REVIEW PAPER

DOI: https://doi.org/10.5114/kitp.2024.141148

Pulmonary embolism in cancer patients. Effectiveness of vitamin K antagonists and direct oral anticoagulants in long-term therapy

Paulina M. Nadziakiewicz[1], Bożena Szyguła-Jurkiewicz[2]

[1]Student's Scientific Society, 3rd Department of Cardiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Poland
[2]3rd Department of Cardiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Poland

Kardiochirurgia i Torakochirurgia Polska 2024; 21 (2): 102-107

Abstract

Patients with cancer are prone to develop pulmonary embolism (PE) in the course of cancer-associated thrombosis. These patients have increased risk of both recurrent venous thromboembolism and major bleeding. Pulmonary embolism treatment in the cancer patient group is challenging. Selection of anticoagulants, duration of anticoagulation, decision of adjuvant therapy, and adjustment of the regimen in special situations are the major problems that need to be considered in the treatment of cancer-associated PE. Current first line treatment in long-term therapy following an episode of PE is low molecular weight heparin (LMWH), with direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs) listed as viable alternatives. This study aims to explore long-term oral anticoagulation therapy for cancer patients. Both VKAs and DOACs are compared to LMWH, which serves as a gold standard in anticoagulation therapy for cancer patients and has proven to be effective.

Key words: cancer, pulmonary embolism, vitamin K antagonists, direct oral anticoagulants.

Introduction

Pulmonary embolism (PE) is one of the leading causes of cardiovascular mortality and morbidity. It is estimated that it contributes to 100,000 deaths per year [1]. It has a significant mortality rate of 30% if left untreated [2].

Especially affected are patients with active cancer as they have a 4–7-fold increased risk of developing venous thromboembolism (VTE) [3]. Pulmonary embolism is a leading cause of death in this group, second only to the cancer itself [4]. Different types of cancer have different VTE risks: pancreatic cancer, hematological malignancies, lung cancer, gastric cancer, and brain cancer carry the highest risk [5]. Due to the fragility of cancer patients and frequent oligosymptomatic presentation of this condition the diagnosis is challenging [6].

Recurrence and mortality of PE in cancer patients

Populational risk of recurrence after the first episode of VTE is between 5 and 7%, while patients with active cancer are at a higher risk of recurrence [7].

The acute PE mortality rate is significantly higher in cancer patients than noncancer patients (19.6% vs. 3.2%, $p < 0.001$) [8]. Gussoni *et al.* reported that the mortality rate in cancer patients during a 3-month follow-up after acute PE was 3% [9].

The mortality rate in the hospital phase of PE can be greatly lowered with the implementation of a pulmonary embolism response team (PERT). The multidisciplinary approach and specialized care those teams provide brought in-hospital mortality rates for both non-cancer and cancer patients to similar levels. Research has also shown that establishing PERT increases access to advanced therapies, while at the same time the number of bleeding complications does not increase in the cancer patient group [10, 11].

Trends in long-term pharmacotherapy of PE in the general population

Current guidelines for PE treatment and diagnosis were established in 2019 by the European Society of Cardiology in collaboration with the European Respiratory Society.

Over the years as medicine progressed, the PE mortality rate decreased. More treatment options became available and new drugs were implemented. This progress is particularly visible in changes in the guidelines between the years 2014 and 2019. Aside from the use of age-specific

Address for correspondence: Paulina Małgorzata Nadziakiewicz, Student's Scientific Society, 3rd Department of Cardiology, Faculty of Medical Sciences, Medical University of Silesia, Zabrze, Poland, e-mail: s81184@365.sum.edu.pl

Received: 18.01.2024, **accepted:** 25.03.2024, **online publication:** 30.06.2024.

