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Guidelines on the prevention and treatment of venous thromboembolism in cancer patients treated surgically, including patients under 18 years of age

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(Approved with the following statement: "I accept the guideline document with the strong believe concerning the necessity of the careful application of antithrombotic prophylaxis in cancer patients, especially the necessity of the combination of heparin prophylaxis and the use of intermittent pneumatic compression during the surgery and postoperative period".)

Abstract

Venous thromboembolism (VTE) is one of the most dangerous complications of cancer. Oncological treatment, surgeries and advanced-stage cancer are only some of the risk factors for VTE, which is still one of the most common causes of death in the population of cancer patients. Differences in the risk of deep-venous thrombosis and its complications, including risk of bleeding, between particular oncological patient groups suggests that there is a need for individual risk assessment and prophylaxis dedicated to specific clinical situations and patients. Cancer-related thrombosis (CAT) is the second most common cause of death in cancer patients. In view of the dynamically growing body of evidence on CAT in recent years, there is a need to update the guidelines for prevention and treatment offered to cancer patients, as evidenced by this document, which is an update of the guidelines published in 2016. This document contains data published after 2016 and the most recent indications for prevention and treatment in the population of cancer patients, with particular emphasis on thromboprophylaxis in those undergoing surgical treatment. Moreover, it was extended to include indications in patients under 18 years of age. The recommendations for the treatment of cancer-related VTE and the use of thromboprophylaxis in the population of children with cancer who are scheduled for surgery were analyzed. The current recommendations confirm the leading role of low-molecular-weight heparins in the pharmacological prevention of VTE in cancer patients and indicate direct oral anticoagulants as an alternative to low-molecular-weight heparin in the treatment of CAT patients.

Key words: venous thromboembolism, cancer, surgery, thromboprophylaxis, anticancer therapy

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Preamble

Cancer patients are a group of patients with a significantly increased risk of both deep vein thrombosis (DVT) and pulmonary embolism (PE). Cancer-associated thrombosis (CAT) is the second most common cause of death in cancer patients [1]. Patients with malignant neoplasm are four to seven times more likely to develop venous thromboembolism (VTE) than patients without cancer, as evidenced by the worldwide increase in CAT cases [2–4]. It should be emphasized that VTE is one of the few diseases that can be effectively prevented. Educational publications, such as these guidelines, aim to reduce the incidence of thromboembolic complications in cancer patients. Therefore, the 2021 guidelines provide information based on up-to-date medical knowledge on the indications and principles of antithrombotic prophylaxis in patients undergoing anticancer treatment, in particular surgical treatment for neoplastic diseases.

These guidelines for the prophylaxis and treatment of VTE apply to the population of adult and pediatric patients treated surgically for cancer.

It was assumed that the audience of the guidelines will be the entire medical community involved in the diagnosis and treatment of cancer.

The authors of this document analyzed the most recent scientific data and current VTE prevention guidelines published in Poland and other countries, with the focus on recommendations for cancer patients. The 2016 "Venous thromboembolism prophylaxis in cancer patients — guidelines focus on surgical patients" was adopted as the basic document [5]. Prophylaxis guidelines were formulated based on medicine-based evidence (EBM) in order to form a universal document dedicated to cancer patients who remain under supervision of a specialist, as well as those who are treated by general practitioners. The authors also attempted to adjust these guidelines as much as possible to the present healthcare system in Poland.

Guidelines represent the standpoint of the authors on most-justified diagnostic and therapeutic procedures; however, they should be interpreted in the context of each individual clinical situation. These guidelines should not be treated as mandatory treatment or a standard of care.

Just like other guidelines, they are above all indications aiming to enable and facilitate rational clinical decisions regarding prophylaxis and treatment of VTE in cancer patients. As stated in the preamble to the previous guidelines, every effort has been made to update the data in line with published reports and the most recent research results.

Every effort has been made to ensure that the information provided is up-to-date and accurate at the time of publication. It is the responsibility of the treating physician to determine the best treatment for a given patient. The authors, editors and publishers shall have no liability for any issues that may arise in connection with the citation of this position statement.

Poznan, 1 September 2021

Abbreviations

aPTT — partial thromboplastin time
AUA — American Urological Association
BMI — body mass index
CAT — cancer-associated thrombosis
CDT — catheter-directed thrombolysis
CI — confidence interval
CNS — central nervous system
CrCl — creatinine clearance
DOAC — direct oral anticoagulants
DVT — deep venous thrombosis
ECF — electrical calf stimulation
eGFR — estimated glomerular filtration rate
FDA — Food and Drug Administration
GPS — good practice statement
INR — international normalized ratio
HIT — heparin induced thrombocytopenia
LMWH — low-molecular-weight heparin
LDUH — low doses of unfractionated heparin
OR — odds ratio
PE — pulmonary embolism
PCDT — pharmacomechanical catheter-directed thrombolysis
RCT — randomized controlled trial
RR — risk ratio
SrCr — serum creatinine
TURP — transurethral resection of the prostate
UFH — unfractionated heparin
VKA — vitamin K antagonist
VTE — venous thromboembolism

Introduction

Aim

These guidelines for the prevention and treatment of venous thromboembolism (VTE) are aimed to improve patients' safety by appropriate prevention and treatment of VTE.

Patient groups to whom the guidelines apply

These guidelines apply to adults and pediatric patients who are at risk of VTE due to cancer and patients with cancer-associated thrombosis (CAT), with particular emphasis on those undergoing surgical procedures.

Target audience

The guidelines are intended for medical professionals of all specialties involved in diagnosis and treatment of the above-mentioned patients, both at the specialist and primary care level.

Types of interventions included in the guidelines

Recommendations in these guidelines include diagnostic tests that can be performed to confirm the diagnosis of VTE and pharmacological and non-pharmacological interventions for VTE prevention and treatment.

Potential barriers to the implementation of the developed recommendations may be the lack or low availability of some drugs/procedures in Poland, for example tinzaparin, catheter-directed thrombolysis (CDT) or pharmacomechanical venous thrombectomy.

Remarks on using the guidelines

The authors of the guidelines encourage the promotion and implementation of these recommendations in the management of adult patients at risk of DVT and PE associated with cancer, patients with CAT. However, the guidelines should not be treated as a legally established standard of care for all patients, as the developed document only contains treatment tips and suggestions, and the recommendations contained therein should help doctors make optimal decisions in their daily practice. Proper care for an individual patient will always depend on their specific situation, available and applicable treatment methods and many other factors; and therapeutic decisions should be made each time by the attending physician or a therapeutic team after consultation with the patient or — if necessary — with the patient's guardian.

Methods

Composition of the Working Group

The guidelines were updated by a working group established by Polish experts in the field of VTE prevention and treatment, specialists in vascular surgery, oncological surgery, urology, thoracic surgery, cardiology, angiology, internal diseases, hematology and other surgical fields dealing with oncological patients.

Working Group meetings

Process for updating guidelines

These guidelines are based on a systematic literature review of the publications available up to 2016 and included in the previous guidelines, and an analysis of the English-language literature published in this area in 2016–2021. The guidelines were developed by a multi-disciplinary panel of experts with knowledge of medical research methodology. In order to communicate with each other, the panelists used tools for on-line meetings and e-mail correspondence. Based on the analysis of the evidence, the literature was searched, systematically reviewed and guidelines developed. A consensus was reached on the final wording of the recommendations.

Other arrangements were made and discussions conducted via emails and phone calls.

The full text of the guidelines was approved by all panelists. Their suggestions were included in the final version of the recommendations. The members of the expert panel were responsible for the review and approval of the penultimate version of the guidelines, which was then sent for external review and submitted to the Editorial Board of Acta Angiologica for editorial review and publication decision.

Overview of the updating process

The update of the guidelines was carried out in accordance with the guidelines of the ADAPTE Collaboration, an interdisciplinary group of experts appointed by the Guideline International Network [The ADAPTE Collaboration (2009). The ADAPTE Process: Resource Toolkit for Guideline Adaptation. Version 2.0] [6]. First, a list of clinical questions was formulated to which Polish recommendations were to be answered. The established range of clinical questions was approved by all members of the Working Group. Then, guidelines for the prevention and treatment of patients with CAT were systematically searched for and reviewed. When formulating the recommendations, the experts took into account the guidelines of the American Society of Hematology [7, 8], European Society for Vascular Surgery [9], American Society of Clinical Oncology [10], and International Initiative on Thrombosis and Cancer [11] on prophylaxis, diagnosis and treatment of venous thromboembolism in cancer patients undergoing surgery.

The information presented as responses to the questions asked was based on publications on the

topic of interest, including randomized controlled trials (RCTs), meta-analyzes and cohort studies, which were published since 2016. Articles were excluded from the systematic review if: 1) they contained abstracts that were not later published in peer-reviewed journals; 2) they were editorials, comments, letters, news articles, case reports and 3) they were published in a language other than English.

The updated search followed a "signals" approach which aims to identify only new data that could potentially change practice — signals that could translate into revised practice recommendations [12]. This approach relies on a targeted routine search of literature and expertise by members of the expert panel to help identify potential signals. The feasibility of implementing the guidelines was also assessed prior to publication. Each recommendation is annotated with the type and strength of the recommendation and the quality of the evidence assessed using standardized criteria that were also used in previous 2016 guidelines [5].

Classification of the strength of recommendations

The strength of a recommendation reflects the belief of its authors that following the recommendation will bring more benefits than harm. In these guidelines, the strength of the recommendations is determined — depending on the source document — according to the classifications of the American College of Chest Physicians, American Heart Association, and European Society of Cardiology. For each recommendation included in the Polish guidelines, the source document of the guidelines and their strength (in square brackets) are given. One of the source documents did not specify the strength of the recommendations, so the authors of the Polish update also did not provide the strength of the recommendations that were based on these guidelines. In the absence of existing recommendations answering the clinical question, the Working Group aimed at formulating the consensus opinion of the expert team, i.e., good practice statement (GPS) (Tables 1–3) [13–16].

During the elaboration of this document all the available references were analyzed and guidelines were formulated based on definitions according to the GRADE Working Group (The Grading of Recommendations Assessment Development and Evaluation Scale). Formulated guidelines were classified as strong recommendations (1) or weak recommendations (2) and supported with an additional description referring to the quality of evidence that they have been based on [17–19]. In the case of recommendations classified as strong, based on the analysis of results of correctly planned and performed studies, the authors are convinced that administration of a particular procedure will bring significant benefits in comparison to restraining from it (recommendation level 1 — "recommended"). In case of a weak recommendation (recommendation level 2 — "suggested") the authors believe that administration of the suggested procedures may be more beneficial than restraining from performing it. However, at this point, there are no high-quality studies that would determine favorable and unfavorable effects of a particular procedure — this recommendation level should be considered as a suggestion for the final clinical decision.

According to the suggestions specified in GRADE, guidelines marked with letter (A) are based on reports sufficient for formulating them and further studies probably will not elicit any changes.

The letter (B) indicates that further studies could possibly influence the change of statement due to the quality of data available at this time.

The letter (C) suggests that due to very low quality of data available, further studies may elicit significant changes to the guidelines.

The levels of recommendation importance:

1A — Strong recommendation, high-quality evidence according to EBM;

1B — Strong recommendation, moderate-quality evidence according to EBM;

1C — Strong recommendation, low- or very low-quality scientific evidence;

2A — Weak recommendation, high-quality evidence according to EBM (further studies probably will not have any significant influence on changes in suggested treatment method);

2B — Weak recommendation, moderate-quality evidence according to EBM (further studies may have significant influence on changes in suggested treatment method);

2C — Weak recommendation, low- or very low-quality scientific evidence (further studies probably will have significant influence on changes in suggested treatment method).

GPS (good practice statement) — in the absence of existing recommendations, the Working Group sought information on good practice, which implies the potential benefit of applying it.

The authors reviewed papers on prophylaxis and treatment of cancer patients using the MEDLINE database from January 2016 to April 2021. The analysis covered available randomized trials, prospective and retrospective studies, as well as meta-analyses, systematic reviews, and previously published Polish and foreign guidelines on prevention and treatment of venous thromboembolism (VTE), including VTE prophylaxis in cancer patients.

Table 1. Classification of recommendations and evidence according to the European Society of Cardiology [13]

Class of recommendation	Definition
I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective (Is recommended/is indicated)
II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
IIA	Weight of evidence/opinion is in favor of usefulness/efficacy (Should be considered)
IIB	Usefulness/efficacy is less well established by evidence/opinion (May be considered)
III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful (Is not recommended)
Level of evidence	
A	Data derived from multiple RCTs or meta-analyses
B	Data derived from a single RCT or large non-randomized studies
C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

RCT — randomized controlled trial

Table 2. Classification and interpretation of the strength of recommendations according to the American College of Chest Physicians [14, 15]

Grade of recommendation	Implications
Strong recommendations ("we recommend")	
1A	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
1B	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
1C	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Weak recommendations ("we suggest")	
2A	The best action may differ depending on circumstances or patient or societal values. Further research is very unlikely to change our confidence in the estimate of effect
2B	Best action may differ depending on circumstances or patient or societal values. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
2C	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate

Chapter 1. Venous thromboembolism prophylaxis — general recommendations

This part of the guidelines has been left unchanged, assuming that the treatment principles described in it have not changed and are still valid. Only recommendations were added regarding the education of cancer patients on thromboembolic complications in neoplastic disease.

Clinical question 1. Should the awareness of cancer care teams and cancer patients be raised about the risk and treatment of VTE?

Recommendation 1.1

It is recommended to elaborate and implement guidelines for VTE prophylaxis in every hospital, department and/or institute, where the cancer patients at risk of venous thromboembolism are treated and consulted [1A].

Recommendation 1.2

It is recommended to elaborate guidelines for VTE prophylaxis on paper or in electronic form, as a standard procedure for particular health care facility [1C].

Recommendation 1.3

It is recommended to use anticoagulants for VTE prophylaxis and treatment according to manufacturer guidelines and drug registration documents [1C].

