Prediction and management of recurrent venous thromboembolism in patients with cancer

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ABSTRACT

Patients with cancer have an increased risk of venous thromboembolism (VTE), often even while on therapeutic dose of anticoagulation. Recent randomized controlled trials show that the 6-month rate of recurrent VTE is 5-8% during anticoagulation. Multiple risk factors are reported to be associated with recurrent cancer-associated thrombosis, including history of VTE, poor Eastern Cooperative Oncology Group performance status, metastatic diseases, and certain cancer types. Several risk assessment models are derived, but better validation is needed before clinical use. Management of patients with recurrent VTE while on anticoagulation is challenging. Necessary considerations include both the risk of further VTE recurrence and the risk of bleeding. In this review, we will summarize pertinent literature and provide suggestions on the management strategies in patients with recurrent cancer-associated thrombosis.

Key words: prediction; recurrence; cancer-associated thrombosis; anticoagulation; malignancy.

Introduction

Patients with cancer have a significantly increased risk of first as well as recurrent venous thromboembolism (VTE) despite anticoagulation. Management of recurrent VTE in the cancer population is challenging, especially when patients are already on therapeutic dose of anticoagulation. In this narrative review, we aim to summarize relevant literature on the epidemiology, risk factors, and management of recurrent VTE in those with cancer-associated thrombosis, as well as to provide expert-driven suggestions on management strategies. Whenever possible, we base our suggestions on available evidence and discuss knowledge gaps and future research directions.

Direct oral anticoagulants (DOACs) are currently first-line options for the treatment of VTE in patients with cancer, and their use is steadily increasing. Consequently, a growing number of recurrences during DOAC therapy in this population can be expected. This review summarizes recent evidence on recurrent VTE during DOAC treatment in patients with cancer and proposes a structured algorithm for their management.

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Epidemiology of recurrent cancer-associated thrombosis

Current international guidelines recommend continuing anticoagulation in patients with cancer-associated thrombosis, if cancer is not in remission and/or anticancer therapies are ongoing.[1-3] This is supported by data as shown in a recent systemic review and meta-analysis including 14 studies and 1,922 patients who had completed at least 3 months of anticoagulation for cancer-associated thrombosis.[4] After anticoagulation discontinuation, there were high pooled rates of recurrent symptomatic VTE: 14.6 events per 100 person-years (95% confidence interval [CI], 6.5 to 22.8) in the first 3 months, with the cumulative incidence of 28.3% (95% CI, 15.6 to 39.6%) at 1 year and 35% (95% CI, 16.8 to 47.4%) at 5 years.[4] These data support the recommendations of continuing anticoagulation in patients with active cancer.

However, despite anticoagulation, there remains a significant risk of recurrent VTE in this population. In contemporary randomized controlled trials (RCTs), the rate of recurrent VTE on therapeutic anticoagulation was 5-8% at 6 months.[5-9] The case-fatality rate of recurrent VTE was also high at 14.8%.[10] Meta-analysis showed that DOACs were associated with a re-

duced risk of recurrent VTE compared to low-molecular-weight heparin (LMWH).[11] Nonetheless, it remains unclear whether this is more related to the anticoagulant class itself or the 25% dose reduction of LMWH after the first month (done in all RCTs comparing DOACs to LMWH). In addition, a meta-analysis of the RCTs showed that the risk of recurrent VTE was lower in those with incidental VTE compared to symptomatic VTE (relative risk [RR] 0.62, 95% CI, 0.44 to 0.87).[12] This could be due to the unclear chronicity of incidental VTE at the time of diagnosis, as well as the types of malignancies, such as gastrointestinal cancers, for which frequent staging computed tomography (CT) scans are more commonly done, resulting in the diagnosis of incidental VTE.

