

EVIDENCE BASED STATEMENT

DOMAIN **06**, Statement **05**

TOPIC: “Cancer-related venous thrombosis management”

SEARCH TERMS & SOURCES

("venous thrombosis" OR "venous thromboembolism" OR "VTE") AND ("cancer" OR "malignancy")
AND ("management" OR "treatment") AND ("meta analysis" OR "systematic Review")

INCLUSION CRITERIA

Systematic review or meta-analysis, 2012-2022
Focused on management of VTE in cancer patients
Available in English

SEARCH RESULT BEFORE - AFTER SELECTION

82 – 17

PERTINENT LITERATURE NOT IDENTIFIED BY THE LITERATURE SEARCH

1. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. Chest. 2021 Dec 1;160(6):e545-608.
2. Ferreira F, Pereira J, Lynce A, et al. Cancer Screening in Patients with Unprovoked Thromboembolism: How to do it and Who Benefits?. Cureus. 2020 Feb 10;12(2)
3. 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 advances. 2021 Feb 23;5(4):927-74.
4. Kakkos SK et al., European Society for Vascular Surgery (ESVS) 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis, Eur J Vasc Endovasc Surg 2020, <https://doi.org/10.1016/j.ejvs.2020.09.023>.

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IDENTIFIED REFERENCES

1. Moik F, Colling M, Mahé 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 Mar;20(3):619-634. doi: 10.1111/jth.15599. Epub 2021 Dec 8. PMID: 34816583.
2. Brandão GMS, Malgor RD, Vieceli T, et al. A network meta-analysis of direct factor Xa inhibitors for the treatment of cancer-associated venous thromboembolism. *Vascular.* 2022 Feb;30(1):130-145. doi: 10.1177/17085381211002726. Epub 2021 Apr 1. PMID: 33794711.
3. Chen Y, Mao M, Chang J, et al. Safety and efficacy of new oral anticoagulants compared to those of warfarin in AF patients with cancer: a meta-analysis of randomized clinical trials and observational studies. *Eur J Clin Pharmacol.* 2021 Jun;77(6):849-857. doi: 10.1007/s00228-021-03132-x. Epub 2021 Apr 1. PMID: 33791828.
4. Carrier M, Blais N, Crowther M, et al. Treatment Algorithm in Cancer-Associated Thrombosis: Updated Canadian Expert Consensus. *Curr Oncol.* 2021 Dec 18;28(6):5434-5451. doi: 10.3390/currenconcol28060453. PMID: 34940092; PMCID: PMC8700468.
5. Mohamed MFH, ElShafei MN, Ahmed MB, et al. The Net Clinical Benefit of Rivaroxaban Compared to Low-Molecular-Weight Heparin in the Treatment of Cancer-Associated Thrombosis: Systematic Review and Meta-Analysis. *Clin Appl Thromb Hemost.* 2021 Jan-Dec;27:1076029620940046. doi: 10.1177/1076029620940046. PMID: 33651658; PMCID: PMC7930650.
6. Lyman GH, Kuderer NM. Clinical practice guidelines for the treatment and prevention of cancer-associated thrombosis. *Thromb Res.* 2020 Jul;191 Suppl 1:S79-S84. doi: 10.1016/S0049-3848(20)30402-3. PMID: 32736784.
7. Brunetti ND, Tricarico L, Correale M, et al. Direct oral anticoagulants more effective than low-molecular-weight heparin for venous thrombo-embolism in cancer: an updated meta-analysis of randomized trials. *J Thromb Thrombolysis.* 2020 Aug;50(2):305-310. doi: 10.1007/s11239-019-01974-y. PMID: 31654194.
8. Chen H, Tao R, Zhao H, et al. Prevention of venous thromboembolism in patients with cancer with direct oral anticoagulants: A systematic review and meta-analysis. *Medicine (Baltimore).* 2020 Jan;99(5):e19000. doi: 10.1097/MD.00000000000019000. PMID: 32000440; PMCID: PMC7004711.
9. Giustozzi M, Agnelli G, Del Toro-Cervera J, et al. Direct Oral Anticoagulants for the Treatment of Acute Venous Thromboembolism Associated with Cancer: A Systematic Review and Meta-Analysis. *Thromb Haemost.* 2020 Jul;120(7):1128-1136. doi: 10.1055/s-0040-1712098. Epub 2020 May 4. PMID: 32365386.
10. Moik F, Posch F, Zielinski C, et al. Direct oral anticoagulants compared to low-molecular-weight heparin for the treatment of cancer-associated thrombosis: Updated systematic review and meta-analysis of randomized controlled trials. *Res Pract Thromb Haemost.* 2020 May 21;4(4):550-561. doi: 10.1002/rth2.12359. PMID: 32548553; PMCID: PMC7292654.
11. Li A, Kuderer NM, Garcia DA, et al. Direct oral anticoagulant for the prevention of thrombosis in ambulatory patients with cancer: A systematic review and meta-analysis. *J Thromb Haemost.* 2019 Dec;17(12):2141-2151. doi: 10.1111/jth.14613. Epub 2019 Sep 17. PMID: 31420937.
12. Dong Y, Wang Y, Ma RL, et al. Efficacy and safety of direct oral anticoagulants versus low-molecular-weight heparin in patients with cancer: a systematic review and meta-analysis. *J Thromb Thrombolysis.* 2019 Oct;48(3):400-412. doi: 10.1007/s11239-019-01871-4. PMID: 31062143.
13. Li A, Garcia DA, Lyman GH, et al. Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): A systematic review and meta-analysis. *Thromb Res.* 2019 Jan;173:158-163. doi: 10.1016/j.thromres.2018.02.144. Epub 2018 Mar 2. PMID: 29506866; PMCID: PMC6119655.
14. Kahale LA, Hakoum MB, Tsolakian IG, et al. Anticoagulation for the long-term treatment of venous thromboembolism in people with cancer. *Cochrane Database Syst Rev.* 2018 Jun 19;6(6):CD006650. doi: 10.1002/14651858.CD006650.pub5. PMID: 29920657; PMCID: PMC6389342.
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16. Vedovati MC, Giustozzi M, Bonitta G, et al. Efficacy and safety of anticoagulant agents in patients with venous thromboembolism and cancer: A network meta-analysis. *Thromb Res.* 2018 Oct;170:175-180. doi: 10.1016/j.thromres.2018.08.023. Epub 2018 Sep 1. PMID: 30196195.
17. Yan YD, Zhang C, Shen L, Su YJ, Liu XY, Wang LW, Gu ZC. Net Clinical Benefit of Non-vitamin K Antagonist Oral Anticoagulants for Venous Thromboembolism Prophylaxis in Patients With Cancer: A Systematic Review and Trade-Off Analysis From 9 Randomized Controlled Trials. *Front Pharmacol.* 2018 Jun 12;9:575. doi: 10.3389/fphar.2018.00575. PMID: 29946255; PMCID: PMC6005885.

