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# **Risk assessment for recurrent venous thromboembolism in patients with cancer**

**Cornelia Englisch<sup>1</sup>, Florian Moik<sup>1</sup>, Cihan Ay<sup>1</sup>**

<sup>1</sup>Clinical Division of Haematology and Haemostaseology, Department of Medicine I, Comprehensive  
Cancer Center Vienna, Medical University of Vienna; Vienna, Austria

**Correspondence:** Cihan Ay. MD

Clinical Division of Haematology and Haemostaseology

Department of Medicine I, Medical University of Vienna

Waehringer Guertel 18-20, A-1090 Vienna, Austria

Phone number: +43 1 40400 44100

Fax number: +43 1 40400 40300

cihan.ay@meduniwien.ac.at

## Abstract

Cancer patients are at high risk for first and recurrent venous thromboembolism (VTE). While various risk factors for a first cancer-associated VTE event have been identified, information on risk factors for recurrent VTE is limited or inconsistent. Therefore, risk assessment for VTE recurrence in cancer patients is challenging at the moment.

Certain patient- and tumor-related factors such as presence of metastasis and high VTE risk tumor types, such as pancreas and lung cancer, have been associated with an increased risk of recurrent VTE in patients with cancer. Previously, a risk assessment model, the Ottawa Score, was established to aid in the clinical decision-making regarding duration of anticoagulant therapy; however, its discriminative capacity could not be validated and therefore it is not implemented in clinical practice. There is an urgent call for meeting this medical need and providing tools for improved risk assessment and stratification for recurrent VTE in patients with cancer.

In this review, we provide an overview of clinical as well as laboratory markers that influence the recurrence risk of cancer-associated VTE and critically appraise existing risk stratification tools and approaches of integrating risk assessment in clinical decision making.

**Key Words:** Venous Thromboembolism, Cancer, Recurrence, Risk, Anticoagulation

## Introduction

Venous thromboembolism (VTE) is a frequent complication in patients with cancer. Contemporary risk estimates indicate that a diagnosis of cancer increases the risk of VTE by the factor of 9 compared to individuals without cancer.(1) VTE events adversely impact the clinical course of disease in cancer patients by contributing to morbidity, mortality, health-care-costs, and adding to the psychological burden of patients as reviewed in (2)Therefore, optimizing therapeutic approaches by personalizing primary prevention of cancer-associated VTE and secondary prevention of recurrent VTE is an unmet medical need, as the risk-benefit ratio of primary and secondary thromboprophylaxis in cancer patients needs to be carefully balanced based on the concurrent high risk of bleeding events. Various risk factors were identified for a first diagnosis of VTE in cancer patients.(3) In contrast, fewer data exist on risk factors for recurrent VTE events. In the present narrative review, we provide an overview of currently available evidence on risk factors, biomarkers, and prediction models for the assessment of risk of VTE recurrence in patients with cancer.

### **Risk of a first VTE in patients with cancer and duration of anticoagulation**

Characterizing the risk of recurrent VTE in cancer patients requires the consideration and knowledge of underlying factors that influence risk of first VTE event. Risk of VTE in cancer patients is highly heterogeneous and strongly depends on treatment-, tumor-and patient-related prothrombotic risk factors.(3) Among those, the underlying tumor type is among the most important factors that influence VTE risk, with the highest rates of up to 20% observed in patients with pancreatic and gastric cancer, and a low risk in patients with breast and prostate cancer. Further, advanced disease stage, certain anti-cancer treatments (e.g. surgery, radiotherapy, cisplatin-based chemotherapy, anti-angiogenic agents), and comorbidities including a prior history of VTE were identified as risk factors for VTE diagnosis.(2, 3) Importantly, the increasingly utilized immune checkpoint inhibitors have lately been shown to be associated with an increased risk.(4) Based on the heterogeneity in VTE risk, in combination with an increased risk of bleeding events in cancer patients compared to

the general population, primary thromboprophylaxis is not routinely recommended in the overall population of patients with cancer, necessitating the implementation of risk prediction strategies to identify high-risk subgroups. Different biomarkers were identified that can help predicting the future risk of VTE in patients with cancer beyond key clinical prothrombotic risk factors, including D-dimer(5, 6), soluble P-selectin (sP-selectin)(6, 7), prothrombin fragment 1+2 (F1+2)(8) and citrullinated histone H3(9) in the general population with cancer, and the expression of podoplanin on cancer cells in patients with glioblastoma(10). Risk assessment scores and models for risk stratification in clinical practice have been developed with guidelines recommending primary thromboprophylaxis in patients with cancer and a high risk of VTE.(11-13) Currently the Khorana score is recommended to evaluate the risk-benefit ratio of primary thromboprophylaxis in ambulatory cancer patients.(11-14) The Khorana score is the most extensively externally validated risk score, however the predictive ability varied in those studies with reported c-statistics between 0.52 and 0.7.(14, 15)