cut-off levels of D-dimers, detailed recommendations for risk stratification and the possibility of outpatient management, there was a shift in the use of anticoagulants [12]. In 2014 vitamin K antagonists (VKAs) were the gold standard in oral anticoagulation both in acute VTE and in further prevention of recurrence, while direct oral anticoagulants (DOACs) were still being evaluated. The results were promising but not revolutionary. Phase III clinical trials indicated that these agents were non-inferior in terms of efficiency and potentially safer than warfarin [13]. Research showed that compared with VKA-treated patients, critical site major bleeding occurred less frequently in DOAC-treated patients. In particular, there was a significant reduction in intracranial bleeding and in fatal bleeding with DOACs compared with VKAs [14]. Paired with their comparable effectiveness were several advantages over VKAs: they have been shown to have predictable pharmacokinetics and pharmacodynamics, a low potential for drug–drug interactions, and are given at fixed doses without the need for routine coagulation monitoring [15]. Their major disadvantage however is the difficulty in DOAC overdose treatment. Both DOAC and warfarin overdosing can be associated with worse outcomes of major bleeding, stroke/systemic embolism, all-hospitalization and all-cause mortality [16, 17]. In the case of warfarin, diagnosis and treatment are relatively simple, with international normalized ratio (INR) monitoring and intravenous vitamin K readily available [18]. When it comes to DOACs, both are challenging. For rivaroxaban, edoxaban and apixaban their plasma concentrations can be measured using anti-factor Xa chromogenic assays, which reflect drug levels if calibrated. Nevertheless, such tests are infrequently available in emergency situations. For dabigatran a normal diluted thrombin time or ecarin chromogenic or clotting assay can be used, but only normal diluted thrombin time is reliable in high drug concentrations and its availability is limited. A normal prothrombin time (PT) or activated partial thromboplastin time (aPTT) cannot be used to exclude clinically relevant plasma concentrations of any of the DOACs [19]. A qualitative dipstick assay that detects DOACs in the urine is available, but the test has not been validated in patients with bleeding [20]. When a patient presents with uncontrolled or life-threatening bleeding in the course of DOAC overdose, reversal should be considered. Two licensed specific DOAC reversal agents are idarucizumab for reversal of dabigatran and andexanet alfa for reversal of apixaban and rivaroxaban. The drug level for dabigatran that requires reversal according to the recent studies is above 30 ng/ml. It is the same for Xa inhibitors. The concentration below 30 ng/ml is clinically irrelevant for reversal [21]. In terms of clinical usage, idarucizumab is a first line agent for dabigatran reversal and it is available in virtually every major hospital. Andexanet alfa is practically unavailable in Poland, due to its high price and controversial role in current clinical practice. To date it has not been proven superior to prothrombin complex concentrate (PCC), which provides a high possibility of reversal of rivaroxaban and apixaban [21].

Long-term pharmacotherapy of PE in cancer patients

The same change cannot be observed in extended PE treatment in patients with active cancer. It has been proven that the use of low molecular weight heparin (LMWH) over conventional VTE treatment (heparin followed by VKA) is beneficial to the patient. A study from 2003 showed significant reduction in VTE recurrence with LMWH compared with conventional (VKA) treatment without an increase in bleeding complications, making LMWH a leading treatment option for cancer patients [22]. LMWH has predictable pharmacokinetic properties and drug interactions, in contrast to VKA, and it does not depend on gastrointestinal absorption due to subcutaneous administration [23]. LMWH therapy does not require such rigorous monitoring and the therapeutic dosage is weight adjusted, making it well suited for cancer patients, whose weight can be very labile. Furthermore, the multiple conditions affecting cancer patients including malnutrition, vomiting, and liver dysfunction can significantly alter the pharmacokinetics of VKAs while LMWH remains notably less affected. LMWH therapy is flexible with a rapid onset of action and predictable clearance, allowing for frequent interruptions in anticoagulation therapy that may be required in cancer patients due to chemotherapy-induced thrombocytopenia, or prior to surgery or other invasive procedures [22]. In VKA therapy there is a delay of several days between the initiation of treatment and the appearance of a full anticoagulant effect as this depends on the clearance of clotting factors from the plasma, which makes required interruptions challenging [24]. In terms of quality of life, patients tend to prefer LMWH over VKAs. In a qualitative study undertaken to determine whether LMWH was acceptable in 40 palliative care patients, both in the community and inpatient units, the majority had been on warfarin and were switched to LMWH due to difficulties in controlling the INR or resistance to therapy. The majority of those patients preferred a daily injection of LMWH over the frequent INR monitoring required to achieve stable anticoagulation on warfarin. Many reported that the discomfort following injection was short lived and the freedom and simplicity of this therapy increased their quality of life [25].

Subcutaneous administration of LMWH is far from perfect in long-term usage as it lowers patients' comfort of life, especially in months-long therapy. However, studies show that despite the discomfort of injections LMWH has a positive impact on quality of life and overall health in cancer patients surviving an episode of VTE [26].

