

Implications of the API-CAT Trial for Extended Secondary Prophylaxis of Cancer-associated Venous Thromboembolism: Guidance from an Expert Panel

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Abstract

Venous thromboembolism (VTE) is an increasingly frequent complication of solid tumors and hematological malignancies, significantly contributing to morbidity and mortality. In patients with acute cancer-associated VTE, therapeutic anticoagulation with direct oral factor Xa inhibitors (DXIs) or low-molecular-weight heparin (LMWH) for 3 to 6 months is recommended by clinical practice guidelines based on randomized controlled trials. Although extended secondary VTE prophylaxis should be considered in patients with persisting active cancer, the type, intensity, and duration of continued anticoagulation have not been rigorously studied until recently. In non-cancer patients, low-dose DXIs (apixaban 2.5 mg BID or rivaroxaban 10 mg OD) are the preferred options to prevent recurrent VTE beyond the first 6 months of treatment. The recently published API-CAT trial compared low-dose with full-dose apixaban for extended secondary VTE prophylaxis in 1,766 patients with active cancer. Over a 12-month period, low-dose apixaban was associated with similar efficacy, but significantly improved safety compared with full-dose apixaban, with cumulative incidence rates of recurrent VTE and major or clinically relevant non-major bleeding of 2.1% versus 2.8% (adjusted subhazard ratio [sHR]: 0.76; 95% confidence interval [CI]: 0.41–1.41; $p < 0.001$ for noninferiority) and 12.1% versus 15.6% (adjusted sHR: 0.75; 95% CI: 0.58–0.97; $p = 0.03$ for superiority), respectively. Based on these findings, extended secondary VTE prophylaxis with low-dose DXIs, preferably apixaban 2.5 mg BID, is proposed for most patients with persisting active cancer. To facilitate informed decision-making in clinical practice, we provide an expert consensus on criteria that either justify cessation of anticoagulation or require continued full-dose anticoagulation.

Keywords

- ▶ cancer
- ▶ thromboembolism
- ▶ anticoagulation
- ▶ API-CAT
- ▶ VTE

received

May 19, 2025

accepted after revision

June 30, 2025

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Georg Thieme Verlag KG,

Oswald-Hesse-Straße 50,

70469 Stuttgart, Germany

DOI [https://doi.org/](https://doi.org/10.1055/a-2645-4927)

10.1055/a-2645-4927.

ISSN 0720-9355.

Introduction

Thrombotic complications, predominantly venous thromboembolism (VTE), are a major clinical concern for patients suffering from active malignancies, adding substantially to morbidity and mortality.¹ As a result, thrombosis ranks as the second leading cause of death in cancer patients.² Commonly termed as cancer-associated thromboembolism (CAT), it may present during the course of the disease, or it may lead to the detection of hitherto occult cancer. Generally, cancer patients have a significantly increased risk of developing VTE, approximately up to 9 times higher than in healthy individuals and up to 30% for some tumor entities.^{3–5} On this account, it comes without surprise that current estimations make CAT responsible for 20 to 30% of all diagnosed VTEs.^{5–7} The mechanisms contributing to CAT are multifactorial. Relevant factors include thrombogenic cellular and molecular pathways associated with distinct tumor entities, immobility resulting from disease progression or cancer surgery, treatment-related effects, such as endothelial damage induced by inflammation, radiotherapy, or anticancer drugs, central venous catheters and ports, and lastly, preexisting comorbidities.⁸ It becomes apparent that proper therapy of acute CAT and secondary prophylaxis are crucial in the management of cancer patients to reduce overall morbidity and mortality.

In the early 2000s, pivotal studies like the CLOT trial (dalteparin versus a coumarin) have established the safe and efficacious use of low-molecular-weight heparins (LMWHs) for the management of CAT, being superior to previously used vitamin K antagonists (VKAs).^{9,10} Since then, the direct oral anticoagulants (DOACs), mostly factor Xa (FXa) inhibitors, have emerged for the treatment and secondary prophylaxis of VTE in the general population and have largely ousted VKAs in the management of VTE not related to cancer. However, dedicated randomized controlled trials (RCTs) later have also investigated their safety and efficacy in the setting of CAT, including the HOKUSAI VTE Cancer (edoxaban), SELECT-D (rivaroxaban), and CARAVAGGIO (apixaban) studies.^{11–13} Pooled analyses of these RCTs revealed superior efficacy of DOACs over dalteparin. The risk of major or clinically relevant non-major (CRNM) bleeding, however, was higher during treatment with DOACs, although findings differed between individual substances: patients with gastrointestinal (GI) or genitourinary tumors experienced increased bleeding during DOAC treatment in the HOKUSAI VTE Cancer study (edoxaban) and in the SELECT-D study (rivaroxaban), while this was not observed in the CARAVAGGIO study (apixaban).

