

Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: updated guidance from the SSC of the ISTH

Scope

Venous thromboembolism (VTE) represents a frequent and clinically relevant complication in patients with active malignancy, substantially contributing to morbidity and mortality [1]. Direct oral anticoagulants (DOACs) and low molecular weight heparins (LMWH) are recommended by clinical practice guidelines for the treatment of cancer-associated VTE. Earlier guideline recommendations were based on limited randomized clinical trial (RCT) evidence in the cancer setting. This document constitutes an update of the previous 2018 ISTH guidance statement to incorporate new RCT evidence, including evidence for treatment of cancer-associated VTE past the initial 6-month phase [2,3]. The structure of the current ISTH guidance follows the previous version [4], with some differences in the wording of recommendations based on changes in general ISTH statements, as outlined below.

Definition

1. Cancer patients

For this guidance document, we define active cancer as either a solid tumor diagnosed within the preceding 6 months; or, recurrent, locally advanced, or metastatic disease; or, cancer for which systemic therapy or other antineoplastic treatment has been administered within the past 6 months; or a hematologic malignancy that has not achieved complete remission. Patients with hematologic malignancies were underrepresented in randomized controlled trials of DOACs, and those included had largely lymphoma, chronic lymphocytic leukemia, or multiple myeloma. Acute leukemia was consistently excluded, as were non-melanoma skin cancers.

2. DOACs

DOACs currently approved in many countries for the treatment of VTE include the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors apixaban, edoxaban, and rivaroxaban.

Methods

For the identification of studies to be included in this guidance, we relied on a previously published systematic review and network meta-analysis that was conducted in accordance with established methodological standards and the PRISMA guidelines [5]. An additional search was performed across biomedical and multidisciplinary scientific databases, including PubMed/MEDLINE, Scopus, and Web of Science, to identify relevant studies published after the meta-analysis.

Iterative discussion and revision ensured that statement decisions and data interpretations were collectively reviewed and agreed upon by the Authors. For recommendations in which consensus of the authors was achieved and the recommendations were informed by higher-quality clinical studies with greater certainty of evidence, the term used for such recommendations is “we advise.” For recommendations in which consensus of the authors was achieved but the recommendations were informed by lower quality clinical studies with lower certainty of evidence, the term used for these recommendations is “we suggest.” The authors followed the ISTH Guidelines and Guidance Committee COI Policy and disclosed any relevant financial relationships with industry within the past 12 months. Authors who reported more than \$5,000 relevant direct financial conflicts and/or had major conflicts recused themselves from voting on the guidance statements.

Background

Evidence from RCTs in cancer patients

Several pivotal randomized trials in cancer patients evaluating DOACs have been performed since the 2018 guidance statement. Trial design and key results are summarized in Table 1. The Caravaggio trial randomized 1170 patients with cancer and acute symptomatic or incidental VTE to receive either oral apixaban (10 mg twice daily for the first 7 days, followed by 5 mg twice daily) or dalteparin (200 IU/kg once daily for the first month, followed by 150 IU/kg once daily) for 6 months [6]. The primary efficacy outcome was objectively confirmed recurrent VTE during the 6-month trial period. Recurrent events occurred in 5.6% of patients assigned to the apixaban group and in 7.9% of patients in the dalteparin group (hazard ratio [HR] 0.63; 95% confidence interval [CI] 0.37–1.07; $P < 0.001$ for non-inferiority; $P = 0.09$ for superiority). The principal safety outcome was major bleeding, which occurred in 3.8% of patients receiving apixaban and in 4.0% of those