Table 3. Classification and interpretation of the strength of recommendations according to the American Heart Association [15]

Estimate of certainty (precision) of treatment effect	Size of treatment effect						
		Class I **Benefit >>> Risk** Procedure/Treatment SHOULD be performer/ administered	Class IIa **Benefit >> Risk** Additional studies with focused objectives needed IT IS REASONABLE to perform procedure/ /administer treatment	Class IIb **Benefit ≥ Risk** Additional studies with broad objectives needed; additional registry data would be helpful Procedure/Treatment MAY BE CONSIDERED	Class III No Benefit Or Class III Harm		
						Procedure/test	Treatment
					Class III: No benefit Class III: Harm	Not helpful Excess cost w/o benefit or harmful	No proven benefit Harmful to patients
	Level of evidence A Multiple populations evaluated Data derived from multiple RCTs or meta-analyses	— Recommendation that procedure or treatment is useful/effective — Sufficient evidence from multiple RCTs or meta-analyses	— Recommendation in favor of treatment or procedure being useful/ /effective — Some conflicting evidence from multiple RCTs or meta-analyzes	— Recommendations's usefulness/efficacy less well established — Greater conflicting evidence from multiple RCTs or meta-analyses	— Recommendation that procedure or treatment is not useful/effective and may be harmful — Sufficient evidence from multiple RCTs or meta-analyses		
	Level of evidence B Limited populations evaluated Data derived from a single RCT or nonrandomized studies	— Recommendation that procedure or treatment is useful/effective — Evidence from single RCT or nonrandomized studies	— Recommendation in favor of treatment or procedure being useful/ /effective — Some conflicting evidence from single RCT or nonrandomized studies	— Recommendations's usefulness/efficacy less well established — Greater conflicting evidence from single RCT or nonrandomized studies	— Recommendation that procedure or treatment is not useful/effective and may be harmful — Evidence from single RCT or nonrandomized studies		
	Level of evidence C Very limited populations evaluated Only consensus opinion of experts, case studies, or standard of care	— Recommendation that procedure or treatment is useful/effective — Only consensus opinion of experts, case studies, or standard of care	— Recommendation in favor of treatment or procedure being useful/ /effective — Only diverging consensus opinion of experts, case studies, or standard of care	— Recommendations's usefulness/efficacy less well established — Only diverging consensus opinion of experts, case studies, or standard of care	— Recommendation that procedure or treatment is not useful/effective and may be harmful — Only consensus opinion of experts, case studies, or standard of care		

RCT — randomized controlled trial

Recommendation 1.4

In patients with a high bleeding risk, benefits and risk of antithrombotic prophylaxis should be evaluated individually. In clinically justified situations, mechanical prophylaxis methods should be applied, until bleeding risk will decrease enabling the administration of pharmacological prophylaxis [1A].

Recommendation 1.5

In each patient with cancer, it is recommended to assess the risk of VTE at diagnosis, and then periodically, especially when systemic anticancer therapy, surgery or hospitalization is planned [1A].

Recommendation 1.6

It is suggested that cancer patients should be educated about VTE by oncologists and cancer care team members, especially during periods of increased risk, such as major surgery, hospitalization, and when receiving systemic anticancer therapy [2C].

Comment

Individual risk assessment of venous thromboembolism is justified considering the unpredictable variety of clinical situations and different characteristics of the treated populations, especially in terms of the type of therapy and risk factors present in a specific patient group. At the same time, significant differences between populations of patients indicate a need for the elaboration of an antithrombotic prophylaxis protocol dedicated to the particular patient group in each healthcare facility considering the characteristics of the treated population, as well as administered therapy. This protocol should contain recommendations on VTE risk assessment and VTE prophylaxis, as well as up-to-date registrations of drugs available and used in this indication. The principles of antithrombotic therapy and prophylaxis in the healthcare facility should be updated, taking into account the current guidelines, as well as individual risk assessment for VTE risk, treatment-related bleeding and potential complications in a specific group of patients.

Chapter 2. The prevention of venous thromboembolism in cancer patients treated surgically

Clinical question 2. Should cancer patients undergoing elective surgery be given anticoagulation prophylaxis?

Recommendation 2.1

The VTE risk as well as the risk of hemorrhagic complications should be individually assessed in each patient undergoing cancer surgery [1A].

Recommendation 2.2

All patients undergoing extensive oncological surgeries in the abdomen and pelvis should receive VTE prophylaxis with prophylactic doses of LMWH or low doses of unfractionated heparin, if there are no contraindications, including active bleeding or high risk of bleeding events [1A].

Recommendation 2.3

It is suggested that pharmacological prophylaxis should be started (2 to 12 hours) before the surgery [2B].

Recommendation 2.4

It is suggested that in cancer patients qualified for surgery, who are at high or very high risk of VTE, pharmacological prevention should be supported with mechanical methods, most preferably intermittent pneumatic compression [2B].

Recommendation 2.5

It is not recommended to use mechanical methods as the only prevention for thromboembolism (without pharmacotherapy) in surgical cancer patients, who are not at higher risk of bleeding [1B].

Recommendation 2.6

In surgical patients at high risk of serious bleeding complications or in patients with contraindications for pharmacological prophylaxis due to active bleeding or a high risk of bleeding relapse, mechanical prophylaxis should be considered (most preferably intermittent pneumatic compression), at least until the bleeding risk decreases and pharmacological prophylaxis is possible [2C].

Recommendation 2.7

In patients undergoing (open or laparoscopic) cancer surgery, it is recommended to continue thromboprophylaxis for at least 7–10 days [1A]. In patients undergoing major abdominal and/or pelvic oncological surgery, who are not at high risk of serious bleeding complications, and who have thrombosis risk factors such as prolonged immobilization, obesity, a history of VTE or other, an extended-duration pharmacological prophylaxis (4 weeks) with LMWH is recommended [1A]. In other cases, it is suggested that an individual decision be made whether to extend the prophylaxis or not, based on the assessment of the relevant benefits and risks [2C].

Recommendation 2.8

In surgical patients with cancer disease, at high risk of thromboembolic complications insertion of an

inferior vena cava filter is not recommended as primary thromboprophylaxis [1A].

In the natural history of neoplastic disease, hemostatic disorders often occur, leading to the activation of the coagulation system and, consequently, VTE [20]. At the same time, however, anticancer treatment, especially surgical procedures, may additionally increase the risk of this complication [20–26]. Surgery affects the risk of thrombosis through multiple factors: tissue trauma due to surgical procedures, periprocedural immobilization, blood and plasma substitution, positive pressure ventilation, potential foci of inflammation or intravenous catheters [24, 27–32].

The best known risk factor for VTE in cancer patients is surgery, and the risk associated with surgical procedures in this group of patients is estimated to be 3–5 times higher compared to patients without diagnosed malignancy [27, 28, 33–37]. The risk factors of CAT are summarized in Table 4 [24, 37]. The majority of cancer patients qualified for surgical treatment for oncological indications should be considered a population at high and very high risk of developing postoperative DVT and/or pulmonary embolism [21, 24, 25]. This increased risk is reflected, inter alia, in the increasingly used Caprini scale, a tool for assessing perioperative VTE risk, in which the presence of cancer is scored 2 points (Table 5). [25, 39–41].

While evaluating VTE risk in patients scheduled for surgery, it is obligatory to take into account the presence of other factors, especially those related to comorbidities and clinical situations that increase the risk of VTE (obesity, prolonged immobilization, varicose veins, hormone therapy, previous stroke resulting in paralysis, history of VTE episode and other) [24, 25, 42]. Medical diseases such as exacerbation of chronic heart failure or inflammatory bowel disease are also considered important risk factors of VTE [24, 25, 43]. One should also keep in mind other potential risk factors, such as postsurgical infection — the presence of an intra-abdominal abscess or other infection of the surgical site following colorectal surgery or other acute infection may increase the risk of VTE [25, 36, 44–45]. Merkow et al. [46] analyzed a population of almost 45,000 cancer patients (9 types of cancers) in order to determine the incidence of postoperative DVT. In 33.4% of cases, VTE occurred occur not immediately after surgery, but after discharge from the hospital. The percentage of CAT patients varied depending on the type of cancer treated. Factors significantly influencing the occurrence of thrombotic complications in this group of patients were age 65 years or more, presence of metastases, high body mass index (BMI), platelet count over 400,000/μL, albumin level <3 g/dL and duration of the procedure being over 2 hours. Postoperative VTE occurred mainly in patients who underwent gastrointestinal, lung and ovarian/uterine procedures, and the occurrence of CAT was associated with a six-fold higher mortality [46]. In another study analyzing the population of patients after "major" cancer surgery involving the abdominal cavity and pelvis, 4.05% of symptomatic VTE cases were identified up to 90 days after surgery, of which 47.5% were diagnosed after discharge from hospital [47]. It should be noted that the increased risk of postoperative thrombotic complications may be influenced by previous anticancer therapy, including preoperative chemo- and radiotherapy [48].

However, not only cancer surgery in the abdominal, pelvic and thoracic areas is linked to the risk of thrombosis. Reports on the occurrence of VTE episodes also concern cancer surgery procedures in the neck and head region, including maxillofacial surgery or commonly performed surgical procedures for breast cancer [49–54]. The risk of symptomatic VTE in the population of patients after breast cancer surgery ranges from 0.12–0.5 [52–54].

The effectiveness of low doses of unfractionated heparin (LDUH) in the prophylaxis of VTE in high-risk surgical patients has been well documented. However, in everyday clinical practice, for various reasons, this method of prophylaxis is less and less important compared with the use of LMWH; and it should be noted that both methods show high and comparable effectiveness [55–66].

In cancer surgery, pharmacological thromboprophylaxis with the use of LMWH or UFH (according to approved indications and studies performed) should be started before the surgery [21, 22, 62, 64]. This is an important difference to general non-cancer surgery. There is still insufficient evidence to support fondaparinux as an alternative to LMWH in postoperative prophylaxis of VTE in cancer patients [11].

The authors of these guidelines believe that it is crucial to adhere to the registration documents of specific drugs and use them in accordance with the manufacturer's instructions. Some of the products containing LMWH have a range of different prophylactic dosage options for the moderate and high risk surgical patients; however, there are suggestions supported by research that higher doses should be used in high- and very-high-risk cancer patients. In a study of 1.375 patients, of whom 70% were patients with cancer, two prophylactic doses of dalteparin (2500 U and 5000 U) were used. The dose of 5000 U was more effective in preventing postoperative VTE than the 2500 U dose (postoperative VTE of 8.5% vs. 14.9%; $p < 0.001$) [67]. Table 6 lists the drugs used in perioperative prophylaxis in cancer patients.

Very few RCTs have been published comparing the efficacy of the different LMWHs in perioperative proph-

Table 4. Risk factors of venous thromboembolism, taking into account the specificity of the population of oncological patients [adapted from 37]

Category	Risk factor
Risk factors depending on the patient and comorbidities	Age (> 40 years) Positive family history Obesity Injuries (especially multi-organ injuries, fractures of the pelvis, fractures of the long bones of the lower limbs) Stroke with paralysis, paresis or restricted mobility Sepsis Acute infection Heart failure class III and IV according to the New York Heart Association History of myocardial infarction Respiratory failure (especially worsening) Autoimmune diseases Nephrotic syndrome Myeloproliferative neoplasms Nocturnal paroxysmal hemoglobinuria Pressure on the venous vessels Pregnancy or postpartum Varicose veins Previous episode of venous thromboembolism Thrombophilia Prolonged immobilization (in hospital, at home or during travel) Antiphospholipid syndrome
Risk factors depend on the type and stage of the cancer	Location of the tumor Cancer stage (the higher the stage, the greater the risk) Histological type Time from diagnosis (increased risk in the first 1–6 months and in advanced neoplasms)
Risk factors dependent on therapy	Surgical treatment Prolonged postoperative immobilization Chemotherapy Hormone therapy, hormone replacement therapy, treatment with selective estrogen receptor modulators Radiotherapy Transfusion of concentrated red blood cells or plasma Use of erythropoiesis stimulating factors Use of angiogenesis inhibitors Central lines or ports Leukocytosis (> 11 × 10^9/L) Anemia (Hb < 100 g/L)

ylaxis in cancer patients. In the SAVE-ABDO study, in which more than 80% of the 4,414 patients were those who underwent major surgery in the abdominal area due to cancer, the patients were randomized to the groups receiving enoxaparin or semuloparin (the beginning of prophylaxis in both groups before the procedure). Endpoints, defined in this study as an episode of VTE or death, occurred in 5.5% of patients receiving enoxaparin and in 6.3% of those receiving semuloparin (OR 1.16; 95% CI, 0.84–1.59), with a smaller percentage of bleeding complications in the group receiving semuloparin [68]. In a study comparing the efficacy of nadroparin and enoxaparin at prophylactic doses (nadroparin 2850 anti-Xa units, enoxaparin 4000 anti-Xa units) in surgical patients with colorectal cancer, symptomatic or asymptomatic DVT or pulmonary embolism occurring up to 12 days of observation was diagnosed respectively in 15.9% and 12.6% of those patients (RR 1.27; 95% CI 0.93 to 1.74, p = NS) with fewer major bleeding complications in the group treated with nadroparin (7.3% vs. 11.5%; p < 0.05). However, when considering the methodology of this study, it should be noted that the time of administration of enoxaparin 40 mg was inconsistent with approved drug labeling (2 hours before the procedure instead of the currently recommended 12 hours) [69]. A study comparing dalteparin at a dose of 5,000 anti-Xa units with fondaparinux 2.5 mg once daily for 5–9 days showed comparable benefit/risk ratios for both drugs used for prophylaxis in patients undergoing general

Table 5. Modified Caprini scale to assess the risk of thromboembolic complications in surgical patients [From 24]

1 point	2 points	3 points	5 points
Age 41–60 years Minor surgery BMI > 25 kg/m2 Swollen legs Varicose veins Pregnancy or postpartum History of unexplained or recurrent spontaneous abortion Oral contraceptives or hormone replacement Sepsis (< 1 month) Serious lung disease, including pneumonia (<1 month) Abnormal pulmonary function Acute myocardial infarction Exacerbation or diagnosis of heart failure (< 1 month) History of inflammatory bowel disease Medical patient at bed rest Acute spinal cord injury (< 1 month)	Age 61–74 years Arthroscopic surgery Major open surgery (>45 minutes) Laparoscopic surgery (>45 minutes) Malignancy Confined to bed (>72 hours) Immobilizing plaster cast Central venous access	Age ≥ 75 years History of VTE Family history of VTE Factor V Leiden Prothrombin gene 20210A mutation Lupus anticoagulant Anticardiolipin antibodies Anti-beta 2-glycoprotein I antibodies Elevated serum homocysteine Heparin-induced thrombocytopenia Other congenital or acquired thrombophilia	Stroke (<1 month) Elective arthroplasty Hip, pelvis or leg fracture Acute spinal cord injury (<1 month)

BMI — body mass index; VTE — venous thromboembolism
Score: 0 points — very low risk; 1–2 points — low risk; 3–4 points — moderate risk; ≥ 5 points — high risk

surgical procedures [70]. In the case of fondaparinux, however, there is still a lack of prospective, randomized studies dedicated specifically to the population of cancer patients — in the previous studies, they represented only a small portion of the population studied [70, 71]. Data on the effectiveness of thromboprophylaxis in laparoscopic procedures in cancer patients are limited [72–74]. Xie et al. [74] in their meta-analysis of 9 randomized clinical trials conducted on 2,606 cases of colorectal cancer, who underwent surgery, did not find any difference in DVT incidence between patients treated with open or laparoscopic surgery.

Factors related to laparoscopic surgery that increase the risk of thromboembolic complications include laparoscopic pelvic surgery, as well as long duration of the surgery (above one hour) [75]. In addition, the presence of cancer, anticancer therapies and other VTE risk factor should be taken into consideration [22, 24, 75].

Due to the limited number of studies on the best method and timespan of thromboprophylaxis in patients undergoing laparoscopic oncological surgery, thus far it is only possible to extend the guidelines referring to the open surgeries. The benefits of prolonged thromboprophylaxis at least in some patients undergoing laparoscopic surgery for oncological reasons are confirmed by the study by Vedovati et al. [76], which included 225 patients undergoing laparoscopic colorectal surgery. The patients were randomly assigned to the group receiving pharmacological thromboprophylaxis for 8 ± 2 days or to the group where prophylaxis was prolonged to 4 weeks. The effectiveness of the prophylaxis was verified by venous ultrasound imaging of the lower extremities. No statistically significant differences were found in the incidence of bleeding complications between the groups. However, prolongation of antithrombotic prophylaxis up to 4 weeks significantrly decreased the DVT rate detected by the means of ultrasound (9.7% in the short-term prophylaxis group vs. 0% in the group of patients receiving extended prophylaxis) [76]. The results of the studies by Vedovati et al. and two meta-analyzes: Fagarasanu et al. [77] and Felder et al. [78] point out that the reduction of VTE events with prolonged prophylaxis was not associated with an increase in the number of bleeding complications. An additional argument for extending pharmacoprophylaxis, especially in patients with colorectal and genitourinary cancers, as well as in those undergoing radiotherapy, is the fact that 54% of patients had thromboembolic complications after discharge from the hospital, many weeks after surgery [79].

