Risk of recurrent venous thromboembolism in cancer patients after discontinuation of anticoagulant therapy

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ABSTRACT

Anticoagulant therapy is recommended for cancer-related venous thromboembolism (VTE). Recurrent VTE prevention is the main goal of this treatment. The majority of evidence-based practice guidelines recommend anticoagulant treatment for at least 6 months. Based on individual assessment of potential benefits and risks, tolerability, drug availability, patient preference, and cancer activity, active cancer patients should continue anticoagulant treatment beyond the 6-month course. When cancer is no longer active or the risk outweighs the benefit, anticoagulant therapy is usually stopped after 3-6 months. Until recently, there was little data on the risk of recurrent VTE in cancer-associated VTE patients after stopping anticoagulants. New results and evidence synthesis have emerged in the last 3 years. Recurring VTE occurs in over 30% in the 5 years after treatment discontinuation. In the first six months, recurrence rates are 10-15%. Recurrences reach 31% at 2 years and stabilize between 2 and 5. Duration of prior anticoagulation does not affect cumulative recurrence. The high risk of recurrent VTE after discontinuing treatment supports guidelines to continue anticoagulant treatment if cancer is active. Stopping anticoagulants after 3-6 months may not be ideal, so randomized clinical trials should be conducted quickly. This review highlights the need to improve cancer patients' primary VTE prevention efforts.

Introduction

Venous thromboembolism (VTE) is a common complication in cancer patients that increases mortality and results in morbidity from recurrent thromboembolism.[1-3] The yearly incidence of VTE among patients with cancer has increased by approximately 3-fold between 1997 and 2017.[1] As the treatment of cancer continues to improve, reducing morbidity from complications such as VTE among cancer survivors is an increasingly important goal. Although primary prevention is the most effective strategy to achieve this goal, reducing the incidence of recurrent VTE can also have an important impact on reducing morbidity and maintaining quality of life among cancer survivors who have experienced VTE complicating their diagnosis of cancer.

Anticoagulant therapy is the treatment of choice for cancer-associated VTE.[1,4-9] The primary goal of this treatment is to prevent recurrent VTE. Current approaches for anticoagulant therapy, including low-molecular-weight heparin and direct oral anticoagulants, are very effective for preventing recurrent VTE while treatment is continued. Evidence-based practice guidelines recommend continuing anticoagulant treatment for at least 3 to 6 months, with most guidelines recommending treatment for at least 6 months.[4-8] There is a consensus from guideline panels and expert narrative reviews that the optimal duration of anticoagulant treatment for patients with cancer-associated VTE remains uncertain due to a lack of definitive data from randomized clinical trials.[1,4-9] In general, extended or indefinite anticoagulant treatment beyond the initial 6-month course is recommended for patients with active cancer,[4-9] based on individual assessment of the potential benefit and risk of continued treatment, tolerability, drug availability, patient preference, and cancer activity. It is common practice to discontinue anticoagulant therapy after 3 to 6 months in patients in whom cancer is no longer considered to be active, or in whom the risk of continued treatment is assessed to outweigh the potential benefit.

A starting point or foundation for assessing the risk-benefit of extended anticoagulation is to have valid and sufficiently precise data on the risk of recurrent VTE over time after discontinuing anticoagulant treatment. This data is critical for the clinician and patient to assess the potential benefit that extended anticoagulant treatment can provide, and to consider this in the context of the risk of bleeding with contemporary long-term anticoagulant treatment. Rigorous data on the risk of recurrent

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VTE in the months to years after discontinuing anticoagulant treatment in patients with cancer-associated VTE has been sparse until relatively recently.

The purpose of this narrative review is to summarize the available evidence quantifying the risk of recurrent VTE after discontinuing anticoagulant treatment in patients with cancer-associated VTE. New results and synthesis of evidence have become available during the last 3 years,[2,10-12] and these reports are the focus of this review.