After a diagnosis of VTE in cancer patients, anticoagulation for treatment and secondary prevention is recommended when risk of VTE recurrence is considered to be elevated.(11-13) In recent randomized-controlled trials, the treatment with either low-molecular weight heparin (LMWH) vs. a direct oral anticoagulant (DOAC) was evaluated and current guidelines recommend at least 6 months of anticoagulation treatment.(11-13, 16-18) Further prolonged anticoagulation treatment beyond 6 months after the index VTE event should be evaluated individually, based on the presence of a still active cancer or ongoing antineoplastic therapies.(11-13) However, to date, patients and treating physicians are left with the challenges of an optimal risk-benefit evaluation of bleeding risk vs. risk of recurrent VTE. The most challenging question to guide the duration of anticoagulation in patients with cancer-associated VTE is the lack of validated evidence-based tools (i.e. prediction models, clinical parameters or biomarkers) for assessing risk of recurrent VTE which could guide clinical decision-making.

## Risk of recurrent VTE in cancer patients

In general, in patients with VTE, cancer significantly increases the risk of recurrence.(19) Data from clinical practice suggest a 3-fold higher risk of VTE recurrence in cancer patients compared to patients with no history of cancer.(20, 21) The 12-month cumulative incidence of recurrent cancer-associated VTE is estimated to be at about 21%, whereas it is reported to be only at about 7% in non-cancer patients.(22) In a recent meta-analysis, aggregating data from 29 studies and 8,000 patients with cancer-associated VTE, the overall risk of recurrent VTE was high, with a rate of 23.7 events per 100-patient years.(23) The risk for recurrence of cancer-associated VTE is the highest in the first 6 months after the index event.(19) The peak of VTE recurrence was observed in the first month after the initial event.(24, 25) In detail, recurrence rates are 22.1 per 100 person-years in the first 6 months and drop to 7.9 per 100 person-years 6-12 months after the index event.(26) Similarly, in large-scale clinical trials evaluating anticoagulation treatment for a first episode of cancer-associated VTE, recurrence rates of 4-9% were reported in the first 6 months, and of 1-4% in months 7-12.(27, 28).

Recurrence rates of VTE in cancer patients differ between patient subgroups and depend on the type of anticoagulation treatment. In patients treated with Vitamin-K-Antagonists (VKA), recurrence rates were between 10-17% in the first 6 months after the index event.(29, 30) With the implementation of LMWH as the standard treatment for cancer-associated VTE in 2003 based on the CLOT trial, lower rates of 7-9% were observed.(29, 30) Recently, three large randomized controlled trials (RCT) have shown an improved efficacy and reduction of VTE recurrences in patients with cancer-associated VTE treated with DOAC.(31) In the SELECT-D trial, 6-month risk of recurrent VTE in patients treated with rivaroxaban was 4%, compared to 11% with LMWH. (31) Further, in the Hokusai VTE Cancer trial, risk of recurrent VTE at 6- and 12- months of follow-up after the index event with edoxaban treatment was 4.4% and 7.9%, compared to 6.7% and 11.3% with LMWH, respectively.(32, 33) In the Caravaggio study, patients treated with apixaban had a risk of VTE recurrence at 6 months of 5.6%, compared to 7.9% with LMWH.(34)

The rates of VTE recurrence during anticoagulant therapy in patients with cancer-associated VTE have been documented in detail, only little data on recurrence risk after the discontinuation of anticoagulant therapy for VTE treatment in cancer patients are available. After stopping anticoagulation, patients with cancer are 2-times more likely to have a recurrent VTE event compared to non-cancer patients with transient risk factors.(21) Lapébie et al. observed a cumulative recurrent VTE incidence of 13.5% at 1 year and 30.2% at 5 years after anticoagulation was stopped.(35)

