Venous thromboembolism treatment in patients with cancer: reflections on an evolving landscape

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ABSTRACT

Cancer is a leading cause of morbidity and mortality worldwide. It is also one of the strongest risk factors for venous thromboembolism (VTE), reported in approximately 20% of all cases of VTE diagnosed. The thrombotic effect of cancer and its treatments, however, is highly variable among patients and changes over the course of their cancer. Anticoagulant therapy remains the cornerstone of VTE treatment, but it is associated with a substantial rate of VTE recurrence and the potential for serious bleeding. The risk of bleeding in patients with cancer is also dependent on the cancer type and its treatments, often revealing underlying tumor invasion of mucosal or parenchymal tissues, and treatment complications such as thrombocytopenia or coagulopathy. Over the past few decades, efforts to improve the efficacy and safety of anticoagulant therapy for the treatment and prevention of cancer-associated thromboembolism have resulted in changes in the standard of practice. This evolution has been made possible largely through the development of new anticoagulants. This review will reflect on the major advances in the treatment of cancer-associated thrombosis and offer insights on how to address unmet needs in this field.

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Introduction

Cancer is a leading cause of morbidity and death worldwide. In 2020, over 19 million new cases of cancer were diagnosed globally, and the annual incidence is continuing to climb.[1] Among these patients, just over 5 million were diagnosed with cancers of the pancreas, liver/biliary, lung, ovary, or stomach. These 5 tumor types are associated with the highest risks of venous thromboembolism (VTE) with incidence rates ranging from 66.4 to 156.0 per 1000-person years within the first 6 months after the cancer diagnosis.[2-4] However, because breast, lung, colorectal, and prostate cancers are the most commonly diagnosed cancers worldwide, they are the most prevalent cancers in patients diagnosed with cancer-associated thrombosis despite the relatively lower risk of thrombosis for breast and prostate (Figure 1).[2] The incidence of cancer-associated thrombosis is rising over time and it is associated with an increased mortality for all tumor types.[3] In addition to the tumor type, the extent of the cancer (*e.g.*, metastatic versus localized) and the prescribed systemic therapies (*e.g.*, surgery, chemotherapy, immunotherapy) contribute to each individual's risk of thrombosis.[5] Patient-specific factors, such as age, sex, race/ethnicity, and the presence of other prothrombotic conditions also influence the overall risk of thrombosis. The risk of bleeding in patients with cancer is also dependent on some of the same factors as thrombosis, along with a history of bleeding, chronic kidney disease, and use of antiplatelet agents.[6] Consequently, providing optimal patient-centered care for the treatment of cancer-associated thrombosis requires balancing a multitude of factors, including patient values and preferences, all of which can also change over time. Furthermore, managing patients with cancer-associated thrombosis has become more complex over the past two decades because of the rapidly changing landscape of cancer therapeutics, prolonged survival of patients with advanced disease, and the availability of more anticoagulant options with variable costs, convenience and accessibility.

Before the 1990s: heparin and vitamin K antagonists

Heparin and vitamin K antagonists (VKAs) were the only available anticoagulants for over half a century.[7] Heparin was discovered in 1916 and came into clinical use in the 1930s. The first randomized trial demonstrating the efficacy of anticoagulant therapy with unfractionated heparin in patients with pulmonary embolism was published in 1960.[8] Dicoumarol, a VKA no longer in use, was introduced for clinical use in the 1950s, and other VKAs, such as warfarin, remained the only long-term oral anticoagulant option for the next 5 decades. Although heparin and VKAs are cumbersome to use because of the requirement for laboratory monitoring and dose adjustments to achieve blood levels within a narrow therapeutic range, they remain in common use today for managing venous and arterial thrombosis. In fact, unfractionated heparin is still the drug of choice for coronary bypass surgery and critically ill or unstable patients with acute thrombotic events, while VKA is the drug of choice for thrombosis prevention in mechanical heart valves and antiphospholipid syndrome. Their 'reign' is expected to continue given their established efficacy in these settings, their low cost, and their rapid reversibility.