The efficacy and safety of prolonged thromboprophylaxis has been confirmed in cancer patients undergoing major (open or laparoscopic) abdominal and pelvic surgeries.

Table 6. Perioperative thromboprophylaxis dosing in cancer patients

Drug	Prophylactic doses
Dalteparin	5000 IU subcutaneously in the evening before the procedure. After the procedure, administer 5,000 IU subcutaneously every evening OR initiation of drug administration on the day of surgery: 2,500 IU subcutaneously within 2 hours before surgery and 2,500 IU subcutaneously 8 to 12 hours later, but not earlier than 4 hours after the end of the procedure. Postoperatively, starting from the day after surgery, administer 5,000 IU subcutaneously every morning
Enoxaparin	40 mg subcutaneously once daily, first dose 12 hours before surgery
Nadroparin	0.3 ml (2850 IU anti-Xa) once daily for at least 7 days. The first dose should be given 2 to 4 hours before surgery
Fondaparinux	In oncology, 2.5 mg once daily subcutaneously; give the first dose 6 hours after surgery, provided that hemostasis is preserved. Treatment should be continued until the risk of VTE is reduced, usually for 5–9 days (until the patient is able to walk). In postoperative patients after hip fracture, the risk usually lasts more than 9 days and an additional 24-day extension treatment is recommended

Since 2016, four new meta-analyzes have been published confirming the benefits of prolonged prophylaxis after oncological procedures [77, 78, 80, 81]. The first one assessed the administration of prophylactic doses of heparins for a period of 2–6 weeks after surgery, which significantly reduced the risk of any VTE events (2.6% vs. 5.6%, RR 0.44, 95% CI 0.28– 0.70) and proximal deep vein thrombosis (1.4% vs. 2.8%, RR 0.46, 0.23–0.91), but it had no effect on asymptomatic pulmonary embolism (0.8% vs. 1.3%, RR 0.56, 0.23–1.40) [77]. This treatment was not associated with an increase in the incidence of major bleeding (1.8% vs. 1.0%, RR 1.19, 0.47–2.97). In the second meta-analysis, extended thromboprophylaxis was associated with a significant reduction in the incidence of deep vein thrombosis (RR 0.57, 95% CI 0.39–0.83), without a significant increase in bleeding (RR 1.48, 0.78–2.8) [80]. Another meta-analysis showed that extended prophylaxis significantly reduced the risk of all VTE events (OR 0.38, 95% CI 0.26–0.54), all reported cases of deep vein thrombosis (OR 0.39, 95% CI 0.27–0.55) and proximal deep vein thrombosis (0.22, 0.10–0.47), with a non-significant reduction in symptomatic VTE (0.30, 0.08–1.11) and a non-significant increase in major bleeding (1.10, 0.67–1.81) [78]. The fourth meta-analysis [81] provided data confirming the results published by Felder et al. [78].

Three other observational studies (two prospective and one retrospective) have demonstrated a beneficial effect of prolonged thromboprophylaxis after radical cystectomy and liver resection [82–84]. The above observational studies and meta-analyzes published after 2016 confirm data from previous studies cited in the 2016 document. In two RCTs: ENOXACAN II — extended-duration thromboprophylaxis after abdominal or pelvic cancer surgery, and FAME — prolonged thromboprophylaxis after major abdominal and pelvic procedures, the use of 4-week antithrombotic prophylaxis with LMWH proved to be effective in reducing the incidence of VTE compared with the standard duration of prophylaxis, without increasing the rate of bleeding complications [85, 86]. Based on the data from the RIETE registry (Registro Informatizado Enfermedad ThromboEmbolica), Bustos Merlo et al. [79] showed that in patients after surgical treatment of colon and genitourinary cancers, in more than 50% of the patients thromboembolic complications were detected after discharge from hospital. Therefore, it can now be assumed that there is strong evidence to extend the duration of anticoagulation prophylaxis to 4 weeks after oncological surgery, provided that patients are not at high risk of bleeding.

Early and aggressive mobilization of the patient after surgery is currently the standard of perioperative care. Often other mechanical methods of thromboprophylaxis are also used. A number of already completed studies related to surgically treated patients highlight the beneficial effects of mechanical prophylaxis methods on the reduction of VTE incidence in this group of patients [23]. Most of them, however, relate only to mixed groups of patients, in terms of risk as well as in terms of indications for surgery. Reports dedicated to homogenous groups of cancer patients are very limited [70, 87–91]. There seems to be no reason at present to amend the recommendations on mechanical methods of thromboprophylaxis. It is emphasized that they should not be used as the only method in patients at

high risk of VTE, unless the patient has a high risk of bleeding complications, which is a contraindication to pharmacological prophylaxis [20, 21, 23, 24]. On the other hand, concomitant prophylaxis with mechanical methods, in particular intermittent pneumatic compression (IPC), may have a beneficial additive effect on the reduction of thrombotic events in patients with a high and very high risk of VTE qualified for surgery [20, 21, 23, 24]. In a meta-analysis, the results of 25 prospective randomized clinical trials concerning the combined DVT prophylaxis based on anticoagulation and mechanical methods were compared with VTE prevention regimens using only one method of prophylaxis in surgical patients [92]. Based on this report, pharmacological prophylaxis with mechanical methods together resulted in 49% DVT risk reduction. The pharmacological VTE prophylaxis added to mechanical methods led to the 44% DVT risk decrease; however, a significant increase in the bleeding rate was observed (RR = 1.74, 95% CI: 1.29–2.34) [92].

In the last 5 years, there has been only one RCT assessing the clinical efficacy of mechanical antithrombotic prophylaxis in 682 cancer patients [93]. Patients who used only intermittent pneumatic compression had a higher risk of VTE compared with patients who received a combination treatment with intermittent pneumatic compression and LMWH (3.6% in the group with intermittent pneumatic compression only vs. 0.6% in the group with intermittent compression plus LMWH, $p = 0.008$), although the risk of bleeding was higher in the LMWH group (1.2% vs. 9.1%, $p < 0.001$). Two small RCTs of 30 patients and 90 patients found no benefit of adding LMWH to mechanical prophylaxis [94, 95]

Compared with the 2016 guidelines, the recommendations regarding the use of mechanical methods of prophylaxis have not been changed and their use as monotherapy is not recommended, except when pharmacological methods are contraindicated.

Chapter 3. Specific guidelines regarding cancer patients in selected surgical fields

3.1. General remarks on data published after 2016

Guidelines presented in Chapter 2 are dedicated to oncological surgical patients and contain the rules of prophylaxis in oncological surgery. For practical implementation of the proposed guidelines, it is necessary to take into account the characteristics of the treated patient population and the differences arising from the different bleeding risk as well as the type of procedures performed. The authors of these updated guidelines, taking into account the literature review and recommendations included in the previous version of the guidelines from 2016, decided to omit from the present document detailed recommendations for all surgical specialties treating cancer patients (they are available to readers in the original version of the document).

Lung cancer is associated with a high risk of thromboembolic complications. Patients undergoing major thoracic surgery because of cancer (including extensive lung resection, pneumonectomy, resection of the lung and pleura, or esophageal oncological resection) should be classified as at high risk of VTE [23, 96–99].

After 2016, two new meta-analyzes were published confirming that in patients with lung cancer, LMWH prophylaxis reduces the risk of VTE, but at the cost of an increase in bleeding [100, 101]. The results of a cohort study by Hachey et al. [102] in a population of surgically treated lung cancer patients confirmed the usefulness of the modified Caprini scale for assessing VTE risk in selecting patients who would benefit from extended prophylaxis. A later published study by Sterbling et al. [103] confirmed this conclusion and additionally showed that the therapy is safe and does not increase the bleeding rate in cancer patients after thoracic surgery.

A meta-analysis of pancreatic cancer patients showed a significant benefit from antithrombotic prophylaxis, i.e., a marked reduction in VTE incidents (RR 0.18, 95% CI 0.08–0.40), without a significant increase in the bleeding rate [104].

Taking into account, as mentioned above, the information contained in the previous guidelines, the authors of the current update also concluded that the two surgical specialties should be discussed more broadly, due to their distinctiveness in the context of bleeding complications or a high risk of VTE, i.e., neurosurgery and urology.

3.2. Antithrombotic prophylaxis in neurosurgical cancer patients

Studies of limited quality on antithrombotic prophylaxis in the field of cancer neurosurgery indicate that the risk for VTE is high when no prophylaxis is administered in this group of patients [105–107].

Available studies on thrombosis prophylaxis in neurosurgery suggest the possibility to reduce the VTE risk effectively by the means of mechanical methods, as well as pharmacological prophylaxis [105–107]. However, most of these reports apply to the patients operated not only due to cancer. Prospective trials on effectiveness and safety of thrombosis prophylaxis in the oncological patient population undergoing neurosurgery are still very rare [105].

According to the literature, VTE risk in patients suffering from malignant glioma is exceptionally high

in subjects who underwent craniotomy and surgical treatment, ranging from 21 to 32%, whereas deep venous thrombosis occurs in 3–25% of cases [108–114].

Most studies focusing on thrombosis prophylaxis analyze heterogeneous groups of neurosurgical patients, among whom only some suffered from a malignant tumor of the central nervous system. The report based on the analysis of 2,000 neurosurgical patients estimated the average risk of symptomatic VTE within 30 days of follow-up at 3.9%. However, the risk was significantly higher in patients, who underwent craniotomy due to a primary brain tumor (7.5%) or brain metastases 19%. In this study 67% of the patients received antithrombotic prophylaxis [115].

Kimmel and Walter [116] specified the following VTE risk factors in patients undergoing craniotomy (in their study 56% of 3,098 patients underwent craniotomy due to malignancy): poor functional performance, age > 60 years, surgery duration > 4 hours, and postoperative complications such as: pneumonia, cerebrovascular events, sepsis, septic shock, unplanned and/or prolonged intubation [116].

Administration of appropriate prophylaxis for VTE prevention in neurosurgical patients, including those who were operated because of a tumor, requires an individual bleeding risk assessment in the context of disease etiology, projected surgery, and particular VTE prevention method. Postoperative intracranial bleeding requires further consideration. The review of 20 studies performed on 31,000 craniotomy patients who did not receive VTE prophylaxis suggests that the risk of intracranial bleeding amounts on average to 1.1%; however, however, the differences were significant depending, inter alia, on the indications for surgery [106].

Application of mechanical methods of VTE prophylaxis in neurosurgical patients is a focus of interest, especially for procedures having a high bleeding risk, including neurosurgical oncological procedures [23, 105, 106]. Apart from early patient mobilization, which is not always possible, mechanical methods of prophylaxis available for this group include intermittent pneumatic compression (IPC), graduated compression stocking, and electric calf muscle stimulation. In two trials, the effectiveness of IPC was compared with controls who did not receive any prophylaxis. The studies proved that IPC is beneficial for neurosurgical patients [117, 118].

Graduated compression stockings are usually more commonly used for VTE mechanical prophylaxis than IPC because of many reasons, including economic ones. However, data regarding their effectiveness, when used as a single prevention method in patients undergoing oncological neurosurgical procedures, are limited and controversial. Bucci et al. [119] in a study involving a small group of neurosurgical patients, among whom 56% suffered from brain tumors, did not find any significant difference in the incidence of symptomatic deep venous thrombosis between patients using intermittent pneumatic compression and those using gradated compression stockings. Angelli et al. [120] conducted a study comparing outcomes of graduated compression stockings used along with enoxaparin and graduated compression stockings used with placebo. In the arm of the study where only compression stockings were used, the thrombosis incidence amounted to 33% (evaluation based on phlebography) [120]. In this trial, opposed to the previous one, patients with brain or spinal cord tumors constituted 97% of analyzed population. The study conducted by Turpie et al. [121] on the incidence of asymptomatic deep venous thrombosis also confirmed that differences in characteristics and risk rates between analyzed neurosurgical patient populations are significant. Deep venous thrombosis was diagnosed in 8.75% of patients using graduated compression stockings (in patients without prophylaxis the incidence amounted to 20%). However, only 48% of patients in this study were operated due to a brain tumor (and only some patients suffered from malignant brain tumors). Although this study revealed a decrease in VTE incidence, when graduated compression stockings as well as complex prophylaxis with graduated compression stockings combined with intermittent pneumatic compression were used, there was no statistically significant difference between groups, in which mechanical prophylaxis was applied. Therefore, further studies are required in order to evaluate the role and efficacy of graduated compression stockings in neurosurgical patients and to directly compare the effectiveness of IPC with graduated compression stocking application [121]. In the study conducted by Wautrecht et al. [122] on a small group, none of the 18 neurosurgical patients (100% of enrolled subjects suffered from a brain tumor), who received intermittent pneumatic compression combined with compression stockings developed DVT, whereas 2 of 5 patients, who used compression stockings only, developed deep venous thrombosis [122].

Recently, there is increased interest in other methods of mechanical prophylaxis such as electrical calf stimulation (ECF). The study conducted in order to assess the effectiveness of ECF in high-risk neurosurgical patients found that deep venous thrombosis incidence dropped from 18.7% to 4%, including proximal deep vein thrombosis rate decrease from 8% to 2.7%, and symptomatic DVT reduction from 2.7% to 0% [123].

Pharmacological prophylaxis in patients at a high and very high risk of VTE, especially those combining pharmacological prophylaxis with mechanical methods, potentially reduces the thromboembolic complication

incidence in other medical fields [23]. Due to characteristics of neurosurgical patients operated for oncological indications and a potential neurosurgery- as well as pharmacological prophylaxis-related bleeding risk, this subject requires further studies also in the field of the cancer neurosurgical treatment. Meta-analysis of 4 randomized controlled clinical trials on pharmacological prophylaxis for thrombosis prevention in neurosurgery (three of them involving antithrombotic prophylaxis with LMWH and one of them LDUH, with or without mechanical prophylaxis methods, proved that DVT incidence decreased from 29% in controls to 16.1% in patients, who received pharmacological prophylaxis (proximal DVT incidence decreased from 12.5 % to 6.25%). Regarding the hemorrhagic complications at the time, the risk of "major" bleedings increased from 2.5% to 3.1%, and the overall bleeding incidence increased from 2.9% to 5.9% [124].

The timing of the antithrombotic pharmacological prophylaxis administration plays an important role in neurosurgical patients. Due to the fact that most of the intracranial bleedings in neurosurgical patients occur within the first 12–24 hours after craniotomy, and half of thromboembolic events occur later (after the first week after surgery), in patients at a high risk of VTE, it is justified to start VTE pharmacological prophylaxis postoperatively (after obtaining proper hemostasis) [113, 125].

