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Updates in anticoagulant therapy for cancer-associated venous thromboembolism

Dana **Pop** [1, 2], Diana Andrada **Irimie** [1, 2] *, Alexandra **Dădârlat-Pop** [1, 3]

[1] Department of Internal Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[2] Department of Cardiology, Clinical Rehabilitation Hospital, Cluj-Napoca, Romania
[3] Department of Cardiology, N. Stancioiu Heart Institute, Cluj-Napoca, Romania

*** Correspondence to:** Diana Andrada Irimie, Department of Cardiology, Clinical Rehabilitation Hospital, 46-50 Viilor Str., Cluj-Napoca, 400066, Romania. E-mail: gurzaudiana@yahoo.com

Abstract

Venous thromboembolism (VTE) is a frequent complication in patients with cancer and a major cause of morbidity and mortality in this population. The risk of developing VTE in cancer patients varies according to the stage and type of cancer and increases during cancer treatment. Even with traditional anticoagulant therapy, patients with cancer and venous thromboembolism are more likely to experience recurrences and major bleeding compared with patients without malignant disease. Traditional treatment with low–molecular-weight heparins is associated with a lower recurrence rate of venous thromboembolism compared with vitamin K antagonists, but with a similar rate of major bleeding and extremely low adherence. In this context, studies on direct oral anticoagulants have emerged, leading to the development of guidelines that include them as a treatment option for managing cancer-associated venous thromboembolism.

Keywords: venous thromboembolism, anticoagulant therapy, cancer

Introduction

The presence of active cancer is associated with a 4- to 7-fold increase in the risk of developing venous thromboembolism (VTE) [1]. Moreover, patients with cancer account for 20% to 30% of new VTE cases in the general population [2]. VTE-related mortality is 2–3 times higher among oncologic patients [1].

Initiating anticoagulant therapy in this category of patients represents a real challenge, as outcomes are poorer compared with those in patients without cancer. Even with traditional anticoagulant therapy, patients with cancer and diagnosed VTE are more likely to develop recurrent VTE and major bleeding than patients without malignancies. Thus, the risk of VTE recurrence is more than three times higher [3], the risk of major bleeding doubles [3], and the risk of mortality is approximately threefold higher [1].

The risk of developing VTE in neoplastic diseases depends on several factors—related to the patient, the treatment administered, the location of the cancer, as well as certain biomarkers. The most important patient-related factors include obesity, poor nutrition, advanced age, race, the presence of genetic mutations (*e.g.*, Factor V Leiden), chronic diseases, and a history of thromboembolic events [4]. Treatment-related factors include chemotherapy, anti-angiogenic agents, hormone therapy, surgical interventions, radiotherapy, blood transfusions, central venous catheters, immobilization, and hospitalization [5].

The location of the cancer is another determinant factor. The risk is particularly high in cancers of the esophagus, stomach, pancreas, and biliary

tract. There is also an increased risk in lung, gynecologic, testicular, renal, bladder, intracranial, and hematologic malignancies. In colorectal cancer, the risk is considered intermediate [4, 5]. The histologic grade of the tumor, cancer stage, the presence of metastases, and time since diagnosis are also important factors [5]. Elevated levels of certain biological biomarkers—such as D-dimers, P-selectin, prothrombin fragments 1+2, C-reactive protein, and hematologic elements (*e.g.*, platelet count, hemoglobin, leukocytes)—are further indicators of increased thrombotic risk [4, 5].

Treatment with low–molecular-weight heparins (LMWH)

Several important studies have evaluated low–molecular-weight heparins (LMWHs) compared with warfarin in cancer patients with VTE: CLOT (dalteparin), LITE (tinzaparin), ROMERA (tinzaparin), CATCH (tinzaparin), ONCENOX (enoxaparin), and CANTHANOX (enoxaparin). It is worth mentioning that the CLOT study, which used dalteparin, was a pivotal trial that led to LMWHs being established as the standard of care for patients with cancer-associated VTE [6, 7].