DOACs are as effective as VKAs for the treatment of VTE and are associated with less frequent and less severe bleeding [21, 27]. They offer a promising treatment option, combining the lack of rigorous monitoring that was appealing to the patients when taking LMWH with oral administrations of VKA. The treatment is more convenient in patients with cancer, due to their oral administration in fixed-dose regimens and their lower cost compared with LMWH. Similarly to LMWH they can be used in patients

with renal impairment, up to the level CrCl = 15 ml/min for some agents, with appropriate dosage adjustment and caution. None of the DOACs is recommended for CrCl < 15 ml/min [28]. When it comes to cancer-related thrombocytopenia they are not recommended if the platelet count is below 50 000/µl [29]. However, the number of cancer patients included in phase III trials of DOACs made up only 3–9% of total patients [28]. A randomized, open-label, non-inferiority trial compared edoxaban with LMWH in the secondary prevention of VTE in 1050 patients with cancer-associated thrombosis [30]. This trial showed that treatment with a fixed once-daily dose of oral edoxaban was non-inferior to dalteparin in the prevention of VTE recurrence or major bleeding over 12 months after randomization. The rate of recurrent VTE was numerically lower with edoxaban than with dalteparin (7.9% and 11.3%), with edoxaban showing a lower rate of recurrent symptomatic deep-vein thrombosis (DVT) (3.6% and 6.7%). The rate of PE was similar in both groups, 5.2% in edoxaban and 5.3% in the dalteparin group. Major bleeding occurred in 6.9% of the patients in the edoxaban arm and 4.0% in the dalteparin arm. The difference was associated mainly with the higher rate of upper gastrointestinal bleeding with edoxaban [28], which is consistent with results of previous studies of DOACs [21]. The increase in upper gastrointestinal major bleeding occurred mainly in patients who had entered the trial with gastrointestinal cancer [30]. A randomized, open-label pilot trial comparing rivaroxaban with dalteparin in 406 patients with VTE and cancer, 58% of whom had metastases, reported similar results [31]. The cumulative VTE recurrence rate at 6 months was 11% for dalteparin and 4% for patients receiving rivaroxaban. The 6-month cumulative rate of major bleeding-was 6% for rivaroxaban and 4% for dalteparin. Most major bleeding events were gastrointestinal; no central nervous system bleeds occurred. Patients with esophageal or gastroesophageal cancer tended to experience more major bleeds with rivaroxaban than with dalteparin. The cumulative rate of clinically relevant non-major bleeding at 6 months was 4% for dalteparin and 13% for rivaroxaban [31]. Although not mentioned in the guidelines due to their late publication, two separate studies regarding apixaban were conducted. Conducted in 2018, the ADAM VTE trial randomized 300 patients with cancer and VTE to receive either apixaban for 6 months or subcutaneous dalteparin [32]. Oral apixaban therapy was associated with very low rates of bleeding and significantly lower VTE recurrence. Major bleeding up to 6 months occurred in none assigned to apixaban and 1.4% assigned to dalteparin. Recurrent VTE occurred in 0.7% in the apixaban group and 6.3% in the dalteparin group [32]. The second trial comparing apixaban to dalteparin was conducted in 2020 on 1155 recruited patients, of whom 97% had active cancer [33]. Patients with basal-cell or squamous-cell carcinoma of the skin, primary brain tumors, intracerebral metastasis, and acute leukemia were excluded. It was a randomized, controlled, investigator-initiated, open-label, noninferiority trial with blinded adjudication of the outcomes. Recurrent VTE occurred in 5.6% of patients from the apixaban group compared with 7.9% from the dalteparin group. Recurrent PE rates were lower in the apixaban arm (3.3% vs. 5.5%). The rates of major bleeding were similar between the two groups: 3.8% and 4% for apixaban and dalteparin, respectively. There was no significant difference between the groups in the rate of gastrointestinal bleeding, which contrasts with the results of previous studies [33]. The aforementioned trials provide evidence for DOAC therapy in patients without gastrointestinal cancer, with an anticipated low risk of bleeding who have no contradiction for oral treatment (Table I) [31–34].

