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Management of Cancer-Associated Thrombosis

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Abstract

Purpose of review Low molecular weight heparin (LMWH) has been the standard of care for patients with cancer-associated thrombosis (CAT) for over 10 years; however, its adoption has been limited. The appearance of direct acting oral anticoagulants (DOACs) revolutionized the treatment of non-cancer venous thromboembolism (VTE) through their attractive fixed dose regimens; however, a lack of dedicated trial experience had relegated their position to off-label use in patients with cancer. The goal of this review is to review the evidence that has been generated over the last 3 years for factor Xa inhibitors, summarize their current position in the guidelines, and highlight areas of ongoing uncertainty with respect to the management of CAT.

Recent findings Four dedicated trials of patients with CAT have been published comparing edoxaban, rivaroxaban, or apixaban with the LMWH, dalteparin. While these trials all have differences in sample size and inclusion/exclusion criteria, the totality of evidence suggests these agents have similar (if not superior) efficacy for reducing the risk of VTE recurrence without a significant excess in major bleeding. These overall favorable results have translated to guideline recommendations with caveats for patients at high bleeding risk or those with anticipated drug-drug interactions.

Summary Direct-oral anticoagulants now feature prominently in the treatment guidelines for patients with CAT. These agents are, however, not for everyone and ongoing research will need to identify which patients are most, and least likely to benefit from a DOAC-based regimen, and the optimal duration. Furthermore, the incorporation of these data with emerging results from patient-preference research is required to personalize decisions in these patients.

Background

Approximately 20–30% of all cases of venous thromboembolism (VTE) are considered cancer-associated thrombosis (CAT) [1]. Patient, cancer, and treatment factors all influence the risk of developing VTE which is 5 to 8 times more common than in patients without cancer [2, 3]. The overall rates of CAT appear to be increasing through a combination of increasing oncological treatment thrombogenicity (e.g., hormonal therapy, immunomodulators, erythropoiesis stimulating drugs), increasing use of central venous catheters for chemotherapy, prolonged cancer survivorship with an overall aging population, and greater detection through widespread CT imaging [1, 2, 4].

Compared with the general population, CAT tends to be more extensive, bilateral, and found in high-risk locations such as the ileocaval, splanchnic, and upper limb vessels. Once established, CAT portends a poor prognosis from both a malignancy and thrombosis perspective. Cancer and thrombosis have a bidirectional relationship; cancer growth is not only capable of activating (and potentiating) the coagulation cascade but there is also evidence that thrombosis may drive tumorigenesis and metastasis [5]. In patients that are six times more likely to suffer a bleeding event and three times more likely to sustain a recurrent VTE, it is unsurprising that achieving the competing aims of both thrombosis resolution and bleeding avoidance is incrementally more challenging in patients with cancer [6, 7]. More so than the non-cancer patient, the traditional bleeding risk factors in CAT are dynamic owing to both treatment and cancer-related lability in renal function, body weight, and platelet count, as well as a higher frequency of treatment-related procedural interruption [8].

For over 15 years, the standard of care for CAT management has been anticoagulation with low-molecular weight heparin (LMWH). However the last 3 years has witnessed the growth of a large body of evidence supporting the use of direct-acting oral anticoagulants. Here we review the current management of CAT in the context of this new evidence, how it has shaped guideline direction, and the current unanswered questions.

Seminal evidence for current therapeutic options

Low-molecular weight heparin

Vitamin-K antagonists had been the standard of care for management of VTE irrespective of cancer diagnosis until the early 2000s when the pivotal CLOT (Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer) trial was performed [9]. In an attempt to address unmet thrombotic and bleeding risk, the CLOT trial randomized 676 participants with CAT to either the LMWH dalteparin or VKA. At 6 months, administration of dalteparin was associated with a profound 50% reduction in VTE recurrence (9 vs. 17%, HR 0.48 [0.30–0.77], $p = 0.002$) without a significant price to pay in bleeding events (6 vs. 4%, $p = 0.26$). Almost 10 years later, the CATCH (Comparison of Acute Treatments in Cancer Haemostasis) trial evaluated a similar, albeit lower risk than CLOT, population and showed the LMWH tinzaparin to offer directionally consistent reductions in the rates of recurrent VTE (7.2% vs. 10.5% HR 0.65 [0.41–1.03] although this did not reach statistical significance [10]. A meta-analysis dominated by these two trials confirmed thrombotic risk reduction without excess bleeding reaffirming LMWH's superiority over VKA and its role as a high level recommendation in CAT care [11]. Yet despite endorsement in multiple guidelines for over 10 years, the inconvenience of daily parental administration and high cost of LMWH have contributed to poor adoption, high rates of discontinuation, and an overall unmet treatment need for patients with CAT prompting evaluation of the DOACs [12–15].