Between the 1970s and early 2000s, VTE treatment with heparin followed by warfarin was the standard of care for all patients, regardless of their cancer status.[9,10] It was recognized that outcomes were worse in patients with cancer, with higher rates of recurrent thrombosis, major bleeding and mortality. But without other anticoagulant options, cancer patients were sometimes treated with warfarin at a higher intensity which often resulted in more bleeding and worse outcomes.[9-11]

1990s: low molecular weight heparin is the new standard of care

To overcome the unpredictable pharmacodynamics of unfractionated heparin, low-molecular-weight heparin (LMWH) was developed in the 1990s.[7] Numerous randomized trials directly compared these agents for the initial treatment of acute VTE and meta-analyses of these studies demonstrated subcutaneous, weight-based dosing of various LMWHs is superior to intravenous heparin in reducing recurrent thrombosis and major bleeding.[12] LMWH also allowed outpatient treatment and thus revolutionized acute care delivery in VTE. But the need to use warfarin for long-term treatment and secondary prevention (because no other oral agents were available) remained unsatisfactory. This was particularly challenging in patients with cancer, in whom the time-in-therapeutic range for the INR was suboptimal because of drug-drug interactions, poor nutrition, and gastrointestinal toxicity.[9,10] The requirement for venipunctures is especially traumatic to patients with difficult venous access after multiple rounds of chemotherapy. This prompted the investigation of using LMWH for initial and long-term treatment, instead of transitioning to warfarin. Following the publication of the CLOT trial and several other randomized trials, all major clinical practice guidelines endorsed using LMWH over VKA as first-line treatment for cancer-associated thrombosis.[13]

Meta-analyses showed LMWH offered a risk reduction of 53% in symptomatic recurrent thrombosis without increasing the risk of major bleeding compared with VKA.[14] However, the lack of survival benefits, the unpleasantness of daily injections and the high cost of LMWH are major barriers in implementing the change in practice and maintaining adherence.[15] Worldwide, VKA

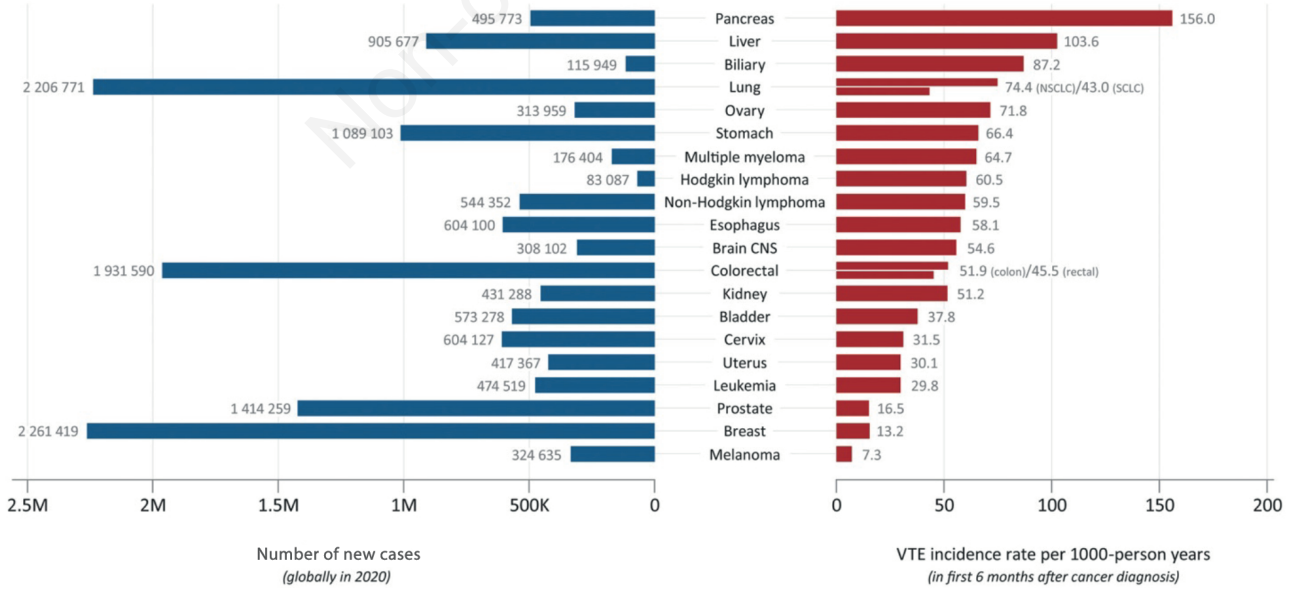

Figure 1. The burden of cancer and thrombosis in patients with cancer. This figures summaries the estimated number of new cases of cancer for major types of cancer reported globally in 2020 and the incidence rate of thrombosis per 1000-person years in the first 6 months after cancer diagnosis.[1,4]

