk of bleeding or VTE recurrence, should be regularly re-assessed.

Drug-drug interactions

It should be noted that many DDIs are based on theoretical knowledge, and there is a paucity of data to establish their clinical relevance. This can lead to a reluctance to prescribe direct factor Xa inhibitors. A significant proportion of clinical trials assessing novel SACT exclude patients who are prescribed direct factor Xa inhibitors because of the lack of understanding of DDIs, which in turn restricts the availability of high-quality data on DDIs. In general, we advise to check for major drug interactions for acute VTE treatment, particularly those interacting with cytochrome P450 (CYP) 3A4 enzymes or P-glycoprotein (P-gp), to ensure there is a clear understanding of the risk of DDIs. Edoxaban has minimal CYP3A4 enzyme interaction and hence may be suitable in patients receiving concomitant therapy with drugs metabolized *via* this pathway[53].

A published analysis of DDI databases and summaries of product characteristics (SmPCs) concluded that warfarin has greater DDI potential than other anticoagulants, while LMWH had the lowest potential[53]. It also reported that there was no difference in DDI potential between DOACs as a whole, although each DOAC may have different degrees or types of interactions. More specifically, a *post hoc* analysis of Caravaggio trial data considered interactions with cytotoxic agents, demonstrating that patients on apixaban or dalteparin showed no increased risk of VTE recurrence or major bleeding when receiving concomitant anti-cancer therapy[54]. Before prescribing any anticoagulant, the SmPCs of the anticoagulant and SACTs should be reviewed to ensure safe use.

The anticoagulant of choice is a shared decision with the patient and they should be made aware of the likelihood of any potential DDIs, preferably with assistance from pharmacists to optimize treatment to reduce DDIs[55]. Some patients with moderate risk of DDI may be willing to have assessment of anti-factor Xa levels to avoid regular injectable therapies; therefore, personalized care should always be provided. However, regular monitoring is of no value in ensuring therapeutic anti-factor Xa levels since target ranges have not been established and there is no evidence to guide changes in management based on anti-factor Xa levels. Nevertheless, where DDIs are of concern, measuring anti-factor Xa plasma levels, on an individual basis, may be considered. In addition to SACT, we suggest supportive care and concomitant medication such as anticonvulsants or antifungal therapy should be reviewed for potential DDIs. Caution should also be given to concomitant prescription of antiplatelet agents, specifically thienopyridines (clopidogrel) and/or aspirin, as evidence suggests elevated bleed risk in those receiving oral anticoagulants[56]. As a consensus group, we recommend that the decision to extend treatment with anticoagulants should be regularly evaluated to consider the dynamic risk of VTE and bleeding related to the cancer (response or progression), cancer treatment, which can include sudden wholesale change of "line of treatment" and individual patient factors.

Quality of life considerations

Patients generally prefer orally administrable options over injectable treatments, assuming it causes minimal disruption to current SACT[57]. Patients have shown improved treatment satisfaction for DOACs compared to VKAs[58], and LMWH[59–61]. In the SELECT-D trial, there was no difference in measurable health-related quality of life or coping with LMWH vs rivaroxaban[15], but the COSIMO study found that patients with cancer-associated VTE who switched from LMWH to rivaroxaban had improved treatment satisfaction[59]. A similar outcome was seen in the ADAM-VTE trial, whereby patient satisfaction

scores favored apixaban over dalteparin[10]. Furthermore, greater treatment satisfaction is associated with better adherence, compliance and persistence[62], thereby improving treatment outcomes. With this in mind, our consensus view is that DOACs should be used where there is patient preference for oral administration over parenteral, unless DOAC use disrupts anti-cancer regimens or is contraindicated.

Appropriate use of anticoagulation therapy in palliative care

Existing guidelines for cancer-associated VTE do not consider optimal anticoagulation treatment in palliative care, and recommend indefinite anticoagulation for patients with active cancer[63]. However, for terminally ill cancer patients, we suggest to balance priorities when prescribing anticoagulants, with particular regard to the inconvenience and discomfort of parenteral agents. We therefore suggest that anticoagulants may be discontinued altogether in circumstances where there is limited benefit and patients are at the end of life.