Evidence from systematic reviews

Moik *et al.*[10] performed a systematic review of the evidence on the incidence of recurrent VTE and bleeding between 6 and 12 months after a diagnosis of cancer-associated VTE. The authors identified 11 studies, which were either randomized trials or cohort studies, that included 3,019 patients 18 years of age or older with active cancer at the time of diagnosis of VTE, and appropriate follow-up to document the outcomes of recurrent VTE and bleeding during the period of 6 to 12 months after diagnosis. There was substantial heterogeneity in the reported rates of recurrent VTE during this period, ranging from 1% to 12%.[10] The studies varied in the anticoagulation strategies, and the authors were not able to determine an aggregate rate of recurrence for patients on or off anticoagulation. In general, the reported risk of recurrent VTE was highest (13-15%) for patients not receiving anticoagulation in whom there was evidence of residual vein thrombosis by imaging at 6 months. The rates of recurrence were 1% to 4% for patients receiving anticoagulation, except for one prospective observational study which reported a rate of recurrence of 12%.[10] The authors suggested the latter result was due to the very high thrombotic risk of the cohort due to both advanced stage of disease and a preponderance of very prothrombotic tumor types.[10] The rates of major bleeding were 1-4% among patients receiving continued anticoagulation.[10]

A recent systematic review and meta-analysis by van Hylckama Vlieg *et al.* [11] provides important new data on the risk of recurrent VTE after discontinuing anticoagulation in patients with cancer-associated VTE. These authors assessed the rate of recurrent VTE and the cumulative rate of VTE recurrence in patients with a first cancer-associated VTE who completed at least 3 months of anticoagulant treatment and were followed up after discontinuation of this treatment. The analysis was performed using the data from 14 studies involving 1,922 patients. The methodology was rigorous and followed current best practices for meta-analysis. The pooled rates of recurrent VTE for the time intervals of 0 to 3, 3 to 6, 6 to 12, 12 to 24, 24 to 36, and 3 to 5 years after discontinuing treatment are summarized in Table 1. The rate of VTE recurrence for these intervals ranged from 14.6% to 1.1%, with the highest risk during the early periods after discontinuing therapy.[11] The cumulative rates of recurrent VTE for up to 5 years after discontinuing treatment are summarized in Table 2. The results document high cumulative rates of recurrent VTE, ranging from 23% at 6 months after discontinuation of anticoagulant treatment to more than one-third of patients having a recurrence within 5 years.[11] The authors discussed several limitations of the study, several of which would likely cause the results to be an underestimate of the recurrence rate after discontinuing therapy. The cumulative rates of recurrent VTE are so high that the limitations of the study would be unlikely to lead to different conclusions.

Table 1. Rate of recurrent venous thromboembolism after discontinuation of anticoagulant therapy in patients with cancer-associated venous thromboembolism. Reproduced with permission from van Hylckama Vlieg *et al.*[11]

Time	No. of studies	No. of patients at risk	Recurrent VTE events	Event rate per 100 person-years
0-3 months	15	1922	63	14.6
3-6 months	15	1375	69	10.3
6-12 months	13	888	57	6.4
12-24 months	11	615	60	4.0
24-36 months	9	366	10	1.1
3-5 years	5	128	10	2.2

VTE, venous thromboembolism.

Table 2. Cumulative rate of recurrent venous thromboembolism after discontinuation of anticoagulant therapy. Reproduced with permission from van Hylckama Vlieg *et al.*[11]

Time after discontinuation	Cumulative rate of VTE recurrence, %	95% CI
6 months	23.4	12.9-33.3
1 year	28.3	15.6-39.6
2 years	31.1	16.5-43.8
3 years	31.9	16.8-45.0
5 years	35.0	16.8-47.4

VTE, venous thromboembolism; CI, confidence interval.