Direct-acting oral anticoagulants

DOACs, in particular the factor Xa inhibitors (edoxaban, rivaroxaban, apixaban), are attractive anticoagulants due to their fixed dosing regimens and predictable pharmacology which obviates the need for therapeutic drug monitoring. These agents have transformed the care of patients with non-cancer VTE with similar efficacy and modest reductions in the risk of major (and particularly intracranial) bleeding; however, until recently, the evidence supporting their use in CAT was scarce. Despite patients with cancer being routinely underrepresented in the seminal trials of these agents (< 5% of enrolment), meta-analysis of those with a cancer comorbidity appeared to derive equivalent, if not greater, efficacy (risk of recurrent VTE 4.1% vs. 6.1%, RR 0.66 [0.38–1.2]) with similar rates of bleeding (15 vs. 16%, RR 0.94 [0.7–1.3]) compared with VKA [16, 17]. However, the use of a VKA comparator arm which is not the standard of care for CAT, in addition to a lack of granularity on the cancer population (e.g., cancer type, stage, treatment modality), did not meet evidentiary standards for high level guideline recommendations. Of note, despite the lack of professional society endorsement, registry data from 2016 had already started to reveal early (off label) adoption with as many as 20% of patients with active cancer prescribed DOACs in routine clinical care of CAT [18]. Over the last 3 years, however, there have been four dedicated, open-label, blinded-endpoint prospective trials (Table 1) which have evaluated Factor Xa inhibitors and with rapid uptake in the guidelines, established their role as a first-line treatment for many patients with CAT.

The Hokusai-VTE cancer trial randomized 1046 participants with active cancer (or a diagnosis within 2 years), to open-label edoxaban or dalteparin after receiving at least 5 days of LMWH [19]. The primary composite outcome was recurrent VTE or major bleeding at 12 months which occurred in 12.8% of the edoxaban-treated participants and 13.5% in those treated with dalteparin. The modified intention to treat comparison suggested edoxaban was well within the prespecified non-inferiority margin for the composite endpoint (HR 0.97, 95% CI 0.70–1.36, $p = 0.006$). Numerically fewer recurrent VTE events were observed (7.9 vs. 11%, $p = 0.09$) with the cumulative incidence curves suggesting a late benefit that may have been driven by improved persistence on DOAC. There was however more frequent major bleeding events (6.9 vs. 4.0%, $p = 0.04$) in those treated with edoxaban with the majority of excess being GI-related in the cohort of patients with a GI malignancy. Some limitations are worth noting. Although the endpoint was measured at 12 months, treatment between 6 and 12 months of follow-up was at the discretion of the investigator. Thus, at the end of 12 months, only 200 (38.3%) and 154 (29.4%) retained randomization fidelity in the edoxaban and dalteparin groups respectively, not only forfeiting statistical power but also generating uncertainty about management strategy beyond 6 months.

The SELECT-D trial randomized 406 patients to open-label rivaroxaban (15 mg BID loading for 3 weeks followed by 20 mg OD maintenance) or dalteparin [20]. At 6 months, the primary efficacy outcome was the cumulative incidence of recurrent VTE which occurred less frequently in the rivaroxaban group compared with LMWH (4 vs. 11%, HR 0.43 [0.19–0.99]). Major bleeding events were numerically higher in patients treated with rivaroxaban (6 vs. 4%, HR 1.83 [0.68–4.96]) although the differences were more pronounced in the

Table 1. Seminal trials of LMWH and DOACs in patients with cancer-associated thrombosis. Number (%) of patients in the *investigational* arm