It is important to note that the primary focus of these RCTs was the treatment phase, not specifically investigating extended secondary CAT prophylaxis.

Several clinical guidelines and practical recommendations for the management of CAT have been published, generally acknowledging the recent FXa inhibitor CAT trials and adding them as a primary option for most patients.^{14,15} While in non-cancer patients, low-dose FXa inhibitors, i.e., apixaban or rivaroxaban, are the preferred option to prevent

recurrent VTE beyond 6 months of treatment, patients with active cancer may require full-dose anticoagulation for extended secondary prophylaxis due to the high risk of VTE recurrence.^{15,16} As part of the treatment decision process, it should be considered that cancer patients generally have an increased bleeding risk, which might affect the risk-benefit ratio of extended secondary prophylaxis when compared with the non-cancer population.¹⁷ It is important to note that current guideline recommendations regarding extended secondary CAT prophylaxis are largely based on expert testimonies and merely represent extrapolations from FXa inhibitor trials on CAT treatment. The EVE trial, which was published in 2024, was the first properly designed RCT investigating extended anticoagulation with apixaban for secondary prophylaxis in patients with cancer-associated VTE and has only recently been complemented by findings from API-CAT.^{18,19} Considering the availability of important new evidence from dedicated RCTs, updated guidance for the treatment and secondary prophylaxis of CAT seems warranted.

FXa Inhibitors for the Treatment of VTE in Cancer

As outlined earlier, HOKUSAI VTE Cancer (edoxaban), SELECT-D (rivaroxaban), and CARAVAGGIO (apixaban) were dedicated RCTs that paved the way for adoption of FXa inhibitors into CAT guidelines (–Table 1). Apixaban and edoxaban were evaluated in large phase III trials, rivaroxaban in a smaller sized phase III pilot study. All studies investigated treatment for at least 6 months compared with dalteparin, with the primary outcome of either recurrent VTE or the composite of recurrent VTE and major bleeding. Two types of cancer patients were eligible for participation in HOKUSAI VTE Cancer and CARAVAGGIO: patients who were diagnosed with cancer and/or treated for cancer within 6 months prior to enrollment (i.e., patients with active cancer, which accounted for >97% of study subjects in both trials) and patients who were diagnosed with cancer up to 2 years prior to enrollment (i.e., patients with a history of cancer). SELECT-D only allowed cancer diagnosis and/or treatment within 6 months prior to enrollment.^{12,13,20} All studies showed noninferior efficacy of FXa inhibitors regarding VTE recurrence, whereas the risk for major bleeding was heterogenous. Both edoxaban and rivaroxaban were associated with more major or clinically relevant non-major bleeding events compared with dalteparin, predominantly GI hemorrhages, which were highly frequent in patients with GI tumors, whereas apixaban had comparable safety to dalteparin.^{11,13,21–23}

While the CARAVAGGIO trial had a defined treatment phase of 6 months, followed by a 1-month follow-up period, in the HOKUSAI VTE Cancer study all patients were treated for at least 6 months and up to 12 months, with the duration beyond 6 months being determined by the treating physician. About 38% of patients in the edoxaban group and approximately 29% of patients in the dalteparin group completed treatment for 12 months or until study closure. A post-hoc analysis of the HOKUSAI VTE Cancer study focusing on

Table 1 Comparison of DOAC CAT trials^{11,13,21}

	CARAVAGGIO (apixaban)	HOKUSAI VTE Cancer (edoxaban)	SELECT-D (rivaroxaban)
Design	Randomized, open label, blinded end-point evaluation		
	Phase III		Phase III pilot study
	N = 1,155	N = 1,046	N = 406
Treatment	10 mg BID for 7 days, followed by 5 mg BID versus dalteparin	60 mg OD (after ≥5 days LMWH) versus dalteparin	15 mg BID for 3 weeks, followed by 20 mg OD versus dalteparin
Duration	6 months	6–12 months	6 months
Primary outcome	Recurrent VTE	Composite of recurrent VTE or major bleeding	Recurrent VTE
Cancer definition	Active cancer ^a (97.3%) History of cancer ^b (2.7%)	Active cancer ^a (97.9%) History of cancer ^b (2.1%)	Active cancer ^a (100%)
Safety and Efficacy Outcomes			
VTE recurrence	HR 0.63 (95% CI 0.37–1.07)	HR 0.71 (95% CI 0.48–1.06)	HR 0.43 (95% CI 0.19–0.99)
Major bleeding	HR 0.82 (95% CI 0.40–1.69)	HR 1.77 (95% CI 1.02–3.04)	HR 1.83 (95% CI 0.68–4.96)
Major or CRNM bleeding	HR 1.16 (95% CI 0.77–1.75)	HR 1.40 (95% CI 1.03–1.89)	HR 2.77 (95% CI 1.51–5.06)