In the Hokusai VTE cancer study, a significant proportion of VTE recurrences occurred off-treatment; 22 events of a total of 41 observed VTE recurrences occurring on-treatment in the per-protocol population in the edoxaban group.(32) In contrast, in the Caravaggio trial, 27 of 33 recurrent VTE events in the apixaban group and 41 of 46 events in the LMWH group occurred in patients on anticoagulation treatment.(34)

### **Case fatality rate of VTE recurrence and bleeding**

Importantly, cancer patients represent a particularly challenging patient population, characterized not only by a higher rate of VTE recurrence, but also a higher case-fatality rate of VTE recurrence and an increased risk of bleeding compared to patients without cancer. While the case-fatality-rate of recurrent VTE in the non-cancer population after an unprovoked index event is estimated to be about 3.8% (36), a recent systematic review and meta-analysis suggested a much higher rate in cancer patients. Abdulla et al.(23) found a VTE recurrence rate of 23.7 per 100 patient-years. A relatively high VTE recurrence case fatality rate of 14.8% was reported in this meta-analysis.(23)

The risk of bleeding in patients with cancer is 2.5-fold (HR 2.48, 95% confidence interval [CI] 1.90–3.23; HR, 2.77, 95% CI 2.03–3.79) higher compared to the non-cancer population according to real life data.(20, 21) The overall incidence in cancer patients was reported to be at 15.3% for clinically relevant bleeding events.(37) Interestingly, in patients with cancer under anticoagulation therapy, the case fatality rate of major bleeding was reported to be 8.9%, which is lower compared to the case-fatality rate of recurrent VTE.(23)

## Risk factors for recurrent VTE in cancer

In patients with a VTE diagnosis in the absence of underlying cancer, the recurrence risk of VTE depends on the presence of risk factors and triggers, with the highest risk observed in patients with an unprovoked VTE (i.e. without an triggering event or identifiable risk factor). In contrast, VTE due to major transient provoking risk factors is associated with the lowest risk for recurrence.(38) Thus, guidelines recommend at least 3 months of anticoagulation, with long-term anticoagulation or indefinite treatment in those with an unprovoked index event. If the balance between risk and benefit of prolonged or indefinite anticoagulation is unclear, the use of risk assessment strategies for VTE risk is suggested. Patients with persistent risk factors should continue anticoagulant treatment for prevention of VTE recurrence, while in those with transient risk factors, individual risks and benefits should be evaluated.(39)

In patients with cancer, based on currently available evidence, anticoagulation treatment for at least 6 months is recommended, with prolonged treatment suggested in those with an ongoing high risk of VTE recurrence based on personalized risk evaluation.(11-13) However, individual risk assessment remains ill-defined in this setting. Therefore, knowledge of factors that are associated with an increased or decreased risk of VTE recurrence might be helpful in clinical practice to guide clinical decision-making regarding duration of anticoagulation based on risk-benefit ratio. In **Table 1**, an overview of previously reported predictors and risk factors for recurrent VTE in cancer patients is provided.

### Tumor-specific risk factors

Similar to risk of a first cancer-associated VTE, the risk for VTE recurrence seems to be strongly influenced by the characteristics of the underlying cancer. The presence of distant metastatic disease seems to be a strong risk factor for VTE recurrence, as consistently reported in different studies.(20, 35, 40-43) Chee et al.(41) found a 1.5- to 2.9-fold (HR: 1.50, 95% CI: 1.03-2.17 and HR: 2.85, 95% CI: 1.74-4.67) increased recurrence risk in patients

with metastatic disease compared to those with localized tumors during and after stopping anticoagulation (details provided in Table 1). VTE recurrence rates seem also to vary between individual tumor types. (40, 41, 44-46) For example, patients with known high thrombotic risk tumor types seem to also have higher rates of VTE recurrences, with a 6-fold (HR 6.38, 95% CI: 2.69-15.13) higher risk in pancreatic cancer, and a 4-fold (HR 3.8, 95% CI: 2.6-5.6) increased risk in lung cancer compared to lower risk tumor types (details provided in Table 1). (41, 45, 46)