	LMWH (vs. VKA)		DOAC (vs. LMWH)			
	CLOT	CATCH	Hokusai-VTE cancer	SELECT-D	ADAM VTE	CARAVAGGIO
First author, year	Lee, 2003 [9]	Lee, 2015 [10]	Raskob, 2018 [19]	Young, 2018 [20]	McBane, 2020 [21]	Agnelli, 2020 [22]
Design	Randomized Open-label Non-inferiority Blinded adjudicated endpoint	Randomized Open-label Non-inferiority Blinded adjudicated endpoint	Randomized Open-label Non-inferiority Blinded adjudicated endpoint	Randomized Open-label Pilot Blinded adjudicated endpoint	Randomized Open-label Exploratory Blinded adjudicated endpoint	Randomized Open-label Non-inferiority Blinded adjudicated endpoint
Sample	676	900	1046	406	300	1155
Allocation	Dalteparin 200 IU/kg OD 1/12 then 150 IU/kg OD vs. LMWH 5–7/7 then VKA (INR 2–3)	Tinzaparin 175 IU/kg OD vs. LMWH 5–10/7 then VKA (INR 2–3)	LMWH for 5/7 then edoxaban 60 mg OD vs. dalteparin*	Rivaroxaban 15 mg BID 3/52 then 20 mg OD vs. dalteparin*	Apixaban 10 mg BID 1/52 then 5 mg BID vs. dalteparin*	Apixaban 10 mg BID 1/52 then 5 mg BID vs. dalteparin*
Duration	6 months	6 months	6–12 months	6 months	6 months	6 months
ECOG strata	0: 80 [23] 1: 135 (41) 2: 118 [35] 3: 5 [1]	0 or 1: 343 (76) 2: 106 [24]	0: 155 [30] 1: 243 (47) 2: 123 [23]	0: 61 [30] 1: 95 (47) 2: 43 [21]	0: 60 (40) 1: 70 (47) 2: 20 [13]	0: 183 [32] 1: 281 (49) 2: 109 [19]
Incidental VTE	0 (0)	0 (0)	167 [32]	105 (52)	NR	116 [20]
CrCl 30–50	NR	59 [13]	38 [7]	NR	14 [9]	51 [9]
Plt 50–100	NR (excluded plt < 75)	NR	32 [6]	NR	10 [7]	21 [4]
GI cancer						
- Upper	0	66 [15]	33 [6]	11 (5)	7 (5)	23 (4)
- Lower	54 [18]	56 [12]	83 (16)	55 (27)	18 (12)	121 (21)
Hematologic cancer	40 (12)	44 (9)	56 (11)	14 (7)	13 (9)	33 (6)
Brain tumor	14 (5)	NR	NR	1 (1)	3 (2)	13 (9)
Metastatic cancer	223 (66)	247 (55)	274 (53)	118 (58)	98 (65)	389 (68)*
Recurrent VTE	9% vs. 17% (27/336 vs. 53/336) HR 0.48 [0.30–0.77]	7.2% vs. 10.5% (31/449 vs. 45/451) HR 0.65 [0.41–1.03]	7.9% vs. 11.3% (41/522 vs. 59/524)	3.9% vs. 8.9% (8/203 vs. 18/203)	0.7% vs. 6.3% (1/145 vs. 9/142)	5.6% vs. 7.9% (32/576 vs. 46/579)

Table 1. (Continued)

	LMWH (vs. VKA)		DOAC (vs. LMWH)			
	CLOT	**CATCH**	**Hokusai-VTE cancer**	**SELECT-D**	**ADAM VTE**	**CARAVAGGIO**
			HR, 0.71 [0.48–1.06]	HR, 0.43 [0.19–0.99]	HR, 0.10 [0.01–0.78]	HR, 0.63 [0.37–1.07]
Major bleeding	6% vs. 4% (19/338 vs. 12/335) $p = 0.27$ (log-rank)	2.7% vs. 2.4% (13/449 vs. 12/451) HR 0.89 [0.40–1.99]	6.9% vs. 4.0% (36/522 vs. 21/524) HR 1.77 [1.03–3.04]	5.4% vs. 3.0% (11/203 vs. 6/203) HR 1.83 [0.68–4.96]	0.0% vs. 1.4% (0/145 vs. 2/142) HR N/A	3.8% vs. 4.0% 22/576 vs. 23/579 HR 0.82 [0.40–1.69]
Treatment	discontinuation	NR	NR	6 months: 41.2% vs. 45.6% (219 vs. 239)	42.4% vs. 44.3% (86 vs. 90)	37.9% vs. 45.8% (55 vs. 65)
36.8% vs. 44.6% (212 vs. 258)						
Mortality	39 vs. 41% (130/338 vs. 136/335); $p = 0.53$	33.4 vs. 30.6% (150/449 vs. 138/451) HR [0.85–1.36]	39.5% vs. 36.6% 206/522 vs. 192/524 HR, 1.12 [0.92–1.37]	23.6% vs. 27.6% (48/203 vs. 56/203)	16% vs. 11% (23/145 vs. 15/142) HR, 1.40 [0.82–2.43]	23.4% vs. 26.4% 135/576 vs. 153/579 HR, 0.82 [0.62–1.09]

*Dalteparin standard arm: 200 IU/kg OD for 1 month then 150 IU/kg OD thereafter

rates of non-major bleeding (13 vs. 4%, HR 3.76 [1.63–8.69]). Midway through the trial after 220 patients were recruited, the trial's data safety and monitoring board noted an imbalance in bleeding events in 19 participants with esophageal cancers and thus subsequent enrolment for these patients was halted. As observed in the trial of edoxaban, GI major bleeding was similarly more common among those receiving rivaroxaban (3.9 vs. 2.0%) and particularly among those with esophageal malignancy (36.4 vs. 5.3%).