A meta-analysis that included all these studies demonstrated that the use of LMWHs is associated with a lower recurrence rate of venous thromboembolism compared with vitamin K antagonists but with a similar rate of major bleeding [8]. Furthermore, real-world data have shown very low adherence when LMWHs are prescribed for six months. A real-world Canadian study conducted across 12 centers, which included 868 outpatients, found that only 60% of patients received LMWH monotherapy, and after three months, only 43% remained on this treatment [9]. Similarly, data from European clinical practice show that in a prospective, multicenter study including 372 cancer patients with VTE who received LMWH therapy for up to 180 days, one in five discontinued treatment due to adverse effects [10].

Treatment with direct oral anticoagulants (DOACs)

In this context, in which studies have shown no reduction in major bleeding with prolonged therapy using low–molecular-weight heparins compared with vitamin K antagonists, increasing attention has been given to the potential beneficial role of direct oral anticoagulants (DOACs). Therefore, further analyses of established clinical trials involving DOACs in VTE were required, focusing on the subset of patients with cancer who had been included.

A meta-analysis of the sub-analyses from phase III clinical trials demonstrated that DOACs were non-inferior to vitamin K antagonists for the treatment of VTE in cancer patients, without increasing the risk of major bleeding [11]. Six studies were analyzed: two with dabigatran (RE-COVER I and II), two with rivaroxaban (EINSTEIN-DVT and EINSTEIN-PE), one with edoxaban (Hokusai), and one with apixaban (AMPLIFY). These studies included a total of 1,132 patients with cancer and VTE.

In the next stage, studies specifically dedicated to patients with malignancies and VTE began to appear (Table 1).

The Hokusai-Cancer study compared the efficacy of edoxaban with that of a low–molecular-weight heparin, dalteparin [12]. Orally administered edoxaban was non-inferior to subcutaneous dalteparin regarding the composite endpoint

Table 1. Major studies with DOACs in patients with cancer and VTE.

Completed studies	Number of patients	Study plan	DOAC	Comparison	Primary objective	Duration of treatment
Hokusai-VTE Cancer	1050	Randomized, open-label, non-inferiority	Edoxaban	Dalteparin	Composite of recurrent VTE and/or major bleeding	12 months
SELECT-D	406	Prospective, randomized, open-label, blinded primary endpoint (PROBE), pilot	Rivaroxaban	Dalteparin	Recurrent VTE	6 months
ADAM-VTE	300	Randomized, open	Apixaban	Dalteparin	Major bleeding	6 months
CARAVAGGIO	1170	PROBE, non-inferiority	Apixaban	Daltepatin	Recurrent VTE	6 months

VTE – Venous thromboembolism.

of recurrent venous thromboembolism or major bleeding. The rate of recurrent venous thromboembolism was lower, but the rate of major bleeding was higher in the edoxaban group than in the dalteparin group (6.1% *vs.* 3.1%) [12]. Gastrointestinal bleeding occurred in 4.2% of patients treated with edoxaban compared with 1% among those receiving dalteparin. The frequency of life-threatening or fatal hemorrhage was similar between edoxaban (1.9%) and dalteparin (2.1%) [12].

The efficacy of rivaroxaban was evaluated in the Select-D study. Treatment with rivaroxaban was associated with a relatively lower recurrence rate of VTE but with a higher rate of major and clinically relevant non-major bleeding compared with dalteparin [13]. Patients with esophageal or gastroesophageal cancer tended to experience more major bleeding under rivaroxaban than under dalteparin (36% *vs.* 11%). Consequently, these cancer types were later excluded from enrollment as a precautionary measure [13].

Apixaban was compared with dalteparin in the ADAM-VTE study, in which the primary endpoint was the rate of major bleeding [14]. The study concluded that oral apixaban was associated with low rates of major bleeding and VTE recurrence in the treatment of VTE among cancer patients [14].

Another trial investigating apixaban, the CARAVAGGIO study, also compared it with dalteparin in patients with cancer-associated VTE [15]. The study found that apixaban was non-inferior to dalteparin in preventing recurrent VTE in patients with cancer-associated thrombosis and showed a slightly higher event-free survival rate. Likewise, the rates of clinically relevant non-major bleeding, both gastrointestinal and non-gastrointestinal, were comparable between the two anticoagulant classes.