### **Residual vein thrombosis**

The presence of residual vein thrombosis (RVT) after 6 months of anticoagulation treatment has been reported as major risk factor for VTE recurrence. Napolitano et al. (47) evaluated the impact of RVT after 6 months of anticoagulant treatment on risk of VTE recurrence in cancer patients. They reported that RVT increases the risk of recurrence approximately 10-fold (HR 9.6, 95%CI: 2.8-28.5). Conversely, the absence of RVT in patients with DVT as index event could allow identification of a low risk population for VTE recurrence (2.8% cumulative 12-month recurrence rate compared to 15.1% under anticoagulation with RVT and 21.9% without anticoagulation with RVT). (47) These findings are supported by data from the SELECT-D trial, which evaluated the presence of RVT at 6-months to guide prolonged anticoagulation treatment. Patients with RVT and/or index PE were randomized to continue anticoagulation with rivaroxaban or placebo (n=92), and those without RVT and index DVT were stopped and observed up to month 12 (n=35). Importantly, none of the patients with index DVT and absence of RVT at 6-months did experience VTE recurrence between 6-12 months after the index event. (48)

### **Characteristics of index VTE**

Data on the association of characteristics of the index event and risk of VTE recurrence are conflicting. (24, 47-49) While in some studies index PE was associated with a 2-fold (OR: 1.9, 95% CI: 1.2-3.1) higher recurrence risk in patients on anticoagulation treatment (50), other

studies have reported a 2-fold (SHR: 1.93, 95% CI: 1.25-2.99) risk elevation in patients with DVT as index event (details provided in Table 1).(49)

Further, the presence of symptoms at VTE diagnosis might affect risk of recurrence.

Incidental VTE, diagnosed in asymptomatic patients in imaging studies conducted for other reasons than suspicion of VTE (e.g. restaging CT to evaluate response to anticancer therapy), is frequently observed in cancer patients, and its prevalence is expected to rise as the numbers of imaging procedures and advances in imaging resolution increase.(51) In clinical practice it is frequently discussed whether patients with incidental index event should be managed differently than those presenting with symptomatic VTE. Seemingly, risk of VTE recurrence is similar between incidental and symptomatic events, with a recurrence rate of 7.9% at 12 months compared to 10.9% (HR 0.68, 95% CI 0.43–1.06) in those with symptomatic events reported in a post-hoc analysis of the Hokusai VTE cancer trial during anticoagulation.(51) However, these data are challenged by a recent meta-analysis including the Caravaggio, Hokusai VTE cancer and Select D studies reporting a significant decrease in recurrence risk for incidental compared to symptomatic VTE.(52)

With respect to extent of PE, no difference in recurrence risk between patients on anticoagulation with subsegmental PE and patients with more proximal PE has been found (12-month incidence of recurrent VTE 6.4% versus 6.0%, respectively).(53)

### **Biomarkers for VTE recurrence in cancer patients**

Various biomarkers have been identified as predictors of occurrence of a first VTE in patients with cancer.(2) Similarly, effort has been put into evaluating their utility for estimating recurrence risk. However, D-dimer levels, which predict risk of VTE recurrence in the general population, do not seem to have the same predictive utility for risk of recurrence in patients with cancer.(25, 44) Interestingly, elevated baseline levels of soluble (s)P-selectin at diagnosis of the index VTE event was reported to increase the recurrence risk 4-fold (SHR 4.0, 95%CI: 1.1-14).(25) However, the results could not be reproduced in a subsequent study.(44)

Recently, a novel longitudinal biomarker-based risk assessment approach was investigated.(54, 55) Upon evaluating different biomarkers at the time point of anticoagulation termination, and subsequently 21 days later, a significantly higher risk of VTE recurrence was observed for a >2-fold increase in D-Dimer levels between the two time points (SHR 7.53, 95%CI: 1.97-28.71), and for elevated levels of high-sensitivity C-reactive protein (hs-CRP) (>4.5mg/L) at day 21 (SHR 9.82, 95%CI: 1.86-51.7), D-dimer >600ng/mL (SHR 5.81, 95%CI: 1.06-31.72) and P-selectin at day 21 (SHR 5.60, 95%CI: 1.48-21.08).(54, 55) However, it should be mentioned that a specific D-dimer cut off has limited validity as various kits have different normal ranges. The kit used by Jara-Palomares et al.(54) had a normal range of <500 mg/L and an increased risk was noted at levels higher than >600ng/mL. Further, Otero Candelera et al.(55) did not mentioned the kit that was used.