Role of direct factor Xa inhibitors in cancer patients with complex clinical needs

Cancer patients often have complex needs that require careful consideration when prescribing anticoagulants, including those with kidney or liver impairment, gastrointestinal disorders, nausea/vomiting, extremes of body weight, increased risk of bleeding, increased risk of VTE recurrence and patients hospitalized with COVID-19.

Kidney impairment

Kidney function must be taken into account when considering an anticoagulation regimen. In line with the phase III direct factor Xa inhibitor registration studies, we suggest calculating creatinine clearance (CrCl) instead of estimated glomerular filtration rate (eGFR) in patients receiving a direct factor Xa inhibitor to avoid overestimating kidney function. Due to the exclusion criteria of many trials, there are limited clinical data surrounding the use of anticoagulants in patients with cancer-associated VTE and moderate to severely impaired kidney function. However, a *post hoc* analysis of Caravaggio showed that moderate kidney impairment (CrCl 30–59 mL/min) was not associated with an increased risk of major bleeding or recurrent VTE in cancer patients treated with apixaban or dalteparin, supporting the use of direct factor Xa inhibitors in patients with moderate kidney impairment[64]. We suggest initiating apixaban in patients with kidney impairment owing to the reduced dependence on renal clearance versus other direct factor Xa inhibitors[65]. Based on our consensus, we recommend that patients with cancer can be offered apixaban if CrCl is greater than 30 mL/min. The SmPC allows patients for CrCl as low as 15 mL/min to be prescribed apixaban[66], but this should be considered carefully on a case by case basis, similarly to comparable patients without cancer.

For patients with CrCl $<$ 15 mL/min or on kidney replacement therapy we recommend LMWH at a reduced dose and, should kidney function improve, we support switching to a direct factor Xa inhibitor. It is important to note that therapeutic doses of LMWH may also accumulate in patients with severe kidney impairment and subsequent measurement of anti-Xa levels may be indicated.

Elevated risk of VTE recurrence is an important factor to consider in patients with kidney impairment. Additionally, prescribing anticoagulants in these patients may be further complicated by the presence of comorbidities and/or end-stage kidney disease, where anticoagulation may be affected by dialysis. Kidney function may also fluctuate significantly over relatively short periods. We therefore recommend regular monitoring of kidney function to ensure treatment remains optimized.

Liver impairment

A reduction in liver function is likely to affect the safety and effectiveness of anticoagulant treatment, as well as the detoxification of chemotherapy. We consider direct factor Xa inhibitors to be the preferred anticoagulant option unless liver impairment is sufficiently severe for them to be contraindicated (as defined in the individual SmPCs). Patients with hepatocellular or pancreatic cancer may be at an increased risk of liver impairment. For this reason, we recommend liver function tests and assessment of patients according to the Child-Pugh score; low serum albumin may also be a sign of significant liver impairment in this patient group[67]. We recommend special consideration should be given to potential DDIs in liver-impaired patients prescribed anticoagulants, and we suggest individualized treatment decisions should be made according to patient condition.

Gastrointestinal disorders and nausea/vomiting

In general, we suggest patients with GI conditions can be given direct factor Xa inhibitors for cancer-associated VTE management. However, patients with acute nausea, persistent vomiting or dysphagia who are unable to take oral medication and do not receive nasogastric intubation, may be managed temporarily with LMWH[68]. Should GI complications subside, we suggest that treatment should be reverted to direct factor Xa inhibitors. We consider that there is a need for caution when prescribing DOACs to patients with possible impaired GI absorption such as those with bowel disease or substantial resection. Limited evidence suggests that DOAC absorption varies depending on the resection site[69]; however, further research is required to confirm such associations. Many patients are able to absorb DOACs despite resection, but we recommend measuring a drug-specific anti-factor Xa level or to assess plasma concentration and confirm absorption. However, it is important to note that measuring DOAC levels is of limited use as therapeutic ranges are yet to be clearly defined[70]. The dynamic nature of GI complications in cancer patients should be considered

and we recommend that anticoagulation regimens should be adapted accordingly.