therapy remains a commonly used anticoagulant, especially in those with limited government reimbursement or insurance coverage, living in low-income areas, and in patients who are unable to inject.[16-18]

Early 2000s: specific factor inhibition with fondaparinux and direct thrombin inhibitor

Development of fondaparinux in 1997 delivered the proof of concept that selective inhibition of activated factor X (FXa) alone was effective and safe in treating acute VTE.[7] Fondaparinux was the first synthetic, small molecule parenteral anticoagulant that can be given at a fixed dose as a once-daily subcutaneous injection. Clinical trials demonstrated that fondaparinux was comparable to LMWH in efficacy and safety but a subgroup, post-hoc analysis of patients with cancer in the Matisse-DVT trial suggested that fondaparinux was less efficacious than LMWH in this population.[19] Further studies were not done to verify this finding and the lack of any practical advantage (in terms of cost and route of administration) over LMWH likely made fondaparinux a less attractive alternative to LMWH. Further development of small molecules that were selective and potent inhibitors of FXa or thrombin followed.[7] Dabigatran became the first direct oral anticoagulant (DOAC) that showed efficacy and safety compared with VKA for the acute and long-term treatment for VTE. Although a lead-in period of 5 days of LMWH prior to dabigatran use is required, the convenience of this direct thrombin inhibitor with a fixed, twice-daily dosing regimen and far fewer drug and food interactions compared with warfarin was obvious. A subgroup, post-hoc analysis also suggested that dabigatran could be potentially useful in patients with cancer and thrombosis.[20] However, dabigatran has not been compared directly with LMWH and it is not recommended for use in this setting by most clinical practice guidelines.[21,22]

2010s: direct oral anticoagulant in cancer-associated thrombosis

On the heels of dabigatran, randomized trials of oral FXa inhibitors in VTE treatment were published between 2010 and 2013.[23] All were of similar design and showed that each DOAC was non-inferior to standard treatment with heparin/LMWH followed by VKA in reducing recurrent thrombosis. The risks of major and clinically relevant non-major bleeding were also similar between DOAC and VKA. About 6% of patients in these studies had active cancer or a history of cancer and the subgroup analyses of these highly selected patients with cancer suggested DOAC is comparable with warfarin.[24] However, it was evident that the cancer patient populations enrolled in DOAC *vs*. VKA trials were *healthier* than those in LMWH *vs*. VKA trials, as the rates of recurrent VTE, bleeding and mortality were lower in DOAC trials.[24] Network meta-analyses of these early trials suggested that DOAC would be comparable to warfarin and also LMWH for treatment of cancer-associated thrombosis.[25]

Cancer-associated thrombosis treatment studies comparing DOAC directly with LMWH soon followed.[26] The first randomized trial (Hokusai VTE Cancer) studying edoxaban was published in 2018 and the largest trial (Caravaggio) evaluating apixaban was reported in 2020. Smaller studies (SELECT-D and CASTA-DIVA) described the outcomes for rivaroxaban. Some studies excluded certain types of cancer, such as primary brain cancers, and all studies excluded patients with a high risk of bleeding, hepatic impairment or severe renal dysfunction, or poor performance status (Eastern Cooperative Oncology Group 3-4).[26] They demonstrated that DOAC is non-inferior to LMWH in efficacy but varied in the relative risk of clinically relevant bleeding. A meta-analysis combining the results of all randomized controlled trials demonstrated that DOAC, compared with LMWH, is associated with a significantly lower risk of recurrent VTE [relative risk (RR), 0.67 (95% CI, 0.52-0.84)], a non-significant increased risk of major bleeding [RR, 1.17 (95% CI, 0.82-1.67)], and a significant increase in clinically relevant non-major bleeding [RR, 1.66 (95% CI, 1.31-2.09)].[27] The higher rates of bleeding were largely driven by gastrointestinal bleeding, occurring mostly in patients with gastrointestinal cancers and particularly in those with unresected luminal tumors.[28,29] Other sites of clinically relevant bleeding included hematuria, abnormal uterine bleeding or epistaxis. Although real-world data have also emerged to suggest that DOACs may carry different bleeding risks, head-to-head comparisons are needed to verify these observations given the significant heterogeneity of the patient populations. Other clinically important differences among DOACs include mechanisms of drug-drug interactions, oral bioavailability and sites of gastrointestinal absorption.[21,22,26]

