Cancer-Associated Venous Thromboembolism—Diagnostic and Therapeutic Considerations: An Update Based on the Revised AWMF S2k Guideline

Diagnostik und Therapie der Malignom-assoziierten venösen Thromboembolie

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Abstract

Patients with cancer are prone to develop venous thromboembolism (VTE) with negative impact on quality of life, morbidity, and mortality. Treatment of established VTE is often complex in patients with cancer. Treatment of cancer-associated VTE (CAT) basically comprises initial and maintenance treatment, for 3 to 6 months, secondary prevention, and treatment in special situations. Therapeutic anticoagulation is the treatment of choice in CAT. In addition to the efficacy and safety of low-molecular-weight heparin (LMWH) that had been recommended for decades, direct oral anti-factor Xa inhibitors, a subgroup of direct oral anticoagulants (DOACs), demonstrated their advantages along with the accompanying concerns in several randomized controlled treatment trials of CAT. The latest guidelines, such as the German AWMF-S2k Guideline "Diagnostics and Therapy of Venous Thrombosis and Pulmonary Embolism," agree with each other on most aspects with respect to the treatment of CAT. Encompassing recent clinical studies, and meta-analyses, as well as the focus on some special management aspects of CAT, the objective of this review is to present a current overview and recommendations for the treatment of CAT.

Keywords

- venous thromboembolism
- cancer
- anticoagulation

Background

The risk to develop venous thromboembolism (VTE) is strongly increased in cancer patients. Overall, the cumulative incidence of experiencing a VTE event within the first 12 months after cancer diagnosis is ~2.3% compared with 0.35% in non-tumor patients[1] with wide variability depending on the underlying entity, stage, and therapy.[2] Thus, in about every fourth to fifth patient with a symptomatic VTE, an underlying cancer is diagnosed.[1,2] Cancer-associated VTE

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Table 1 Six-month results from RCTs comparing DOACs and LMWH in CAT

Trial	*n*	DOAC	Recurrent VTE		Major bleeding		CRNMB	
		LMWH	%	HR (95% CI)	%	HR (95% CI)	%	HR (95% CI)
HOKUSAI-VTE CANCER	1,050	Edoxaban	7.9	0.71 (0.48–1.06)	6.9	1.77 (1.03–3.0)	14.6	1.38 (0.98–1.94)
		Dalteparin	11.3		4.0		11.1	
SELECT-D	406	Rivaroxaban	4.0	0.43 (0.19–0.99)	6.0	1.83 (0.68–1.96)	13.0	3.76 (1.63–8.69)
		Dalteparin	11.0		4.0		4.0	
ADAM-VTE	300	Apixaban	0.7	0.099 (0.013–0.780)	0	Not estimable	6.2	Not reported
		Dalteparin	6.3		1.4		4.9	
CARAVAGGIO	1,170	Apixaban	5.6	0.63 (037–1.07)	3.8	0.82 (0.40–1.69)	9.0	1.42 (0.88–2.30)
		Dalteparin	7.9		4.0		6.0	
CASTA-DIVA	158	Rivaroxaban	6.4	0.75 (0.21–2.66)	1.4	0.36 (0.04–3.43)	10.8	Not reported
		Dalteparin	10.1		3.7		6.1	
CANVAS[a]	671	DOAC[a]	6.1	Not reported	5.2	Not reported	5.8	Not reported
		LMWH[a]	8.8		5.6		2.6	
ITT-Meta-analysis	**3,680**	**(DOAC[a])/DXI**	**3.4**	**0.67 (0.52–0.85)**	**4.3**	**1.17 (0.82–1.67)**	**9.6**	**1.66 (1.31–2.09)**
		LMWH	**8.3**		**3.7**		**5.7**	
OT-Meta-analysis	***2,440***	***DXI***	***4.8***	***0.60 (0.38–0.95)***	***4.4***	***1.43 (0.51–1.70)***	***8.8***	***1.93 (0.70–5.13)***
		Dalteparin	***8.1***		***3.2***		***4.6***	

Abbreviations: CRNMB, clinically relevant non-major bleeding; DOAC, direct oral anticoagulant; DXI, direct oral factor Xa inhibitors; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.
[a]In the Canvas study,[12] the choice of a specific DOAC or LMWH was open to the study physicians. In fact, most patients on DOAC got apixaban (57%) or rivaroxaban (39%).
Note: An intention-to-treat meta-analysis of all six published RCTs (Frere et al[11]) and an on-treatment meta-analysis from Hokusai-VTE cancer, Select-d, and Caravaggio (Mulder[8,16]) are given.