Risk factors of recurrent VTE in cancer

Clinical risk factors

Multiple studies have reported different risk factors for recurrent VTE in the cancer population. A recent systematic review and meta-analysis including 33 studies (n=96,753) comprehensively summarized current literature published prior to December 2024 regarding factors associated with an increased risk of recurrent cancer-associated VTE.[13] The majority of the studies (except for two) included patients who developed recurrent VTE on anticoagulation. The main risk factors associated with increased risks included: history of VTE, ECOG (Eastern Cooperative Oncology Group) performance status ≥1, metastatic cancer, several cancer types including lung, hepatobiliary, pancreatic, and genitourinary cancers (Table 1). On the other hand, a few factors were possibly associated with reduced risks of recurrent VTE: female sex, older age, surgery within 3 months, breast cancer, and deep vein thrombosis (DVT) alone as the index VTE (Table 1).[13] Although understanding key risk factors for recurrent VTE may inform anticoagulation decisions, the extent to which current evidence influences clinical decision-making and management strategies remains unclear.

Biomarkers

In addition to clinical risk factors, many studies have investigated biomarkers and their association with recurrent cancer-associated thrombosis. Baseline P-selectin was found to be associated with a 4-5 fold increased risk of recurrent VTE in this population and could be promising, but it is limited by its lack of availability in routine clinical care.[14,15]

Elevated D-Dimer and tissue factor are inconsistently associated with the risk of recurrent VTE, which is likely related to different study designs and populations, as well as modest sample sizes in each study.[16,17] Unfortunately, the afront-mentioned systemic review did not find sufficient data to allow a meta-analysis on the effects of any biomarkers.[13] Biomarkers may not be widely available outside research settings and, given their associated costs and uncertain impact on clinical decision-making, their role in routine practice remains limited. More studies are needed to explore the effects of biomarkers in predicting recurrent VTE in the cancer population.

Risk prediction models of recurrent VTE in cancer

Thus far, several clinical risk assessment models have been derived in patients with cancer-associated thrombosis (Table 2). The first model, the Ottawa score, was derived from a retrospective cohort study, and included sex, history of VTE, cancer site and cancer stage as risk factors.[18] This is the only model that has been externally validated in multiple cohorts, but with variable results.[19-22] Another predictive model was derived retrospectively using machine learning methods based on data from nine Spanish hospitals including 2,224 patients with cancer-associated throm-

Table 1. Risk factors for recurrent cancer-associated venous thromboembolism.

Risk factors	Pooled aHR (95% CI)	Certainty grade
Factors associated with increased risk		
History of VTE	1.50 (1.08-2.09)	High
ECOG performance status >0	1.81 (1.34-2.46)	High
ECOG performance status >1	2.44 (1.55-3.84)	High
Metastatic cancer	1.38 (1.15-1.65)	High
Lung cancer	1.78 (1.29-2.46)	High
Hepatobiliary cancer	2.37 (1.70-3.30)	High
Pancreatic cancer	3.20 (2.06-4.96)	High
Genitourinary cancer	1.38 (1.14-1.67)	High
DVT alone as index VTE	1.49 (1.06-2.08)	Moderate
Factors associated with reduced risk		
Sex (female)	0.89 (0.82-0.97)	Moderate
Age (increasing)	0.97 (0.97-0.98)	Moderate
Surgery within 3 months	0.56 (0.40-0.76)	High
Breast cancer	0.43 (0.23-0.81)	High

aHR, adjusted hazard ratio; CI, confidence interval; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; VTE, venous thromboembolism.