The totality of evidence and major clinical practice guidelines to date indicate that direct oral FXa inhibitors (apixaban, edoxaban and rivaroxaban), LMWH and warfarin all have important roles and limitations in the treatment of cancer-associated thrombosis.[21,22,26] The complexity of this patient population demands individualized therapy that cannot be met with any single class of these anticoagulants. For example, many clinical scenarios associated with a higher risk of bleeding lack high-quality evidence to guide management.[26,30] Up to 13% of cancer patients on anticoagulant therapy experience major bleeding, with a case-fatality rate of 8.9% in patients with cancer.[6,31]

2020s: factor XI inhibition is the new frontier

To reduce the risk of anticoagulant-related bleeding, new targets in the coagulation cascade are being examined. The most promising of these is factor XI (FXI) in the contact pathway.[32] Based on epidemiology data, observational studies and animal models, selective inhibition FXI could be effective in reducing thrombosis without interfering with hemostasis.[32,33] Inhibition of the contact pathway might also offer improved efficacy in management of thrombosis associated with foreign materials in medical devices such as central venous catheters and mechanical heart valves. Currently, this upstream blockade approach is being investigated in clinical trials for stroke prevention in atrial fibrillation, treatment of acute coronary syndrome, thromboprophylaxis in total joint arthroplasty, and cancer-associated thrombosis.

Abelacimab, a human IgG1 monoclonal antibody that binds to FXI and blocks its activation by activated FXII or thrombin, is the first FXI inhibitor being evaluated for treatment of cancer-associated thrombosis. Two complementary phase 3 randomized trials are currently enrolling patients with active cancer and VTE. The ASTER trial (NCT05171049) is comparing abelacimab with

apixaban in patients who are eligible for DOAC therapy, while the MAGNOLIA trial (NCT051171075) is comparing abelacimab with LMWH in patients with gastrointestinal or genitourinary cancers. Potential drawbacks of abelacimab are that it has a half-life of about 20 days, and it is a parenteral agent. But some argue that once-monthly subcutaneous injection could improve persistence and adherence with therapy over the long term if administration is timed with regular oncology visits. Abelacimab also does not rely on gastrointestinal absorption or renal or hepatic clearance, which are barriers for DOAC use in some patients. But unlike DOACs which are short-acting and have rapid reversal agents available, abelacimab has a prolonged anticoagulant effect and there are no proven methods for controlling serious bleeding.[34] Shorter-acting, small molecules that block the active site of FXIa, such as asundexian and milvexian, are also under investigation in a number of cardiovascular settings, but studies of these oral agents in cancer-associated thrombosis are not yet available.[33]

Unmet clinical needs: more work ahead

Without a doubt, the effectiveness, convenience and lower cost of DOACs have made treatment of cancer-associated thrombosis more accessible and acceptable for many patients. Still, there are many areas where DOAC and other anticoagulants fall short in the treatment of thrombosis in these complex and heterogeneous patients.[26,30]

Anticoagulant-related bleeding poses one of the biggest challenges and fears in treating patients with cancer-associated thrombosis. FXI inhibition might improve the risk-benefit profile but there may be other ways to reduce bleeding. For example, avoiding unnecessary invasive procedures and paying closer attention to renal and hepatic function will help to reduce iatrogenic instances of bleeding, and primary prophylaxis with proton pump inhibition might reduce upper gastrointestinal bleeding.[35] Using non-anticoagulant agents that target pathways (*e.g.*, complement system) that can activate coagulation or the vascular endothelium is also worthy of investigation.[36-38] Also, as we learn more about cancer-specific mechanisms of thrombosis, targeting the molecular pathways involved might offer even more precise therapy.[39]