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(CAT) has a dramatic negative impact on quality of life, morbidity, and mortality, with a fourfold increased mortality as compared with cancer patients without VTE.[2,3] In addition, a high number of incidental VTE cases (i.e., clinically not suspected), accidentally detected by screening or staging examinations, are diagnosed.[4,5]

Based on several randomized clinical trials (RCTs) demonstrating improved efficacy and unchanged bleeding risk of subcutaneously applied low-molecular-weight heparin (LMWH) as compared with vitamin K antagonists (VKAs),[6] LMWH became the unanimously recommended standard of care for the initial and maintenance treatment of CAT for decades. Guidelines recommend anticoagulation therapy for at least 3 to 6 months, but most patients with CAT complete anticoagulation therapy prior to 6 months.[7] The recently updated German AWMF-S2k Guideline "Diagnostics and Therapy of Venous Thrombosis and Pulmonary Embolism"[8] offers up-to-date guidance on how to diagnose and treat patients with CAT.

Diagnostic Considerations

VTE symptoms in cancer patients are similar to those of non-cancer patients[9,10], but there is an increased awareness warranted not to misinterpret VTE symptoms (e.g., dyspnea) as a consequence of the neoplastic disease or anticancer therapy—as it is probably the case in some patients with incidental CAT. It is important to consider VTE as a possible alternative diagnosis, that needs to be objectively confirmed or ruled out.[8] Since the presence of cancer increases the probability of VTE and since D-dimers are usually elevated in manifest neoplastic disease, the diagnostic workup of a suspicion of CAT should primarily be performed using suitable imaging procedures.[9,10] Normal D-dimer levels in combination with low VTE probability, however, can exclude VTE even in cancer patients.[11]

Management Strategies in Cancer Patients with Symptomatic VTE

Initial and Maintenance Treatment

Until a few years ago, LMWH was the anticoagulant drug of choice for initial CAT treatment, and parenteral anticoagulation with LMWH was maintained for 3 to 6 months or longer in case of persistent active cancer.[6] With the introduction of the direct oral anticoagulant drugs (DOACs) into VTE therapy of non-cancer patients a decade ago, the use of DOACs also became more frequent in CAT despite a lack of trial evidence or guideline recommendations to support the use of DOAC in CAT.[7,12]

Five recent RCTs investigated the efficacy and safety of direct oral factor Xa inhibitors (DXI; apixaban, edoxaban, and rivaroxaban)—a specific subgroup of DOACs—in comparison to LMWH (dalteparin) in CAT. Although individual trial outcomes differed in details, an overall similar benefit–risk balance could be seen across these trials, making DXI a valid treatment alternative also in CAT.[13] In addition, a pragmatic RCT close to every-day care confirmed the results of the previous RCT.[13,14] These studies differed considerably in terms of cancer entities, exclusion criteria, and endpoint definitions, thus DXI endpoint rates cannot be compared across these studies. However, meta-analyses of the 6-month outcome found less VTE recurrences for DXI therapy numerically or statistically significant, depending on methodology and included trials, similar rates for major bleeding (MB) but a significant increase in clinically relevant non-major bleeding (CRNMB; ►Table 1). As treatment persistence with the study drugs was significantly increased with DXI,[15] on-treatment meta-analysis[16] resulted in a significantly better efficacy of DXI (HR: 0.60; 95% CI: 0.39–0.95) but—in contrast to intention-to-treat analyses—without a significant negative effect on MB or CRNMB (►Table 1). Updated international and German guidelines thus recommend DXIs for CAT treatment as an at least equivalent or even superior and less expensive alternative to LMWH.[8] However, even with the use of DXI, the rates of VTE recurrences are still in the range of 5 to 10%. If recurrent VTE occurs in previously anticoagulated patients, it is important to reassess and modify the anticoagulation therapy[17].