receiving dalteparin (HR 0.82; 95% CI 0.40–1.69; P=0.60). Clinically relevant non-major bleeding occurred in 9.0% of patients in the apixaban arm and in 6.0% of those in the dalteparin arm (HR 1.42; 95% CI 0.88–2.30). The composite of recurrent VTE or major bleeding occurred in 8.9% and 11.4% of patients, respectively (HR 0.70; 95% CI 0.45–1.07). Death from any cause occurred in 23.4% of patients in the apixaban group and 26.4% in the dalteparin group. The CASTA-DIVA study compared rivaroxaban with dalteparin for the treatment of cancer-associated VTE over a 3-month period [7]. Overall, 158 patients with active cancer and acute VTE were randomized to either rivaroxaban (15 mg twice daily for 3 weeks followed by 20 mg once daily) or dalteparin (200 IU/kg once daily for 1 month followed by 150 IU/kg once daily). The primary endpoint, recurrent VTE at 3 months, occurred in 6.4% of patients treated with rivaroxaban and 10.1% of those treated with dalteparin (subdistribution hazard ratio 0.75; 95% CI 0.21–2.66). The predefined non-inferiority criterion was not met, primarily for early trial discontinuation due to slow accrual and limited statistical power. Major bleeding was infrequent, occurring in 1.4% of patients in the rivaroxaban group and 3.7% in the dalteparin group. The composite of major or clinically relevant nonmajor bleeding occurred in 12.2% and 9.8%, respectively. Overall mortality at 3 months was high and comparable between groups (25.7% vs 23.8%), largely driven by cancer progression. The CANVAS trial enrolled 671 patients with cancer and acute VTE to receive either a DOAC or LMWH for 6 months (the choice of anticoagulants was left to investigator's discretion) [8]. Recurrent VTE occurred in 6.1% of patients treated with a DOAC and 8.8% treated with LMWH, meeting criterion for noninferiority. Major bleeding occurred in 5.2% and 5.6% of patients, while clinically relevant nonmajor bleeding occurred in 5.8% and 2.6%, respectively. All-cause mortality at 6 months was 21.5% in the DOAC group and 18.4% in the LMWH group.

Additional new RCTs include ADAM VTE, ONCO PE, EVE and API-CAT trials [9-12]. ADAM VTE included 287 patients and compared apixaban with dalteparin for treating cancer-associated VTE over 6 months [9]. The primary endpoint was major bleeding, which occurred in none of the apixaban patients and in 1.4% of those receiving dalteparin. Recurrent VTE occurred in 0.7% vs 6.3%, respectively. The composite of major bleeding plus clinically relevant nonmajor bleeding was 6% in both groups. Mortality was mainly related to cancer progression. While quality-of-life outcomes measured monthly showed patients had more confidence that dalteparin provided protection against blood clots at one month, all other measures, including excess bruising, psychological distress and frustration, satisfaction with treatment, all favored apixaban.

ONCO-PE randomized 178 patients to receive 18 months versus 6 months of rivaroxaban [10]. Recurrent VTE occurred in 5.6% of patients in the 18-month group versus 19.1% in the 6-month group. Major bleeding occurred in 7.8% and 5.6% of patients, respectively, with no significant differences between the arms. The EVE trial included 360 cancer who had completed 6–12 months of anticoagulation for cancer-associated VTE and compared apixaban 2.5 mg versus 5 mg twice daily for an additional 12 months [11]. The composite of major bleeding plus clinically relevant nonmajor bleeding occurred in 8.9% in the 2.5-mg group and 12.2% in the 5-mg group (HR 0.72; $p=0.39$). Recurrent VTE occurred in 5.0% and 5.0% of patients, respectively, and all-cause mortality was similar at 13% vs 12%, with no significant difference in outcomes between the two doses. The API-CAT trial evaluated extended anticoagulation with reduced-dose apixaban in patients with cancer-associated VTE who had completed at least 6 months of anticoagulant therapy [12]. A total of 1,766 patients were randomized to receive apixaban 2.5 mg twice daily (reduced dose) or 5 mg twice daily (full dose) for an additional 12 months. The primary efficacy outcome was recurrent symptomatic or incidental VTE during the treatment period. Recurrent events occurred in 2.1% of patients receiving reduced-dose apixaban and in 2.8% of those receiving full-dose therapy, meeting criteria for non-inferiority (HR 0.76; 95% CI 0.41–1.41; p for non-inferiority <0.01). The principal safety outcome was clinically relevant bleeding (defined as the composite of centrally adjudicated major bleeding and clinically relevant non-major bleeding occurring during the 12-month treatment period), which occurred in 12.1% of patients in the reduced-dose group and 15.6% in the full-dose group (HR 0.75; 95% CI 0.58–0.97). Rates of major bleeding were numerically lower with the reduced dose. Overall mortality was comparable between groups, largely driven by the underlying malignancy.

Evidence from meta-analyses in cancer patients

Additional data about the use of DOACs for treatment of cancer-associated thrombosis have emerged from meta-analyses. A network meta-analysis of 17 RCTs ($n=6,623$) showed that DOACs have comparable efficacy in preventing recurrent VTE, with apixaban ranking highest and demonstrating superiority over LMWH without increasing bleeding risk. However, safety profiles slightly differ across DOACs: apixaban seemed to be associated with lower major bleeding compared with edoxaban, whereas rivaroxaban and edoxaban showed

higher rates of clinically relevant bleeding compared to apixaban. [5]. This difference in bleeding among DOAC is consistent with results from the COBRRA trial, which enrolled 2760 patients with acute VTE to receive apixaban or rivaroxaban for 3 months [13]. A significantly lower risk of clinically relevant bleeding with apixaban compared to rivaroxaban (3.3% vs 7.1%, HR 0.46; 95% CI 0.33-0.65 $p < 0.001$) was observed. However, cancer patients were excluded from COBRRA and therefore, these results should be interpreted with caution for those with cancer.