Patients with unusual site thrombosis (*e.g.*, splanchnic vein thrombosis), primary brain cancer, untreated intracranial metastasis, severe thrombocytopenia, and shorter life expectancy are routinely excluded from clinical trials participation. Yet, these patients might experience the most harm when it comes to anticoagulant therapy.[40,41] Reluctantly, clinicians extrapolate findings from clinical trials and often rely on retrospective analyses from administrative data sets. Results from such *real world* studies are often outdated and contain inherent biases (*e.g.*, confounding by indication). More organized and collaborative research efforts are needed to provide higher-quality evidence to manage these vulnerable patients.

Another area where data are lacking is in the management of refractory or 'breakthrough' thrombosis, when patients develop recurrent thrombosis despite being on therapeutic anticoagulation. This is a common outcome and yet little therapeutic advancement has been made over the past decades. The best available evidence remains small, retrospective studies and registries that reported dose escalation of LMWH can be effective and appears safe.[42] Applying the same principle by using higher doses of DOAC has not been studied and carries a heightened concern for bleeding. Importantly, drug-drug interaction, reduced gastrointestinal absorption and poor treatment adherence should be excluded as potential causes of refractory thrombosis before concluding there is true treatment failure.[26,42]

Optimal duration and dosing for extended anticoagulation, an issue that is encountered in all patients, remains inadequately addressed in cancer-associated thrombosis.[42] One randomized trial has shown that treatment of cancer patients with isolated distal DVT with edoxaban for 12 months reduced symptomatic recurrent VTE or VTE-related death compared with 3 months.[43] An ongoing randomized trial (APICAT NCT03692065) is comparing standard- with low-dose apixaban for secondary prevention after 6 months or more of full-dose anticoagulation.[44] Guideline recommendations to continue anticoagulant therapy beyond 6 months in patients with active cancer, metastatic disease or who are receiving anticancer therapy are largely based on expert experience. This seems reasonable when the risk of recurrent thrombosis remains at 5-15% even after the first 6 months of anticoagulant therapy, but information on thrombosis and bleeding beyond the first year of the thrombotic event is scarce.[2,45,46] Nevertheless, we do recognize now that the risk-benefit balance might be tipped towards avoiding anticoagulant therapy in patients in the palliative phase of their cancer.[47] It is also important to note that advancements in cancer care have further complicated this decision process as an increasing number of cancer patients enjoy extended survival. For example, as maintenance therapy becomes the standard of care for a multitude of malignancies (*e.g.*, immunomodulatory therapy for myeloma, check-point inhibitors in non-small cell lung cancer), identifying when it is safe to stop anticoagulant therapy for patients with metastatic cancer will have a substantial impact. Biomarkers and risk assessment models might play an important role in risk prediction in this setting.[45,48]

Targeting tumor growth might be an essential strategy to manage cancer-associated thrombosis.[49] Experimental data in the 1950s first offered plausible mechanisms of anticancer effects for anticoagulants and this hypothesis was then tested in an observational study in 1964, which reported a beneficial effect of VKA on mortality in patients with cancer.[50] Almost 20 years later, this field of research was ignited when a randomized trial in 1981 showed that warfarin was associated with significant improvement in overall survival in patients with small-cell lung cancer.[51] However, enthusiasm dimmed when subsequent studies in other types of cancer provided negative results.[52] Over the past 20 years, a similar cycle of research studying heparins and LMWH followed, with preclinical studies continuing to provide evidence that anticoagulants, particularly LMWH, may have antitumor effects (*e.g.*, antiangiogenesis) while clinical studies in different settings (*e.g.*, tumor type and stage) produced provocative but inconsistent results on cancer patient survival.[53,54] Now, 60 years later, we are circling back to the hypothesis that warfarin, compared with LMWH or DOAC, is associated with a survival benefit in cancer patients.[55] Since none of the randomized controlled trials comparing warfarin with LMWH or DOAC demonstrated any difference in 6-month survival, these recent observations from administrative databases might reflect confounding by indication from the selection of patients with better prognosis to receive warfarin. It remains uncertain if anticoagulant therapy has any meaningful antitumor effects, and if present, in what specific clinical scenarios.