In a retrospective study including 5,100 patients with VTE and cancer, therapy with DOACs was associated with a 50% reduction in the risk of VTE recurrence compared with LMWH and warfarin. Furthermore, treatment with DOACs was linked to a 60% reduction in all-cause mortality compared with LMWH. The risks of major and gastrointestinal bleeding were also lower among patients treated with DOACs than with LMWH [16].

A particular challenge is represented by patients with acute pulmonary embolism and primary or metastatic brain tumors, who have a high risk of recurrent VTE. However, initiating anticoagulant therapy in these patients increases the risk of intracranial hemorrhage (ICH). Several meta-analyses have shown that the baseline (non-anticoagulated) risk of ICH is higher in patients with metastatic brain cancer than in those with primary brain tumors, and that anticoagulant therapy is associated with an increased risk of both overall and major ICH in patients with primary brain cancer, but not in those with metastatic brain cancer [17–19]. Furthermore, the risk of ICH is lower in patients with primary or metastatic brain tumors treated with DOACs compared with those treated with LMWH [17–19].

Treatment after 6 months

The risk of recurrent venous thromboembolism (VTE) in patients with cancer-associated VTE may persist beyond six months [20]. This is particularly true in patients with active or metastatic cancer. In these cases, treatment with direct oral anticoagulants (DOACs) should be continued beyond six months — as extended therapy. Unfortunately, most pivotal clinical trials on DOACs were conducted over only a six-month period.

A meta-analysis published in 2023 showed that discontinuation of anticoagulant therapy in patients with cancer-associated VTE was linked to recurrence rates of 8.3% at 1 year, 31.1% at 2 years, 35% at 3 years, and 35% at 5 years after treatment cessation [21]. Real-world evidence also supports the benefit of extended anticoagulation beyond six months, showing reduced rates of VTE recurrence [22].

In 2024, results of the EVE trial were published, comparing long-term (1-year) efficacy of apixaban 2.5 mg *vs.* 5 mg twice daily. The primary endpoint was the composite of major and clinically relevant non-major bleeding [23]. The study concluded that in secondary prevention of cancer-associated VTE, apixaban 2.5 mg twice daily did not reduce the rate of combined bleeding events compared with the 5 mg twice-daily dose [23].

The API-CAT study, published in 2025, evaluated the same apixaban doses over one year. Extended anticoagulation with reduced-dose apixaban was non-inferior to full-dose apixaban for prevention of VTE in patients with active cancer. The lower dose led to a reduced incidence of clinically relevant bleeding complications compared with standard dosing [24].

Treatment with edoxaban for 12 months in the ONCO DVT trial, dedicated to patients with cancer-associated isolated distal deep vein thrombosis, proved consistently superior to a 3-month regimen in reducing thrombotic risk. However, caution was advised with the standard edoxaban dose due to the potential for increased bleeding risk with prolonged anticoagulation [25].

A meta-analysis including these three major studies concluded that regarding VTE recurrence, bleeding events, and all-cause mortality, reduced-dose DOACs demonstrated a safety profile comparable or superior to full-dose regimens [26].

Taken together, these findings support the approach that when extended therapy beyond six months is considered for cancer-associated VTE, low-dose DOACs should be preferred.

What do the guidelines say?

In the 2022 ESC Guidelines on Cardio-Oncology, developed in collaboration with the European Hematology Association (EHA), the European Society for Radiotherapy and Oncology (ESTRO), and the International Cardio-Oncology Society (IC-OS), the following recommendations are provided regarding anticoagulant therapy in patients with cancer-associated VTE [27]:

- Apixaban, edoxaban, or rivaroxaban are recommended for the treatment of symptomatic or incidentally discovered VTE in cancer patients, provided there are no contraindications;
- Low-molecular-weight heparins (LMWHs) are recommended for the treatment of symptomatic or incidentally discovered VTE in cancer patients with a platelet count >50,000/μL;
- In patients with cancer and a platelet count between 25,000 and 50,000/μL, half-dose LMWH anticoagulation may be considered after multidisciplinary discussion;
- Extension of anticoagulant therapy beyond 6 months should be considered in selected patients with active cancer, including those with metastatic disease;
- For catheter-associated VTE in cancer patients, anticoagulant therapy is recommended for at least 3 months and may be extended as long as the catheter remains in place;
- In ambulatory cancer patients receiving systemic therapy and at high risk of thromboembolism, prophylactic therapy with DOACs (apixaban or rivaroxaban) or LMWH may be considered, provided there is no significant bleeding risk.