Dickinson et al. [126] conducted a study on patients with brain tumors and attempted to compare effectiveness of antithrombotic prophylaxis in 3 groups of patients, who received intermittent pneumatic compression, LMWH (enoxaparin) and combination therapy with two of the aforementioned methods. In this study, LMWH was administered before surgery. The trial was discontinued due to a high bleeding rate in patients in whom pharmacological prophylaxis was administered before surgery (the hemorrhagic events occurred mostly in an early postoperative period and 3 patients required surgical reintervention). The authors suggest that patients receiving low-molecular-weight heparin should undergo intracranial procedures no sooner than after an appropriate time after the last dose of LMWH. Agnelli et al. [120] and Nurmohamed et al. [127] evaluated effectiveness and safety of LMWH at prophylactic dose administered within the first 24 hours after surgery (LMWH + graduated compression stockings vs. LMWH). In the first trial, DVT and proximal DVT incidence amounted to 33% and 13% respectively in the group of patients, who used only graduated compression stockings in comparison with 17% and 5% in the group, who received combined prophylaxis [168]. In the second trial, the incidence amounted to 26% and 12% respectively in patients using only compression, and 19% and 7% for combination of mechanical and pharmacological prophylaxis (with LMWH prophylaxis started postoperatively).

Also in phlebography based studies, a decrease in the incidence of proximal deep venous thrombosis from 28.9% to 17.9% was observed in patients, who received combination prophylaxis (along with a decrease in proximal DVT rate from 12% to 5.7%, and an increase in incidence of "major" bleeding complications from 2.0% in patients receiving graduated compression to 3.4% in patients, who additionally received LMWH) [120, 127].

Effectiveness and safety of unfractionated heparin administered at low doses for pharmacological prophylaxis in neurosurgical patients, including a substantial number of patients operated for a brain tumor, was also assessed. Unfortunately, the outcomes of these studies also raise doubts regarding especially the characteristics of the treated population. Cerrato et al. [128] analyzed the effect of antithrombotic prophylaxis with low doses of unfractionated heparin (prophylaxis began before surgery) in a group of patients, 87% of whom were suffering from a brain tumor, and discovered a decrease in incidence of asymptomatic VTE from 34% to 6%. Constantini et al. [129] using a similar VTE prophylaxis algorithm did not observe "major" bleedings; however, at the same time did not report a decrease in incidence of symptomatic DVT compared with placebo. Two other studies comparing prophylactic administration of LMWH and LDUH combined with mechanical prophylaxis (63–93% of patients in this group suffered from a brain tumor) did not find significant differences in incidence of "major" bleedings between the groups [130, 131].

The analysis performed by Collen et al. [106] on 18 randomized clinical trials and 12 prospective trials on application of IPC, LMWH and low-dose unfractionated heparin for thromboembolism prevention in neurosurgery confirms the effectiveness of both methods (mechanical prophylaxis — IPC and pharmacological prophylaxis — LMWH). Application of LMWH, as well as IPC, decreased the risk of DVT simultaneously increasing the risk of minor bleedings and increasing the incidence of the composite end-point defined as "minor" bleeding and intracranial bleeding events in the group of patients treated with LMWH [106]. Meta-analysis conducted by Hamilton et al. [107] that compared results of VTE prophylaxis in 1170 patients (6 randomized clinical trials on low dose unfractionated heparin or low-molecular-weight heparin administration in comparison with the controls not receiving pharmacological prophylaxis), who underwent neurosurgical operations within the skull, confirmed that prophylactic heparin doses reduce DVT incidence and, at the same time, increase

the risk of intracranial bleeding. Based on this analysis, pharmacological prophylaxis used in 1,000 patients who undergo craniotomy will potentially prevent 91 venous thromboembolism events (including 35 proximal deep venous thrombosis or pulmonary embolism cases), and at the same time will put 7 patients at risk of intracranial bleeding, and 28 patients at risk of "minor" bleeding complications [107]. Perioperative use of LMWH may be associated with little or no difference in mortality compared with UFH (RR 0.34; 95% CI, 0.04–3.21). The use of LMWH results in little or no difference in symptomatic PE (RR, 0.20; 95% CI, 0.01–4.03) [132].

The systematic literature review by Salmaggi et al. [105] based on the treatment results of 1932 patients, from which 1,558 were operated for a brain tumor should be also mentioned in the context of these guidelines. The authors concluded that administration of mechanical prophylaxis before surgery and its continuation until discharge reduce the incidence of VTE without an increase in bleeding risk. Administration of pharmacological prevention with LMWH further reduces VTE incidence and increases the risk for "major" bleeding complications. Due to significant heterogeneity of analyzed populations, various prophylaxis regimens used as well as the differences in bleeding complication risk related to the type of procedure performed, there is a need for further research in order to define an optimal antithrombotic prevention method in patients undergoing neurosurgical oncological procedures.

The American Society of Hematology (ASH) guideline panel advises against the use of pharmacoprophylaxis in patients undergoing major neurosurgery (Conditional recommendation based on very weak evidence). Pharmacological prophylaxis may be justified in a higher-risk subset of patients, such as those who are post-operatively immobilized for long periods. Moreover, this type of VTE prevention can be considered in patients undergoing major neurosurgical procedures who are at low risk of major bleeding [7].

Recommendation 3.2.1

The risks of venous thromboembolism and bleeding complications should be assessed individually for each patient undergoing neurosurgical oncological procedures [1A].

Recommendation 3.2.2

Due to potential bleeding risk, patients undergoing intracranial oncological neurosurgery should receive mechanical prophylaxis for prevention of venous thromboembolism, most preferably by the means of intermittent pneumatic compression, in the perioperative and postoperative period [2C].

Recommendation 3.2.3

In patients undergoing intracranial oncological neurosurgery related to high or very high risk of venous thromboembolism, who are not at high risk of bleeding, in the postoperative period the pharmacological thromboprophylaxis with low doses of unfractionated heparin or low-molecular-weigth heparin should be added to mechanical methods of prophylaxis [2C].

Recommendation 3.2.4

In patients undergoing intracranial oncological neurosurgery qualified for pharmacological antithrombotic prevention, the pharmacological prophylaxis should be started postoperatively, if proper hemostasis is achieved [2C]. The time, when pharmacological prophylaxis should begin must be assessed individually considering bleeding risk and local hemostasis [1C].

Recommendation 3.2.5

In patients undergoing intracranial oncological neurosurgery, inferior vena cava filter should not be used for primary antithrombotic prevention [2C].

3.3. Antithrombotic prophylaxis in surgical urological cancer patients

The bleeding risk associated with urinary-tract surgery is often difficult to estimate, and the number and quality of studies on this issue are limited, which hinder the elaboration of final guidelines on VTE prophylaxis in patients undergoing urologic oncological surgeries [23, 133]. Because of that fact, many up-to-date guidelines extrapolate results of the studies conducted on patients undergoing abdominal and pelvic surgery [23, 42, 134, 135]. Lack of research of sufficient quality hinders elaboration of guidelines dedicated to anti-thrombotic prophylaxis in the particular urologic procedures. Hitherto, such guidelines were formulated only by the American Urological Association (AUA) as the Best Practice Statement in 2008 [136]. Although, this document determines cancer as a significant VTE risk factor, the AUA statement applies to patients undergoing urological surgery because of various reasons, including cancer-unrelated ones [136].

The characteristics of urology itself, high percentage of endoscopic and laparoscopic procedures along with a high bleeding risk justify taking them into account in elaboration of guidelines for antithrombotic prophylaxis and individual approach to each patient qualified for urologic oncological surgery.

In patients undergoing transurethral resection of the prostate (TURP), the ASH guidelines do not recommend pharmacological prophylaxis; however, it was pointed out that patients with other risk factors for VTE (e.g. thrombophilia or malignancy) may benefit from

pharmacological prophylaxis. For patients undergoing radical prostatectomy, the ASH guidelines suggest not to use prophylaxis. Patients undergoing additional extended nodal resection and/or radical classic prostatectomy may have a higher risk of VTE and may potentially benefit from pharmacological prophylaxis [7].

In extensive and open urologic oncological surgeries within the lesser pelvis (prostatectomy, cystectomy) the VTE risk, when no prophylaxis is given, corresponds to the risk observed for extensive procedures in general surgery (VTE risk at 10–30%, pulmonary embolism risk at 1–10%) [23, 133, 137–139]. Symptomatic venous thromboembolism occurs on average in 1–5% of patients after extensive urologic surgeries within the pelvis [23]. This risk seems to be even higher in some extensive urologic intraabdominal oncological surgeries. Radical oncological cystectomy with ileal conduit urinary diversion is an example of such a procedure [23, 133, 140]. In the study published in 2014 based on retrospective analysis of 27,455 patients, who underwent extensive urologic oncological surgeries, symptomatic VTE was diagnosed in 2.93% of cases [141]. The highest incidence of symptomatic VTE within 30 days after surgery was observed in patients after radical oncological cystectomy and amounted to 5.5% (there were no data available regarding antithrombotic prophylaxis), whereas the incidence amounted to only 0.7% in patients, who underwent minimally invasive or partial nephrectomy due to cancer [141]. Similar data suggesting high percentage of VTE in patients undergoing radical cystectomy due to cancer can be found in other reports. Potretzke et al. [142] diagnosed 8.3% of clinically overt VTE within 90 days after radical cystectomy due to cancer. VanDlac et al. [143] and Rosario et al. [144] in two independent trials estimated the risk of symptomatic VTE in patients after radical cystectomy at 6%. Based on treatment results of 1,581 patients after radical cystectomy performed due to bladder cancer, James et al. [145] reported that VTE occurred in 10% of the cases within 90 days after surgery [145].

Most of the available data concerning VTE risk and antithrombotic prophylaxis in patients undergoing urologic cancer surgery refers to patients after radical prostatectomy. According to the reports published in recent years, estimated risk of symptomatic VTE ranges from 0.8% to 6.2% in patients, who underwent open prostatectomy, whereas the risk of fatal pulmonary embolism amounts to 0.4–1.1% [146–155]. Dilliogl-ugil et al. [154] found that in the group of 472 patients after prostatectomy, 1.1% suffered from symptomatic pulmonary embolism and 1.3% from DVT. Likewise, Andriole et al. [153] and Catalona et al. [156], based on treatment results of 1,000 patients after this type of surgery, estimated the VTE incidence at 2.6% and 2%, respectively. Hammond et al. [157] analyzed 20,000 extensive oncological surgeries, including urological oncological surgery and found that symptomatic VTE occurred in 1.8% of patients after prostatectomy. In cases where no prophylaxis was applied and thromboembolic complications were assessed by the means of imaging methods after prostatectomy, the risk seems to be significantly higher (16.8–32%), which results from high percentage of asymptomatic DVT cases [158, 159].

The presence of cancer also increases the risk for symptomatic VTE occurrence after upper urinary tract surgery up to 1–5% [23, 133, 139, 160]. A retrospective analysis of the California Patient Discharge Data Set estimated the incidence of symptomatic VTE at 2% after nephrectomy performed because of malignancy [146]. Pettus et al. [161] evaluated the VTE incidence in 2,208 patients after partial or radical nephrectomy (only mechanical methods of VTE prophylaxis were used) and estimated that symptomatic VTE occurred in 1.5% of patients and pulmonary embolism in 0.9%. In renal cancer, risk factors for VTE complications, aside from staging and the presence of metastases, include: the presence of concomitant diseases, long surgery duration, non-radical operation, cancer infiltration into the renal vein and/or inferior caval vein [162–164].

Thanks to advances in laparoscopic techniques, also in urology more and more procedures are performed by the means of minimally invasive surgery, such as robotic surgical systems. However, even these procedures, despite of significantly less severe surgical trauma and faster mobilization of the patient, are not free from thromboembolic complications. VTE occurs in 0.13–4.8% of patients who underwent urologic laparoscopic surgery, whereas incidence of pulmonary embolism is estimated at 0.08–1% [165–172]. Chalmers et al. [173] analyzed VTE incidence in 1,486 patients after radical robotic prostatectomy and antithrombotic prophylaxis with intermittent pneumatic compression combined with low doses of unfractionated heparin or intermittent pneumatic compression prophylaxis alone. In both groups the incidence of symptomatic VTE was comparable (1.0% vs. 0.7%). Other authors also report relatively low incidence of symptomatic VTE (0.5–0.6%) in laparoscopic or robotic prostatectomy [172, 174]. On the other hand, some reports suggest higher risk for such complications despite antithrombotic prophylaxis in this clinical setting. Abel et al. [175] found that within 30 days after radical robotic prostatectomy, VTE occurred in 1.8% of patients (despite the use of mechanical methods of antithrombotic prevention as well as pharmacological prophylaxis with single heparin dose administered before surgery). The authors of this study indicate that surgery duration is also important in the context of an increased VTE risk.

Urologic endoscopic procedures (transurethral urological surgery) are also not free from thromboembolic complications, although the incidence of symptomatic VTE is significantly lower in these procedures (symptomatic VTE: 0.1–0.75%; PE 0.1–0.84%). The presence of cancer and other concomitant diseases may significantly increase the risk of DVT and PE in patients who undergo transurethral procedures such as transurethral electro-resection of the prostate and resection of bladder cancer [23, 138, 146, 176]. The analysis of the extensive California Patient Discharge Data Set assessed symptomatic VTE incidence at 0.3–0.5% in patients who underwent transurethral resection of prostate adenoma within 3 months after surgery. On the other hand, according to White et al. [146], the percentage of diagnosed VTE cases in patients undergoing nephrostomy due to cancer was 3.6% [146].

Clinical application of guidelines on antithrombotic prophylaxis and progress in the surgical techniques, resulting among others in the reduction of procedure duration, significantly decreased incidence of thromboembolic complications after extensive urologic procedures [23, 133, 177]. On the other hand, application of minimally invasive techniques reduced the incidence of thromboembolic complications but did not eliminate them entirely, whereas pulmonary embolism remained the most common nonsurgical cause of death in this group [23, 136]. Like in the other surgical specialties, assessment of VTE risk and bleeding risk is crucial for the proper qualification for antithrombotic prophylaxis [23, 136, 178]. Because of the fact that there are no studies referring to the particular clinical situations (the same type of surgery, same bleeding risk and VTE risk) of sufficient quality, individual approach and treatment in each patient is encouraged.

The number of prospective clinical trials on antithrombotic prophylaxis in patients undergoing urologic surgery, including cancer surgery, is limited. Kutnowski et al. [179] and Sebeseri et al. [180] reported that the DVT incidence decreased after administration of low doses of unfractionated heparin for VTE prophylaxis in patients undergoing urologic surgery (from 36–58% to 9–12%). Bigg and Catalona [181] obtained similar results in the group of patients after open prostatectomy (PE: 0% vs. 11%); the incidence of pulmonary embolism was significantly lower after prophylactic heparin administration. Vandendris et al. [182] used low doses of unfractionated heparin for prophylaxis in patients qualified for open prostatectomy and reported a decrease in deep venous thrombosis incidence from 39.4% to 9.7%. In a review of 7 prospective randomized clinical trials on pharmacological antithrombotic prevention, Collins et al. [183] documented a significant decrease in DVT incidence accompanied by a significant increase in the risk of bleeding in patients receiving low doses of unfractionated heparin for prophylaxis (incidence of clinically significant bleeding complications ranged from: 3.8% to 5.9%).