Finally, patient quality of life of and racial, ethnic and social disparities have not been well studied in cancer-associated thrombosis.[56,57] Evidence available indicates that thrombosis is a dramatically adverse event that is under estimated by the medical community and vulnerable populations might be affected more negatively.[57-59] While the incidence of thrombosis varies among Blacks, Whites and Asians, the bulk of published literature on epidemiology, prevention and treatment are largely derived from White populations and from higher-income nations.[58,60] Across many parts of the world, the anticoagulant choices made may be less dependent on science and more dictated by practical issues such as accesibility.[16-18,60]

Conclusions

Major achievements have been made in the management of cancer-associated thrombosis over the past decades. The availability of more anticoagulant options and a better appreciation of patient preferences and values have changed clinical practice. Further improvements will require novel approaches, such as inhibiting coagulation without disturbing hemostasis, adopting innovative research methodologies, embracing risk in challenging clinical settings, and broadening research collaboration around the globe. We must also pay more attention to equity, inclusion and diversity; so that as we march forward to break new ground, we must also look back, look outside the box, and look beyond *the usual suspects*.

References

1. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, et al. Cancer statistics for the year 2020: an overview. Int J Cancer 2021.
2. Cohen AT, Katholing A, Rietbrock S, et al. Epidemiology of first and recurrent venous thromboembolism in patients with active cancer. A population-based cohort study. Thromb Haemost 2017;117:57-65.
3. Mahajan A, Brunson A, Adesina O, et al. The incidence of cancer-associated thrombosis is increasing over time. Blood Adv 2022;6:307-20.
4. Mulder FI, Horvath-Puho E, van Es N, et al. Venous thromboembolism in cancer patients: a population-based cohort study. Blood 2021;137:1959-69.
5. Khorana AA, Connolly GC. Assessing risk of venous thromboembolism in the patient with cancer. J Clin Oncol 2009;27:4839-47.
6. Frere C, Font C, Esposito F, et al. Incidence, risk factors, and management of bleeding in patients receiving anticoagulants for the treatment of cancer-associated thrombosis. Support Care Cancer 2022;30:2919-31.
7. Hirsh J, Eikelboom JW, Chan NC. Fifty years of research on antithrombotic therapy: achievements and disappointments. Eur J Intern Med 2019;70:1-7.
8. Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet 1960;1:1309-12.
9. Levine M, Hirsh J. The diagnosis and treatment of thrombosis in the cancer patient. Semin Oncol 1990;17:160-71.
10. Sutherland DE, Weitz IC, Liebman HA. Thromboembolic complications of cancer: epidemiology, pathogenesis, diagnosis, and treatment. Am J Hematol 2003;72:43-52.
11. Chan A, Woodruff RK. Complications and failure of anticoagulation therapy in the treatment of venous thromboembolism in patients with disseminated malignancy. Aust N Z J Med 1992;22:119-22.
12. van Dongen CJ, van den Belt AG, Prins MH, Lensing AW. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database Syst Rev 2004:CD001100.
13. Khorana AA, Streiff MB, Farge D, et al. Venous thromboembolism prophylaxis and treatment in cancer: a consensus statement of major guidelines panels and call to action. J Clin Oncol 2009;27:4919-26.
14. Akl EA, Kahale L, Barba M, et al. Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer. Cochrane Database Syst Rev 2014:CD006650.
15. Khorana AA, McCrae KR, Milentijevic D, et al. Current practice patterns and patient persistence with anticoagulant treatments for cancer-associated thrombosis. Res Pract Thromb Haemost 2017;1:14-22.
16. Athanazio RA, Ceresetto JM, Marfil Rivera LJ, et al. direct oral anticoagulants for the treatment of cancer-associated venous thromboembolism: a latin american perspective. Clin Appl Thromb Hemost 2022;28:10760296221082988.
17. Chew TW, Gau CS, Wen YW, et al. Epidemiology, clinical profile and treatment patterns of venous thromboembolism in cancer patients in Taiwan: a population-based study. BMC Cancer 2015;15:298.
18. Rahme E, Feugere G, Sirois C, et al. Anticoagulant use in patients with cancer associated venous thromboembolism: a retrospective cohort study. Thromb Res 2013;131:210-7.
19. van Doormaal FF, Raskob GE, Davidson BL, et al. Treatment of venous thromboembolism in patients with cancer: subgroup analysis of the Matisse clinical trials. Thromb Haemost 2009;101:762-9.
20. Schulman S, Goldhaber SZ, Kearon C, et al. Treatment with dabigatran or warfarin in patients with venous thromboembolism and cancer. Thromb Haemost 2015;114:150-7.
21. Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol 2020;38:496-520.
22. Lyman GH, 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.
23. van Es N, Coppens M, Schulman S, et al. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood 2014;124:1968-75.
24. Carrier M, Cameron C, Delluc A, Castellucci L, Khorana AA, Lee AY. Efficacy and safety of anticoagulant therapy for the treatment of acute cancer-associated thrombosis: a systematic review and meta-analysis. Thromb Res 2014;134:1214-9.
25. Rossel A, Robert-Ebadi H, Combescure C, et al. Anticoagulant therapy for acute venous thrombo-embolism in cancer patients: a systematic review and network meta-analysis. PLoS One 2019;14:e0213940.
26. Carrier M, Blais N, Crowther M, et al. Treatment algorithm