### **Prediction models for VTE recurrence in cancer patients**

Based on the availability of prediction scores to estimate individual risk for recurrent VTE in the non-cancer population, the same was desired for cancer patients. Therefore, the Ottawa-score was derived, which includes female sex, lung cancer and previous VTE as risk factors, as well as breast cancer and TNM stage I as indicators of lower risk. The original score allocates one point for female sex, lung cancer and previous VTE, whereas one point for breast cancer and two points for TNM stage I are subtracted. Patients were grouped into low (-3 to 0 points) and high (1 to 3 points) clinical probability classes. As the exact TNM classification is not always available for patients in observational studies, a modified version was also implemented, with TNM stages I+II summarized as low-risk category (-1 point in the score). This score divides patients into low ( $\leq -1$  point), intermediate (0 points) and high ( $\geq 1$  point) clinical probability groups. In the derivation study, a sensitivity for VTE recurrence of 100% and a negative predictive value of 98.1% were reported.(56) Unfortunately, this score could not be externally validated by others. In the framework of a prospective cohort study, the Ottawa score could not discriminate high and low risk patients with a low c-statistic of 0.6 (95%CI: 0.55-0.65).(57) Further, in the RIETE registry, the score was evaluated in over

11,000 patients and showed a low sensitivity, specificity, PPV and a c-statistic of 0.58 (95%CI: 0.56–0.61).(58) Especially in cancer patients with incidental index events, the Ottawa score was reported to perform poorly, as demonstrated in another prospective cohort study (c-statistic 0.45, 95% CI: 0.36-0.54). (56, 57, 59) Given the results of these external validations, the Ottawa score was not implemented in clinical practice.(11-13)

There is clearly a need to develop and validate improved risk assessment models for predicting risk of VTE recurrence in cancer patients. Such models could include clinical parameters and biomarkers, and may aid in risk stratification and clinical decision making on duration of anticoagulation for treatment of cancer-associated VTE.

## Discussion

Taken together, solid data for optimal risk assessment for recurrence of cancer-associated VTE is currently scarce. As no consistent approach to evaluate risk factors was used, the comparison of the existing data is hampered. Nevertheless, there are few risk factors that increase the risk of recurrence. In analogy to risk for a first event of cancer-associated VTE, the most relevant predictors seem to be the presence of metastasis and certain high-risk tumor types, such as pancreatic and lung cancer.(20, 35, 40-46) For patients with index DVT, the presence of RVT after 6 months of anticoagulation also indicates enhanced risk of recurrence, as the absence of RVT may identify patients at low risk of recurrence.(47, 48) In non-cancer patients, biomarkers such as D-Dimer were found to be helpful in evaluating recurrence risk of VTE. However, evidence of the usefulness of D-dimer levels to predict VTE recurrence – as in non-cancer patients - in the setting of recurrent cancer-associated VTE is lacking.(25, 44) Data on the association of characteristics of the index event (e.g. incidental vs. symptomatic VTE, extent of the clot burden, etc.) are conflicting. Incidental events are clinically as important as symptomatic events, however, incidental subsegmental PE might be associated with a lower recurrence risk. This is also reflected in the recommendations of the current guidelines for management of VTE in cancer patients, as

incidental subsegmental PE may not require anticoagulant therapy in every patient.(11, 51, 52)

The Ottawa score is the only risk predication score for recurrent cancer-associated VTE available at the moment. As it did not reliably differentiate between high and low risk patients in external validation, it has not been implemented in clinical routine practice.(56-59)

Therefore, identification of new and reliable risk factors for predicting recurrent cancer-associated VTE is needed. This can only be achieved with dedicated studies to explore patient- and tumor-related risk factors, which further could be used to create an improved risk prediction model for risk of recurrent VTE in patients with cancer, which is of urgent need.

The duration of anticoagulation in patients with cancer associated VTE beyond 6 month is still unclear, and risk assessment for recurrent VTE may aid in decision-making of stopping or continuing anticoagulation. According to current practice, it is recommended to continue anticoagulation as long as patients have active cancer or undergo anti-cancer treatment.(11-13) However, solid data supporting these recommendations is limited and especially data regarding recurrence risk after stopping anticoagulation treatment is lacking.

In future studies investigating new and predictive biomarkers the best time-point to measure such biomarkers for risk assessment needs to be addressed. Lately a novel longitudinal biomarker-based risk assessment approach was implemented for the first time (54, 55) and seems to be a promising way to answer both questions. However, caution should be applied when using different specific D-dimer cut off levels and measurement approaches as it makes comparisons complicated.