Patient preferences and values

While DOAC use offers practical advantages such as oral administration, fixed dosing, and no need for routine laboratory monitoring, these potential benefits should be balanced against potential drawbacks including bleeding risk, drug–drug interactions with anticancer therapies, and disease-related clinical features. Furthermore, the choice of anticoagulant for VTE treatment should not rely solely on efficacy and safety outcomes reported in clinical trials, but should also reflect patient preferences and values. VTE is often experienced as an unexpected complication and associated with psychological distress, irrespective of the attributed symptom burden. Preference studies using discrete-choice methodology have provided insight into the relative importance patients assign to each treatment characteristic. These analyses consistently indicate that avoiding interference with ongoing cancer therapy is the most valued attribute of anticoagulant treatment, followed by the reduction of recurrent VTE risk and then safety outcomes such as the risk of major bleeding. In contrast, route of administration, although relevant, appears to be less crucial when compared with efficacy and safety aspects [14,15]. In this context, anticoagulation therapy with LMWH is generally acceptable with the daily subcutaneous injection and is considered tolerable by many patients. Overall, these findings underscore the importance of shared decision-making in the management of cancer-associated VTE and the need for a thorough discussion with the patient, including their concerns and priorities.

Limitations and precautions

Several limitations exist regarding the evidence base. All three direct factor Xa inhibitor rivaroxaban, edoxaban and apixaban were evaluated in RCTs conducted in cancer patients and there is consensus about their higher efficacy, while concerns regarding an increased risk of bleeding (major bleeding and clinically relevant non-

major bleeding remain. However, there were discrepancies in the results between these trials. In contrast to HOKUSAI-VTE and SELECT-D trials [16, 17], in which higher risk of bleeding was observed with edoxaban and rivaroxaban respectively, in CARAVAGGIO, there was no excess risk of major bleeding [3.8% with apixaban vs 4.0% with dalteparin (HR 0.82; 95% CI 0.40–1.69); clinically relevant non-major bleeding was 9.0% vs 6.0% (HR 1.42; 95% CI 0.88–2.30)]. However, the studies of apixaban were conducted after the higher risk of bleeding in the original DOAC trials had already been noted, thus raising concerns for selection bias (in terms of bleeding risk or cancer types) in later studies. In this context, a prospective cohort study of 1,392 patients (not randomly allocated to treatment arms) demonstrated an overall rate of major and clinically relevant non-major bleeding in patients with GI cancer were similar to those in patients with non-GI cancer across apixaban, rivaroxaban, and enoxaparin treatment groups [18]. However, apixaban was associated with a significantly higher major bleeding rate in luminal GI cancer compared with non-GI cancer and with enoxaparin in luminal GI cancer. Therefore, for patients with GI tumors or high luminal bleeding risk, LMWH remains the preferable choice, with DOAC being a less desirable alternative.

All direct factor Xa inhibitors are susceptible to drug-drug interactions due to their dependence on the P-glycoprotein transporter, whereas rivaroxaban and apixaban, and to a lesser extent edoxaban, are additionally influenced by cytochrome P450 3A4 (CYP3A4)-dependent metabolism. Consequently, the concomitant administration of strong inhibitors or inducers of CYP3A4 and P-glycoprotein, such as certain tyrosine kinase inhibitors, may alter the pharmacokinetics of direct factor Xa inhibitors. While there has been some evidence that concomitant administration of anticancer agents does not impact the efficacy and safety of DOACs [19], LMWHs are preferred when there are concerns for strong or potent drug-drug interaction because they lack pharmacokinetic interactions. Given that DOACs are administered orally, the use of LMWH in cases of dysphagia, upper digestive tract obstruction, as well as emesis from highly emetogenic chemotherapy regimens, need to be considered and discussed with patients. Since patients with severe renal impairment (CrCl < 30 ml/min) were excluded from pivotal trials, data on DOACs' efficacy are lacking and, therefore, dose-adjusted LMWH may represent the most suitable option in these patients. Other patient characteristics, e.g., extremes of body weight, require additional caution and may warrant dose adjustment [20,21]. Finally, the use of DOACs in the setting of thrombocytopenia is not recommended below a platelet count of 50,000/uL as no robust evidence is available [22].