Differences within the DOAC group

The 2019 ESC pulmonary embolism guidelines approve of edoxaban and rivaroxaban use in the long-term anticoagulation therapy following an episode of PE, with edoxaban having a higher level of evidence. However, both edoxaban and rivaroxaban are excluded from the use in therapy of patients with gastrointestinal cancer [28]. The 2019 pulmonary embolism treatment guidelines were the first guidelines that put LMWH on par with rivaroxaban and edoxaban. In the newer 2022 ESC cardio-oncology guidelines, edoxaban, rivaroxaban, and apixaban are recommended for the treatment of VTE in cancer patients. Patients with any of the following bleeding risk factors are excluded: unoperated gastrointestinal (GI) or genitourinary malignancies, history of recent bleeding or within 7 days of major surgery, significant thrombocytopenia (platelet count < 50 000/µl), severe renal dysfunction (creatinine clearance (CrCl < 15 ml/min), or GI comorbidities. LMWH should be used in case of unfavorable drug-drug interactions, for patients with inoperable gastrointestinal cancer, severe renal impairment (eGFR < 15 ml/min), gastrointestinal toxicity or other gastrointestinal conditions such as gastric ulcers [29, 35].

In an observational study at the Mayo Clinic, comparing apixaban to rivaroxaban and enoxaparin, there was no significant difference in the rate of recurrence or major bleeding among patients from different treatment groups. Rivaroxaban therapy was associated with a higher rate of clinically relevant non-major bleeding. The Mayo clinic study is the first study reporting a difference in mortality rates in high-risk cancer patients based on anticoagulant assignment with rivaroxaban showing lower mortality compared to apixaban and enoxaparin [36].

Another Mayo clinic study focused on bleeding in patients with gastrointestinal cancer treated with apixaban, rivaroxaban, or enoxaparin. In luminal GI cancer apixaban had a higher rate of major bleeding compared with enoxaparin and compared with patients with non-GI cancer treated with apixaban. However, previous reports that patients with GI cancer treated with rivaroxaban have an increased risk of bleeding were not substantiated. The aforementioned higher rate of clinically relevant non-major bleeding was also observed in this study both in patients with GI cancer and in patients with non-GI cancer [37].

Table I. Comparison of DOAC vs. LMWH trials

Parameter	Hokusai VTE-Cancer, 2018 [34]	SELECT-D, 2018 [31]	ADAM-VTE, 2020 [32]	Caravaggio, 2020 [33]
Trial design	Open-label, noninferiority	Open-label, pilot	Open-label, investigator-initiated	Open-label, controlled, investigator-initiated, noninferiority
Number of patients	942	406	300	1155
Mean age	64	67	64	67
DOACs	Edoxaban	Rivaroxaban	Apixaban	Apixaban
Comparators	Daltepatin	Dalteparin	Dalteparin	Dalteparin
Inclusion criteria	Patients with active cancer and acute symptomatic or incidental proximal DVT and/or PE	Patients with active cancer and symptomatic or incidental PE, or symptomatic lower extremity proximal DVT	Patients with active cancer and acute extremity DVT, PE, splanchnic or cerebral vein thrombosis	Patients with active cancer and acute symptomatic or incidental proximal DVT or PE
Cancer types	Gastrointestinal, lung, urogenital, breast, hematological, and gynecological cancer	Solid and hematologic malignancies (other than basal-cell or squamous-cell skin carcinoma)	Solid and hematologic malignancies	Cancers other than basal-cell or squamous-cell carcinoma of the skin, primary brain tumor, intracerebral metastases, or acute leukemia
Primary outcome meassurements	The composite of VTE recurrence or major bleeding	VTE recurrence	Episode of major bleeding	VTE recurrence
Primary outcome results	Edoxaban 19.4%; Dalteparin 15.0% (RD = 4.4%; 95% CI: −4.1 to 12.8%)	Rivaroxaban 4% (95% CI: 2 to 9%); Dalteparin 11% (95% CI: 7 to 16%); (HR = 0.43; 95% CI: 0.19 to 0.99)	Apixaban 0%; Dalteparin 1.4% (p = 0.138)	Apixaban 5.6%; Dalteparin 7.9% (HR = 0.63; 95% CI: 0.37 to 1.07; p < 0.001 for noninferiority)

There was also a retrospective study utilizing U.S. electronic health record (EHR) data from January 2013 to December 2020 comparing apixaban and rivaroxaban. It included adults diagnosed with active cancer, excluding esophageal, gastric, unresected colorectal, bladder, noncerebral central nervous system cancers and leukemia, who experienced VTE and received a therapeutic VTE dose of rivaroxaban or apixaban. Similar effectiveness and safety were reported for treatment of cancer-associated VTE through 6 months with both drugs [38]. Rivaroxaban and apixaban were the only anticoagulants from the DOAC group that were compared in cancer-associated VTE. As of this date, dabigatran has not been specifically studied in a randomized trial in patients with cancer-associated VTE.