According to the revised AWMF-S2k guideline, anticoagulation therapy in CAT may be initiated orally with DXI (apixaban or rivaroxaban) or parenterally with LMWH, which is similar to non-cancer patients.[9] Maintenance treatment may be continued orally with DXI (apixaban, edoxaban, or rivaroxaban) or parenterally with LMWH.[8]

These new differential treatment options require a careful case-by-case evaluation of the clinical situation, practicability of oral versus parenteral therapy, and should also include the patient's preferences. The reduced treatment burden, superior adherence to anticoagulation, and better efficacy of an oral DXI therapy needs to be balanced against the experience gained in the past with LMWH in "complicated" CAT patients, especially those at increased risk of bleeding. Furthermore, it should be considered that the DXI demonstrate individually different drug–drug interactions mediated by the cytochrome P_{450} enzyme and p-GP transporter systems,[18] which might complicate treatment. Clinical data, moreover, suggest that mucosa-associated lesions may increase the bleeding risk to a greater extend with DXI than with LMWH in CAT patients.[16,17] Taken these factors into account, ►Fig. 1 outlines a possible differential treatment algorithm. In clinical practice, it is important to realize that due to the similar pharmacokinetics and dosing intervals of LMWHs and DXIs, a direct, overlap-free switch from parenteral LMWH to oral DXI and vice versa can easily be made, thus offering the option to quickly adapt anticoagulation therapy to unexpected or planned situations such as anticancer treatment-associated nausea, acute interventions, or others.[8]

Secondary VTE Prevention

Guidelines recommend secondary anticoagulation prophylaxis of CAT as long as the neoplastic disease is still active and there are no (new) contraindications.[8] This recommendation is based on the extension from other VTE situations with persistent high-grade risk factors for recurrences, such as severe thrombophilia.[9] Since RCTs for anticoagulation of CAT