Abbreviations: BID, twice daily; CI, confidence interval; CRNM, clinically relevant non-major; CAT, cancer-associated thromboembolism; DOAC, direct oral anticoagulant; HR, hazard ratio; LMWH, low-molecular-weight heparin; OD, once daily; VTE, venous thromboembolism.

Notes: ^aActive cancer is defined as diagnosis or treatment within 6 months prior to inclusion.

^bHistory of cancer is defined as diagnosis up to 2 years prior to inclusion.

the period from 6 to 12 months showed relatively low rates of VTE recurrence and major bleeding with edoxaban or dalteparin.²⁴ The SELECT-D trial featured a treatment phase of 6 months. Patients with cancer-associated VTE who had residual deep vein thrombosis (DVT) after 6 months of anticoagulation or an index pulmonary embolism (PE) were further randomized to receive either rivaroxaban or placebo for an additional 6 months.²⁵ Although the study was underpowered due to early termination, extended rivaroxaban treatment showed a lower recurrence rate of VTE (4% versus 14%) with a slightly increased risk of bleeding.

Where Does Current CAT Guidance Place FXa Inhibitors?

To review where FXa inhibitors have been placed in comparison to LMWHs following release of their respective trial results, we evaluated nine guidance documents published between 2019 and 2024, which are recognized and utilized in Germany (→ **Supplementary Table S1**). FXa inhibitors are either preferred over LMWHs or they receive equally strong recommendations as LMWHs. The rationale for the broad implementation of FXa inhibitors has been based on their comparable efficacy, good safety profile, and ease of administration when compared with LMWH, which requires subcutaneous injections and, occasionally, monitoring of plasma anti-FXa activity levels, e.g., in case of impaired renal function. In summary, FXa inhibitors are generally preferred in patients with CAT, but LMWHs still remain the

anticoagulants of choice in certain clinical scenarios characterized by an exceedingly high risk of bleeding, uncertain drug absorption, or potentially relevant drug–drug interactions (→ **Fig. 1**). Regarding treatment duration of CAT, anticoagulation for at least 3 to 6 months is usually recommended.

Extended Secondary CAT Prophylaxis—Status Quo

CAT guidelines agree on potential extension of anticoagulation beyond 6 months if cancer remains active, therapy is ongoing, or other individual factors call for continued secondary prophylaxis. Both FXa inhibitors and LMWHs, usually without dose adjustment, are reasonable options in this indication (→ **Supplementary Table S1**). Nevertheless, so far, no dedicated RCTs with adequate power have specifically investigated the efficacy and safety of FXa inhibitors in extended secondary CAT prophylaxis. Continued anticoagulation with certain FXa inhibitors beyond the treatment phase is a well-established, safe, and efficacious strategy in patients with unprovoked VTE or in patients with persisting risk factors other than active cancer or severe thrombophilia, as evidenced by the AMPLIFY-EXT (apixaban) and EINSTEIN CHOICE/EXT (rivaroxaban) trials.^{26–28} However, until recently, the available literature concerning extended secondary VTE prophylaxis in cancer patients has not allowed for informed, high-grade, evidence-based recommendations. Therefore, available guidance is largely based