bosis.[23] Factors identified included: age, family history of VTE, VTE characteristics (DVT or pulmonary embolism -PE), metastasis, adenocarcinoma histological type, hemoglobin, serum creatinine levels, platelet and leukocyte count. Model performance was modest (Area Under the Receiver Operating Curve [AUROC] 0.66-0.69), and the model has not been externally validated. In addition, the accuracy of recurrent VTE diagnosis in this cohort (based on Natural Language Processing) was unclear, as well as the type and dose of anticoagulation at the time of VTE recurrence. A recent individual patient data meta-analysis combined data from 2,245 patients receiving either LMWH or DOACs in four RCTs of cancer-associated thrombosis: CLOT, CATCH, Hokusai VTE Cancer, and Select-D.[24] A model was derived containing five risk factors: age, breast cancer, metastatic disease, anticoagulant type (LMWH or DOAC), and DVT only as index VTE.[24] The model showed modest discrimination (c-statistics 0.63 after internal-external cross validation) and calibration. The population was limited to patients enrolled in RCTs, which restricted generalizability to the real world. This model also has not been externally validated. Another model, the Caravaggio score, was derived from the Caravaggio trial (1,155 patients with acute cancer-associated thrombosis randomized to apixaban *vs* dalteparin) and validated in the prospective TESEO registry cohort (N=3,506).[25] Six risk factors were included in the model: symptomatic VTE, ovarian or uterine cancer, pancreatic cancer, metastasis, adenocarcinoma, and receipt of platinum/fluoropyrimidine based regimens. The model was also derived from patients enrolled in an RCT, with similar limitations as the previous model. All existing models have limitations and currently there is no single well-validated risk prediction model that can be recommended for routine use in clinical practice. The modest performance of current risk assessment models may be due to multiple reasons including heterogeneity in study populations, variability in cancer types and stages, differences in anticoagulant exposure, and the limited inclusion of dynamic or treatment-related variables.

Given the limited data, the ongoing CAN-CATCH (NCT06894576) study aims to develop a novel risk assessment model for recurrent VTE and anticoagulant-related bleeding in patients with acute cancer-associated thrombosis on therapeutic dose of anticoagulation. Approximately 1000 patients are planned for enrollment with follow-up of 6 months. Blood samples are collected for future investigation of promising biomarkers in the prediction of recurrent VTE and bleeding complications as well.

Management of recurrent VTE

As noted above, patients with cancer-associated VTE are at high risks of recurrent thrombosis despite appropriate anticoagulant treatment. Recurrent VTE represents a distressful event for patients and their relatives who may feel depressed and anxious for an additional burden that further complicates the disease course. Recurrent thrombosis also poses relevant challenges to physicians who may need to adapt the type and dose of anticoagulants in a relatively frail patient population, presenting a delicate balance between the risk of thrombosis extension and bleeding complications.

After detection of recurrent VTE, it is important to establish whether the event is truly new or rather represents residual throm-

Table 2. Risk assessment models for recurrent cancer-associated thrombosis.

Model	N	Risk factors	Model performance	Limitations
Ottawa score[18]	543	• Sex • History of VTE • Lung cancer • Breast cancer (negative) • Cancer stage	AUROC: 0.7 (original) 0.5 (modified)	- Retrospective - Variable discriminations on external validation
Munoz *et al.*[23]	2,224 for model build (total cohort 16,407)	• Age • Family history • VTE type • Metastasis • Adenocarcinoma • Hemoglobin • Serum creatinine • Platelet count • Leukocyte count	AUROC: 0.66-0.69	- No external validation - Outcome of VTE recurrence was defined by Natural Language Processing
Lanting *et al.*[24]	2,245	• Age • Breast cancer (negative) • Metastasis • Anticoagulant type • DVT only as index	c-statistics: 0.63 (95% CI 0.54-0.72)	- Limited to patients included in RCTs-No external validation
Caravaggio score[25]	1,155 derivation cohort (validation cohort 3,506)	• Symptomatic VTE • Ovarian/uterine cancer • Pancreatic cancer • Metastatic cancer • Adenocarcinoma • Platinum/fluoropyrimidine based regimens	c-statistics: Derivation: 0.64 (95% CI 0.58-0.69) Validation: 0.61 (95% CI 0.56-0.65)	- Derived from RCT patients - *Post-hoc* derivation

CI, confidence interval; DVT, deep vein thrombosis; RCT, randomized controlled trial; AUROC, area under the receiver operating characteristic curve; VTE, venous thromboembolism.

bosis. Diagnosis is usually confirmed when the thrombus occurs in a new vessel or segment not involved in the initial VTE. However, uncertainty may still linger for small clots within distal vessels, especially when detected incidentally by imaging tests that are not optimally set-up for vessels' visualization. A second opinion by another radiologist, when feasible, may help to confirm the diagnosis or exclude false positive findings. In cases of recurrent thrombosis in the ipsilateral veins, it is useful to review prior images, and if these are not available, to consider further testing such as magnetic-resonance direct thrombus imaging or quantitative ultrasonography for DVTs which cannot be easily distinguished from chronic residual thrombus by standard ultrasonography.[26,27] While these imaging techniques are promising, they are not readily available and their use is currently limited to research purposes.