Two studies have been published evaluating apixaban in patients with active cancer. The ADAM-VTE trial was a comparatively small, investigator initiated study which randomized 300 participants to open-label apixaban (10 mg BID loading then 5 mg BID maintenance) or dalteparin for 6 months [21]. The primary safety outcome was major bleeding which occurred in only two patients in the dalteparin arm; however, the rates of the secondary safety endpoint (major and non-major bleeding) were similar between the groups (9%). While the number of events were low, there was a significant reduction in the rate of VTE recurrence for patients treated with apixaban compared with dalteparin (3.4 vs. 14.1%, HR 0.26 (0.09–0.8). The CARAVAGGIO Trial is the largest of any of the CAT trials which randomized 1155 participants to either apixaban (same loading strategy as ADAM-VTE) or dalteparin [22]. At 6 months, the rates of the recurrent VTE primary endpoint were lower in the apixaban group compared with dalteparin (5.6 vs. 7.9%, HR 0.63, [0.37–1.07] which met its non-inferiority margin ($p < 0.001$) but narrowly missed superiority ($p = 0.09$). Notably there was no significant difference between the groups with respect to the primary safety endpoint of major bleeding (3.8 vs. 4.0%, HR 0.82 (0.40–1.69)); however, there were numerically more non-major bleeds (9.0% vs. 6.0%, (HR = 1.42, 95% CI 0.88–2.30) in the apixaban group. While excess GI bleeding had been observed in the trials of edoxaban and rivaroxaban, increased rates of genitourinary (19/52 vs. 10/34) and upper airway bleeds (12/52 vs. 3/52) were observed rather than GI bleeds (10/52 vs. 11/52) in apixaban-treated patients.

Vitamin K antagonists

As mentioned earlier, VKA was the standard of care prior to the CLOT trial and the emergence of LMWH. While VKAs generally have a similar bleeding profile, they are clearly inferior with respect to the prevention of VTE recurrence in patients with CAT. Furthermore, VKAs present multiple practical challenges for patient and prescriber, the most prominent being therapeutic drug monitoring. Even in the two largest and carefully conducted RCTs [9, 10], participants in the VKA arms spent less than 50% of the time in a therapeutic range which is likely to have been impacted by frequent drug-drug interactions, labile nutritional status, and treatment interruption that commonly affects cancer patients. Nonetheless, the low cost and physician comfort have kept VKAs as a third option in most guidelines when cost, availability, or contraindications prevent the administration of either LMWH or DOACs.

Inferior vena cava filters

For patients with acute CAT with an absolute contraindication to anticoagulation or in whom CAT recurrence on LMWH has occurred, an inferior

Table 2. Current treatment guidelines for cancer-associated thrombosis from 2019 onwards

	NCCN	ITAC, endorsed by ISTH	ASCO
Lead author, year	Streiff, 2020 [28]	Farge, 2019 [26]	Key, 2019 [27]
Guidance	Patients without gastric or esophageal lesions: - Category 1: apixaban or edoxaban (after LMWH/UFH for 5/7) - Category 2A: rivaroxaban Patients with gastric or esophageal lesions: - Category 1: dalteparin - Category 2A: enoxaparin If above unavailable: - Category 2B: dabigatran, fondaparinux, UFH and warfarin Contraindications (key): Kidney disease: - CrCl < 30: edoxaban, rivaroxaban, dabigatran - CrCl < 25: apixaban Strong inducers/inhibitors of - CYP3A4: rivaroxaban, apixaban; OR - P-gp rivaroxaban, apixaban, edoxaban, dabigatran.	Initial - Grade 1B: LMWH if CrCl ≥ 30 - Grade 1B: Rivaroxaban or edoxaban (after 5/7 parenteral anticoagulation) if CrCl ≥ 30 and not high risk of GI or genitourinary bleeding. - Grade 2C: UFH can be used if LMWH/DOAC contraindicated or not available. - Grade 2D: fondaparinaux may be used as an alternative. Early maintenance (up to 6 months) - Grade 1A: LMWH preferred over VKA if CrCl ≥ 30 - Grade 1A: Rivaroxaban or edoxaban if CrCl ≥ 30 in the absence of drug-drug interactions or GI absorption impairment. Use in caution with upper GI malignancy. Extended - (consensus) After 6 months, termination or continuation of any anticoagulant based on individual risk-benefit ratio, tolerability, patient preference	Initial (high/strong) - LMWH, UFH, fondaparinux, or rivaroxaban. - CrCl ≥ 30 LMWH is preferred over UFH for the initial 5/7 to 10/7 Early maintenance (high/strong) - LMWH, edoxaban, or rivaroxaban for at least 6 months preferred over VKAs - VKA inferior but permitted if LMWH or DOAC inaccessible. - Caution with DOAC in GI ± GU malignancy and other settings of mucosal bleeding risk. Drug-drug interactions need to be checked. Extended (low/weak) - Anticoagulation with LMWH, DOACs, or VKAs beyond the initial 6 months should be offered to select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy. - Needs to be assessed on an intermittent basis to ensure a continued favorable risk-benefit profile

ASCO, American Society of Clinical Oncology; *CrCl*, creatinine clearance; *GI*, gastrointestinal; *GU*, genitourinary; *ITAC*, International Initiative on Thrombosis and Cancer; *LMWH*, low-molecular weight heparin; *NCCN*, National Comprehensive Cancer Network; *UFH*, unfractionated heparin

vena cava (IVC) filter may be considered. The evidence supporting this approach is retrospective, underpowered, and subject to confounding by indication. The majority of studies show increased risk of VTE recurrence without an appreciable impact on mortality [23, 24] although those at greatest absolute risk (such as the elderly) may represent a subgroup that derives net benefit [25].