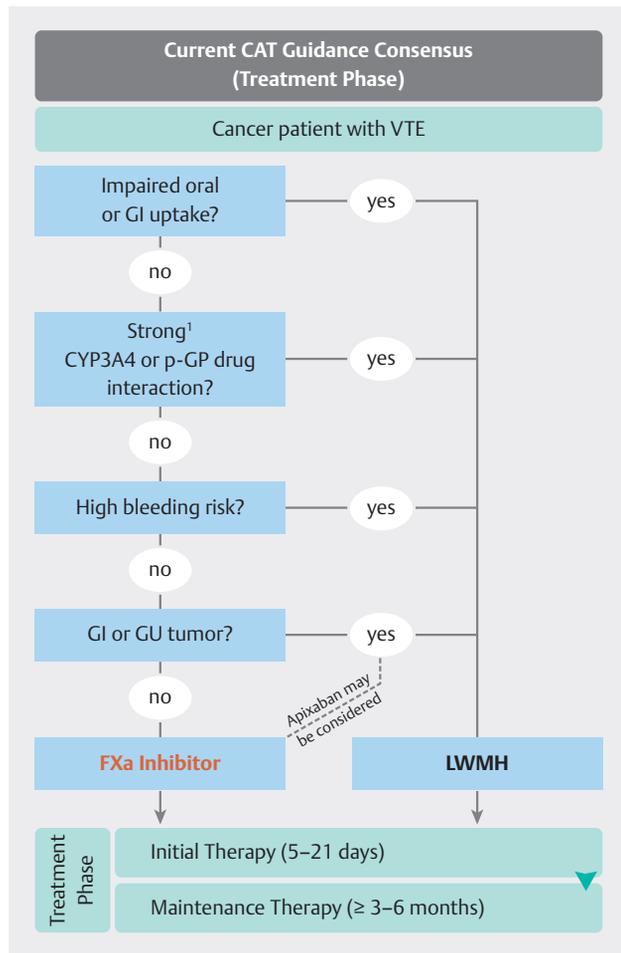


Fig. 1 Overview of cancer-associated thromboembolism (CAT) guidance consensus. ¹Weak to moderate interactions allow for direct oral anticoagulant (DOAC) use but caution is warranted. ²For example, thrombocytopenia or other coagulopathies. ³Apixaban presents with comparable safety to low-molecular-weight heparins (LMWHs) and might be considered. Regularly reassess patient's risk factors. FXa, factor Xa; GI, gastrointestinal; GU, genitourinary; VTE, venous thromboembolism.

on extrapolation of other FXa inhibitor trials and expert testimony. The relevance of the subject is further highlighted by a survey from the Netherlands, evaluating the actual clinical practice of treatment and secondary prevention of CAT.²⁹ In fact, extended secondary prophylaxis beyond 3 to 6 months of initial treatment was reported for 96% of patients, with 75% remaining on the initially chosen anticoagulant and 21% either switching the anticoagulant or adjusting its dose.²⁹ These findings support the notion that almost all CAT patients receive prolonged anticoagulation based on guidance with low-level evidence and lacking strong RCT-based validation. The absence of definitive information leads to uncertainty and inconsistent approaches among clinicians of various specialties regarding the choice and dosage of anticoagulants. Dedicated RCTs are needed to allow clinical guidelines to adopt high-grade evidence for definitive and data-driven treatment decisions.

Predictors for CAT Recurrence

Although for the prediction of cancer-associated VTE various risk assessment models like the Khorana score or the Vienna CATScore are available to inform clinical decision-making regarding primary thromboprophylaxis, there is no validated tool available that reliably predicts the risk of recurrent VTE beyond 6 months of anticoagulation in patients with established CAT.^{30–35} Thus, there is a clear unmet need to precisely define patient groups at high risk for VTE recurrence beyond the treatment phase. A summary of published risk factors predicting recurrent VTE that were identified in either univariate or multivariate analyses is found in **–Supplementary Table S2**. Cancer-related predictors include tumor entity as well as disease progression and active anticancer therapy. This is well in line with currently available guidelines pointing out these predictors as indicators for extended secondary VTE prophylaxis (**–Supplementary Table S1**). Yet, patient-related factors have also been identified that, so far, have not been incorporated into currently available guidelines. These factors include: (1) the type of thromboembolic index event (mostly DVT), (2) the presence, amount, and localization of residual thrombosis, (3) obesity, (4) renal impairment, (5) male sex, and (6) (younger) age. Regarding clinical trial evidence, residual DVT after completion of 6 months of anticoagulation and PE as an index event may indicate a particularly high risk of VTE recurrence.^{13,36} It should be considered to additionally incorporate the most relevant of these patient-related risk factors in future guidance statements on the necessity of anticoagulation beyond 6 months after CAT.

Recent Evidence on Extended Secondary CAT Prophylaxis—The API-CAT Trial

After establishing relevant predictors for recurrent VTE in patients with CAT, there is one more decision left to make—which anticoagulant and which dose should be used beyond the first 6 months of treatment? So far, there have been no studies available for an evidence-guided decision-making, as trials such as TiCAT, DALTECAN, HOKUSAI VTE Cancer, or SELECT-D were either not randomized or not adequately powered.^{12,13,37,38} The EVE trial was the first dedicated RCT investigating the safety of a DOAC, low-dose apixaban (2.5 mg twice daily [BID]) compared with full-dose apixaban (5 mg BID), in the setting of extended secondary VTE prophylaxis in 360 patients with active cancer, confirmed VTE, 6 to 12 months of prior anticoagulant therapy, and a life expectancy of equal or longer than 6 months.³⁹ Results indicated no difference in the rate of clinically relevant bleeding, a composite of major and clinically relevant non-major (CRNM) bleeding, between low- and full-dose apixaban (8.9% versus 12.2%; hazard ratio [HR]: 0.72; 95% confidence interval [CI]: 0.38 to 1.37; $p = 0.39$), which was also true for the number of recurrent thromboembolic events (5.0% versus 5.0%; HR: 1.00; 95% CI: 0.40 to 2.53; $p = 1.00$).¹⁹ Although absolute bleeding rates were higher in the EVE trial, the comparability of low- and full-dose apixaban matches