Once the diagnosis of recurrent VTE has been confirmed, physicians need to determine if VTE is a true breakthrough event related to anticoagulant treatment failure or the result of inadequate dosing (Figure 1). In this regard, poor patient adherence to

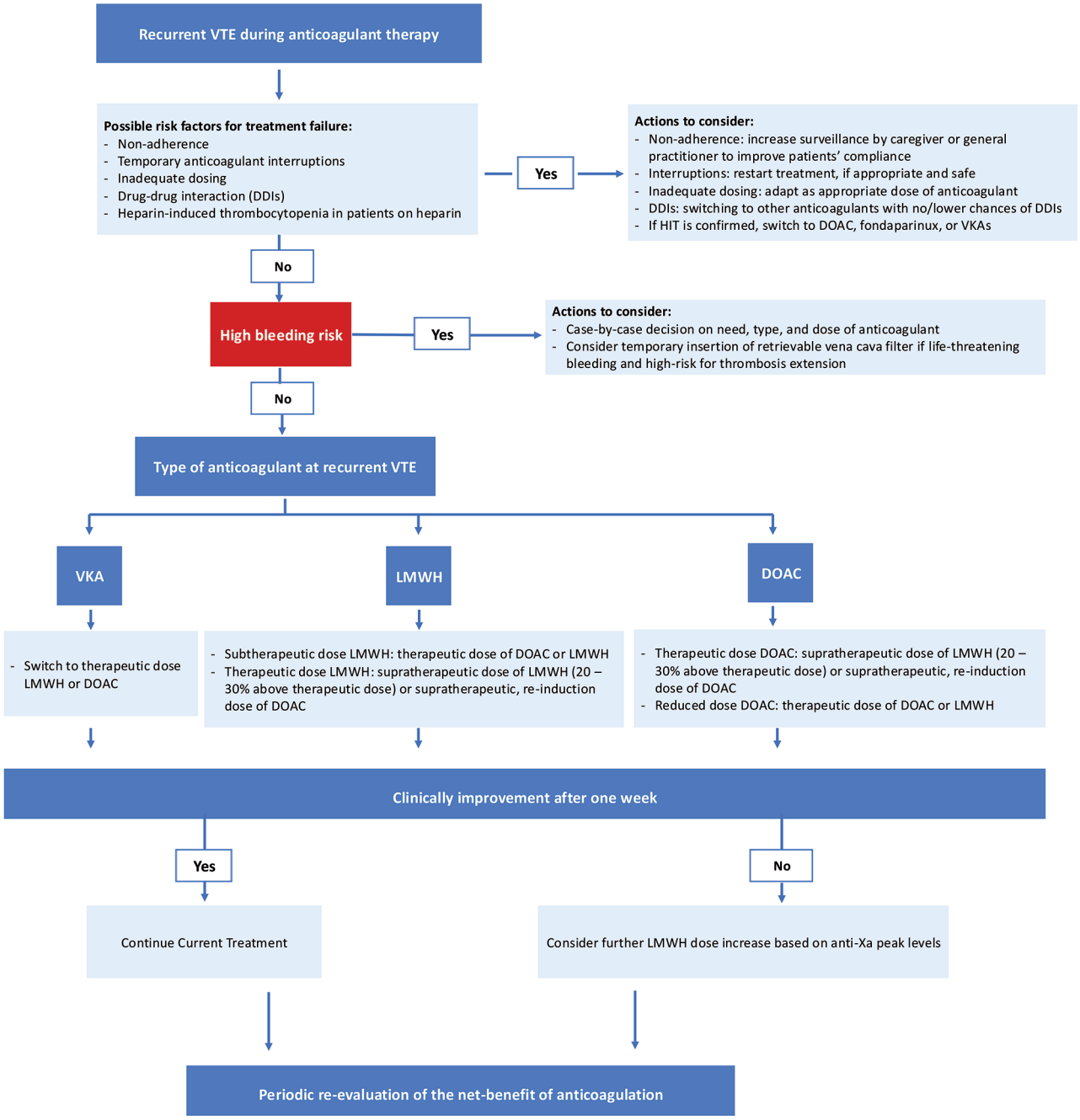

Figure 1. Schematic re-evaluation of the net-benefit of anticoagulation.

anticoagulation is common, even in the early phases of treatment, and it can represent an important risk factor for recurrent thrombosis.[28,29] Inadequate patient education about VTE risks and anticoagulation, or fear of anticoagulant-related bleeding could affect treatment adherence and persistence, leading to suboptimal anticoagulation.[30] In addition, patients with cancer frequently receive multiple concomitant medications which increase the risks of drug–drug interactions and potentially lead to interference with the efficacy and safety of anticoagulants. While these interactions should be carefully assessed, their clinical relevance and the value of monitoring anticoagulant activity remain unclear. Furthermore, temporary interruption of anticoagulation in those undergoing surgery or invasive procedures may expose patients to a higher perioperative risk of thrombosis recurrence. Lastly, heparin-induced thrombocytopenia should be excluded in patients with high clinical suspicion, such as exposure to heparin in the past 10 to 14 days or with an abrupt reduction of platelet count.

If recurrent VTE represents an actual treatment failure, physicians should cautiously consider the risks of bleeding *vs* VTE progression when deciding on adjusting anticoagulant regimen. Aspects to consider include the overall patients' prognosis, the type and stage of cancer, the presence of comorbidities, the patients' quality of life and preferences. Estimating the risk of bleeding remains challenging as multiple patient-, disease- and treatment-related factors may play a role, including history of bleeding, the presence of severe thrombocytopenia, renal or liver failure, brain lesions, and concomitant antiplatelet agents. Unfortunately, risk estimation remains empiric given the lack of validated, accurate, and reproducible assessment models.