Recent evidence from registries or population-based studies

Using the *Registro Informatizado de la Enfermedad ThromboEmbolica* cohort, Lapebie *et al*.[12] evaluated the rate of recurrent VTE and predictors of recurrence during the 1 year after discontinuation of anticoagulation among patients with an index VTE associated with active cancer, and who completed a course of at least 3 months of anticoagulant therapy. From a total of 14, 318 patients with cancer-associated VTE, 3,414 patients had anticoagulant treatment discontinued after at least 3 months of therapy. The length of anticoagulant treatment was 3 to 6 months in 1699 patients (49.8%), 6 to 12 months in 1146 patients (33.6%), and >1 year among 569 patients (16.7%). The cumulative incidence of recurrent VTE after discontinuation was 10.2% [95% confidence interval (CI), 9.1 to 11.5 %] at 1 year, 19.7% (95% CI, 17.0 to 22.5%) at 5 years, and 27.6% (95% CI, 22.1 to 33.3%) at 10 years.[11] The cumulative incidence of recurrence after discontinuing anticoagulant therapy did not change according to the length of previous treatment. In a cohort comparison of 6,532 patients with cancer-associated VTE who did not have a recurrence during the first 3 months and were receiving continued anticoagulant treatment, the corresponding cumulative rates of recurrent VTE at 1, 5 and 10 years were 3.2% (95% CI, 2.6 to 4.0%), 6.0% (95% CI, 4.2 to 8.3%) and 13.5% (95% CI, 5.9 to 9.5%).[12]

Several potential predictors of recurrent VTE were evaluated using multivariable analysis. The features most strongly associated [hazard ratio (HR) >2] with recurrent VTE were the type of cancer, the post-thrombotic syndrome, residual pulmonary artery obstruction, and the presence of an inferior vena cava filter.[12] Surgery in the 2 months prior to the diagnosis of VTE was associated with a lower hazard for recurrent VTE (HR 0.60).[12] The HRs for recurrent VTE for different groups of the type of cancer are shown in Table 3; the 95% CIs for the HRs overlap widely across these groups.[12]

A recent population-based prospective study provides new data on the incidence and burden of cancer-associated VTE,[2] and the rate of recurrent VTE up to 2 years after diagnosis among patients with active cancer and among those with a history of cancer >6 months prior to diagnosis of VTE. The age-adjusted incidence of cancer-associated VTE among adults aged 18 years or more was 70.0 (95% CI, 65.1 to 75.3) per 100,000 general population.[2] Recurrent VTE documented by imaging during the 2 years after the initial diagnosis occurred in 38 of 304 patients (12.5%) with active cancer (of whom 37% were receiving anticoagulant therapy at the time of recurrence), and in 34 of 424 patients (8.0%) with a history of cancer >6 months prior to their index diagnosis (of whom 38% were receiving anticoagulant treatment).[2] Among this latter group, the majority of recurrences occurred within the first 6 months, but approximately one-third of the recurrent events accumulated later throughout the 2-years follow-up period.[2] The time course of the recurrent VTE among patients with active cancer, and in patient with a history of cancer >6 months previously is shown in Figure 1; the cohorts of patients without cancer, stratified by the presence or absence of transient or persistent provoking risk factors are also shown for comparison.[2]

Discussion and Conclusions

This review of the data on the risk of recurrent VTE following discontinuation of anticoagulant therapy leads to several inferences. First, there is a high cumulative incidence of recurrent VTE, more than 30%, during the 5 years following discontinuation of treatment.[11] The risk of recurrence is highest during the initial 6 months, with reported rates of approximately 10% to 15% (Table 1). Recurrences continue to accumulate significantly to 31% at 2 years, with the cumulative incidence stabilizing between years 2 and 5 (Table 2). The cumulative recurrence rate appears to not be influenced by the duration of prior anticoagulation.[12] This pattern is similar to that observed in patients without cancer who have unprovoked VTE.[13]

Second, the high risk of recurrent VTE after discontinuing treatment provides support for the recommendation from guidelines that anticoagulant treatment be continued if the cancer is active unless the risk of bleeding is too great.[4-8] Among the 14 studies in the systematic review by van Hylckama Vlieg,[11] 10 studies included information on the stage of cancer, although the precise number of patients with active versus non-active cancer was not available. The proportion of patients with metastatic disease, indicating active cancer, ranged from approximately 18% to 76% of patients in these studies. More granular information is needed on the risk of recurrence in the groups with active versus non-active cancer at the time of discontinuing treatment. This is particularly important since it is common practice to discontinue treatment after 6 months if the cancer is no longer active, a practice which may need to be revisited. The relative benefit and risk of continuing versus stopping anticoagulant treatment among patients whose cancer is no longer considered active should be evaluated by a randomized trial.