Comparison of current clinical guidelines

Most contemporary guidelines now include rivaroxaban and edoxaban as equal first-line therapy with LMWH for the initial and maintenance phase of VTE treatment (Table 2). Each of the main guidelines that have been published within the last 3 years makes a point of expressing caution with (or in the NCCN guideline, avoidance of) rivaroxaban and edoxaban in the context of gastric/esophageal cancer and genito-urinary cancer [26–28]. DOACs are recommended only in patients with CrCl ≥ 30 which is consistent with the inclusion/exclusion criteria from their respective CAT clinical trials. Consensus documents continue to favor the use of LMWH in patients where the oral route may be problematic (e.g., nausea/vomiting, GI luminal pathology) and in the context where interruption of therapy is anticipated (e.g., perioperatively, thrombocytopenia, intercurrent bleeding). In this context, the extensive clinical experience with LMWH and its dose adjustment is clearly superior to the off-label use of reduced dose DOAC formulations.

In the most recent ITAC and ASCO guidelines, apixaban (like dabigatran) is currently relegated as an option only in those patients in whom LMWH, edoxaban, or rivaroxaban are unavailable. This is unsurprising as neither of the prospective apixaban studies had been completed at the time of their writing and with the subsequent publication of CARAVAGGIO, apixaban is likely to receive the same level of endorsement as the other Factor Xa agents. Of note, the April 2020 update of the 2018 NCCN guideline [29] elevated apixaban to a category 1 recommendation on the account of the modestly sized ADAM-VTE trial. It remains to be seen whether the relative GI safety of apixaban observed in CARAVAGGIO may soften the current guidance to avoid Factor Xa inhibitors in patients with upper GI malignancy. Furthermore, updated meta-analyses of 2894 participants which include those in the CARAVAGGIO trial both suggest the Factor Xa class may be superior for reduction in VTE recurrence (5.2 vs. 8.2%, HR 0.62 (0.43–0.91), I^2 = 30%) without a significant increase in major bleeding (4.3 vs. 3.3%, HR 1.31 (0.83–2.08), I^2 = 23%) [30, 31]. Whether this is sufficient evidence for guidelines to consider positioning the Factor Xa class above LMWH as the "preferred" anticoagulant in CAT seems unlikely without more real-world experience, particularly with respect to safety. Even in the event of overall similar efficacy and bleeding profiles, the explicit inclusion of patient preferences into guidelines, as has been proposed in several expert consensus algorithms (Fig. 1), may ultimately determine the decision for either LMWH or DOAC.

Areas of guideline and clinical uncertainty

Duration of treatment

The majority of trials evaluating anticoagulants in CAT have consisted of 3–6-month follow-up with few reporting 12-month outcomes. With the above seminal trials all reporting their primary endpoint at 6 months, most guidelines recommend at least 6 months of therapy and in the setting of persistent malignancy or ongoing chemotherapy, indefinite anticoagulation. The nature of the risk beyond 6 months is incompletely understood. Data from the TiCAT and DALTECAN single arm studies of LMWH in CAT patients showed the highest risk