Guidance statements

1. We advise individualized treatment regimens after shared decision-making with patients, incorporating patient preferences and values. In particular, the choice of anticoagulant may be influenced by the risk of bleeding, potential drug-drug interactions, integrity of the GI tract for oral medication administration, and renal function.
2. We advise the use of full-dose DOACs (either apixaban, edoxaban or rivaroxaban) for cancer patients with an acute diagnosis of VTE, a low risk of bleeding, and no concerns for drug–drug interactions for at least six months of treatment. LMWHs constitute an acceptable alternative and are preferred in case of concern for drug-drug interactions and severe renal impairment.
3. We suggest the use of LMWH monotherapy in the setting of gastrointestinal or genitourinary cancers with a luminal primary lesion that are at high risk of bleeding. DOACs are an acceptable alternative based on patient preference and willingness to accept an increased risk of bleeding.
4. We advise the use of reduced-dose apixaban (2.5 mg twice daily) after six months of anticoagulation in cancer patients for whom extended use of anticoagulation is being considered.

References

1. Mulder FI, Horváth-Puhó E, van Es N, et al. Venous thromboembolism in cancer patients: a population-based cohort study. *Blood*. 2021;137:1959–1969.
2. Agnelli G, Becattini C, Meyer G, et al. Apixaban for the treatment of venous thromboembolism associated with cancer (Caravaggio). *N Engl J Med*. 2020;382:1599–1607
3. Planquette B, Bertolotti L, Charles-Nelson A, et al. Rivaroxaban vs Dalteparin in Cancer-Associated Thromboembolism: A Randomized Trial. *Chest*. 2022;161(3):781-790. doi:10.1016/j.chest.2021.09.037
4. Khorana AA, Noble S, Lee AYY, et al. Role of direct oral anticoagulants in the treatment of cancer-associated thrombosis: guidance from the ISTH. *J Thromb Haemost*. 2018;16:1891–1894.
5. Fujisaki T, Sueta D, Yamamoto E, et al. Comparing Anticoagulation Strategies for Venous Thromboembolism Associated With Active Cancer: A Systematic Review and Meta-Analysis. *JACC CardioOncol*. 2024;6(1):99-113. Published 2024 Jan 9. doi:10.1016/j.jacc.2023.10.00
6. Agnelli G, Becattini C, Meyer G, et al. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. *N Engl J Med*. 2020;382(17):1599-1607. doi:10.1056/NEJMoa1915103
7. Planquette B, Bertolotti L, Charles-Nelson A, et al. Rivaroxaban vs Dalteparin in Cancer-Associated Thromboembolism: A Randomized Trial. *Chest*. 2022;161(3):781-790. doi:10.1016/j.chest.2021.09.037
8. Schrag D, Uno H, Rosovsky R, et al. Direct Oral Anticoagulants vs Low-Molecular-Weight Heparin and Recurrent VTE in Patients With Cancer: A Randomized Clinical Trial. *JAMA*. 2023;329(22):1924-1933. doi:10.1001/jama.2023.7843
9. 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;18(2):411-421. doi:10.1111/jth.14662
10. Yamashita Y, Morimoto T, Muraoka N, et al. Rivaroxaban for 18 Months Versus 6 Months in Patients With Cancer and Acute Low-Risk Pulmonary Embolism: An Open-Label, Multicenter,

Randomized Clinical Trial (ONCO PE Trial). *Circulation*. 2025;151(9):589-600.