Third, the available data support the concept that tumor type influences the risk of recurrent VTE (Table 3),[12] with some tumors being especially strong in promoting recurrent thromboembolism. Further studies are needed; however, to determine precisely how information on tumor type should be incorporated

Table 3. Effect of the type of cancer on the risk of recurrent venous thromboembolism after discontinuation of anticoagulant therapy in patients with cancer-associated venous thromboembolism. Adapted with permission from Lapebie *et al.*[12]

Site of the cancer	sHR	95% CI
Oropharynx, larynx, melanoma	Reference	-
Others, hematological, colorectal, uterus, bladder, kidney, prostate, breast, vulva	2.94	0.91-9.52
Lung, cerebral, stomach, esophagus, liver, ovary	3.56	1.07-11.80
Pancreas, biliary system, carcinoma of unknown origin	6.86	1.89-24.85

sHR, sub-hazard ratio; CI, confidence interval.

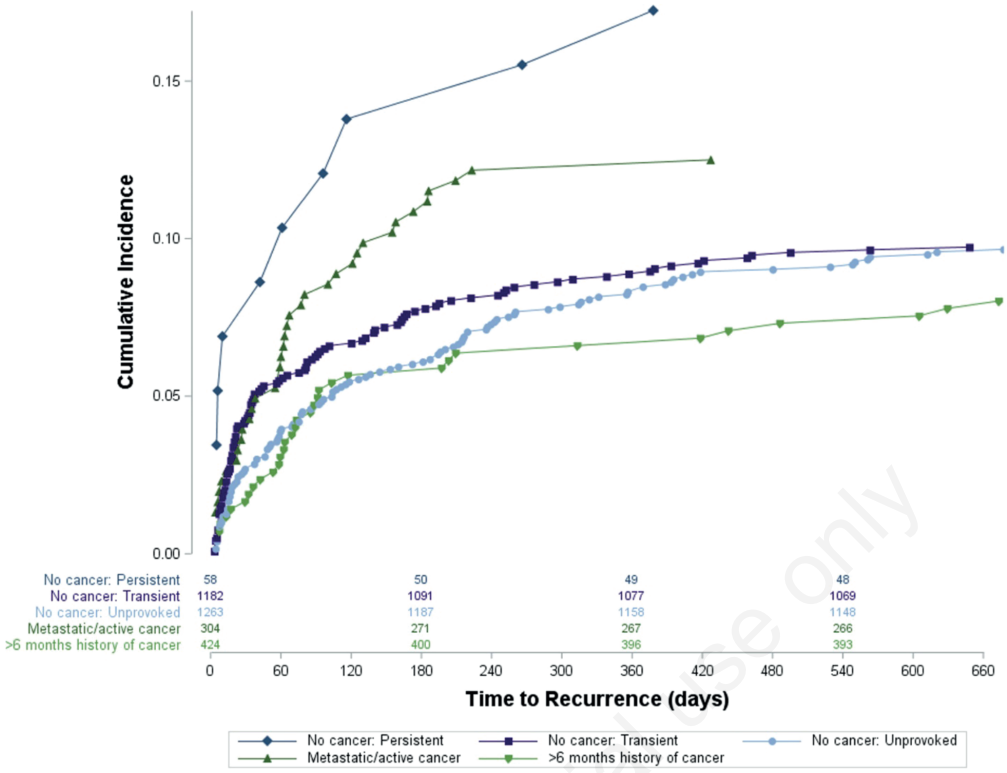

Figure 1. Cumulative incidence of the first recurrent venous thromboembolism stratified by status of cancer and provoking risk factor status. Reproduced with permission from Raskob *et al.*[2]

into the individual patient's decision to continue or discontinue anticoagulant therapy. Because contemporary oncology, clinical decision-making, and patient care are "tumor specific", future clinical trials of anticoagulant treatment should also focus on specific tumors, or stratify by tumor type, to be most helpful to the practicing oncologist.