Additionally, the AHA/ACC guidelines highlight that in patients with primary or metastatic brain tumors and acute pulmonary embolism who are candidates for oral anticoagulation, a DOAC may be considered instead of LMWH to reduce the risk of intracranial hemorrhage (ICH) [28].

Conclusion

In conclusion, in patients with cancer-associated VTE, the initiation of anticoagulant therapy is associated with a higher risk of recurrence, bleeding, and mortality compared to patients with non-cancer-associated VTE. Based on the results of studies in cancer-associated VTE using DOACs, guidelines have been developed, some of which have been recently updated, supporting the safe use of this drug class.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

References

1. Pavlovic D, Niciforovic D, Markovic M, Papic D. Cancer-Associated Thrombosis: Epidemiology, Pathophysiological Mechanisms, Treatment, and Risk Assessment. Clin Med Insights Oncol. 2023 Dec 26;17:11795549231220297. doi: 10.1177/11795549231220297.
2. Ashrani AA, Gullerud RE, Petterson TM, Marks RS, Bailey KR, Heit JA. Risk factors for incident venous thromboembolism in active cancer patients: a population based case-control study. Thromb Res. 2016;139:29-37.
3. Falanga A, Ay C, Di Nisio M, et al.; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Venous thromboembolism in cancer patients: ESMO Clinical Practice Guideline. Ann Oncol. 2023 May;34(5):452-467. doi: 10.1016/j.annonc.2022.12.014.
4. Nusrat S, Khan S, Beg K, Raskob G. Unmet Needs and Challenges in Cancer-Associated Venous Thromboembolism. Int J Mol Sci. 2026 Feb 12;27(4):1756. doi: 10.3390/ijms27041756.
5. Ay C, Pabinger I, Cohen AT. Cancer-associated venous thromboembolism: Burden, mechanisms, and management. Thromb Haemost. 2017 Jan 26;117(2):219-230. doi: 10.1160/TH16-08-0615.
6. Wang TF, Li A, Garcia D. Managing thrombosis in cancer patients. Res Pract Thromb Haemost. 2018 May 1;2(3):429-438. doi: 10.1002/rth2.12102.
7. Lee AY, Levine MN, Baker RI, et al.; Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003 Jul 10;349(2):146-53. doi: 10.1056/NEJMoa025313.
8. Posch F, Königsbrügge O, Zielinski C, Pabinger I, Ay C. Treatment of venous thromboembolism in patients with cancer: A network meta-analysis comparing efficacy and safety of anticoagulants. Thromb Res. 2015 Sep;136(3):582-9. doi: 10.1016/j.thromres.2015.07.011.
9. Kahn SR, Springmann V, Schulman S et al. Management and adherence to VTE treatment guidelines in a national prospective cohort study in the Canadian outpatient setting. The Recovery Study. Thromb Haemost. 2012 Sep;108(3):493-8. doi: 10.1160/TH12-03-0169.
10. van der Wall SJ, Klok FA, den Exter PL, et al. Continuation of low-molecular-weight heparin treatment for cancer-related venous thromboembolism: a prospective cohort study in daily clinical practice. J Thromb Haemost. 2017 Jan;15(1):74-79. doi: 10.1111/jth.13563.
11. Vedovati MC, Germini F, Agnelli G, Becattini C. Direct oral anticoagulants in patients with VTE and cancer: a systematic review and meta-analysis. Chest. 2015 Feb;147(2):475-483. doi: 10.1378/chest.14-0402.
12. Raskob GE, van Es N, Verhamme P, et al.; Hokusai VTE Cancer Investigators. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. N Engl J Med. 2018 Feb 15;378(7):615-624. doi: 10.1056/NEJMoa1711948.
13. Young AM, Marshall A, Thirlwall J, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). J Clin Oncol. 2018 Jul 10;36(20):2017-2023. doi: 10.1200/JCO.2018.78.8034.