doi:10.1161/CIRCULATIONAHA.124.072758

11. McBane RD 2nd, Loprinzi CL, Zemla T, et al. Extending venous thromboembolism secondary prevention with apixaban in cancer patients. The EVE trial. *J Thromb Haemost*. 2024;22(6):1704-1714. doi:10.1016/j.jtha.2024.03.011
12. Mahé I, Carrier M, Mayeur D, et al. Extended Reduced-Dose Apixaban for Cancer-Associated Venous Thromboembolism. *N Engl J Med*. 2025;392(14):1363-1373. doi:10.1056/NEJMoa2416112
13. Castellucci LA, Chen VM, Kovacs MJ, et al. Bleeding Risk with Apixaban vs. Rivaroxaban in Acute Venous Thromboembolism. *N Engl J Med*. 2026;394(11):1051-1060. doi:10.1056/NEJMoa2510703
14. Noble S, Matzdorff A, Maraveyas A, Holm MV, Pisa G. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. *Haematologica*. 2015;100(11):1486-1492. doi:10.3324/haematol.2015.127126
15. Noble S, Prout H, Nelson A. Patients' Experiences of Living with CANcer-associated thrombosis: the PELICAN study. *Patient Prefer Adherence*. 2015;9:337-345. Published 2015 Feb 24. doi:10.2147/PPA.S79373
16. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. *N Engl J Med*. 2018;378(7):615-624. doi:10.1056/NEJMoa1711948
17. 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;36(20):2017-2023. doi:10.1200/JCO.2018.78.8034
18. Houghton DE, Vlazny DT, Casanegra AI, et al. Bleeding in Patients With Gastrointestinal Cancer Compared With Nongastrointestinal Cancer Treated With Apixaban, Rivaroxaban, or Enoxaparin for Acute Venous Thromboembolism. *Mayo Clin Proc*. 2021;96(11):2793-2805. doi:10.1016/j.mayocp.2021.04.026

19. Verso M, Munoz A, Bauersachs R, et al. Effects of concomitant administration of anticancer agents and apixaban or dalteparin on recurrence and bleeding in patients with cancer-associated venous thromboembolism. *Eur J Cancer*. 2021;148:371-381. doi:10.1016/j.ejca.2021.02.026
20. Boonyawat K, Caron F, Li A, et al. Association of body weight with efficacy and safety outcomes in phase III randomized controlled trials of direct oral anticoagulants: a systematic review and meta-analysis. *J Thromb Haemost*. 2017;15(7):1322-1333. doi:10.1111/jth.13701
21. Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2016;14(6):1308-1313. doi:10.1111/jth.13323
22. Kopolovic I, Lee AY, Wu C. Management and outcomes of cancer-associated venous thromboembolism in patients with concomitant thrombocytopenia: a retrospective cohort study. *Ann Hematol*. 2015;94(2):329-336. doi:10.1007/s00277-014-2198-6

Table 1. Randomized trials of anticoagulation for cancer-associated VTE published after 2018

Study	Study design	Treatment Arms	Follow-up	Recurrent VTE (%)	HR / OR (95% CI)	Major Bleeding (%)	HR / OR (95% CI)
CARAVAGGIO ⁶	Randomized, open-label, non-inferiority trial with blinded outcome adjudication	Apixaban vs Dalteparin	6 mo	5.6 vs 7.9	HR 0.63 (0.37–1.07)	3.8 vs 4.0	HR 0.82 (0.40–1.69)
ADAM-VTE ⁹	Randomized, open-label superiority trial	Apixaban vs Dalteparin	6 mo	0.7 vs 6.3	HR 0.099 (0.013–0.780)	0 vs 1.4	NE*
CASTA-DIVA ⁷	Randomized, open-label non-inferiority trial with blinded central adjudication	Rivaroxaban vs Dalteparin	3 mo	6.4 vs 10.1	SubHR 0.75 (0.21–2.66)	1.4 vs 3.7	SubHR 0.36 (0.04–3.43)
CANVAS ⁸	Randomized, unblind, non-inferiority comparative-effectiveness trial	DOAC vs LMWH	6 mo	6.1 vs 8.8	Risk diff –2.7%	5.2 vs 5.6	Risk diff –0.4%
ONCO-PE ¹⁰	Adjudicator-blinded randomized, open-label, superiority trial	Rivaroxaban 18 mo vs 6 mo	18 mo	5.6 vs 19.1	OR 0.25 (0.09–0.72)	7.8 vs 5.6	OR 1.43 (0.44–4.70)
EVE ¹¹	Randomized, double-blind trial	Apixaban 2.5 mg vs 5 mg	12 mo	5.0 vs 5.0	HR 1.0 (0.40–2.53)	2.8 vs 2.2	HR 1.26 (0.34–4.66)
API-CAT ¹²	Randomized, double-blind non-inferiority trial with blinded outcome adjudication	Apixaban 2.5 mg vs 5 mg	12 mo	2.1 vs 2.8	SubHR 0.76 (0.41–1.41)	—	SubHR 0.75 (0.58–0.97)

*NE = hazard ratio not estimable because of zero events in one arm; SubHR = subdistribution hazard ratio.

CRNMB = clinically relevant non-major bleeding; DOAC = direct oral anticoagulant; LMWH = low-molecular-weight heparin; VTE = venous thromboembolism.