Bleeding complications are also a major concern of physicians when treating patients with cancer associated VTE, and thus studies dedicated to identifying reliable risk factors are needed to help evaluating the benefit-harm ratio of anticoagulation for cancer patients.

## **Conclusion**

Recently, treatment of cancer-associated VTE has been transformed with implementation of DOAC in clinical practice. However, optimal evaluation of VTE recurrence risk remains a

challenging clinical scenario as of the lack and low data quality tools in the setting to support clinical decision-making.

Conflicts of interest:

CA has received honoraria for lectures from Bayer, Daiichi Sankyo, BMS/Pfizer, and Sanofi; and participation in advisory boards for Bayer, Daiichi Sankyo, BMS/Pfizer and Sanofi.

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**Table 1. Risk factors and predictors for recurrent VTE in cancer patients.**

Study	Study type	Treatment	n	Finding	Risk estimate	Setting
Chee CE et al. 2014(41)	Cohort study	Long term treatment: 74% heparin followed by warfarin, 9% inferior vena cava filter	477	Metastasis Stage IV pancreatic cancer Brain cancer Myeloproliferative or myelodysplastic disorders Ovarian cancer Stage IV cancer (non-pancreatic) Lung cancer Neurological disease with leg paresis Cancer stage progression	HR 1.5 [95% CI: 1.03-2.17] HR 6.38 [95% CI: 2.69-15.13] HR 4.57 [95% CI: 2.07-10.09] HR 3.49 [95% CI: 1.59-7.68]  HR 3.22 [95% CI: 1.57-6.59] HR 2.85 [95% CI: 1.74-4.67]  HR 2.73 [95% CI: 1.63-4.55] HR 2.38 [95% CI: 1.14-4.97]  HR 2.14 [95% CI: 1.30-3.63]	Recurrence during and after stopping anticoagulation
Khorana AA et al. 2017(44)	Posthoc analysis of RCT	Tinzaparin or warfarin for 6 months	900	Venous compression Hepatobiliary cancer	SHR 3.0 [95% CI: 1.8-4.9] SHR 2.9 [95% CI: 1.2-7.0]	Recurrence during anticoagulation
Young AM et al. 2018(45)	RCT	Dalteparin or rivaroxaban for 6 months	406	Stomach or pancreas versus other malignancies Lung, lymphoma, gynecologic, or bladder versus other malignancies Symptomatic VTE versus incidental PE	HR 5.55 [95% CI: 1.97-15.66] HR 2.69 [95% CI: 1.11-6.53] HR 2.78 [95% CI: 1.2-6.41]	Recurrence during anticoagulation
Bosch FTM et al. 2021(49)	Posthoc analysis of RCT	Edoxaban or LMWH for 6 months (up to 12 months)	1050	Age <50 years Body weight > 110kg DVT only as index event Upper GI tumor	SHR 2.0 [95% CI: 1.12-3.58] SHR 2.3 [95% CI: 1.14-4.62] SHR 1.93 [95% CI: 1.25-2.99] SHR 3.35 [95% CI: 1.07-10.57]	Recurrence during and after stopping anticoagulation
Louzada ML et al. 2012(56)	Retrospective cohort	37% Vitamin K antagonist, 63% LMWH	543	Sex Primary tumor		Recurrence during anticoagulation

Trujillo-Santos J et al. 2008(50)	Prospective registry	49% long term LMWH, 43% long term vitamin K antagonists, 3.8% inferior vena cava filter	3805	Patients aged <65 years  Clinically overt PE at entry Cancer detected <3 months earlier	OR 1.6 [95% CI: 1.0-2.4] for DVT; OR 3.0 [95% CI: 1.9-4.9] for PE  OR 1.9 [95% CI: 1.2-3.1] for PE OR 2.4 [95% CI: 1.5-3.6] for DVT; OR 2.0 [95% CI: 1.2-3.2] for PE	Recurrence during anticoagulation
Napolitano M et al. 2014(47)	Prospective study	LMWH 6 months, if RVT then randomization: LMWH 6 more months or stop, no RVT anticoagulation stop	347 (242 patients with RVT)	RVT after 6 months of LMWH or PE as index event	HR 9.56 [95% CI: 2.8-28.5]	Recurrence during and after stopping anticoagulation
Marshall A et al. 2020(48)	RCT	Dalteparin or rivaroxaban for 6 months, then second randomization rivaroxaban or placebo for 6 more months	92	RVT after 5.5 months or PE as index event		Recurrence during and after stopping anticoagulation
Bauersachs R et al. 2018(60)	Posthoc analysis of RCT	Tinzaparin or warfarin for 6 months	900	Renal impairment	RR 1.74 [95% CI: 1.06-2.85]	Recurrence during anticoagulation
Van Es N et al. 2018(25)	Prospective observational study	Full dose heparin for 1 month, followed by 75% dose for 5 months	117	Baseline P-selectin levels	SHR 4.0 [95% CI: 1.1-14]	Recurrence during anticoagulation