in cancer-associated thrombosis: updated canadian expert consensus. Curr Oncol 2021;28:5434-51.
27. Frere C, Farge D, Schrag D, et al. Direct oral anticoagulant versus low molecular weight heparin for the treatment of cancer-associated venous thromboembolism: 2022 updated systematic review and meta-analysis of randomized controlled trials. J Hematol Oncol 2022;15:69.
28. Ageno W, Vedovati MC, Cohen A, et al. Bleeding with apixaban and dalteparin in patients with cancer-associated venous thromboembolism: results from the Caravaggio Study. Thromb Haemost 2021;121:616-24.
29. Kraaijpoel N, Di Nisio M, Mulder FI, et al. Clinical impact of bleeding in cancer-associated venous thromboembolism: results from the Hokusai VTE cancer study. Thromb Haemost 2018;118:1439-49.
30. Wang TF, Khorana AA, Agnelli G, et al. Treatment of cancer-associated thrombosis: recent advances, unmet needs, and future direction. Oncologist 2023;28:555-64.
31. Abdulla A, Davis WM, Ratnaweera N, et al. A meta-analysis of case fatality rates of recurrent venous thromboembolism and major bleeding in patients with cancer. Thromb Haemost 2020;120:702-13.
32. Weitz JI, Chan NC. Novel antithrombotic strategies for treatment of venous thromboembolism. Blood 2020;135:351-9.
33. Santagata D, Donadini MP, Ageno W. Factor XI inhibitors for the prevention of cardiovascular disease: a new therapeutic approach on the horizon? Blood Rev 2023;62:101119.
34. Salomon O, Gailani D. A proposal for managing bleeding in patients on therapeutic factor XI(a) inhibitors. J Thromb Haemost 2022;20:32-8.
35. Ray WA, Chung CP, Murray KT, et al. Association of oral anticoagulants and proton pump inhibitor cotherapy with hospitalization for upper gastrointestinal tract bleeding. JAMA 2018;320:2221-30.
36. Joseph P, Glynn R, Lonn E, et al. Rosuvastatin for the prevention of venous thromboembolism: a pooled analysis of the HOPE-3 and JUPITER randomized controlled trials. Cardiovasc Res 2022;118:897-903.
37. Stopa JD, Zwicker JI. The intersection of protein disulfide isomerase and cancer associated thrombosis. Thromb Res 2018;164:S130-S5.
38. Beckman JD, DaSilva A, Aronovich E, et al. JAK-STAT inhibition reduces endothelial prothrombotic activation and leukocyte-endothelial proadhesive interactions. J Thromb Haemost 2023;21:1366-80.
39. Hisada Y, Mackman N. Cancer-associated pathways and biomarkers of venous thrombosis. Blood 2017;130:1499-506.
40. Carney BJ, Wang TF, Ren S, et al. Anticoagulation in cancer-associated thromboembolism with thrombocytopenia: a prospective, multicenter cohort study. Blood Adv 2021;5:5546-53.
41. Cohen O, Caiano LM, Levy-Mendelovich S. Cancer-associated splanchnic vein thrombosis: clinical implications and management considerations. Thromb Res 2024;234:75-85.
42. Sanfilippo KM, Moik F, Candeloro M, et al. Unanswered questions in cancer-associated thrombosis. Br J Haematol 2022;198:812-25.
43. Yamashita Y, Morimoto T, Muraoka N, et al. Edoxaban for 12 months versus 3 months in patients with cancer with isolated distal deep vein thrombosis (ONCO DVT study): an open-label, multicenter, randomized clinical trial. Circulation 2023;148:1665-76.