previous findings from the AMPLIFY-EXT trial in primarily non-cancer patients (major or CRNM bleeding: 3.2% versus 4.3%; HR: 0.74; 95% CI: 0.46 to 1.22). It has to be mentioned, however, that the EVE trial was primarily powered for safety and had the aim to demonstrate superiority of the lower dose over the full dose of apixaban, which was not reached. Based on these findings, adoption of the lower apixaban dose for extended secondary CAT prophylaxis cannot be strongly advised. The recently published API-CAT trial closes this knowledge gap toward efficacy. Here, 1,766 CAT patients who had initially experienced either a symptomatic or incidental PE or symptomatic or incidental iliac, inferior vena cava, or proximal lower-limb DVT and completed 6 months of anticoagulation were randomized to receive either low- or full-dose apixaban for an additional 12 months. The API-CAT trial had a primary composite efficacy endpoint (testing for noninferiority) of adjudicated fatal or nonfatal recurrent VTE, defined as a new symptomatic (distal or proximal DVT of the leg, PE, upper-limb or central-venous catheter-related thrombosis) or incidental event (proximal DVT or PE).^{18,40} In the final analysis, low-dose apixaban was noninferior to full-dose apixaban regarding VTE recurrence (2.1% versus 2.8%; adjusted sHR: 0.76; 95% CI: 0.41 to 1.41; $p=0.001$ for noninferiority).⁴⁰ With regards to safety, analysis of the key secondary outcome of clinically relevant bleeding (defined as major or CRNM bleeding) showed superiority of low-dose over full-dose apixaban (12.1% versus 15.6%; adjusted sHR: 0.75; 95% CI: 0.58 to 0.97; $p=0.03$ for superiority). When focusing only on major bleedings, 24 patients in the low-dose group and 37 patients in the full-dose group experienced an event (2.9% versus 4.3%; adjusted sHR: 0.66; 95% CI: 0.40 to 1.10), while fatal bleedings were rare, with two events per group. Major GI bleedings were reported in 37 patients in total, including upper GI bleeding in 6 patients in the low-dose group and in 13 patients in the full-dose group, and lower GI bleeding in 7 and 13 patients, respectively. Two patients in each group experienced both upper and lower GI bleeding. CRNM bleedings occurred in 84 patients in the low-dose group and in 107 patients in the full-dose group (10.0% versus 12.3%; adjusted sHR: 0.79; 95% CI: 0.59 to 1.05), with the majority located in the urogenital or GI system or presenting as nasal hemorrhage. Mortality rate, defined as death from any cause, was 17.7% for low-dose apixaban and 19.6% for full-dose apixaban. More than 80% of deaths were related to the underlying cancer. Other secondary outcomes, i.e., regarding incidence of major VTE, showed no difference between low- and full-dose apixaban.

Discussion and Recommendations

CAT patients with persisting active malignancies or ongoing anticancer therapy are at high risk for VTE recurrence. Although current guidelines unanimously advocate extended secondary prophylaxis in these individuals, recommendations are not consistent regarding the type and, specifically, the dosing of anticoagulants. The decision on which patients benefit from extended secondary prophylaxis,