Lapébie FX et al. 2021(35)	Prospective registry	Full dose anticoagulation for at least 3 months, then stop of anticoagulation and follow-up of 1 year	3414	Age Obesity Renal insufficiency Previous VTE Type of cancer (pancreas, lung, kidney, carcinoma of unknown origin, metastasis) Association of pulmonary embolism and deep vein thrombosis Inferior vena cava filter Direct oral anticoagulant (compared to low molecular weight heparin) in the first 7 days Post-thrombotic syndrome and residual venous or pulmonary artery obstruction after 3 months No recent surgery Not catheter-related thrombosis		Recurrence after stopping anticoagulation
Sakamoto J et al. 2019(20)	Retrospective cohort study	Long term treatment: warfarin 83%, DOAC 2.9%, LMWH 2.6%	695	Metastasis		Recurrence during and after stopping anticoagulation
Mulder FI et al. 2020(51)	Post hoc analysis of RCT	Edoxaban or LMWH for 6-12 months	331	ECOG 2 versus 0 for recurrent incidental VTE	HR 5.24 [95% CI: 1.81-15.18]	Recurrence during anticoagulation

Louzada ML et al. 2011(40)	Systematic review (6 prospective studies)	Vitamin K antagonist or LMWH	4573	Metastatic versus localized disease	RR 1.36 [95% CI: 1.06-1.74]	Recurrence during and after stopping anticoagulation
Otero Candellera R et al. 2021(55)	Prospective study	More than 3 months of anticoagulation than stop and blood draw, 21 days later blood draw again	166	Male sex Ratio basal D-dimer to 21 days D-dimer >2 Increasing hs-CRP (day 21) Increasing P-selectin (day 21)	SHR 4.32 [95% CI: 1.10-16.96] SHR 7.53 [95% CI: 1.97-28.71] SHR 5.15 [95% CI: 1.37-19.34] SHR 5.60 [95% CI: 1.48-21.08]	Recurrence after stopping anticoagulation
Mahé I et al. 2017(46)	Prospective registry	Long-term treatment: 67% LMWH, 20% Vitamin K antagonists, 1.1% rivaroxaban, 1.6% fondaparinux	3947	Lung cancer versus breast cancer	HR 3.8 [95% CI: 2.6-5.6]	Recurrence during anticoagulation
Jara-Palomares L et al. 2018(54)	Prospective study	At least 3 months of LMWH, then anticoagulation stop and blood draw, 21 days later blood draw again	114	hs-CRP >4.5 mg/L D-dimer >600 ng/mL	SHR 9.82 [95% CI: 1.86-51.7] SHR 5.81 [95% CI: 1.06-31.72]	Recurrence after stopping anticoagulation

HR – hazard ratio, OR – odds ratio, hs-CRP – high-sensitivity C-reactive protein, SHR – subdistribution hazard ratio, RCT – randomized controlled trial, LMWH – low molecular weight heparin, RVT – residual vein thrombosis, DVT – deep vein thrombosis, PE – pulmonary embolism, DOAC – direct oral anticoagulant

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**Declaration of interests**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare they have ethics committee approval and informed consent from patients or volunteers.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

CA has received honoraria for lectures from Bayer, Daiichi Sankyo, BMS/Pfizer, and Sanofi; and participation in advisory boards for Bayer, Daiichi Sankyo, BMS/Pfizer and Sanofi.

Each author declares substantial contributions through the following:

- (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data,
- (2) drafting the article or revising it critically for important intellectual content,
- (3) final approval of the version to be submitted.

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