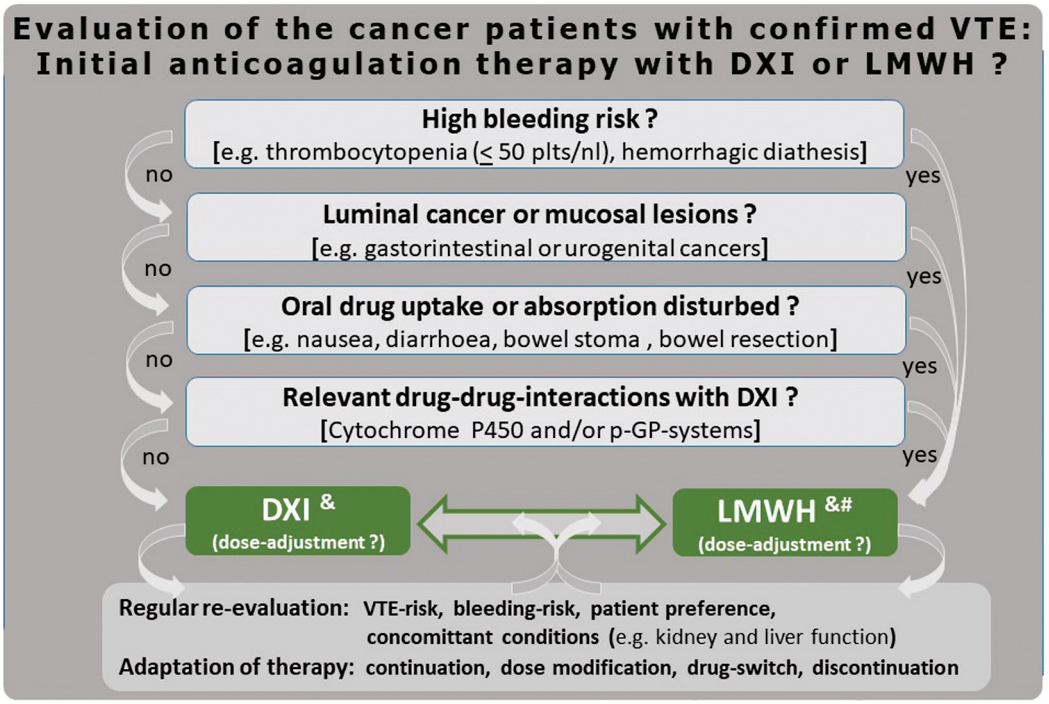

Fig. 1 Differential therapy with DXI or LMWH for cancer-associated VTE (modified from [8]). Abbreviations: DXI, direct oral factor Xa inhibitor; LMWH, low-molecular weight heparin: consider unfractionated heparin in severe renal insufficiency; pay attention to heparin-induced thrombocytopenia type II

beyond 6 months after the index event are missing, the optimal regimen with regard to anticoagulation type or dosage is unclear. Therefore, secondary VTE prevention can be given with DOAC (preferentially DXI), LMWH, or VKA.[8] Usually a full therapeutic dosage of anticoagulation is recommended, again without higher-grade evidence.

Study data of secondary VTE prevention in non-cancer patients with apixaban (2× 2.5 mg/d vs. 2× 5 mg/d) or rivaroxaban (1× 10 mg/d vs. 1× 20 mg/d) demonstrated non-inferiority of the lower dose.[21] Furthermore, these dosages proved to be effective in primary VTE prevention in moderate to high-risk cancer outpatients.[22,23] The consequent use of lower dosages for secondary prevention in CAT was recently prospectively studied in a single-center, single-arm setting, demonstrating feasibility and suggesting a reduction in anticoagulation-associated bleeding without increase in VTE recurrences.[24] Very recently, results of a—primarily negative — RCT reported numerically lower rates for bleeding (primary endpoint was a combination of major and clinically relevant non-major bleeding: 8.9 vs. 12.2%) and similar VTE recurrences (5.0 vs. 4.4%) in 179 versus 181 CAT patients treated after 6 to 12 months of anticoagulation therapy for 12 additional months with 2× 2,5 mg/d versus 2× 5 mg/d apixaban.[25] These data, presented at the ISTH-meeting 2023, are not yet (10/2023) fully published and final results need to be evaluated in closer detail. Taken together, the available evidence supports the alternative use of lower dose anticoagulation—with (preferentially) 2× 2.5 mg/d apixaban or 1× 10 mg/d rivaroxaban—for secondary VTE prevention after CAT.

CAT and Thrombocytopenia

In clinical practice, many cancer patients experience temporary or persistent thrombocytopenia, most often due to the malignancy or anticancer treatment. The risk of bleeding depends on etiology, extent, and duration of the thrombocytopenia, as well as on individual bleeding risk factors such as age or arterial hypertension. In CAT patients with low platelet counts, a regular reevaluation of indication for continuation and intensity of anticoagulation has to be done, which should include the clinical assessment of bleeding signs and kidney and liver function tests in regular intervals. Against this bleeding risk, the risk of VTE recurrence has to be balanced, which is especially high in the first few weeks after CAT diagnosis and in patients with high thrombus burden.[8] The result of this careful reevaluation is the determination of an individual anticoagulation strategy. As long as thrombocytopenia is the only relevant bleeding risk factor and based on longstanding experience with LMWH, it is usually recommended to maintain the full therapeutic dosage down to a platelet count of ~50/nL. If the platelet count is lower, the anticoagulant drug should be reduced in dosage or—particularly in case of platelet counts below 25/nL—paused.[26] Platelet counts less than 10/nL are often complicated by spontaneous bleeding events even without antithrombotic drugs, supporting the temporary interruption of anticoagulation. However, in CAT cases with a very recent VTE diagnosis and high thrombus burden, it may be expedient to maintain a dosage-reduced therapy even at very low platelet counts.[8] Repetitive platelet transfusions may also be considered in individual patients to

allow continuation of anticoagulation[27]—but this is not widely accepted in clinical praxis.