Available studies also refer to postoperative antithrombotic prophylaxis as one of the VTE prevention methods [184, 185]. Nakamura et al. used enoxaparin at the dose of 40 mg (prophylaxis began 6–8 hours after surgery) in a group of 47 patients who underwent open prostatectomy and reported VTE incidence at 4% [184]. Grasso et al. [185] retrospectively analyzed 500 patients after radical prostatectomy who received hemodilution, compression stockings, and pharmacological prevention administered up to 24 hours after surgery and found only two VTE episodes as well as two bleeding events that required surgical intervention. As for now there are no prospective randomized trials on prophylaxis for thrombosis after transurethral oncological surgery, whereas few available reports on VTE prevention mostly refer to the patients undergoing urological surgery due to other reasons. Retrospective analysis of 883 patients who underwent transurethral radical prostatectomy (TURP) and used graduated compression stockings indicated that symptomatic pulmonary embolism occurred in 0.45% of the patients [186]. In the @RISTOS study conducted on patients undergoing cancer urological surgery (mostly due to bladder and prostate carcinoma, 61% of whom underwent laparoscopic surgery), symptomatic VTE was found in 0.87% of patients, while 71% of the patient population received prophylaxis during hospitalization, and in 32% of them prophylaxis was continued after discharge [187].

In both endoscopic and open urological procedures, an important element of qualification for antithrombotic prophylaxis is the assessment of the risk of bleeding complications. [178, 188]. In this context, in the patients with elevated bleeding risk, mechanical prophylaxis methods such as intermittent pneumatic compression are of special interest. According to the performed studies, intermittent pneumatic compression in patients undergoing open urologic surgery causes a reduction in VTE incidence [189]. Koya et al. [190] found VTE incidents only in 0.21% of 1,364 patients undergoing radical prostatectomy, who used early mobilization and intermittent pneumatic compression for thromboprophylaxis [190]. On the other hand, Cisek i Wals [191] suggest that application of intermittent pneumatic compression in high-risk patients does not decrease the total VTE risk in this population, but significantly delays thrombosis event occurrence (the average time of VTE diagnosis in this study was 20 $\pm$ 2 days vs. 11 $\pm$ 5 days after surgery). In this group of patients (patients at high risk and very high risk of VTE), it seems reasonable

to use pharmacological prophylaxis or combination treatment instead of only mechanical methods of VTE prophylaxis [23, 136].

Due to limited invasiveness and often short duration of gradually more commonly performed laparoscopic procedures (e.g., in the field of general surgery), up-to-date guidelines on laparoscopic surgery do not encourage routine administration of pharmacological prophylaxis, permitting for early mobilization and mechanical methods implementation [23, 74, 136]. Other risk factors such as prolonged laparoscopic surgery, lesser pelvis surgery and cancer increase the risk justify the use of prevention methods (including pharmacological prophylaxis), according to the individual assessment of VTE and bleeding risks.

Recommendation 3.3.1

The risks of venous thromboembolism and bleeding complications should be assessed individually for each patient undergoing urologic surgery due to cancer [1A].

Recommendation 3.3.2

In patients undergoing major urological surgery due to cancer and in those undergoing other urological procedures, who are at high risk of venous thromboembolism, it is recommended to consider the use of thromboprophylaxis based on LDUH [1B] or LMWH [1C], if the risk of bleeding do not significantly outstands potential benefits associated with the use of pharmacoprophylaxis. Due to the limited availability of research and the specificity of the treated population, the optimal moment of starting pharmacological prophylaxis in these patients has not been defined and therefore should be based on individual evaluation of the benefits and risks of this type of prophylaxis [2C]. In case of a significant bleeding risk in the perioperative period, it is recommended to use mechanical methods of VTE prevention (most preferably intermittent pneumatic compression) [1C].

Recommendation 3.3.3

In cancer patients with moderate VTE risk undergoing other surgical urologic procedures other than major urologic surgery, it is recommended to decide about the method and the time for administration of thromboprophylaxis according to the current risk assessment of VTE and bleeding complications [2C].

Recommendation 3.3.4

In patients undergoing urologic surgery due to cancer at high risk of VTE and bleeding complications, or in patients with contraindications for pharmacological prophylaxis, it is suggested to use mechanical prophylaxis (most preferably intermittent pneumatic compression), at least until the bleeding risk decreases and administration of pharmacological prophylaxis becomes possible [2C].

Recommendation 3.3.5

It is suggested that in cancer patients undergoing major urologic surgery, qualified for pharmacological prophylaxis due to high or very high risk of VTE, pharmacological prevention should be supported with mechanical methods (most preferably intermittent pneumatic compression) [2C].

Recommendation 3.3.6

In patients undergoing major urologic surgeries in the abdominal cavity and/or pelvis, who are not at high risk of serious bleeding complications, it is suggested to prolong pharmacological prophylaxis (4 weeks) with LMWH [2C]. In the other cases, the decision regarding prolongation of prophylaxis should be made individually based on benefits and risk of such treatment [2C].

Recommendation 3.3.7

In laparoscopic cancer surgery, it is suggested to assess the risk of VTE individually [1A] and to use the same rules of thromboprophylaxis as in patients operated by the means of laparotomy performed due to cancer [2C].

Recommendation 3.3.8

In patients undergoing transurethral and percutaneous endoscopic procedures due to cancer it is suggested to assess the risk of venous thromboembolism and the risk of bleeding complications individually and to decide on prophylaxis administration based on evaluation of benefits and risks of such treatment [2C]. The decision on prophylaxis administration as well as the chosen prevention method and the right time for its administration should be based on characteristics of the particular procedure and bleeding risk assessed individually in each patient [2C]. In the case of high risk of bleeding, in the first place, early patient mobilization as well as mechanical prophylaxis should be used [2C], and pharmacological prophylaxis should be added, when hemostasis is satisfactory [2C].

Chapter 4. Treatment of venous thromboembolism in cancer patients

Clinical question 4. What is the best treatment for patients with cancer-related VTE to prevent recurrence?

The goal of treatment of venous thrombosis in cancer patients is the same as in cancer-free patients, i.e., prevention of thrombus extension and pulmonary

Table 7. Absolute and relative contraindications to therapeutic anticoagulation in cancer patients

Absolute contraindications	Relative contraindications
I. Common to all anticoagulants • Active major, major, or potentially life-threatening bleeding that cannot be stopped by therapeutic intervention (medication or surgery), including any active bleeding at a critical site (e.g. intracranial, pericardial, retroperitoneal, intraocular, intra-articular, intramedullary) • Severe, uncontrolled malignant hypertension • Severe, uncompensated coagulopathy (e.g. liver failure) • Severe platelet dysfunction or congenital bleeding disorder • Persistent severe thrombocytopenia (20,000/mL) • High-risk invasive surgery at a critical site, such as lumbar puncture, spinal anesthesia, epidural catheter placement II. Specific to DOACs • Concomitant use of potent inhibitors or inducers of P-glycoprotein or CYP3A4	I. Common to all anticoagulants • Intracranial or spinal injuries with a high risk of bleeding • Active gastrointestinal ulcer with a high risk of bleeding • Active, but not life-threatening bleeding (e.g. microscopic hematuria) • Intracranial or CNS bleeding in the last 4 weeks • Recent high-risk surgery or bleeding • Persistent thrombocytopenia (< 50 000/μL) • Patients in whom the benefits of anticoagulation are uncertain – Palliative care patient – Very limited life expectancy with no benefit in terms of palliative treatment or symptom reduction – Asymptomatic thrombosis with high risk of major bleeding • Patient characteristics – Patient preference or refusal to take medication – Failure to adhere to the dosing, observation or monitoring schedule

DOAC — direct oral anticoagulant; CNS — central nervous system

embolism, prevention of recurrences and long-term sequelae such as post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension.

The basic contraindications (Table 7) for the pharmacological treatment of acute VTE in this group of patients are the same as for patients without cancer.

Cancer-associated thrombosis (CAT) may be a symptom preceding or a consequence of neoplastic disease, and the occurrence of CAT is strongly associated with poorer prognosis and shorter survival. Cancer-associated thrombosis is defined as a thrombosis that occurs in patients with active cancer or as a result of cancer treatment. Treatment of VTE in cancer patients remains one of the most difficult clinical challenges, as it is often administered concurrently with cancer treatment. Oncological therapy often requires invasive surgery, increases the risk of infections, and may cause thrombocytopenia and, consequently, increase the risk of bleeding [192]. Treatment of VTE in patients with cancer must additionally take into account the higher frequency of recurrent thrombosis and the high risk of bleeding complications in this group of patients [193]. In most guidelines published in 2016, the treatment of VTE consisted of the initial treatment of 7–10 days of anticoagulation and its continuation in the form of long-term treatment (up to 3 months) and, if necessary, subsequent extended (chronic) treatment. Long-term treatment following initial treatment during the first 3 months of thrombosis is also known as maintenance therapy [194]. The durations of these treatment phases are only conventional, especially in relation to the preferred treatment in CAT patients, where treatment with a full dose of LMWH for the first month is suggested. Kearon et al. [195] proposed in 2012 different antithrombotic treatment phases, i.e., the active treatment phase (first 3 months), in which there is a significantly higher risk of VTE recurrence, and the so-called secondary prevention of disease recurrence (after 3 months). The most recent division of anticoagulant treatment, which takes into account the increasing use of DOACs and their registration documents (with the proviso that patients treated with LMWHs were not included) was proposed by ASH in 2020 (see diagram in Figure 1) [7]. [7]. The treatment phases are as follows: initial management (5–21 days), followed by primary treatment for 3–6 months and the period after the decision to continue or discontinue treatment (> 6 months), the so-called secondary prevention.

4.1. Initial (5–21 days) and primary (3–6 months) treatment of VTE

In the 2016 American College of Chest Physicians (ACCP) guidelines for the treatment of VTE, the indications for the treatment of VTE depended on whether the thrombosis was diagnosed as CAT or not related to cancer [14]. For CAT, initial/primary anticoagulant therapy may be based on the use of parenteral anticoagulants without subsequent administration of oral anticoagulants [14, 196]. The classification of patients depending on whether they suffer from CAT or VTE caused by other factors is currently less important due to, among others, new registrations of rivaroxaban, apixaban and edoxaban. The guidelines for the treatment of VTE issued by the ASH in 2020 also point to the change in the approach to patients with CAT and list cancers along with other chronic risk factors for VTE, treating this group as a whole [7].

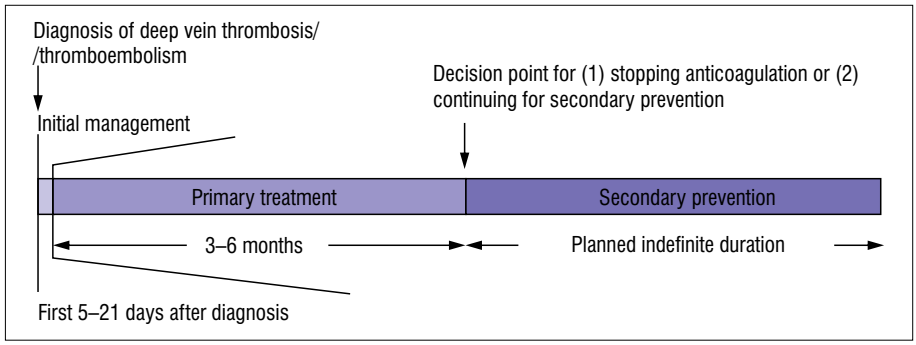

Figure 1. Phases of anticoagulation treatment [adapted from 7]

Table 8 presents the chronic and transient risk factors for VTE. Currently, ASH qualifies patients for different treatment regimens based on the type of risk factors [7].

When analyzing the impact of heparins on the outcomes of VTE treatment in cancer patients, it can be considered in the context of the CLOT study (i.e., before and after the CLOT study), which, until the registration of selected DOACs in cancer patients, was the standard of care in CAT patients [197].

Initial treatment of CAT may include UFH, LMWH, and fondaparinux for 5–10 days. In a 2014 meta-analysis of 16 RCTs, of which 13 compared LMWH to UFH, two studies compared fondaparinux vs. heparin, and one compared dalteparin to tinzaparin. Eleven studies confirmed a statistically significant reduction in mortality in the 3-month follow-up period in favor of LMWH in relation to UFH (RR 0.71; 95% CI: 0.52–0.98) [66]. There was no difference in recurrence of thrombosis between LMWH and UFH used as initial treatment (RR 0.78; 95% CI: 0.29–2.08). In the conclusions, the authors suggest that the primary treatment with LMWH, due to the lower number of bleeding complications and lower mortality, has an advantage over UFH in CAT therapy [66].

The CLOT study (677 randomized patients) compared the treatment with dalteparin at a therapeutic dose of 200 IU/kg bw for one month, followed by 75–83% of the full dose (on average 150 IU/kg bw) for 5 months with the group of patients who, after 5–7 days of using dalteparin at a dose of 200 IU/kg together with an oral anticoagulant, received secondary prophylaxis with warfarin. Over the six-month treatment period, 8% of patients in the heparin group had recurrent venous thrombosis, compared with 15.8% in the VKA group ($p = 0.002$). There was no significant difference between the dalteparin and oral anticoagulant groups in the incidence of major bleeding (6% and 4%, respectively) or any bleeding (14% and 19%, respectively).

Table 8. Transient and chronic risk factors of venous thromboembolism (VTE) [from 7]

Chronic (persistent) risk factors (risk factors that persist after the development of VTE)†; these include:
Active cancer (e.g., ongoing chemotherapy, recurrent or progressive disease)
Inflammatory bowel disease
Autoimmune disorders (e.g., antiphospholipid syndrome, rheumatoid arthritis)
Chronic infections
Chronic immobility (e.g., spinal cord injury)
Transient risk factors (risk factors that resolve after they have provoked VTE*)
Major transient risk factors (occur within 3 months of VTE diagnosis); these include:
Surgery with general anesthesia for ≥ 30 min
Confined to bed in hospital for ≥ 3 days with an acute illness ("bathroom privileges" only)
Cesarean section
Minor transient risk factors (occur within 2 months of VTE diagnosis); these include:
Surgery with general anesthesia for < 30 min
Admission to hospital for < 3 days with an acute illness
Estrogen therapy (e.g., oral contraceptives, hormone replacement therapy)
Pregnancy and puerperium
Confined to bed out of hospital for ≥ 3 days with an acute illness
Leg injury associated with decreased mobility for ≥ 3 days

†Chronic risk factors may fluctuate over time, which may impact the relative risk of recurrent VTE.
*For patients with VTE and a major transient risk factor > 3 months prior to the VTE or a single minor transient risk factor > 2 months prior to the VTE, clinical judgment is essential when considering the contribution of this variable to the initial VTE and the risk of recurrence

The mortality at six months was 39% in the dalteparin group and 41% in the VKA group [197].