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TEXT FOR INCLUSION IN THE DOCUMENT

DOMAIN 06, Statement 05, TOPIC: “Cancer-related venous thrombosis management”

Patients with cancer are at high risk of developing VTE as well as a higher risk of VTE recurrence and should be evaluated with validated risk assessment tools to determine the need for prophylaxis. In particular, VTE risk is much higher in patients with pancreatic, stomach, brain, lung, and ovarian cancer. Chemotherapy and hormonal therapy also independently increase VTE risk. Hospitalized patients with cancer should still undergo individualized risk screening with validated tools such as the Caprini and Padua assessments to determine the utility of thromboprophylaxis (**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 advances. 2021 Feb 23;5(4):927-74.**)

For patients that develop VTE, current guidelines recommend initial management with low molecular weight heparin (LMWH), although recently published guidelines also endorse the use of direct oral anticoagulants (DOACs) (**Kakkos SK et al., European Society for Vascular Surgery (ESVS) 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis, Eur J Vasc Endovasc Surg 2020, <https://doi.org/10.1016/j.ejvs.2020.09.023>**). Both DOACs and LMWH are recommended for short-term (3-6 months) and long-term (over 6 months) VTE management. The most recent update to the CHEST guidelines favors DOACs over LMWH for acute VTE in cancer patients for both initiation and treatment phases (**Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. Chest. 2021 Dec 1;160(6):e545-608.**) Randomized clinical trial data in cancer patients show that direct oral anticoagulants (DOACs) have lower rates of recurrent VTE than LMWH, but may have a slightly higher rate of clinically significant bleeding events. In particular, edoxaban and rivaroxaban may increase the risk of GI bleed in luminal GI malignancies. Evidence clearly favors the use of oral anticoagulants or LMWH over warfarin for VTE treatment in cancer patients (**Kakkos SK et al., European Society for Vascular Surgery (ESVS) 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis, Eur J Vasc Endovasc Surg 2020, <https://doi.org/10.1016/j.ejvs.2020.09.023>; Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. Chest. 2021 Dec 1;160(6):e545-608.**) See section 6.9 for further detail on the use of DOACs. One area of controversy is screening for occult cancer in patients with unprovoked VTE, an association first noted by Trousseau in the 1860s. A number of studies have found that aggressive screening strategies were not associated with improved outcomes in patients with unprovoked VTE. Based on subgroup analyses, however, it has been suggested that aggressive screening with abdomino-pelvic ultrasound or PET/CT may benefit patients with unprovoked VTE and three of the following risk factors: male, age > 70, chronic lung disease, anemia, thrombocytosis, previous VTE, and recent surgery (**Ferreira F, Pereira J, Lynce A, et al. Cancer Screening in Patients with Unprovoked Thromboembolism: How to do it and Who Benefits?. Cureus. 2020 Feb 10;12(2).**) There is some evidence for early diagnosis that does not affect outcomes.

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STATEMENT FOR PUBLIC EVIDENCE-BASED AWARENESS

DOMAIN 06, Statement 05

Venous thrombosis is common in cancer patients, and must be treated with anticoagulation. A specialist should discuss your options for anticoagulation if you develop a venous thrombosis while you have cancer.

4 SELECTED REFERENCES

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1. Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, Huisman MV, Kearon C, King CS, Knighton AJ, Lake E. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. *Chest*. 2021 Dec 1;160(6):e545-608.
2. Ferreira F, Pereira J, Lynce A, Marques JN, Martins A. Cancer Screening in Patients with Unprovoked Thromboembolism: How to do it and Who Benefits?. *Cureus*. 2020 Feb 10;12(2).
3. Kakkos SK et al., European Society for Vascular Surgery (ESVS) 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis, *Eur J Vasc Endovasc Surg* 2020, <https://doi.org/10.1016/j.ejvs.2020.09.023>.
4. Lyman GH, Kuderer NM. Clinical practice guidelines for the treatment and prevention of cancer-associated thrombosis. *Thromb Res*. 2020 Jul;191 Suppl 1:S79-S84. doi: 10.1016/S0049-3848(20)30402-3. PMID: 32736784.

identified LITERATURE BIAS

Many large studies comparing DOACs and LMWH or vitamin K antagonists include less of high-risk cancer patients , which could affect outcomes. Rather big amount of pancreatic cancer patients was included in the trials comparing DOACs and LMWH

SUGGESTED NEXT LINES OF RESEARCH

More studies comparing differences between various DOACs for the optimal treatment of VTE in cancer patients.