weighing the risks for bleeding and recurrence as well as the dosing strategy in case of FXa inhibitors, has so far been largely based on expert testimony and extrapolations from other CAT trials, rather than on definitive studies specifically addressing these questions. Current consensus is that CAT patients with persisting active malignancies need full-dose anticoagulation for extended secondary prophylaxis to address the high risk of VTE recurrence. So far, no evidence has been available to support the use of low-dose anticoagulation with adequate efficacy in the setting of extended secondary CAT prophylaxis. However, in the setting of primary CAT prophylaxis, low-dose apixaban and rivaroxaban have been the subject of interest in the AVERT and CASSINI trials, respectively, investigating their efficacy and safety for thromboprophylaxis in cancer outpatients with a Khorana score of ≥ 2 and, thus, at high risk of VTE.^{41,42} Here, lack of efficacy in the case of rivaroxaban and increased bleeding risk in the case of apixaban (as compared with placebo) led to LWMH remaining the preferred option in most cases. It is noteworthy, however, that a post-hoc analysis of the AVERT trial demonstrated a favorable safety and efficacy profile for low-dose apixaban in the subgroup of patients with GI cancers, including those with pancreatic tumors.⁴³ These findings suggested that in the case of primary VTE prophylaxis, low doses of apixaban were sufficient to prevent thromboembolic events even in highly thrombogenic GI tumors. Furthermore, in a prespecified supportive analysis of the CASSINI trial, assessing the more conventional period during the intervention (first receipt of trial agent to last dose plus 2 days), an absolute difference of 4 percentage points in favor of rivaroxaban (2.6%) over placebo (6.4%) was found with regard to the primary composite endpoint of VTE and VTE-related death (HR: 0.40; 95% CI: 0.20 to 0.80).⁴² These results sparked the idea that low-dose DOACs could also be sufficiently efficacious in the setting of extended secondary CAT prophylaxis. In the following, the EVE trial focused on low- versus full-dose apixaban in the setting of extended secondary prophylaxis in CAT patients who had already completed at least 6 months of treatment.¹⁹ With a primary safety endpoint, low-dose apixaban showed comparable bleeding rates to full-dose apixaban, though not reaching the study aim of superiority. VTE recurrence rates were also similar between the two doses; however, the study was not properly powered for efficacy. On this account, the RENOVE trial was the first RCT comparing low-dose versus full-dose FXa inhibitors (apixaban or rivaroxaban) for extended secondary prophylaxis in patients with VTE at high risk of recurrence after an initial uninterrupted treatment for 6 to 24 months with a primary efficacy endpoint.⁴⁴ Here, the low-dose regimens did not reach significance for noninferiority regarding efficacy, yet the overall low recurrence rates paired with a lower bleeding risk were still judged as supportive for a potential use of low-dose FXa inhibitors in the extended phase of anticoagulation. A question that remained unanswered in this study was whether there were substance-specific differences with regards to efficacy and safety. In parallel, the aforementioned API-CAT trial set out to investigate whether low-dose

apixaban was noninferior to full-dose apixaban regarding efficacy in preventing recurrent VTE within a similar, yet significantly larger, patient cohort who predominantly suffered from primary breast, colorectal, gynecological, lung, or prostate cancers.¹⁸ The recently published results could prove the noninferiority regarding efficacy and a superiority regarding safety (clinically relevant bleeding) for the low versus the full dose.⁴⁰ These findings allow physicians for the first time to make an informed treatment decision toward choice of substance and dosage for extended anticoagulation with confidence based on reliable data. The value of the recent data is underlined in the study by Kaptein et al who surveyed treatment decision for anticoagulation in CAT patients.²⁹ They highlighted that while participating physicians widely agreed on extended anticoagulation for almost all patients, the drug choice and dosage varied and seemed to be partially influenced by physician specialty. This might be the result of previously missing data that left considerable therapeutic discretion even when referring to relevant guidelines. It is unclear whether findings from the API-CAT trial on apixaban can be extrapolated to other FXa inhibitors, because strong evidence for the efficacy and safety of low-dose edoxaban and rivaroxaban in extended secondary prophylaxis of cancer-associated VTE is lacking. Although low-dose FXa inhibitors should be generally recommended in this setting, apixaban is preferred over edoxaban and rivaroxaban based on the underlying trial evidence. Recommendations on (temporary) use of LMWH in cases of hemorrhagic diathesis, thrombocytopenia with platelets $\leq 50/nL$, disturbed oral drug uptake or absorption (e.g., nausea, bowel resection), and drug-drug interactions with FXa inhibitors remain unaffected. However, it is imperative that treatment deci-

sions should be well balanced, considering all relevant (patient-related) factors as outlined by the proposed algorithm depicted in **Fig. 2**. It should be mentioned that patients investigated in the API-CAT trial seem to represent a population with only intermediate VTE recurrence risk based on the reported low overall VTE recurrence rates. In fact, inclusion criteria ruled out enrollment of patients who previously had recurrent VTE during anticoagulation and also patients with a low likelihood of survival beyond 12 months. Thus, patients suffering from more aggressive types of cancer and those already showing progressive disease were likely underrepresented. On this account, recommendations derived from API-CAT regarding low-dose FXa inhibitors for extended secondary VTE prophylaxis should primarily apply to patients matching the characteristics of the trial population with intermediate risk for VTE recurrence. **Table 2** provides an author consensus on factors favoring the cessation or continuation of anticoagulation with either low- or full-dose FXa inhibitors. A decision to stop anticoagulation should be based on patient's preference and a low risk of VTE recurrence. The latter likely accounts for patients who have undergone radical tumor resection and/or concluded systemic anticancer therapy with no remaining malignancy, who have no residual thrombotic burden and no evidence of chronic thromboembolic pulmonary hypertension (CTEPH), and who have no other underlying condition calling for anticoagulation in line with the AWMF traffic light scheme.¹⁶ Continued anticoagulation with low-dose FXa inhibitors, preferably apixaban, is recommended in patients with an intermediate risk of VTE recurrence. This may include subjects with persistently active (i.e., non-cured), but well-controlled, stable cancer (especially in