Further studies with similar goals and study groups are ONCENOX and CATCH [198, 199]. The former investigated a relatively small number of cancer patients (122) treated with enoxaparin (1 mg/kg every 12 hours

for 5 days, then 1 mg/kg/day or 1.5 mg/kg/day) or treated initially with enoxaparin (1 mg/kg every 12 hours for at least 5 days) followed by warfarin. During 180 days, there were no significant differences in the incidence of VTE recurrence or bleeding events between the two groups studied [215]. In 2013, Lee et al. [199] published the results of the CATCH study, the main aim of which was to assess the efficacy of tinzaparin in the prevention of VTE recurrence in patients with active cancer and acute symptomatic proximal deep vein thrombosis and/or pulmonary embolism. The observation period was 6 months. The rate of VTE recurrence was insignificantly lower in patients receiving long-term treatment with tinzaparin (7 vs. 11%). Likewise, there was no difference in mortality or the number of major bleeding events. A meta-analysis of studies comparing long-term LMWH treatment with VKA showed no effect of heparin use on mortality (HR 0.96; 95% CI 0.81–1.14) with a significant reduction of VTE recurrences in parenterally treated patients (HR 0.47; 95% CI 0.32–0.71) [200].

Therefore, it seems that in patients who develop CAT, the use of LMWH for both primary treatment and secondary prevention is more effective than the use of VKA in the second phase of therapy in the prevention of CAT recurrence [200].

However, it should be noted that the results of similar studies (Lopez-Beret 2001, CANTHANOX — Meyer 2002, CLOT — Lee 2003, LITE — Hull 2006, ONCENOX — Deitcher 2006, Romera 2009, CATCH — Lee 2013, DALTECAN — Francis 2015) indicate no class effect for LMWH with regard to the prevention of recurrent VTE in the group of cancer patients [197–199, 201–208].

Lopez-Beret et al. [208], in a study with nadroparin at a dose adjusted to body weight administered twice a day, demonstrated the efficacy and safety of this therapy and a reduction in the incidence of deep venous valve insufficiency in VKA, but with no effect on VTE recurrence.

In the Main-LITE study, 200 CAT patients were divided into two groups of 100 people each; one group was treated with tinzaparin at the dose of 175 anti-Xa units/kg bw/day for 3 months, and patients in the second group received conventional UFH treatment with VKA for the same period. The assessments were performed after 3 and 12 months. There were no differences in endpoints between the studied groups at 3 month. After 12 months, the group treated with the oral anticoagulant had a significantly higher rate of DVT recurrences (16%) compared with 7% in those treated with LMWH ($p = 0.044$) [201].

The CANTHANOX study (146 patients) compared warfarin with enoxaparin (1.5 mg/kg once daily for four days followed by warfarin or enoxaparin for three months without dose adjustment) in CAT patients. During the 3-month follow-up, 15 patients (21.1%) treated with warfarin had major bleeding or VTE recurrence (95% CI: 12.3–32.4%) compared with 7 patients (10.5%) treated with enoxaparin (95% CI: 4.3–20.3%). The CATHANOX study showed no difference in the frequency of VTE recurrences between enoxaparin- and warfarin-treated cancer patients ($p = 0.09$) [203].

A meta-analysis of 5 RCTs on the use of tinzaparin in patients with CAT was published in 2012, which showed a statistically insignificant 38% reduction in the risk of VTE recurrence compared with oral anticoagulant therapy [205].

Most of the meta-analyzes of the initial treatment with UFH vs. LMWH conducted so far indicate that LMWH treatment is comparable in terms of efficacy and has a better safety profile in terms of the risk of bleeding [208–215].

In the initial phase of VTE treatment, an alternative to LMWH or UFH is the indirect factor Xa inhibitor, fondaparinux. Büller et al. [216] showed that fondaparinux was not inferior in efficacy and as safe as enoxaparin (both drugs were used for 5 days before VKA was started).

The 2018 Cochrane meta-analysis comparing the initiating treatment with UFH, LMWH and fondaparinux only highlights the advantage of LMWH over UFH in the conclusions [217]. Regarding the comparison of fondaparinux with heparin (UFH or LMWH), no conclusions could be drawn as most of the parameters assessed, such as bleeding and recurrences, were not significantly different.

The 2020 American Society of Clinical Oncology (ASCO) guidelines list LMWH, UFH, fondaparinux and rivaroxaban as drugs for the initiation of VTE therapy (5–21 days), pointing out that low-molecular-weight heparins have an advantage over unfractionated heparin [10]. If LMWH is selected due to the risk of bleeding, it is suggested that this drug is used once a day rather than twice a day, at the dose recommended by the manufacturer [11].

Recently published studies in patients with thrombosis in the course of neoplastic disease suggest that rivaroxaban, apixaban and edoxaban can be used in the treatment of VTE in this group of patients (Table 9).

In previous studies in patients with VTE, assessing the efficacy and safety of DOAC compared with standard warfarin therapy, the percentage of patients with CAT was relatively low, at the level of 2–9% [218]. In the 2016 ACCP guidelines, this group of drugs is recommended in the primary and long-term treatment of VTE [14].

In 2017 and 2018, the results of three studies on CAT treatment with edoxaban, rivaroxaban and apix-

aban were presented at ASH conferences and were later published in full versions [219–221].

In the Hokusai-VTE study on CAT (symptomatic and incidental VTE), 1,050 cancer patients were randomized into two groups: the edoxaban group (dalteparin for at least 5 days, followed by a single dose of 60 mg edoxaban daily) or dalteparin group (200 IU/kg once daily for one month, followed by 150 IU/kg per day) for 6–12 months.

The primary composite endpoint (recurrent VTE or major bleeding within 12 months of randomization, irrespective of duration of treatment) occurred in 67 (13%) of 522 patients in the edoxaban group compared with 71 (14%) of 524 patients in the dalteparin group (HR 0.97, 95% CI 0.70–1.36, p = 0.006). The percentage of patients with recurrent VTE was statistically insignificantly lower for edoxaban (8% in the edoxaban group vs. 11% in the dalteparin group, p = 0.09). The proportion of patients with major bleeding was higher in the edoxaban group than in the dalteparin group (7% v. 4%, p = 0.04), whereas the percentage of patients with clinically significant bleeding and overall survival were comparable between the groups [219]. The SELECT-D study enrolled 406 patients with pulmonary embolism (symptomatic or accidental) or symptomatic proximal DVT. In this study, patients were randomized into two groups receiving rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg daily for 2-6 months) or dalteparin (200 IU/kg daily for the first month, then 150 IU/kg daily for up to 6 months). The primary endpoint was VTE recurrence within 6 months of randomization. Patients with cancers of the upper gastrointestinal tract were excluded from the study. The 6-month cumulative VTE recurrence rate in the rivaroxaban group was significantly lower compared with that of dalteparin group (4% in the rivaroxaban group vs. 11% in the dalteparin group, HR 0.43, 95% CI, 0.19–0.99). The percentage of patients with clinically significant minor bleeding was significantly higher in the rivaroxaban group compared with the dalteparin group (13% vs. 4%, HR 3.76, 95% CI 1.63–8.69, respectively). The cumulative rate of major bleeding was 6% in the rivaroxaban group compared with 4% in the dalteparin group (p = NS). It should be emphasized that most of the bleeding events in the rivaroxaban group were in people with cancers of the gastrointestinal tract or urinary tract.

The ADAM VTE study recruited 300 patients with CAT, including thrombosis of the veins of the upper limbs and visceral veins. Patients were randomized to receive apixaban (10 mg twice daily for 7 days, then 5 mg twice daily) compared with dalteparin (200 IU/kg daily for 1 month, then 150 IU/kg daily) for 6 months. The proportion of patients with major bleeding, which was the primary endpoint, was not significantly different [0 patients in the apixaban group vs. 3 patients (2%) in the dalteparin group, p = 0.99]. The percentages of patients with the composite endpoint (major bleeding and clinically significant minor bleeding) were similar — 9% in each group. Recurrent VTE occurred in 0.7% of patients in the apixaban group compared with 6.3% in the dalteparin group (HR 0.099, 95% CI 0.013–0.780, P = 0.0281) [221].

In 2018, the results of another RCT on CAT treatment with apixaban were also published [222]. In this study, patients with cancer and symptomatic or incidental acute thrombosis of the proximal limbs or pulmonary embolism were randomized to receive apixaban (dosing as for treatment of deep vein thrombosis) or subcutaneous LMWH (dalteparin). Treatment was carried out for 6 months. The primary endpoint of the study was recurrence of venous thrombosis during the study period and the primary safety endpoint was the occurrence of major bleeding. Recurrence was observed in 32 of 576 patients (5.6%) in the apixaban group and 46 of 579 patients (7.9%) in the heparin group (HR, 0.63; 95% CI, 0.37 to 1.07; p <0.001 for non-inferiority). Major bleeding occurred in 22 patients (3.8%) in the apixaban group and in 23 patients (4.0%) in the heparin group (HR, 0.82; 95% CI, 0.40–1.69; p = 0, 60). At the same time, the number of gastrointestinal bleeding events was not higher in the apixaban group than in the subcutaneous LMWH group. Data from the Caravaggio study therefore indicate that apixaban does not increase the risk of bleeding in patients with gastrointestinal cancer.

Major studies of CAT treatment with DOACs are summarized in Table 9.

It is important to be aware of the limitations of the use of DOACs. Treatment with any DOAC in cancer patients is dependent on gastrointestinal absorption, and drug interactions, including those used in chemo-, hormone, and immunotherapy, can occur. P-glycoprotein inhibitors or inducers may interact with edoxaban, apixaban, and rivaroxaban, and cytochrome P450 34A inhibitors or inducers — with rivaroxaban [223, 224]. The latest list of DOAC interactions with drugs used in the treatment of oncological patients can be found in the recommendations of the 2021 guidelines of the European Heart Rhythm Association [225]. The most important drug interactions with anticancer drugs are listed in Table 10. Nausea or vomiting may also influence adherence to treatment with DOACs, due to the oral route of administration [226]. A suggested treatment strategy for vomiting is shown in Figure 2 [227].The limitations of CAT treatment with DOAC are summarized in Table 11 [228].

Table 9. Summary of major randomized controlled trials of CAT treatment with DOAC

Trial	Hokusai-VTE-cancer	SELECT-D	ADAM VTE	CARAVAGGIO
Size (N)	1050	406	300	1170
Design*	Non-inferiority, international	Pilot, carried out in the USA	Superiority, international	Non-inferiority, international
Drug**	Edoxaban 60 mg QD following 6 days of LMWH	Rivaroxaban 15 mg BID for 3 weeks, then 20 mg QD thereafter	Apixaban 10 mg BID for 1 week, then 5 mg BID thereafter	Apixaban 10 mg 2 BID for 1 week, then 5 mg BID thereafter
Treatment duration	At least 6 and up to 12 months	6 months	6 months	6 months
Primary outcome	Composite of recurrent VTE and major bleeding	Recurrent VTE	Major bleeding	Recurrent VTE
Cancer inclusion criteria***	Diagnosed within the previous 2 years and was objectively confirmed or active cancer: cancer diagnosed within the previous 6 months; recurrent, regionally advanced, or metastatic cancer; cancer for which treatment had been administered within 6 months before randomization; or hematologic cancer that was not in complete remission	Diagnosis of cancer in the previous 6 months, any treatment for cancer within the previous 6 months, recurrent or metastatic cancer, or cancer not in complete remission (hematologic malignancy). Excluded: esophageal or gastroesophageal cancer	Histologically proven active cancer: metastatic disease; evidence of cancer on CT or PET imaging; cancer-related surgery, chemotherapy, or radiation therapy within the past 6 months	Any type of confirmed active cancer: diagnosed within the past 6 months, receiving treatment at inclusion or within the past 6 months; recurrent locally advanced or metastatic disease. History of cancer: those with cancer diagnosed within 2 years before study inclusion. Excluded: primary brain tumor or brain metastases
Results (recurrent VTE)	Edoxaban: 7.9% Dalteparin: 11%	Rivaroxaban: 4% Dalteparin: 11%	Apixaban: 0.7% Dalteparin: 6.3%	Apixaban: 5.6% Dalteparin: 7.9%
Results (major bleeding)	Edoxaban: 6.9% Dalteparin: 4%	Rivaroxaban: 6% Dalteparin: 4%	Apixaban: 0% Dalteparin: 2%	Apixaban: 3.8% Dalteparin: 4%

*All studies were/are randomized, open-label studies; **All comparators were/are subcutaneous dalteparin 200 IU per kg body weight once daily for 1 month followed by dalteparin at a dose of 150 IU per kg once daily for the remainder of treatment; ***All studies exclude non-melanoma skin cancers (e.g., basal cell carcinoma of the skin); CAT — cancer-associated thrombosis; DOAC — direct oral anticoagulants; VTE — venous thromboembolism

Table 10. The most important interactions with anticancer drugs (adapted from [225])

No effect on dosing of DOACs	
Antimetabolites	Methotrexate, purine analogs, pyrimidine analogs
Topoisomerase inhibitors	Topotecan, irinorecan, etoposide
Anthracyclines	Daunorubicin, mitoxantrone
Alkylating agents	Busulfan, bendamustine, chlorambucil, melphalan, carmustine, procarbazine, dacarbazine, temozolomide
Platinum-based agents	Cisplatin, carboplatin, oxaliplatin
Intercalating agents	Bleomycin, dactinomycin, mitomycin C
Tyrosine kinase inhibitors	Erlotinib, gefitinib
Drugs that increase the effect of DOACs. Consider dose reduction	
Immune-modulating agents	Cyclosporine, tacrolimus (strongest for dabigatran – do not use in combination)
Hormonal agents	Tamoxifen
Alkylating agents	Ifosfamide, cyclophosphamide, lomustine (for rivaroxaban and apixaban)
Tyrosine kinase inhibitors	Nilotinib, dasatinib
Do not use, strong interaction with DOACs. Effect on DOACs	
Hormonal agents	Abiratorene (increased effect), enzalutamide (increased effect)
Tyrosine kinase inhibitors	Imatinib, crizotinib (increased effect)
Antimitotic agents	Vinblastine (decreased effect)
Anthracyclines	Doxorubicin (decreased effect)