Patterns of anticoagulant utilization

Currently the pharmacological anticoagulant agents most frequently used for cancer-associated VTE are LMWH and DOACs, with LMWH being the first choice for initial anticoagulation treatment, as shown in a real-world analysis, from September 2018 to January 2020 [39]. In the retrospective cohort study utilizing data from January 1, 2015, to May 31, 2018, the results were similar. LMWH and unfractionated heparin (UFH) were the most common initial treatments (35.2 and 27.4%, respectively) with DOACs being used in 9.6% of the cases. DOACs were the most common initial post-discharge outpatient option. Within 3 months after discharge, DOACs were most frequently used in the outpatient setting (40.3%), followed by LMWH (18.0%) and warfarin (10.7%); nearly one-third of patients (30.5%) had no outpatient anticoagulants. Persistence and adherence in outpatients appeared higher in patients using DOACs or warfarin versus LMWH or UFH [40]. Furthermore, a comparative effectiveness study from 2023, which included 5100 patients, reported a general preference for DOAC therapy use, with nearly twice as many patients receiving this class of medication compared with other classes [41].

Conclusions

The treatment of cancer-associated thrombosis presents several challenges, including increased risks of bleeding and recurrent VTE. Both VKAs and DOACs were proven to be an effective treatment option in cancer-associated PE [28], with DOACs having a lower risk of bleeding and better results than LMWH. The DOACs provide an improved therapeutic option for many patients, while having fewer limitations and drug-drug interactions. VKAs, while less effective, still should be considered as a valid alternative, due to their high persistence and adherence rates compared to LMWH and UFH. Overall, assessment of patient- and cancer-related variables, and patient preference, are key to choosing an anticoagulant regimen.

Funding

No external funding.

Ethical approval

Not applicable.

Disclosure

The authors report no conflict of interest.