[31] In patients deemed to be at high risk of anticoagulant-related bleeding, the decision on the need, type, and dose of anticoagulant therapy should be individualized. In cases with absolute contraindications to anticoagulant therapy and a high risk for thrombosis extension and/or embolization, retrievable inferior vena cava filters represent a possible yet controversial option.[1,32] It can be associated with potential complications including filter migration or fracture with embolization, higher long-term risk of recurrent DVT, and no clear survival advantage. If a decision is made to use a retrievable filter, removal should be attempted as soon as bleeding risks wane and resumption of anticoagulation is deemed feasible.

Evidence for anticoagulant treatment of recurrent VTE

Two retrospective cohorts including a total of 125 cancer patients with recurrent cancer-associated thrombosis evaluated a similar management strategy consisting of 4-week dose escalation to supra-therapeutic LMWH followed by therapeutic doses in patients on LMWH at recurrent VTE and switch to therapeutic dose of LMWH in patients on VKAs (Table 3).[33,34] In the first cohort of 70 patients, the 3-month incidence of any bleeding and second recurrence were 4.3% and 8.6%, respectively.[33] In the other study including 55 cancer patients, the corresponding values for major bleeding and second recurrence were 5.5% and 7.3%.[34] In a larger prospective registry of 212 patients with cancer and recurrent VTE during anticoagulant treatment, only one third had dose escalation after the recurrence, whereas the remainder received highly heterogenous treatment regimens.[35] During the 3-month follow-up period, 11% of patients experienced a second recurrent VTE and 8% had major bleeding. Dose escalation seemed to be not associated with a reduced risk of recurrent VTE nor higher risk of bleeding in this cohort.