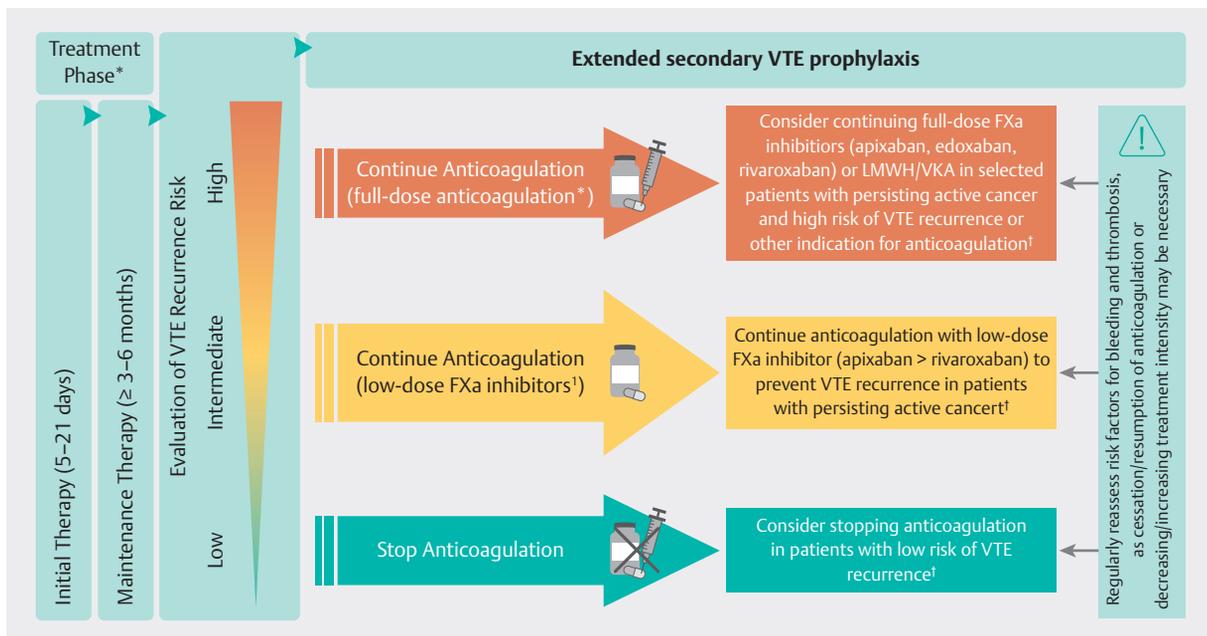


Fig. 2 Decision flowchart toward extended secondary venous thromboembolism (VTE) prophylaxis in patients with cancer. *Refer to **Fig. 1** for details on this phase. [†]Refer to **Table 2** for details. [‡]Always consider low-molecular-weight heparin (LMWH) or vitamin K antagonists (VKAs) where factor Xa (FXa) inhibitors are not tolerated/contraindicated. Always consider non-cancer-related indications for anticoagulation before stopping.

Table 2 Factors guiding decision for extended secondary VTE prophylaxis

Factors favoring stopping of anticoagulation*	Factors favoring low-dose anticoagulation for extended secondary VTE prophylaxis*	Factors favoring full-dose anticoagulation for extended secondary VTE prophylaxis*
Completed anticancer therapy with no evidence of remaining tumor, e.g., status post (potentially) curative tumor resection and adjuvant chemotherapy	Well-managed, stable cancer, especially tumor entities with low thrombogenicity, ^a i.e., esophageal, renal, cervical, bladder, uterine, testicular, breast, prostate, melanoma	Rapidly progressing cancer, especially tumor entities with high thrombogenicity, ^b i.e., pancreatic, brain, ovarian, gastric, multiple myeloma, lung, lymphoma, colorectal
No relevant residual thrombotic burden after 6 months of anticoagulation	Incidental index VTE with low thrombotic burden, e.g., (sub)segmental PE without accompanying DVT	Highly symptomatic index VTE with large thrombotic burden, e.g., V. cava superior thrombosis, and/or relevant residual thrombotic burden after 6 months of anticoagulation
No other factors calling for continued anticoagulation according to AWMF traffic light scheme	No other factors calling for continued full-dose anticoagulation according to AWMF traffic light scheme	Other factors calling for full-dose anticoagulation according to AWMF traffic light scheme, e.g., antiphospholipid syndrome or other severe thrombophilia
No CTEPH	High bleeding risk or prior bleeding during full-dose anticoagulation	Transitory intensification of (systemic) anticancer therapy
ECOG performance status ≤ 2		ECOG performance status >2 with low bleeding risk
	Port/CVC-associated DVT	Malignancy-related compression syndromes