References

1. Shatla I, El Iskandarani M, Munir M, Khan M. Sex differences in outcomes among patients hospitalized with pulmonary embolism: insights from National Inpatient Sample 2002-2020. Eur Heart J 2023; 44 (Suppl 2). doi:10.1093/eurheartj/ehad655.1988
2. Bělohlávek J, Dytrych V, Linhart A. Pulmonary embolism, part I: epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. Exp Clin Cardiol 2013; 18: 129-138.
3. Agnelli G, Verso M. Management of venous thromboembolism in patients with cancer. J Thromb Haemostasis 2011; 9: 316-324.
4. Carson JL, Kelley MA, Duff A, Weg JG, Fulkerson WJ, Palevsky HI, Schwartz JS, Thompson BT, Popovich Jr J, Hobbins TE. The clinical course of pulmonary embolism. N Engl J Med 1992; 326: 1240-1245.
5. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. Blood 2013; 122: 1712-1723.
6. Poenou G, Dumitru Dumitru T, Lafaie L, Mismetti V, Ayoub E, Duvillard C, Accassat S, Mismetti P, Heestermans M, Bertoletti L. Pulmonary embolism in the cancer associated thrombosis landscape. J Clin Med 2022; 11: 5650.
7. White RH. The epidemiology of venous thromboembolism. Circulation 2003; 107 (23 suppl 1): I4-8.
8. Cai B, Bedayat A, George E, Hunsaker AR, Dill KE, Rybicki FJ, Kumamaru KK. Malignancy and acute pulmonary embolism. J Thorac Imaging 2013; 28: 196-201.
9. Gussoni G, Frasson S, La Regina M, Di Micco P, Monreal M. Three-month mortality rate and clinical predictors in patients with venous thromboembolism and cancer. findings from the RIETE Registry. Thromb Res 2013; 131: 24-30.
10. Pietrasik A, Gąsecka A, Kurzyna P, Smyk JM, Wasilewski M, Wolański R, Wrona K, Darocha S, Zieliński D, Grabowski M, Torbicki A, Kurzyna M. Cancer-associated thrombosis: comparison of characteristics, treatment, and outcomes in oncological and non-oncological patients followed by pulmonary embolism response team. Pol Arch Intern Med 2023; 133: 16421.
11. Pietrasik A, Gąsecka A, Kurzyna P, Wrona K, Darocha S, Banaszkiewicz M, Zieliński D, Zajkowska D Smyk JM, Rymaszewska D, Jasińska K, Wasilewski M, Wolański R, Procyk G, Szwed P, Florczyk M, Wróbel K, Grabowski M, Torbicki A, Kurzyna M. Characteristics and outcomes of patients consulted by a multidisciplinary pulmonary embolism response team: 5-year experience. J Clin Med 2022; 11: 3812.
12. Erythropoulou-Kaltsidou A, Alkagiet S, Tziomalos K. New guidelines for the diagnosis and management of pulmonary embolism: key changes. World J Cardiol 2020; 12: 161-166.
13. van Es N, Coppens M, Schulman S, Middeldorp S, Büller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood 2014; 124: 1968-1975.
14. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta analysis. J Thromb Haemostasis 2014; 12: 320-328.
15. Mueck W, Stampfuss J, Kubitza D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. Clin Pharmacokinet 2013; 53: 1-16.
16. Santos J, Antônio N, Rocha M, Fortuna A. Impact of direct oral anticoagulant off-label doses on clinical outcomes of atrial fibrillation patients: a systematic review. Br J Clin Pharmacol 2020; 86: 533-547.
17. Hirsh J, Fuster V, Ansell J, Halperin JL. American Heart Association/American College of Cardiology Foundation Guide to warfarin therapy. Circulation 2003; 107: 1692-1711.
18. Deaton JG, Nappe TM. Warfarin Toxicity. [Updated 2023 Jul 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK431112/
19. Samuelson BT, Cuker A, Siegal DM, Crowther M, Garcia DA. Laboratory assessment of the anticoagulant activity of direct oral anticoagulants. Chest 2017; 151: 127-138.
20. Martini A, Harenberg J, Bauersachs R, Beyer-Westendorf J, Crowther M, Douxfils J, Elalamy I, Weiss C, Hetjens S. Detection of direct oral anticoagulants in patient urine samples by prototype and commercial test strips for DOACs – a systematic review and meta-analysis. TH Open 2021; 5: e438-e448.
21. van Es N, De Caterina R, Weitz JI. Reversal agents for current and forthcoming direct oral anticoagulants. Eur Heart J 2023; 44: 1795-1806.
22. Lee AYY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, Rickles FR, Julian JA, Haley S, Kovacs MJ, Gent M; 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; 349: 146-153.
23. Weitz JI. Low-molecular-weight heparins. N Engl J Med 1997; 337: 688-698.
24. Falanga A, Zacharski L. Deep vein thrombosis in cancer: the scale of the problem and approaches to management. Ann Oncol 2005; 16: 696-701.
25. Noble SI, Finlay IG. Is long-term low-molecular-weight heparin acceptable to palliative care patients in the treatment of cancer related venous thromboembolism? A qualitative study. Palliat Med 2005; 19: 197-201.
26. Farge D, Cajfinger F, Falvo N, Berremili T, Couturaud F, Bensaoula O, Védrine L, Bensalha H, Bonnet I, Péré-Vergé D, Coudurier M, Li V, Rafii H, Benzidia I, Connors JM, Resche-Rigon M. Quality of life in cancer patients undergoing anticoagulant treatment with LMWH for venous thromboembolism: The QUAVITEC study on behalf of the groupe francophone thrombose et cancer (GFTC). Oncotarget 2018; 9: 26990-26999.
27. Bleker SM, Brekelmans MPA, Eerenberg E, Cohen A, Middeldorp S, Raskob G, Büller HR. Clinical impact of major bleeding in patients with venous thromboembolism treated with factor XA inhibitors or vitamin K antagonists. Thromb Haemostasis 2017; 117: 1944-1951.
28. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, Huisman MV, Humbert M, Jennings CS, Jiménez D, Kucher N, Lang IM, Lankeit M, Lorusso R, Mazzolai L, Meneveau N, Ní Áinle F, Prandoni P, Pruszczyk P, Righini M, Torbicki A, Van Belle E, Zamorano JL; ESC Scientific Document Group. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2019; 41: 543-603.
29. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, Boriani G, Cardinale D, Cordoba R, Cosyns B, Cutter DJ, de Azambuja E, de Boer RA, Dent SF, Farmakis D, Gevaert SA, Gorog DA, Herrmann J, Lenihan D, Moslehi J, Moura B, Salinger SS, Stephens R, Suter TM, Szmit S, Tamargo J, Thavendiranathan P, Tocchetti CG, van der Meer P, van der Pal HJH; 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; 43: 4229-4361.
30. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, Grosso MA, Kakkar AK, Kovacs MJ, Mercuri MF, Meyer G, Segers A, Shi M, Wang TF, Yeo E, Zhang G, Zwicker JI, Weitz JI, Büller HR; Hokusai VTE Cancer Investigators. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018; 378: 615-624.
31. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, Hale D, Dunn JA, Lyman GH, Hutchinson C, MacCallum P, Kakkar A, Hobbs FDR, Petrou S, Dale J, Poole CJ, Maraveyas A, Levine M. 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: 2017-2023.
32. McBane RD, Wysokinski WE, Le-Rademacher J. Apixaban, dalteparin, in active cancer associated venous thromboembolism, the ADAM VTE trial. Blood 2018; 132 (Suppl 1): 421.
33. Agnelli G, Becattini C, Meyer G, Muñoz A, Huisman MV, Connors JM, Cohen A, Bauersachs R, Brenner B, Torbicki A, Sueiro MR, Lambert C, Gussoni G, Campanini M, Fontanella A, Vescovo G, Verso M; Caravaggio Investigators. Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med 2020; 382: 1599-1607.
34. Mulder FI, van Es N, Kraaijpoel N, Di Nisio M, Carrier M, Duggal A, Gaddh M, Garcia D, Grosso MA, Kakkar AK, Mercuri MF, Middeldorp S, Royle G, Segers A, Shivakumar S, Verhamme P, Wang T, Weitz JI, Zhang G, Büller HR, Raskob G. Edoxaban for treatment of venous thromboembolism in patient groups with different types of cancer: results from the Hokusai VTE Cancer study. Thromb Res 2020; 185: 13-19.
35. Leszek P, Klotzka A, Bartuś S, Burchardt P, Czarnecka AM, Długosz-Danecka M, Gierlotka M, Koseła-Paterczyk H, Krawczyk-Ożóg A, Kubiatowski T, Kurzyna M, Maciejczyk A, Mitkowski P, Prejbisz A, Rutkowski P, Sierko E, Sterliński M, Szmit S, Szwiec M, Tajstra M, Tycińska A, Witkowski A, Wojakowski W, Cybulska-Stopa B. A practical approach to the 2022 ESC Cardio-Oncology Guidelines: Comments by a team of experts – cardiologists and oncologists. Kardiol Pol 2023; 81: 1047-1063.
36. Wysokinski WE, Houghton DE, Casanegra AI, Vlazny DT, Bott-Kitslaar DM, Froehling DA, Hodge DO, Peterson LG, Mcbane RD. Comparison of apixaban to rivaroxaban and enoxaparin in acute cancer-associated venous thromboembolism. Am J Hematol 2019; 94: 1185-1192.