14. McBane RD 2nd, Wysokinski WE, Le-Rademacher JG, et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. J Thromb Haemost. 2020 Feb;18(2):411-421. doi: 10.1111/jth.14662.
15. Agnelli G, Becattini C, Meyer G, et al. Caravaggio Investigators. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. N Engl J Med. 2020 Apr 23;382(17):1599-1607. doi: 10.1056/NEJMoa1915103.
16. Riaz IB, Fuentes H, Deng Y, et al. Comparative Effectiveness of Anticoagulants in Patients With Cancer-Associated Thrombosis. JAMA Netw Open. 2023 Jul 3;6(7):e2325283. doi: 10.1001/jamanetworkopen.2023.25283. PMID: 37486628; PMCID: PMC10366701.
17. Giustozzi M, Proietti G, Becattini C, et al. ICH in primary or metastatic brain cancer patients with or without anticoagulant treatment: a systematic review and meta-analysis. Blood Adv. 2022;6:4873–4883.
18. Iyengar V, Agrawal S, Chiasakul T, et al. Comparison of direct oral anticoagulants versus low-molecular-weight heparin in primary and metastatic brain cancers: a meta-analysis and systematic review. J Thromb Haemost. 2024;22:423–429.
19. Yang J, He Z, Li M, et al. Risk of intracranial hemorrhage with direct oral anticoagulation versus low molecular weight heparin in the treatment of brain tumor-associated venous thromboembolism: a meta-analysis. J Stroke Cerebrovasc Dis. 2023;32:107243.
20. Marshall A, Levine M, Hill C et al. Treatment of cancer-associated venous thromboembolism: 12-month outcomes of the placebo versus rivaroxaban randomization of the SELECT-D Trial (SELECT-D: 12m). J Thromb Haemost. 2020 Apr;18(4):905-915. doi: 10.1111/jth.14752.
21. 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. EClinicalMedicine. 2023 Sep 8;64:102194. doi: 10.1016/j.eclinm.2023.102194.
22. Khorana AA, McCrae KR, Milentijevic D et al. Duration of anticoagulant therapy and VTE recurrence in patients with cancer. Support Care Cancer. 2019 Oct;27(10):3833-3840. doi: 10.1007/s00520-019-4661-3.
23. McBane RD 2nd, Loprinzi CL, Zemla T et al. EVE trial investigators. Extending venous thromboembolism secondary prevention with apixaban in cancer patients. The EVE trial. J Thromb Haemost. 2024 Jun;22(6):1704-1714. doi: 10.1016/j.jtha.2024.03.011. Epub 2024 Mar 25.
24. Mahé I, Carrier M, Mayeur D et al. API-CAT Investigators. Extended Reduced-Dose Apixaban for Cancer-Associated Venous Thromboembolism. N Engl J Med. 2025 Apr 10;392(14):1363-1373. doi: 10.1056/NEJMoa2416112.
25. Chatani R, Yamashita Y, Morimoto T et al. Edoxaban for 12 vs. 3 months in cancer-associated isolated distal deep vein thrombosis according to different doses: insights from the ONCO DVT study. Eur Heart J Cardiovasc Pharmacother. 2024 Aug 14;10(5):422-431. doi: 10.1093/ehjcvp/pvae028.
26. Bakht D, Arham M, Rashid Z et al. Reduced Versus Full-Dose Direct Oral Anticoagulants for Venous Thromboembolism in Cancer Patients: A Systematic Review and Meta-Analysis. EJHaem. 2025 Sep 24;6(5):e70155. doi: 10.1002/jha2.70155.
27. Lyon AR, López-Fernández T, Couch LS et al. ESC Scientific Document Group. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J. 2022 Nov 1;43(41):4229-4361. doi: 10.1093/eurheartj/ehac244.
28. Writing Committee Members; Creager MA, Barnes GD, Giri J et al. 2026 AHA/ACC/ACCP/ACEP/CHEST/SCAI/SHM/SIR/SVM/SVN Guideline for the Evaluation and Management of Acute Pulmonary Embolism in Adults: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2026 Mar 24;153(12):e977-e1051. doi: 10.1161/CIR.0000000000001415.