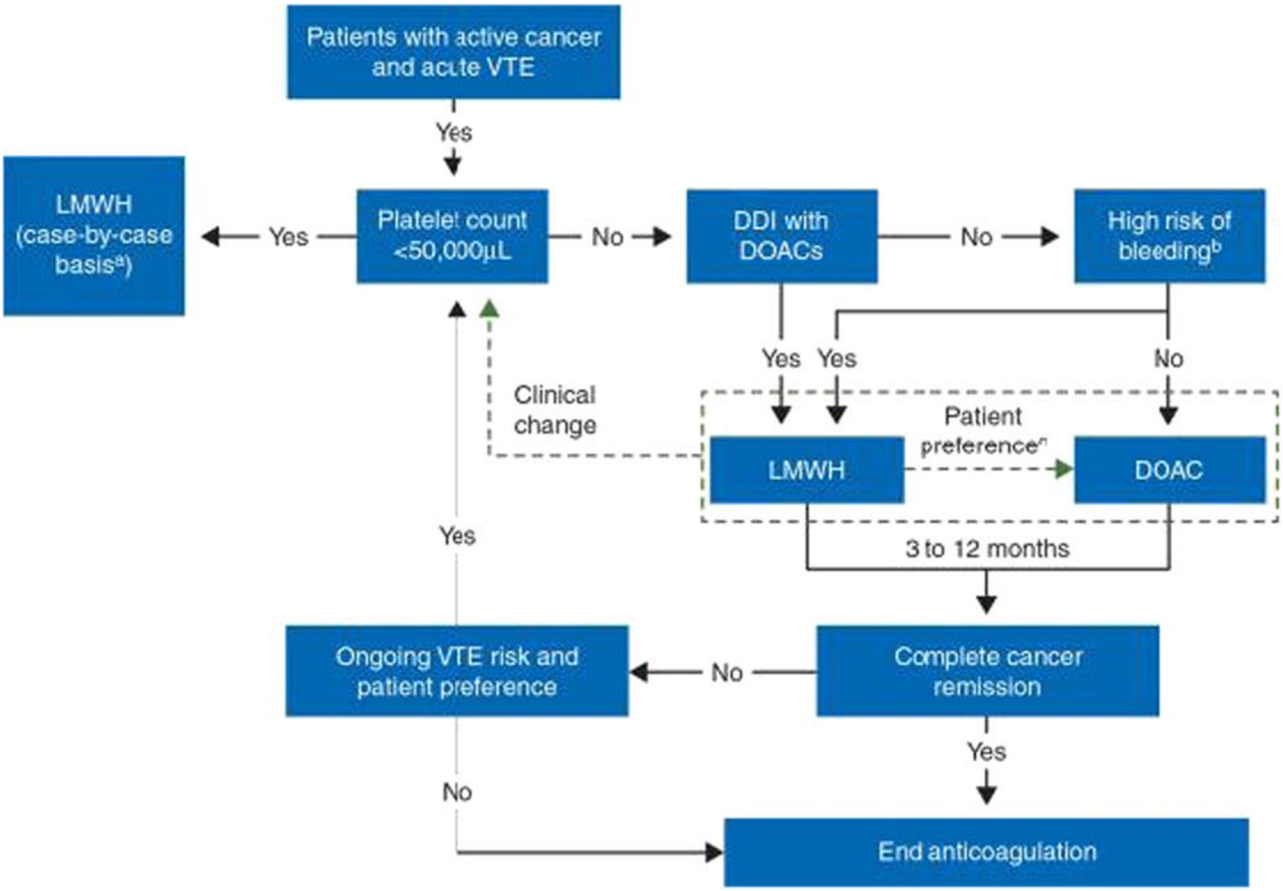

Fig. 1. Reproduced from Ay et al. [37] under the cc by-nc 4.0 permissions (http://creativecommons.org/licenses/by/4.0/). Potential treatment approach for cancer-associated VTE based on current treatment guidelines and new randomized controlled trial evidence. [a]Reduced dose or full dose following transfusion. [b]Includes patients with gastrointestinal cancer as well as risk factors unrelated to cancer. [c]On a case-by-case basis with an understanding of the relative risks and benefits. DDI, drug-drug interactions; DOAC, direct oral anticoagulant; LMWH, low-molecular weight heparin; VTE, venous thromboembolism.

of both bleeding and VTE risk in the first 1–3 months following the index event [32, 33]. However, while patients treated with extended LMWH experienced an overall diminution in the rate of bleeding events out to 12 months, the rates of VTE recurrence persisted suggesting a probable net clinical benefit of extended anticoagulation beyond 6 months that was also inferred from a recent meta-analysis [34]. Studies of DOACs with longer term follow-up comparing the use of reduced dose formulations are needed, as are CAT-specific risk scores to assist in individualizing a risk/benefit decision beyond 6 months.

Thrombocytopenia

Thrombocytopenia is a common (and often predictable) consequence of chemotherapy and of malignancy in general. Notably, while thrombocytopenia increases the risk of bleeding, it does not substantially offset the risk of CAT [1]. Once both are established, determining the delicate balance between bleeding and thrombotic risk is complex and dynamic. In the acute phase of VTE, a

platelet count of 50,000 is the generally the minimum established (consensus rather than evidence-based) threshold for administering therapeutic anticoagulation [35]. This threshold has been determined through post hoc analyses of studies with LMWH and extrapolated to DOACs as these patients represented no more than 5% of the above mentioned trials. In platelet counts < 50,000, there is virtually no DOAC data and their administration cannot be recommended. With the modicum of retrospective LMWH data, the expert opinion diverges from full dose LMWH with platelet transfusion to attenuated LMWH dose regimens based on bleeding and thrombotic risk.

Drug-drug interactions

Most guidelines express caution when considering the use of factor Xa inhibitors when anticipating potential CYP3A4 or P-gp drug-drug interactions. Potential interactions not only have implications for under or over-anticoagulating the patient but may also impact the efficacy of both antineoplastic (e.g., hormonal agents, taxanes, tyrosine kinase inhibitors) and supportive care medications (e.g., steroids, antifungals). Definitive studies assessing the clinical significance of each of these interactions are eagerly awaited (NCT04023760); however, until such time given the co-prescription of strong inducers/inhibitors of the 3A4/P-gp pathways led to exclusion from the DOAC trials, caution must be exercised when considering their clinical use.