37. Houghton DE, Vlazny DT, Casanegra AI, Brunton N, Froehling DA, Meverden RA, Hodge DO, Peterson LG, McBane RD, Wysokinski WE. 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: 2793-2805.
38. Caroti KS, Becattini C, Carrier M, Cohen AT, Ekbom A, Khorana AA, Lee AYY, Brescia C, Abdelgawwad K, Psaroudakis G, Rivera M, Schaefer B, Brobert G, Coleman CI. Rivaroxaban versus apixaban for treatment of cancer-associated venous thromboembolism in patients at lower risk of bleeding. TH Open 2023; 7: e206-e216.
39. Tsoukalas N, Tsapakidis K, Galanopoulos M, Karamitrousis E, Kamposioras K, Tolia M. Real World Data regarding the management of cancer-associated thrombosis. Curr Opin Oncol 2020; 32: 289-294.
40. Guo JD, Hlavacek P, Poretta T, Wygant G, Lane D, Gorritz M, Wang X, Chen CC, Wade RL, Pan X, Rajpura J, Stwalley B, Rosenblatt L. Inpatient and outpatient treatment patterns of cancer-associated thrombosis in the United States. J Thromb Thrombolysis 2020; 50: 386-394.
41. Riaz IB, Fuentes H, Deng Y, Naqvi SAA, Yao X, Sangaralingham LR, Houghton DE, Padrnos LJ, Shamoun FE, Wysokinski WE, McBane 2nd RD. Comparative effectiveness of anticoagulants in patients with cancer-associated thrombosis. JAMA Network Open 2023; 6: e232583.