Catheter-Associated VTE in Cancer Patients

One major complication of central venous catheters (CVC; including temporary central venous lines, peripherally inserted central catheters, Demers catheters, or port catheters) in cancer patients is acute catheter-associated deep vein thrombosis (CADVT) of vena jugularis or vena subclavia.[8] When CADVT is diagnosed, immediate therapeutic anticoagulation therapy should be initiated. It is crucial to exclude catheter infection[28] because an infected catheter should be removed as soon as possible after anticoagulation and empirical antibiotic treatment have been started. If catheter infection is sufficiently unlikely, the ongoing need for the CVC should be critically questioned and unneeded CVC should be removed from the CADVT region. If further needed, correct CVC position and function should be assessed. Occasionally, dislocation of the catheter tip may occur and induce thrombus formation. Therefore, correct position of the catheter tip should be checked. If a catheter is necessary for the continuation of therapy, noninfected, nondisplaced, and functional, it can usually be left in place, and used despite CADVT.[29] Thromboses within the catheter lumen or at the catheter tip—with or without CADVT—are not uncommon and not a reason to remove a catheter. In most cases, it is possible to restore patency by instilling a fibrinolytic agent, such as 2 mg rt-PA in 2 mL NaCl-0.9%. If complete patency is not achieved within 2 hours, a second dose may be given, without increase of MB risk.[30,31] A small catheter tip thrombus should be contemplated in particular if aspiration of blood is not possible, but injections or infusions are without any problems. An algorithm for the management of CADVT is shown in ►Fig. 2.

Management of Incidental VTE in Cancer Patients

Incidentally detected VTE in cancer patients usually results from imaging examinations originally requested with a different question in mind (e.g., CT or sonography for cancer staging or assessing complications such as infections). It is estimated that in patients with underlying malignancy, ~30 to 50% of all diagnosed VTE are incidental events.[15] However, about two-thirds of these can be reconciled with nonspecific complaints afterward. PEs account for ~60% of incidental events.[15] Incidental DVT is diagnosed less frequently in clinical practice and often involves the pelvic and proximal leg veins, visceral veins, or the veins of the upper thoracic aperture. In addition, asymptomatic VTE may also be detected when high-risk populations are specifically screened (e.g., in VTE prevention studies in cancer patients).[23]

Staging CTs of the lung do not use the sophisticated protocols for PE detection; therefore, the risk of a false-positive PE diagnosis is increased. This is particularly true in cases where emboli are described only in one pulmonary artery at the subsegmental level. If a venous thrombus cannot be localized peripherally as a PE source, a careful workup of the CAT slides is mandatory. To exclude false-positive findings, the incidental detection of venous thrombi in central or peripheral veins by CT or MRI should be confirmed by adequate ultrasound technics.[8] In the further diagnostic workup of incidental CAT, it is important to reanalyze older imaging studies to estimate VTE age and to differ new thrombi which require therapeutic-dose