Patient preference

Little is known about patient preference in the choice of treatment options for CAT. In a mixed methods study of in-depth interviews and choice-based exercises, the avoidance of any interference to cancer treatment (39%) was the top priority among participants with efficacy (24%), major bleeding (19%), and route of administration all rated below [36]. Thus, while DOACs may offer significant advantages as far as convenience and potentially efficacy, the potential for deleterious drug-drug interactions and bleeding complications that may lead to oncologic treatment interruption should not be minimized. Two clinical trials are presently ongoing and will definitively report on patient-reported outcome measures in patients with CAT treated with anticoagulation. The first is CONKO-011 which is almost identical to SELECT-D in size and design and will report the degree of treatment satisfaction with rivaroxaban compared with dalteparin as the primary endpoint at 3 months in 450 participants [NCT02583191]. The second is a PCORI pragmatic trial called CANVAS which is randomizing 811 patients to either a DOAC or to either LMWH or warfarin for a period of 6 months following CAT diagnosis. The choice of agent following randomization will be left to the discretion of the investigator and patient with a primary efficacy outcome of VTE recurrence and a number of secondary outcomes including patient satisfaction [NCT02744092]. While the results of CONKO-011 are expected late in 2020, the results of CANVAS are not expected until well into 2022.

Summary

The wealth of randomized clinical trial evidence generated in the last 3 years has established DOACs as a comparably safe and efficacious alternative to LMWH

for a large number of patients with CAT. Patients at high bleeding risk, particularly those with gastro-intestinal and genito-urinary malignancy and those with predictable drug-drug interactions, represent relative contraindications to DOAC therapy and in whom LMWH is preferred. Similarly in patients with thrombocytopenia (< 50,000), reduced creatinine clearance (< 30 mL/min), and brain tumors, the DOACs remain largely untested. In determining choice and duration of anticoagulation, cancer type, tumor location, chemotherapy regimen, age, and a plethora of comorbidities have all been shown to variably and dynamically impact bleeding and thrombotic risk in these complex patients. Although personalization and precision are the hallmarks of contemporary oncologic care, even patient-level meta-analysis has inadequate power to confidently evaluate each of these subgroups with respect to each agent's efficacy and safety. Thus, while the answer is always "more data," whether this will come in the form of larger more inclusive registry-based experience with all the limitations of observational data, or from multiple smaller controlled trials in specific cohorts (i.e., patients with brain tumors, or CrCl < 30, or platelets < 50,000) remains to be seen. Furthermore, how these data are incorporated with patient preferences in a shared decision-making process remains a challenge for the field.

Compliance with Ethical Standards

Conflict of Interest
Adam J Nelson declares that there is no conflict of interest. Chiara Melloni declares that there is no conflict of interest.

Human and Animal Rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

1. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. Blood. 2013;122(10):1712–23.
2. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015;12(8):464–74.
3. Horsted F, West J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. PLoS Med. 2012;9(7):e1001275.
4. Ahlbrecht J, Dickmann B, Ay C, Dunkler D, Thaler J, Schmidinger M, et al. Tumor grade is associated with venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. J Clin Oncol. 2012;30(31):3870–5.
5. Sharma BK, Flick MJ, Palumbo JS. Cancer-associated thrombosis: a two-way street. Semin Thromb Hemost. 2019;45(6):559–68.
6. Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG, Buller HR. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. J Clin Oncol. 2000;18(17):3078–83.
7. Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood. 2002;100(10):3484–8.