Abbreviations: AWMF, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften; CTEPH, chronic thromboembolic pulmonary hypertension; CVC, central venous catheter; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; VTE, venous thromboembolism.

Notes: ^aDefined as VTE rate $<4\%$ according to Betts et al.⁴⁵

^bDefined as VTE rate $\geq 4\%$ according to Betts et al.⁴⁵

*No other indications are present that require a specific type and intensity of anticoagulation, e.g., atrial fibrillation, mechanical heart valves

the case of tumor entities with low thrombogenic potential as outlined in **Table 2**), port-a-cath- or central-venous catheter-associated DVT, bleeding during full-dose anticoagulation, and European Cooperative Oncology Group (ECOG) performance status of ≤ 2 . Incidental VTE with low thrombotic burden, e.g., (sub)segmental PE, is also generally perceived to be associated with an intermediate risk of recurrence. A high risk of VTE recurrence is expected in patients with rapidly progressing cancer (especially in the case of tumor entities with high thrombogenic potential as outlined in **Table 2**), transitory intensification of systemic anticancer therapy, highly symptomatic VTE with large thrombotic burden, malignancy-related compression syndromes, and ECOG performance status >2 with low bleeding risk. It is advised to consult the AWMF traffic light scheme for other factors that call for continued full-dose FXa inhibitors or alternative anticoagulation schemes (e.g., antiphospholipid syndrome or other severe thrombophilia).¹⁶ Patients might fulfill criteria from multiple risk categories. In these cases, it is necessary to weigh the overall combined risk at regular intervals. LMWH or VKA should be considered in cases where FXa inhibitors are not tolerated or contraindicated (**Fig. 1**). It is strongly suggested that the final decision for or against extended anticoagulation is made in consultation with the patient and all treating physicians, and is frequently reassessed and, where needed, revised.

In conclusion, the recently published API-CAT trial allows for the first time evidence-based decision-making regarding the use of low-dose FXa inhibitors for extended secondary VTE prophylaxis in cancer patients. In addition, we provide an author consensus among a range of clinical experts practicing in general and specialty care settings toward the cessation or continuation of anticoagulation in CAT patients after the treatment phase, with a special emphasis on dosing strategies. Based on this, upcoming revisions of relevant CAT guidelines should be strongly encouraged to incorporate the API-CAT results in a timely manner to support clinical decision-making and ensure improvement of treatment pathways.

Conflicts of Interest

Parts of the discussion presented in this manuscript are based on consensus views developed during an advisory board meeting that was financially sponsored by the alliance of Bristol Myers Squibb and Pfizer. The authors participated in the advisory board in their individual capacities and were compensated for their involvement. There was no financial or editorial support for the writing of the manuscript. Although the content reflects the authors' independent opinions and professional judgment, the potential influence of the BMS/Pfizer support in initiation of this project is acknowledged. F.L. has

received personal fees for lectures or consultancy from Bayer, Bristol-Myers Squibb, Daiichi Sankyo, LEO Pharma, Pfizer, Sanofi, and Viartis. C.H. has received personal fees for lectures or consultancy from Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, and LEO Pharma. C.P. has received personal fees for lectures or consultancy from Bristol-Myers Squibb, Pfizer, and LEO Pharma. K.M. has received personal fees for lectures or consultancy from Bayer, Bristol-Myers Squibb, LEO Pharma, Pfizer, and Viartis. K.M.K. has received personal fees for consultancy from Pfizer, BeiGene, and Johnson & Johnson and travel support from AOP Health. S.M. has received personal fees for lectures or consultancy from Bayer, Biotest, Pfizer, and Swedish Orphan Biovitrium GmbH. R.B. has received personal fees for lectures or consultancy from Bayer, Bristol Myers Squibb, LEO Pharma, Pfizer, and VIATRIS.

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