Extremes of body weight

The International Society on Thrombosis and Haemostasis (ISTH) guidelines (2021) state that standard doses of rivaroxaban and apixaban are appropriate treatment strategies for VTE regardless of high bodyweight (>120 kg) and BMI (>40 kg/m^2), and regular peak or trough measurements are not considered necessary[71]. However, the NICE guidelines are yet to be updated and only recommend direct factor Xa inhibitors in patients with a body weight lower than 50 kg or greater than 120 kg if therapeutic levels are monitored[22]. As a consensus group, we support direct factor Xa inhibitor use, particularly apixaban and rivaroxaban, in patients with upper extremes of body weight up to 150 kg, given that pharmacokinetic data and real-world evidence suggest that direct factor Xa inhibitors are unlikely to require dose alterations. For example, an observational study of 100 patients weighing over 120 kg reported reassuring pharmacokinetic data for DOACs in patients up to 230 kg[72]. However, the number of patients with weights exceeding 150 kg included in previous studies have been limited, thus we suggest caution may be warranted in this subgroup and checking a trough level may be considered in these patients.

Conversely, for patients with very low body weight (<50 kg), we recommend particular care should be given to the prescription of anticoagulants, in part due to the paucity of data in underweight patients. The Hokusai VTE trial was the only trial assessing a direct factor Xa inhibitor that stratified dosing by body weight, demonstrating efficacy and safety in underweight patients (<60 kg) at a reduced dose (30 mg)[73], a recommendation which can be found in the SmPC[38]. Additionally, a cross-sectional study found that underweight (<60 kg) cancer patients treated with half-dose (2.5 mg, twice daily) apixaban had comparable plasma trough levels to patients with bodyweight greater than 60 kg at full dose[74]. It should be noted that reduced doses of apixaban and rivaroxaban are not specifically licensed in this setting. Nevertheless, we urge caution for prescribing direct factor Xa inhibitors, including edoxaban, in patients with very low body weight as there is insufficient data to confirm their safety. We consider LMWH to be a viable alternative in patients with extreme low body weight, although minimal subcutaneous fat in some patients will complicate administration.

Long-term direct factor Xa inhibitor therapy in patients with cancer-associated VTE at high risk of bleeding

When prescribing anticoagulants, we recommend that the clot type (DVT or PE) and site (distal or proximal DVT; peripheral PE or central PE) should be taken into consideration, as well as the length of time since the VTE event. Additionally, consideration should be given to the reversibility of anticoagulant therapies when prescribing in patients at elevated risk of bleeding[75].

In most patients, anticoagulation therapy should be prescribed for a minimum of 3 months following a VTE event, according to most guidelines (Table 2). After this treatment period, it should be ensured that those with a comparatively low VTE recurrence risk and high bleed risk are not treated with anticoagulants beyond the period where risk outweighs benefit. In those with moderate to low bleeding risks, we suggest that anticoagulation may continue for longer than six months if a patient has an active underlying disease or risk factors for VTE recurrence are still present.

Thrombocytopenia a reduction in the number of circulating platelets that is common in cancer patients, can result in bleeding and bruising, and retard blood clotting after injury. It often presents as a "dynamic risk" to patients during anticancer therapy, as platelet counts can fluctuate significantly[76]. Currently, there is limited data on the use of direct factor Xa inhibitors in patients with significant thrombocytopenia due to exclusion criteria in many trials. Nevertheless, our consensus is that direct factor Xa inhibitors should be prescribed in patients with platelet counts as low as 50×10^9/L. If counts are lower than this, we advise considering platelet support and reduced dose LMWH down to a minimum platelet count of 20–25 $\times 10^9$/L, with careful consideration given to the timing of acute or non-acute VTE recurrence. For those with platelet counts below 20×10^9/L, we advise considering withholding anticoagulation.

Dose reduction is preferable to discontinuing therapy entirely, and platelet transfusions should also be considered for patients with acute VTE to enable therapeutic dose anticoagulation to be administered, particularly in the first month after VTE when VTE-related death and recurrence are particularly high[77].

Where it is possible, we recommend that inferior vena cava (IVC) filters should be avoided, though, they may be necessary in patients with a very recent VTE who are actively bleeding or who have an absolute contraindication to anticoagulation therapy. If required, retrievable IVC filters should be used and should be removed when bleeding risk has subsided and anticoagulants can be used.