8. Yamashita Y, Morimoto T, Amano H, Takase T, Hiramori S, Kim K, et al. Anticoagulation therapy for venous thromboembolism in the real world- from the COMMAND VTE Registry. Circ J. 2018;82(5):1262–70.
9. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349(2):146–53.
10. Lee AYY, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF, et al. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. JAMA. 2015;314(7):677–86.
11. Connell NT, Abel GA, Connors JM. Low-molecular weight heparin versus vitamin K antagonists for the treatment of cancer-associated thrombosis: a cost-effectiveness analysis. Thromb Res. 2017;150:53–8.
12. Delate T, Witt DM, Ritzwoller D, Weeks JC, Kushi L, Hornbrook MC, et al. Outpatient use of low molecular weight heparin monotherapy for first-line treatment of venous thromboembolism in advanced cancer. Oncologist. 2012;17(3):419–27.
13. Khorana AA, McCrae KR, Milentijevic D, Fortier J, Nelson WW, Laliberte F, et al. Current practice patterns and patient persistence with anticoagulant treatments for cancer-associated thrombosis. Res Pract Thromb Haemost. 2017;1(1):14–22.
14. Khorana AA, Yannicelli D, McCrae KR, Milentijevic D, Crivera C, Nelson WW, et al. Evaluation of US prescription patterns: are treatment guidelines for cancer-associated venous thromboembolism being followed? Thromb Res. 2016;145:51–3.
15. Wittkowsky AK. Barriers to the long-term use of low-molecular weight heparins for treatment of cancer-associated thrombosis. J Thromb Haemost. 2006;4(9):2090–1.
16. van Es N, Coppens M, Schulman S, Middeldorp S, Buller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood. 2014;124(12):1968–75.
17. Vedovati MC, Germini F, Agnelli G, Becattini C. Direct oral anticoagulants in patients with VTE and cancer: a systematic review and meta-analysis. Chest. 2015;147(2):475–83.
18. Ageno W, Haas S, Weitz JI, Goldhaber SZ, Turpie AGG, Goto S, et al. Characteristics and management of patients with venous thromboembolism: the GARFIELD-VTE Registry. Thromb Haemost. 2019;119(2):319–27.
19. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med. 2018;378(7):615–24.
20. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clin Oncol. 2018;36(20):2017–23.
21. McBane RD 2nd, Wysokinski WE, Le-Rademacher JG, Zemla T, Ashrani A, Tafur A, et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: the ADAM VTE trial. J Thromb Haemost. 2020;18(2):411–21.
22. Agnelli G, Becattini C, Meyer G, Munoz A, Huisman MV, Connors JM, et al. Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med. 2020;382(17):1599–607.
23. Brunson A, Ho G, White R, Wun T. Inferior vena cava filters in patients with cancer and venous thromboembolism (VTE) does not improve clinical outcomes: a population-based study. Thromb Res. 2017;153:57–64.
24. Coombs C, Kuk D, Devlin S, Siegelbaum RH, Durack JC, Parameswaran R, et al. Outcomes after inferior vena cava filter placement in cancer patients diagnosed with pulmonary embolism: risk for recurrent venous thromboembolism. J Thromb Thrombolysis. 2017;44(4):489–93.
25. Stein PD, Matta F, Lawrence FR, Hughes MJ. Inferior vena cava filters in patients with recurrent pulmonary embolism. Am J Med. 2019;132(1):88–92.
26. Farge D, Frere C, Connors JM, Ay C, Khorana AA, Munoz A, et al. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. Lancet Oncol. 2019;20(10):e566–e81.
27. Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2020;38(5):496–520.
28. Streiff MB. National Comprehensive Cancer Network. Guidelines Version 1.2020: Cancer-Associated Venous Thromboembolic Disease. https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf. Accessed 10 Jul 2020.
29. Streiff MB, Holmstrom B, Angelini D, Ashrani A, Bockenstedt PL, Chesney C, et al. NCCN guidelines insights: cancer-associated venous thromboembolic disease, version 2.2018. J Natl Compr Cancer Netw. 2018;16(11):1289–303.
30. Giustozzi M, Agnelli G, Del Toro-Cervera J, Klok FA, Rosovsky RP, Martin AC, et al. Direct oral anticoagulants for the treatment of acute venous thromboembolism associated with cancer: a systematic review and meta-analysis. Thromb Haemost. 2020;120(7):1128–36.
31. Tao DL, Olson SR, DeLoughery TG, Shatzel JJ. The efficacy and safety of DOACs versus LMWH for cancer-associated thrombosis: a systematic review and meta-analysis. Eur J Haematol. 2020;105:360–2.
32. Francis CW, Kessler CM, Goldhaber SZ, Kovacs MJ, Monreal M, Huisman MV, et al. Treatment of venous thromboembolism in cancer patients with dalteparin for up to 12 months: the DALTECAN study. J Thromb Haemost. 2015;13(6):1028–35.

33. Jara-Palomares L, Solier-Lopez A, Elias-Hernandez T, Asensio-Cruz M, Blasco-Esquivias I, Marin-Barrera L, et al. Tinzaparin in cancer associated thrombosis beyond 6months: TiCAT study. Thromb Res. 2017;157:90–6.
34. Kahale LA, Hakoum MB, Tsolakian IG, Matar CF, Terrenato I, Sperati F, et al. Anticoagulation for the long-term treatment of venous thromboembolism in people with cancer. Cochrane Database Syst Rev. 2018;6:CD006650.
35. Al-Samkari H, Connors JM. Managing the competing risks of thrombosis, bleeding, and anticoagulation in patients with malignancy. Blood Adv. 2019;3(22):3770–9.
36. Noble S, Matzdorff A, Maraveyas A, Holm MV, Pisa G. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica. 2015;100(11):1486–92.
37. Ay C, Beyer-Westendorf J, Pabinger I. Treatment of cancer-associated venous thromboembolism in the age of direct oral anticoagulants. Ann Oncol. 2019;30(6):897–907.

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