In the more recent REDUCE study, an international, multicenter, prospective, observational cohort study of 81 cancer patients with recurrent on-treatment VTE, anticoagulant therapy was left to the discretion of the treating clinician, although the use of a 4-week dose-escalation strategy was encouraged in accordance with clinical guidelines.[36] At recurrence, 55% of patients were on DOACs, 41% on therapeutic-dose LMWH, and 4% on maintenance-dose LMWH. Two-thirds (65%) of patients had a dose increase after the recurrent VTE, whereas the dose was not escalated in the remainder due to physicians' unfamiliarity, uncertainty or perceived associated-bleeding risk with the dose-escalating approach. Among the 45 patients on DOACs, 51% were switched to supratherapeutic-dose LMWH, 42% to therapeutic-dose LMWH, and 4.4% to a higher DOAC dose. After 3 months of fol-

Table 3. Studies evaluating treatment strategies for recurrent cancer-associated venous thromboembolism.

Study/Author	Design	n	Anticoagulant at the time of recurrent VTE	n (proportion of patients) receiving dose escalation	IVC filter	3-month outcomes		
						Second recurrent VTE	Bleeding	Death
Carrier *et al.*[33]	Retrospective, two centers	70	LMWH 67% VKAs 33%	15 (21%)	3 (4%)	8.6% (4.0-17.5%)	All: 4.3% (1.5-11.9%)	NR
Ihaddadene *et al.*[34]	Retrospective, single center	55	LMWH 89% VKAs 11%	18 (33%)	3 (5%)	7.3% (2.0-17.6%)	MB: 5.5% (1.1-15.1%)	25%
Schulman *et al.*[35]	Prospective, multicenter	212	LMWH 70% VKAs 27% Fondaparinux 3%	66 (31%)	5 (2%)	11.0%	MB: 8.0%	27%
REDUCE[36]	Prospective, multicenter	81	DOACs 55% LMWH 45%	53 (65%)	NR	10.0%	MB: 8.6% CRNMB: 3.7%	20%

CRNMB, clinically relevant non-major bleeding; DOACs, direct oral anticoagulants; IVC, inferior vena cava; LMWH, low molecular weight heparin; MB, major bleeding; NR, not reported; VKA, vitamin K antagonist; VTE, venous thromboembolism.

low-up, 10% developed a second recurrent VTE and 12% had clinically relevant bleeding. Patients initially receiving dose escalation had lower 3-month incidences of VTE (7.5% *vs* 14.3%) and clinically relevant bleeding (5.7% *vs* 25%) compared with patients maintained on therapeutic doses. However, the duration of dose escalation was variable, with some patients deescalating early and others continuing with escalated doses beyond the first month, precluding firm conclusions about the net-benefit of the dose-escalation strategy. While the REDUCE study extended previous observations to a contemporary cancer population receiving DOACs at recurrence in over half of the cases and dose escalation in over two thirds, the study was limited by a relatively small sample size and non-randomized study design.

Taken together, these data underscore that therapeutic options in this setting remain limited, as no RCTs and only a few largely hypothesis-generating observational studies, most of which predate the widespread use of DOACs, are available to guide treatment decisions.[1,32]

If the bleeding risk is deemed acceptable, clinical practice guidelines generally suggest supratherapeutic LMWH dosing, with dose escalation of approximately 20-30% in patients already receiving therapeutic doses, or a switch to therapeutic-dose LMWH in those receiving maintenance dosing at the time of recurrent VTE.

In patients who experience recurrence during treatment with vitamin K antagonists (VKAs), switching to a therapeutic dose of LMWH is recommended.