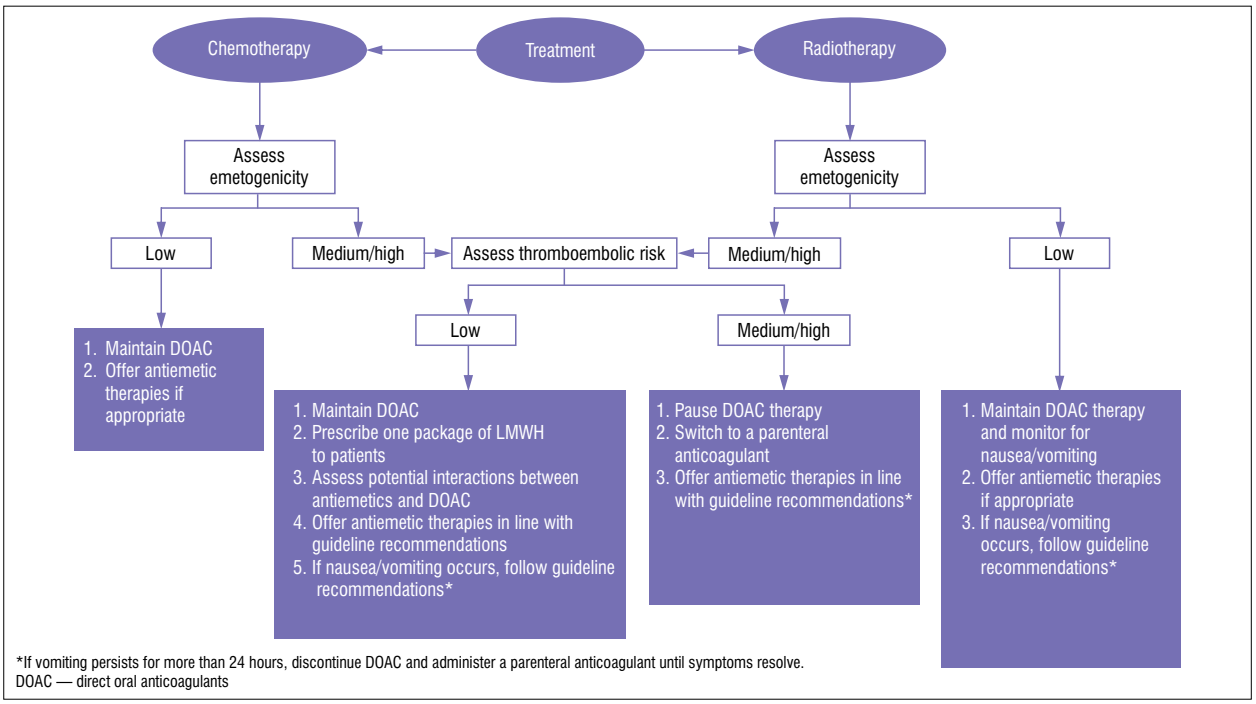

Figure 2. Suggested strategy in the case of vomiting in cancer patients using DOAC [adapted from 227]

Table 11. Limitations on the treatment of cancer-associated thrombosis with direct oral anticoagulants [adapted from 11, 228]

	Rivaroxaban	Apixaban	Edoxaban
Renal insufficiency	Severe: dose adjustment recommended if GFR 15–29 mL/min; not recommended if GFR < 15 mL/min	Severe: not recommended if GFR < 15 mL/min	Severe: dose adjustment recommended if GFR 15–29 mL/min; not recommended if GFR < 15 mL/min
Liver insufficiency	Moderate hepatic insufficiency: caution should be exercised; Liver disease with coagulopathy and risk of clinically significant bleeding: contraindicated (Child-Pugh Classes B and C)	Moderate hepatic impairment: caution should be exercised but no dose adjustment is necessary; Severe hepatic insufficiency: not recommended; liver disease with coagulopathy and risk of clinically significant bleeding: contraindicated (Child-Pugh Class C)	Mild hepatic insufficiency: no dose reduction necessary; Severe hepatic insufficiency: not recommended (Child-Pugh Class C)
Interactions	Inducers or inhibitors of P-glycoprotein, CYP3A4 and CYP2J2	Inducers or inhibitors of P-glycoprotein and CYP3A4	Inducers or inhibitors of P-glycoprotein, CYP3A4
Other limitations	Expected malabsorption at the level of the stomach or small intestine Active genitourinary or gastrointestinal lesions Untreated primary tumor of the central nervous system Body weight: < 50 kg or > 150 kg Concomitant use of an antiplatelet agent other than acetylsalicylic acid		

DOAC — direct oral anticoagulants; GFR — glomerular filtration rate

4.2. Thrombolytic therapy for CAT

According to most of the current recommendations, anticoagulation has so far been the preferred treatment over more aggressive treatments (venous thrombectomy, local thrombolysis) [7]. The main indication for these types of aggressive procedures is the presence of limb ischemia associated with the development of venous thrombosis and the risk of limb loss (phlegmasia coerulea/alba dolens). Interventional methods for the treatment of CAT have large population limitations — they are reserved for patients with proximal deep vein thrombosis, short thrombosis duration (<14 days),

low bleeding risk, good general condition and long life expectancy [229].

Thrombolytic therapy may also be considered in specific subsets of patients with pulmonary embolism (PE) (see Chapter 6) or DVT. Data on thrombolytic therapy in patients with CAT are limited as most studies excluded cancer patients due to a potentially higher bleeding risk. Small, retrospective studies have assessed the degree of venous patency and the safety of CDT treatment in VTE patients with and without cancer, showing that the procedure is equally effective and safe for both groups of patients [135, 230]. The advantage of thrombolytic therapy over anticoagulation is the rapid lysis of the thromboembolic material and, consequently, a faster hemodynamic improvement. Patients with massive thrombosis treated with CDT may benefit from faster symptom relief, restoration of normal limb perfusion, and a reduction in the incidence of post-thrombotic syndrome. Due to the small number of publications on patients who have received thrombolysis in CAT therapy, it should be remembered that this may be associated with a three-fold higher risk of major bleeding, whereas the effect on mortality or the frequency of VTE recurrences is unknown [231]. The basic principle when considering indications for fibrinolytic therapy in CAT is an individual assessment in each patient, taking into account the benefits of therapy and the risk of complications. The exception to this rule is in patients with massive, life-threatening pulmonary embolism who are hemodynamically instable, in the absence of an increased risk of bleeding, for whom thrombolytic therapy is considered the standard of care [14].

Other indications for thrombolysis in patients with CAT, according to the guidelines of the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO), are acute limb- or life-threatening conditions, proximal deep vein thrombosis or massive thrombosis in the ilio-femoral segment, for which rapid venous decompression and restoration of blood flow may be desirable [135].

Brain imaging prior to thrombolysis should be considered in all cancer patients to rule out intracranial tumors or hemorrhage, which are an absolute contraindication to thrombolysis.Other contraindications are history of hemorrhagic stroke, ischemic stroke in the last 3 months, major trauma, surgery or head injury in the last 3 weeks, platelet count less than 100,000/μL, active bleeding or bleeding disorder, treatment-resistant hypertension (i.e., systolic blood pressure> 180 mm Hg and diastolic blood pressure> 100 mm Hg), recent gastrointestinal bleeding and advanced liver disease.

4.3. Insertion of the filter into the inferior vena cava

The insertion of an inferior vena cava filter can only be justified when anticoagulant therapy is contraindicated or in the event of pulmonary embolism despite optimal anticoagulant therapy. The results of the RCT published in 2015 comparing recurrences of pulmonary embolism in patients with IVCF (inferior vena cava filter) used together with anticoagulant therapy (200 patients with active cancer — 16.5%) with anticoagulation therapy alone (2 patients with active cancer — 14.6%). After 3 months of follow-up, PE recurrences were twice as frequent in the filter group, although the difference was not statistically significant [232].

4.4. Recommendations — Initial and primary treatment of cancer-associated thrombosis

Recommendation 4.4.1

LMWH, UFH, fondaparinux, rivaroxaban or apixaban are recommended in the initial treatment period of deep vein thrombosis in cancer patients (direct oral factor Xa inhibitors can be used after ruling out drug interactions according to the SmPC) [1A].

Recommendation 4.4.2

For primary treatment (3–6 months), LMWH, rivaroxaban, apixaban, and edoxaban are recommended, and they are preferred over vitamin K antagonists [1A].

Recommendation 4.4.3

Thrombolytic treatment in patients with DVT of the lower legs can be considered on the individual basis in cases of limb threat, after ruling out contraindications, especially the risk of bleeding. Early endovascular restoration procedures should be performed only in centers with appropriate experience and capabilities in this type of treatment, and in patients with short (up to 14 days) duration of thrombosis who are in good general condition, with a low risk of bleeding and a long life expectancy. Systemic thrombolytic therapy is not recommended in patients with cancer-induced deep vein thrombosis [GPS].

Recommendation 4.4.4

If there are contraindications to anticoagulant treatment or pulmonary embolism despite properly conducted anticoagulant therapy, it is suggested to consider insertion of an inferior vena cava filter [2C].

Recommendation 4.4.5

For incidental DVT, the same treatment is suggested as for symptomatic VTE [3C].

Recommendation 4.4.6

In the case of recurrence or worsening of thrombosis despite proper treatment, it is suggested to increase the dose of LMWH by 20–25% in patients previously treated with these drugs, and in those treated with DOAC or VKA, switch to LMWH at the therapeutic dose for a minimum of 4 weeks [2C].

4.5. Secondary prophylaxis

The indication for extended treatment of VTE in cancer patients is the increased risk of VTE recurrence in this group of patients, and the limitation is the more frequent occurrence of major bleeding. In a prospective cohort study by Prandoni et al. [193], the 12-month cumulative incidence of recurrent VTE in cancer patients was 20.7% versus 6.8% (HR 3.2 [95% CI 1.9–5.4]) in cancer-free patients, and for major bleeding it was 12.4% in cancer patients versus 4.9% (HR, 2.2 [95% CI, 1.2–4.1]) in cancer-free patients.

For many cancer patients, it is not possible to predict for how long a patient will remain at a significantly increased risk of VTE recurrence, which may require so-called "indefinite anticoagulant therapy", for example in patients with deep vein thrombosis and active cancer. In any patient requiring extended anticoagulant therapy, the risk of bleeding complications and the potential benefits of treatment should be re-evaluated periodically.

A Cochrane meta-analysis published by Akl et al. [233], based on the evaluation of the results of 7 prospective RCTs comparing LMWH treatment with extended oral VKA treatment, a statistically significant, almost 50% reduction in the risk of VTE recurrence was shown in the group treated with LMWH (HR 0.47; 95% CI 0.32–0.71), with a comparable risk of major and minor bleeding complications in both groups of patients. Similar conclusions indicating a significant reduction of the risk of VTE recurrence and no effect on the increase of bleeding events in cancer patients receiving extended treatment with LMWH can be found in the previously published meta-analysis by Louzad et al. [234].

The optimal duration of LMWH treatment in patients with DVT associated with cancer is still unknown. The aim of the DALTECAN study was to establish the safety of CAT treatment with dalteparin for 6 to 12 month. Of the 334 patients enrolled in the study, 185 and 109 patients were treated for 6 and 12 months, respectively. In this group, 49.1% of patients were diagnosed with DVT, 38.9% had pulmonary embolism, and 12.0% of patients had both disorders. The overall incidence of major bleeding was 10.2% (34/334). Bleeding events occurred in 3.6% (12/334) of patients in the first month of treatment and with a frequency of 1.1% (14/1237) and 0.7% (8/1086) per patient per month between 2nd and 6th month and between 7th and 12th month, respectively. Recurrent VTE was reported in 11.1% (37/334) of patients, and the incidence was 5.7% (19/334) in the first month, 3.4% (10/296) between 2nd and 6th month and 4.1% (8/194) between 7th and 12th month. During the study, 116 patients died, including 4 deaths due to VTE recurrence and 2 deaths due to bleeding. The incidence of major bleeding was reduced after 6 months of treatment with dalteparin. The risk of bleeding complications such as major bleeding and recurrent VTE was highest in the first month of treatment, and then decreased over the next 11 months [205]. The result of this study confirmed the results of the CLOT study, demonstrating the efficacy and safety of extended use of dalteparin in CAT patients.

In the light of the currently available data, the decision to extend treatment after 3–6 months — either by continuing treatment with the previously used drug or by switching to another drug — should be considered on a case-by-case basis. Both the risk of recurrence and potential complications should be taken into account each time (including events that have already occurred during the current treatment) as well as the patient's preferences (e.g. the drug taken once or twice a day, or avoiding the need for injections). Important from a practical point of view are the results of the meta-analysis by Ferretti et al. [235], which showed that the beneficial effect of LMWH on the reduction of the rate of VTE recurrences compared to traditional anticoagulant therapy is maintained only during the use of LMWHs and is not extended to the period after the end of treatment.

In the pivotal studies evaluating DOACs in the treatment of VTE, there were only a small proportion of patients with CAT [5% in the RECOVER study (dabigatran), 6.8% in the EINSTEIN study (rivaroxaban), and 1.1–1.8% in the AMPLIFY-EXT study (apixaban)]. A meta-analysis of 9 RCTs (2310 CAT patients treated with DOACs) was performed. Compared with VKA, LMWH showed a significant reduction in VTE recurrence rate (RR 0.52; 95% CI 0.36–0.74), which was not found for DOAC (RR 0.66; 95% CI 0.39–1.11)). LMWH administration was associated with a non-significant increase in the risk of major bleeding (RR 1.06; 95% CI 0.5-2.23), whereas patients receiving DOAC showed a non-significant reduction in bleeding (RR 0.78; 95% CI 0.42–1.44) compared with an oral anticoagulant. The annual risk of VTE recurrence and major bleeding in patients in the VKA group was higher compared with LMWH and DOAC [216]. Brunetti et al. [236] performed a meta-analysis of two RCTs in patients with VTE, which included a subgroup of cancer patients. They showed that the number of recurrences in DOAC-treated patients was similar to that of patients

treated with LMWH (OR 0.96; 95% CI, 0.52–1.75), but the use of oral medications was associated with a higher risk of bleeding (OR, 2.72; 95% CI, 1.05–7.01) [236]. An earlier network meta-analysis (performed in 2015) comparing DOAC and LMWH showed no differences between the two drugs in terms of VTE recurrences or bleeding [237].

To date, there were 9 meta-analyzes comparing DOAC with VKA in patients with VTE, in which CAT patients were only subpopulations [218, 236–244]. The drugs analyzed were rivaroxaban, apixaban, dabigatran and edoxaban. In all but one meta-analysis, the risk of VTE recurrence and the risk of major bleeding did not differ significantly between the treatment groups. It should be noted that the majority of cancer patients participated in these studies after completion of cancer treatment, and therefore these results cannot be considered equivalent to studies evaluating the use of DOAC in patients with CAT.

In a paper published in 2014, the indications for extended (by another 6 months) treatment of LMWH in patients with CAT and thromboembolic material found in veins after the initial 6 months of nadroparin treatment (97 IU/kg twice daily) were assessed. Patients with residual thrombosis were randomly assigned to 2 groups: continuation of treatment (119 patients) or discontinuation of anticoagulation (123 patients). In patients with complete recanalization, anticoagulation was discontinued (105 patients). The groups did not differ significantly in terms of the occurrence of major bleeding. Patients with residual thrombosis had a higher risk of recurrent VTE than those who did not have thrombotic material in their veins, whether or not they received 6-month prolonged LMWH prophylaxis [244]. In a multicenter, prospective cohort study of nearly 45,000 patients with VTE, 4,125 patients with CAT were identified. The analysis in this group showed that the proportion of patients with fatal recurrent pulmonary embolism and those with fatal bleeding was similar during the first 3 months of anticoagulation. After 3 months, the number of fatal complications associated with recurrent pulmonary embolism decreased, whereas the rate of fatal bleeding did not change [245].

Limited information is available about the risks and benefits of anti-coagulation for more than 6 months in cancer patients. Continuation of anticoagulant therapy beyond 6 months should be considered only in selected patients due to the persistently high risk of recurrence in people with active cancer. The decision to continue anticoagulation must be balanced against bleeding risk, treatment costs, quality of life, life expectancy, and patient preferences [246].

In the single-arm DALTECAN study (ClinicalTrials.gov ID: NCT00942968), 109 out of 334 patients included completed 12 months of dalteparin therapy [205]. The risk of major bleeding was highest in the first month of treatment (3.6%), then decreased to 1.1% per patient-month in months 2–6 and 0.7% in months 7–12. The risk of VTE recurrence was 5.7% in month 1, 3.4% in months 2–6, and 4.1% in month 7–12. LMWH use over a 6-month period was also assessed in the single-arm TiCAT trial [247]. Of the 247 patients enrolled, 136 completed the 12-month treatment with tinzaparin. The rate of clinically significant bleeding was 0.9% per patient-month in months 1–6 and 0.6% in months 7–12 [248].