Long-term direct factor Xa inhibitor therapy in patients with cancer-associated VTE at high risk of recurrence

All patients should be assessed for their risk of recurrences at 3–6 months, in consultation with their oncologists, evaluating cancer progression and anticoagulation strategies, according to clinical guidelines. Many cancer-associated VTE patients will have long-term risk factors that will maintain the risk of recurrence over longer periods, such as active cancer, metastatic disease, concurrent SACT, a previous history of venous thrombosis, and the ongoing presence of central lines. In these instances, we recommend extended anticoagulation, preferably using direct factor Xa inhibitors, for as long as the risk factors remain present. Should the patient also be deemed to have a high risk of bleeding, we suggest that a reduced dose of apixaban (2.5 mg BD, instead of 5 mg BD) or rivaroxaban (10 mg OD, instead of 20 mg OD) can be considered. Further evidence on the long-term efficacy of reduced

dose apixaban is expected from the API-CAT and EVE trials[30,31]. We suggest that factors such as the presence or absence of residual DVT at 6 months, but not an elevated D-dimer in cancer patients, may be taken into consideration when determining whether to continue anticoagulation.

Recurrent VTE may still occur in patients receiving anticoagulation treatment. Therefore, when managing a suspected recurrence while on treatment, we recommend that it should first be established whether there is a true recurrence. Extensions of existing clots are difficult to diagnose without definitive diagnostic imaging. Next, it should be established whether the patient is on appropriate anticoagulation treatment at the correct dose and is sufficiently adherent. Once these factors are ascertained, other risk factors for recurrence should be considered, including DDIs and progression of the cancer. Evidence is supportive of continuing direct factor Xa inhibitors, which are associated with the lowest rates of VTE recurrence in patients with cancer-associated VTE when compared to LMWH and VKAs[8,78]. Patients on a direct factor Xa inhibitor who have had a recurrence should preferably receive increased dosing, up to the maximum licensed dose if necessary, or switch to alternative direct factor Xa inhibitors. However, we suggest switching to a full therapeutic dose of LMWH may also be considered, and if recurrence arises while already on therapeutic LMWH we advise increasing the dose of LMWH by 20–25% and considering conducting an anti-Xa assay.

The effect of COVID-19 on medical care for patients with cancer-associated VTE

Cancer patients with coronavirus infections are more likely to be hospitalized and develop VTE versus those without cancer[79]. However, there are no specific treatment guidelines regarding extended thromboprophylaxis or VTE treatment in cancer patients with COVID-19 infection[80].

If patients are already receiving anticoagulation therapy before infection we recommend that they should remain on the same therapy. If necessary (for example, if patients are unstable, critically unwell, or unable to ingest oral therapies), we advise that clinicians should consider switching to LMWH for the duration of the inpatient stay, in line with published guidance for VTE prophylaxis in patients with COVID-19[81,82]. Additionally, consideration should be given to potential DDIs when treating with direct factor Xa inhibitors. DOACs may also interact with certain antiviral medication such as ritonavir (a component of Paxlovid), resulting in increased exposure to the DOAC and increased risk of bleeding[83]. Hence, where there is particular concern surrounding DDIs, we suggest LMWHs may be considered as an alternative. Before patients are discharged from hospital, they should generally be re-commenced on the medication they were admitted on where possible.

Conclusion

This article provides guidance on the management of cancer-associated VTE in diverse circumstances based on the consensus opinion of clinicians from a range of specialisms with expertise in treating these patients. Although a systematic approach was used, a limitation of the article is that it does not constitute a formal treatment guideline, as a comprehensive guideline-writing methodology was not applied.

DOACs are typically the standard of care for preventing VTE recurrence in non-cancer patients and should also be considered as the standard of care for first-line treatment for VTE in patients with cancer. Anticoagulation through the use of LMWH reduces VTE recurrences by 40% compared to VKAs[28], and recurrence may be further reduced by 40% when managed with direct factor Xa inhibitors compared to LMWH[27], demonstrating the fundamental benefit of appropriate use of direct factor Xa inhibitors for patients with cancer-associated VTE. The challenges associated with managing cancer patients mean that they should be carefully selected for the most appropriate class of anticoagulant therapy, and consideration should be given to the relative benefits of specific drugs when tailoring individualized care. LMWH may be preferred in some clinical settings, particularly in acutely unwell and/or unstable patients and patients with upper GI cancer, since there is more experience in prescribing LMWH, fewer DDIs and lower bleeding risk. Individualized care personalized to patient requirements and preferences is always required. However, increased use of direct factor Xa inhibitors to manage cancer-associated VTE has the potential to reduce the incidence of VTE recurrence and the associated morbidity and mortality.

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