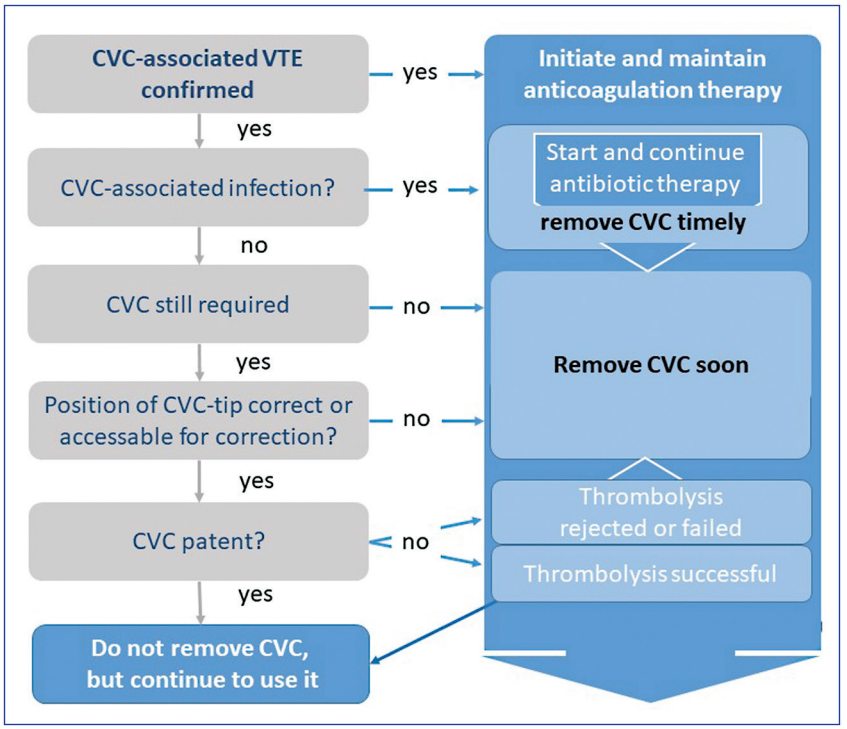

Fig. 2 Management algorithm for confirmed central venous catheter (CVC) associated VTE (modified from [8]).

anticoagulant treatment from older postthrombotic residuals originating from previous VTE events. Furthermore, recording the thrombus burden accurately creates a rational basis for treatment decision and later follow-up assessments.[8,33]

There is limited empirical evidence on the benefit–risk effect of anticoagulation for incidental VTE. The general consensus across current guidelines to treat incidental CAT in the same way as symptomatic CAT[8] is based on the evidence from clinical trials which demonstrated that anticoaculation therapy of incidental CAT is associated with risks of recurrence, bleeding, and death of comparable magnitude to that of symptomatic CAT.[32] Even in case of a low thrombus or embolus burden, there is an increased risk of recurrence.[33] Therefore, the same decision criteria for type, intensity, and duration of anticoagulation have to be considered as for symptomatic CAT. At the same time, detection of a very low thrombus burden (e.g., a single subsegmental PE without a concomitant DVT) may lead to a dosage reduction or even avoidance of anticoagulation if the risk of bleeding is considered to be elevated.[8] There are RCTs ongoing randomizing patients with isolated subsegmental PE to anticoagulation versus observation, which will help optimize treatment in these patients in the future.

Conclusion

VTE is a concerning issue which impacts prognosis of patients with cancer. For established CAT including incidental clots, anticoagulation treatment decisions should be based on risk and benefit assessments and the selection of anticoagulation type and dosage should take into account anticoagulant efficacy, bleeding risk assessment, renal or hepatic function, drug–drug interactions, clinical setting, convenience of use, cost, and patient preference. In addition to long-term parenteral LMWH, DXIs have offered an alternative, cheaper, and more convenient oral treatment option in CAT. As a result, LMWH and DXI are now side-by-side recommendations in the current guideline.[8] A minimum of 3 months of full-dose anticoagulation treatment should be offered to all CAT patients, whereas the continuation or discontinuation of treatment should be based on regular intermittent assessments of risk–benefit ratio. For secondary prevention, lower-dose anticoagulation, too, seems to be effective and safe. Moreover, up-to date guidelines suggest reasonable algorithms to successfully deal with most of the critical situations encountered in CAT patients, such as VTE recurrence,[17] thrombocytopenia, or catheter-related deep venous thrombosis. The future direction of CAT treatment should be focused on how to reduce bleeding rates while on anticoagulation therapy without compromising efficacy.

Conflict of Interest

HR took participation on a Data Safety Monitoring Board or Advisory Board and he got payment or honoraria for lectures, presentations, speakers bureaus or educational events from Bayer, Bristol-Myers Squibb, Pfizer and Viatris.

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