In conclusion, the available literature indicates there is a major burden of morbidity from recurrent VTE after discontinuing anticoagulant treatment in cancer patients with VTE. The optimal duration of anticoagulant treatment in cancer patients with VTE continues to be unresolved. The practice of discontinuing anticoagulants after 3 to 6 months of treatment may not be optimal, and randomized clinical trials to address this issue should be performed expeditiously. The safety of extended anticoagulation is also an important consideration, and the ongoing, larger study of treatment using a lower dose of a factor Xa inhibitor, with the hope of reduced bleeding risk, is awaited with interest.[14] Patients with cancer-associated VTE are also an attractive target patient group for evaluating merging new anticoagulants which are potentially safer, such as the factor XI inhibitors.[15] Finally, while reducing the risk of recurrent VTE can have an important impact on the disease burden of VTE in the cancer patient population, the most effective approach with the greatest potential impact is to prevent VTE in the first place. The results of this review further underscore the importance of strengthened efforts for primary prevention of VTE in cancer patients.

References

1. Khorana A, Mackman N, Falanga A, et al. Cancer-associated venous thromboembolism. Nat Rev 2022:8:1-18.
2. Raskob G, Wendelboe A, Campbell J, et al. Cancer-associated venous thromboembolism: incidence and features in a racially diverse population. J Thromb Haemost 2022;20:2366-78.
3. Mulder F, Horvath-Puho E, vanEs N, et al. Venous thromboembolism in cancer patients: a population-based study. Blood 2021;137:1959-69.
4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Cancer-associated venous thromboembolic disease. Version 2. National Comprehensive Cancer Network 2023. Available from: https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf
5. Falanga A, Ay C, Di Nisio M, et al. Venous thromboembolism in cancer patients: ESMO clinical practice guideline. Ann Oncol 2023;34:452-67.
6. Lyman G, Carrier M, Ay C, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv 2021;5:927-74.
7. Key N, Khorana A, Kuderer N, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer:

ASCO clinical practice guideline update. J Clin Oncol 2020;38:496-520.
8. Farge D, Frere C, Connors J, et al. 2022 International clinical practice guidelines for treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19. Lancet Oncol 2022;23:e334-e347.
9. O'Connell, Escalanti C, Goldhaber S, et al. Treatment of cancer-associated venous thromboembolism with low-molecular-weight heparin or direct oral anticoagulants: patient selection, controversies and caveats. The Oncologist 2021;26:e8-e16.
10. Moik F, Colling M, Mahe I, et al. Extended anticoagulation treatment for cancer-associated thrombosis – rates of recurrence and bleeding beyond 6 months: a systematic review. J Thromb Haemost 2022;20:619-34.
11. Van Hylckama Vlieg MAM, Nasserinejad K, Visser C, et al. The risk of recurrent venous thromboembolism after discontinuation of anticoagulant therapy in patients with cancer-associated thrombosis: a systematic review and meta-analysis. Lancet eClinicalmedicine 2023;64:102194.
12. Lapebie F, Bura-Riviere A, Espitia O, et al. Predictors of recurrence of cancer-associated venous thromboembolism after discontinuation of anticoagulant therapy: a multicenter cohort study. J Thromb Haemost 2023;21:2189-201.
13. Agnelli G, Prandoni P, Santamaria M, et al. for the Warfarin Optimal Duration Italian Trial Investigators. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med 2001;345:165-9.
14. Mahe I, Agnellli G, Ay C, et al. Extended anticoagulant treatment with full or reduced-dose apixaban in patients with cancer-associated venous thromboembolism: rationale and design of the API-CAT study. Thromb Haemost 2022;122: 646-56.
15. Chan N, Weitz J. New therapeutic targets for the prevention and treatment of venous thromboembolism with a focus on Factor XI inhibitors. Arterioscler Thromb Vasc Biol 2023; 43:1755-63.