44. Mahe I, Agnelli 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.
45. Otero R, Solier-Lopez A, Sanchez-Lopez V, et al. Biomarkers of venous thromboembolism recurrence after discontinuation of low molecular weight heparin treatment for cancer-associated thrombosis (HISPALIS-Study). Cancers (Basel) 2022;14.
46. Schmidt RA, Al Zaki A, Desilet N, et al. Patient characteristics and long-term outcomes beyond the first 6 months after a diagnosis of cancer-associated venous thromboembolism. Thromb Res 2020;188:106-14.
47. White C, Noble SIR, Watson M, et al. Prevalence, symptom burden, and natural history of deep vein thrombosis in people with advanced cancer in specialist palliative care units (HIDDen): a prospective longitudinal observational study. Lancet Haematol 2019;6:e79-e88.
48. Candeloro M, Guman NAM, Kraaijpoel N, Di Nisio M. Risk assessment models for thrombosis and anticoagulant-related bleeding in ambulatory cancer patients. Semin Thromb Hemost 2021;47:972-81.
49. Tawil N, Bassawon R, Rak J. Oncogenes and clotting factors: the emerging role of tumor cell genome and epigenome in cancer-associated thrombosis. Semin Thromb Hemost 2019;45:373-84.
50. Michaels L. Cancer incidence and mortality in patients having anticoagulant therapy. Lancet. 1964;2:832-5.
51. Zacharski LR, Henderson WG, Rickles FR, et al. Effect of warfarin on survival in small cell carcinoma of the lung. Veterans Administration Study No. 75. JAMA 1981;245:831-5.
52. Smorenburg SM, Vink R, Otten HM, Swaneveld F, Buller HR. The effects of vitamin K-antagonists on survival of patients with malignancy: a systematic analysis. Thromb Haemost 2001;86:1586-7.
53. Montroy J, Lalu MM, Auer RC, et al. The efficacy and safety of low molecular weight heparin administration to improve survival of cancer patients: a systematic review and meta-analysis. Thromb Haemost 2020;120:832-46.
54. Mousa SA, Petersen LJ. Anti-cancer properties of low-molecular-weight heparin: preclinical evidence. Thromb Haemost 2009;102:258-67.
55. Chiasakul T, Zwicker JI. The impact of warfarin on overall survival in cancer patients. Thromb Res 2022;213:S113-S9.
56. Datta T, Brunson A, Mahajan A, et al. Racial disparities in cancer-associated thrombosis. Blood Adv 2022;6:3167-77.
57. Wiredu C, Haynes N, Guerra C, Ky B. Racial and ethnic disparities in cancer-associated thrombosis. Thromb Haemost 2022;122:662-5.
58. da Costa WL, Jr., Guffey D, Oluyomi A, et al. Patterns of venous thromboembolism risk, treatment, and outcomes among patients with cancer from uninsured and vulnerable populations. Am J Hematol 2022;97:1044-54.
59. Noble S, Prout H, Nelson A. Patients' experiences of LIving with CANcer-associated thrombosis: the PELICAN study. Patient Prefer Adherence 2015;9:337-45.
60. Lee LH, Nagarajan C, Tan CW, Ng HJ. Epidemiology of cancer-associated thrombosis in Asia: a systematic review. Front Cardiovasc Med 2021;8:669288.