Suggested anticoagulant treatment for recurrent VTE

Therapeutic dose of LMWH or DOACs may be considered for patients with recurrent VTE during maintenance (or lower than maintenance) dose of LMWH or reduced dose of DOACs, including rivaroxaban 10 mg daily or apixaban 2.5 mg twice daily. Supratherapeutic doses of LMWH (i.e., therapeutic dose increased by 20-30%) for about four weeks, or re-induction doses of rivaroxaban or apixaban as approved for the frontline treatment phase of acute VTE could be considered in patients on therapeutic LMWH or DOAC at recurrence, if safety is not compromised. The optimal duration of supratherapeutic dosing with LMWH or DOACs for recurrent VTE has not been established and should be individualized, balancing the risks of thrombosis progression and bleeding. Anti-Xa peak level measurements, targeting 1.0-2.0 units/mL for once-daily and 0.8-1.0 units/mL for twice-daily LMWH dosing, may be used to tailor LMWH dosing, although this approach remains empiric and lacks validation. The strategy of resuming a DOAC and measuring circulating drug levels to guide dose adjustment has not been evaluated, and the safety and efficacy of this approach remain unclear. Apixaban has been associated with a bleeding risk comparable to that of LMWH in patients with cancer-associated VTE, whereas other factor Xa inhibitors have been linked to a higher bleeding risk, particularly in patients with gastrointestinal malignancies. However, it remains uncertain whether this safety profile extends to patients with cancer and recurrent VTE. Switching to apixaban may therefore be considered to potentially mitigate bleeding risk, although this strategy requires confirmation in dedicated studies. Switching to therapeutic dose of DOACs in patients on therapeutic LMWH at recurrence may represent an alternative which is supported by RCTs in cancer-associated VTE that showed higher efficacy of DOACs.[11] Of note, dabigatran has not been specifically evaluated for the treatment of VTE in patients with active cancer; therefore, the use of direct factor Xa inhibitors may be preferred in this population.

Cancer patients with recurrent VTE during VKAs' treatment could be switched to either LMWH or DOACs, especially when international normalized ratio values are unstable, subtherapeutic, or recurrence occurs despite values in the therapeutic range. A lower dose of anticoagulant or even treatment discontinuation could be considered in patients with poor prognosis due to the terminal cancer disease, substantial risk of bleeding outweighing risk of thrombosis progression, or recurrent VTE with a relatively low risk of progression (e.g., incidental single subsegmental PE or distal DVT).

All patients with breakthrough VTE need periodic re-evaluation to assess the net-benefit of anticoagulant treatment, especially when the regimen has been modified. Patients without clinical improvement could be considered for further LMWH dose escalation based on anti-Xa peak levels, although this approach may be hampered by the risk of bleeding. In cases with symptomatic improvement, physicians may continue with the same anticoagulant regimen or consider dose de-escalation to mitigate bleeding risk.

Conclusions

Patients with cancer-associated thrombosis remain at high risk of recurrent VTE, often despite therapeutic anticoagulation. Breakthrough events carry significant morbidity and mortality; however, robust evidence to guide management in this setting is limited, and most recommendations rely on low-quality or indirect data.

In clinical practice, suspected recurrence should first be confirmed, distinguishing new events from residual thrombosis before modifying treatment. Potentially reversible causes, such as poor adherence, drug-drug interactions, temporary treatment interruptions, or subtherapeutic dosing should be systematically assessed. Overall, a uniformed treatment approach is unlikely to be appropriate for all patients. Management decisions should be individualized, balancing thrombotic and bleeding risks while considering cancer stage, comorbidities, platelet count, organ function, prognosis, and patient preferences. LMWH dose escalation remains the most commonly suggested strategy, although supporting evidence is limited. Recurrence during DOAC therapy is an increasingly relevant challenge, and approaches such as re-induction dosing or switching agents are biologically plausible but insufficiently validated. Close clinical reassessment after any treatment modification is essential to ensure continued net clinical benefit.

Future research priorities

Well-designed prospective studies and RCTs are urgently needed to define optimal management strategies for recurrent VTE during anticoagulation in cancer-associated thrombosis, particularly in patients receiving DOACs. Comparative evaluations of dose escalation, switching strategies, and re-induction regimens should assess both thrombotic and bleeding outcomes to deter-

mine net clinical benefit. Improved risk stratification tools integrating clinical variables, and potentially biomarkers, require development and external validation. Future research should also address high-risk cancer subgroups, patient-centered outcomes, and the real-world implementation of management strategies.

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