In the DOAC group, only edoxaban was evaluated for over 6 months in CAT patients [219].

Before the DOAC era, acetylsalicylic acid (ASA) was widely studied for the prevention of recurrent VTE. In a pooled analysis of two large RCTs, the rate of DVT recurrence was 13.8% in the ASA group and 19.1% in the placebo group (HR 0.68, 95% CI 0.51–0.90; $p = 0.007$) [249, 250]. This drug has not been evaluated in the group of patients with CAT, and despite the benefits of extended therapy with VTE over placebo at the time of DOAC availability, it is not recommended for secondary prevention in this group of patients.

Although there are currently no data from RCTs in the group of cancer patients, in those at high risk of bleeding complications, the use of sulodexide should be considered to continue long-term therapy, after assessing both the benefits and risks of therapy [250, 251].

The results of many clinical trials to date have shown the multidirectional effect of sulodexide on the hemostatic system, including reduction of thrombin generation, profibrinolytic activity and inhibition of the formation of procoagulant microparticles. Its beneficial effects on blood viscosity and lipid levels have also been documented [252–257]. Sulodexide is recommended for various indications in current guidelines, including the 2019 guidelines of the European Society of Cardiology (ESC) [259] on the management of pulmonary embolism and the recommendations contained in the 2017 Polish Consensus [260] on the treatment of VTE, in which the use of sulodexide as an alternative anticoagulant drug in prolonged anticoagulant prophylaxis is recommended due to the favorable safety profile of this therapy. These recommendations were based on a double-blind RCT (SURVET) in 615 patients with their first unprovoked episode of VTE who completed a 3–12-month treatment with an oral anticoagulant. Patients were randomly assigned to treatment with sulodexide at a dose of 500 lipasemic units twice daily or placebo for 2 years in combination with compression stockings [261]. Venous thromboembolism recurred in 15 of 307 patients who received sulodexide and 30 of 308 patients who received placebo (RR 0.49; 95% CI

Table 12. Dosing of anticoagulation drugs in deep vein thrombosis in patients with cancer-related thrombosis [adapted from 10]

Treatment of established VTE		
Initial	UFH	80 U/kg IV bolus, then 18 U/kg IV and adjust a dose based on aPTT
	Dalteparin	100 U/kg every 12 hours 200 U/kg once daily
	Enoxaparin	1 mg/kg every 12 hours 1.5 mg/kg once daily
	Tinzaparin	175 U/kg once daily
	Fondaparinux	< 50 kg: 5.0 mg once daily 50–100 kg: 7.5 mg once daily > 100 kg: 10 mg once daily
	Rivaroxaban	15 mg orally every 12 hours for 21 days
	Apixaban	10 mg orally every 12 hours for 7 days
Long term	Dalteparin	200 U/kg once daily for 1 month, then 150 U/kg once daily
	Enoxaparin	1.5 mg/kg once daily 1 mg/kg every 12 hours
	Tinzaparin	175 U/kg once daily
	Warfarin	Adjust dose to maintain INR 2–3
	Rivaroxaban	20 mg once daily (with food)
	Edoxaban	Needs at least 5 days of parenteral anticoagulation prior to its start, then switch to edoxaban 60 mg orally once daily or 30 mg orally once daily in those weighing ≤ 60 kg, who have creatinine clearance between 30 and 50 mL/min, or who need concomitant use of a P-glycoprotein inhibitor
	Apixaban	5 mg twice daily

aPTT — activated partial thromboplastin time; INR — international normalized ratio; UFH — unfractionated heparin; VTE — venous thromboembolism

0.27–0.92, p = 0.02). There were no episodes of major bleeding, and clinically significant bleeding episodes were reported in 2 patients in each group. The adverse events were similar in both groups. Sulodexide administered after discontinuation of anticoagulant therapy was found to reduce the risk of recurrence in patients with unprovoked VTE, without a marked increase in the risk of bleeding. When discussing the results of the SURVET study with sulodexide, it should be noted, however, that the assessed population of patients with VTE did not include those with CAT.

Based on the available data, it can be assumed that if CAT patients have active cancer or are on active treatment for more than 6 months, continued anticoagulation is the current standard of care as the risk of recurrence is considered high. The drugs used in the treatment of CAT and their dosing are listed in Table 12.

4.6. Recommendations — secondary prophylaxis

Recommendation 4.6.1

Drugs suggested for secondary prophylaxis of VTE in cancer patients are LMWH, DOAC or VKA. When deciding on secondary prophylaxis, risk factors should be analyzed, including active cancer (the presence of metastases) and oncological treatment (especially chemotherapy). The decision on the method of further anticoagulant therapy (LMWH, VKA, DOAC) should be made on the basis of an individual risk-benefit assessment of proposed treatments and the patient's preferences [2C].

Recommendation 4.6.2

In all patients receiving anticoagulant therapy for cancer-related VTE, periodic assessment of the risk of bleeding and the potential benefit-risk balance of continuing anticoagulant therapy, taking into account patients' preferences, is suggested [2C].

Recommendation 4.6.3

In cancer patients with VTE, it is suggested to continue anticoagulant therapy as long as the risk factors for recurrent VTE persist (including active cancer) or when the risk of continuing anticoagulant treatment outweighs the potential benefits [2C].

Recommendation 4.6.4

In patients at high risk of bleeding complications, sulodexide may be considered as secondary prevention of CAT [GPS].

4.7. Treatment of recurrent venous thromboembolism in cancer patients

In the event of recurrence of CAT in patients receiving anticoagulant therapy, the type and quality of current treatment as well as other potential factors for disease recurrence should be assessed. None of the above methods of anticoagulant therapy result in a complete lack of recurrence of VTE during the treatment. If recurrent VTE is diagnosed, it is suggested to consider one of the following methods of treatment after an individual assessment of the risks and benefits of the treatment:

- in patients using oral VKA anticoagulants: switch to low-molecular-weight heparin or DOAC at the full therapeutic dose;
- in patients on long-term treatment with low-molecular-weight heparin at the full therapeutic dose: increase the dose of low-molecular-weight heparin by 20–25%
- in patients using DOAC: switch to LMWH;
- consider insertion of an inferior vena cava filter in the case of recurrent VTE in the form of pulmonary embolism in patients properly treated with anticoagulants (and continuation of treatment) [14].

Chapter 5. Prevention and treatment of cancer-related venous thromboembolism in children – general recommendations

Previously published international guidelines for the treatment of cancer-related VTE in children, including 2018 ASH guidelines, did not take into account the results of RCTs (such as the EINSTEIN Junior study in children of 0–17 years of age with acute VTE treated with rivaroxaban [262] or DIVERSITY study in children aged 3 months to 12 years receiving dabigatran for secondary VTE prophylaxis [263]) that showed efficacy in preventing recurrent thrombosis without significantly increasing bleeding risk both in children with cancer and in those with central catheter-related thrombosis. In addition, the data available to date have shown that oral direct anticoagulants are at least as effective as traditional anticoagulants [264].

5.1. Treatment of cancer-related venous thromboembolism in children

Clinical question 5A. What is the best treatment for children with cancer-related VTE to prevent recurrence of VTE?

Recommendation 5.1.1

Anticoagulants are recommended for the treatment of VTE and should be used in accordance with the manufacturer's recommendations and registration documents [1C].

Recommendation 5.1.2

The risk of bleeding should always be assessed in all children receiving anticancer therapy with or without a central catheter [1A].

Recommendation 5.1.3

LMWHs or UFHs are routinely recommended in children with cancer and acute VTE [1A].

Recommendation 5.1.4

In a selected group of children with CAT (0–18 years of age) at low risk of bleeding or thrombocytopenia and in the absence of drug interactions, it is recommended to consider rivaroxaban or dabigatran [1B].

Recommendation 5.1.5

In the presence of risk factors for bleeding complications, including recent major bleeding, abnormal renal function, gastrointestinal symptoms that interfere with the absorption of oral medications, tumor location in the genitourinary system or a gynecological cancer, thrombocytopenia ($<100{,}000/\mu L$) or a high probability of its occurrence and uncontrolled coagulopathy, it is recommended to treat VTE in pediatric cancer patients with LMWHs or UFHs, unless there are contraindications to pharmacotherapy or a high risk of bleeding complications [1B].

Recommendation 5.1.6

Due to the increased risk of major bleeding in gastrointestinal cancer and, potentially, in genitourinary cancer, LMWHs are recommended over DOACs for the treatment of VTE in pediatric cancer patients. DOACs should be used with caution in patients with a high risk of mucosal bleeding [1A].

Recommendation 5.1.7

LMWHs are the drugs of choice in patients with impaired renal function and should be used in accordance with the SmPC [1A].

Recommendation 5.1.8

When treating VTE in children with cancer, interactions between anticoagulants, especially DOACs, and anticancer therapy and supportive therapy should be taken into account [1A].

Recommendation 5.1.9

In the case of simultaneous use of drugs that are strong inhibitors or inducers of P-glycoprotein or CYP3A4, the use of LMWH is recommended [1A].

Recommendation 5.1.10

Incidental VTE in children receiving oncological treatment should be treated in the same way as symptomatic VTE [2B].

Table 13. Dosing of primary anticoagulation drugs in children

LMWH — dose adjustment in children		
Treatment of acute VTE with enoxaparin		
	The dose depends on age	
Enoxaparin	≤ 2 months of age	> 2 months of age
	1.5 mg/kg every 12 hours	1 mg/kg every 12 hours
Treatment of acute VTE with dalteparin		
Dalteparin	≤ 2 months of age	> 2 months of age
	150 IU/kg every 24 hours	100 IU/kg every 24 hours
LMWH monitoring	Target range: anti-Xa between 0.5 and 1 U/mL in samples taken 4 hours after the last subcutaneous injection	
VTE — warfarin/acenocoumarol		
Initiate VKA with LMWH; Discontinue LMWH when INR exceeds 2.0		
VKA monitoring	Therapeutic dose to maintain INR within the range of 2.0–3.0	
Rivaroxaban		
The recommended dose of rivaroxaban in children and adolescents from full-term newborns (following at least 10 days of oral feeding and weighing at least 2.6 kg) to children weighing <30 kg (granules 1 mg/mL) (Table 14)	administer after at least 5 days of parenteral anticoagulation treatment	
	Body weight 30–50 kg	Body weight > 50 kg
	15 mg/day	20 mg/day (maximum dose in children)
Dabigatran		
The dose depends on age and weight (capsules or suspension) (Table 15)		

LMWH — low-molecular-weight heparin; INR — international normalized ratio; VKA — vitamin K antagonist; VTE — venous thromboembolism

Recommendation 5.1.11

It is suggested that the decision regarding the treatment of isolated subsegmental pulmonary embolism or visceral vein thrombosis in children with cancer should be made on a case-by-case basis, taking into account potential benefits and complications [2C].

Recommendation 5.1.12

LMWHs or DOACs should be used for at least 6 months [1A].

Recommendation 5.1.13

For long-term anticoagulation, LMWHs or selected DOACs for at least 6 months are preferred over VKAs [2C].

Recommendation 5.1.14

It is suggested that the decision to continue treatment after 6 months should be made on the basis of an individual benefit-risk assessment, drug tolerability and availability, patient preferences and cancer activity [2B].

Recommendation 5.1.15

In selected cases, in children with CAT, targeted thrombolysis or thrombectomy can be considered, depending on the expertise and experience of the medical center as well as availability and feasibility of these treatments, based on an individual benefit-risk assessment [2C].

Recommendation 5.1.16

In children with cancer, treatment of central catheter-related thrombosis should follow the general guidelines [2B].

Pediatric doses of anticoagulants are shown in Table 13.

Comment

Due to the variety of clinical situations, ages of children, types and locations of cancer, therapy with the risk of thrombocytopenia and individual risk factors for recurrence of a thrombotic event and the occurrence of bleeding complications, the choice of the drug

Table 14. Dosing of rivaroxaban in children — recommended dose for rivaroxaban in pediatric patients from full-term neonates (following at least 10 days of oral feeding and weighing at least 2.6 kg) to children weighing less than 30 kg (granules 1 mg/mL) [265]

Body weight [kg]	Rivaroxaban dosing regimen			Total daily dose	Suitable blue syringe
1 mg rivaroxaban corresponds to 1 mL of the suspension					
Min. Maks.	Once a day	2 times a day	3 times a day		
2.6 < 3			0.8 mg	2.4 mg	1 mL
3 < 4			0.9 mg	2.7 mg	1 mL
4 < 5			1.4 mg	4,2 mg	5 mL
5 < 7			1.6 mg	4.8 mg	5 mL
7 < 8			1.8 mg	5.4 mg	5 mL
8 < 9			2.4 mg	7.2 mg	5 mL
9 < 10			2.8 mg	8.4 mg	5 mL
10 < 12			3.0 mg	9.0 mg	5 mL
12 < 30		5 mg		10 mg	5 mL or 10 mL
30 < 50	15 mg			15 mg	10 mL
≥ 50	20 mg			20 mg	10 mL

Table 15. Dosing of dabigatran — a single dose of dabigatran in milligram by weight in kilograms [kg] and age in years of the patient to be administered twice daily [266]

Weight [kg]	Wiek w latach									
	8 do < 9	8 do < 10	10 do < 11	11 do < 12	12 do < 13	13 do < 14	14 do < 15	15 do < 16	16 do < 17	17 do < 18
> 81			300 mg (two 150 mg capsules or four 75 mg capsules)							
71 to 81										
61 to < 71										
51 to < 61	260 mg (110 mg plus 150 mg)									
41 to < 51	220 mg (2 x 110 mg)									
31 to < 41	185 mg (75 mg plus 110 mg)									
26 to < 31	150 mg (1 x 150 mg or 2 x 75 mg)									
21 to < 26										
16 to < 21	1 x 110 mg									
13 to < 16										
11 to < 13	1 x 75 mg									
	Means that no dosing recommendation can be provided									

should be individualized. Thromboembolic lesions are not often observed in children and are secondary to other diseases. They are very often associated with the presence of a central catheter. Children with cancer are at increased risk of VTE. Clinical symptoms are diverse, depending on the location and extent of the disease.

The main medications for thrombosis in children are LMWHs and UFHs. Tissue plasminogen activator is the drug of choice with thrombolytic activity but with limited indications.

For all children with cancer, an individual VTE risk assessment is recommended, including:

— surgical treatment (especially extensive surgery) and prolonged postoperative immobilization;
— chemotherapy, anti-cancer treatment (e.g., asparaginase, corticosteroids);

- central lines or ports;
- the type, location and stage of the cancer;
- obesity;
- idiopathic thrombosis (congenital thrombophilia, mutations of coagulation factors with a prothrombotic effect, antibodies present in the antiphospholipid syndrome).

Treatment of VTE in children is in most cases not evidence-based, as clinical trials in pediatric populations and studies with anticoagulants have not been performed extensively, especially in children with cancer. For this reason, treatment guidelines are mainly extrapolated from adult studies. However, the pathophysiology of VTE, changes in the hemostatic system, and underlying diseases and their treatment in children differ significantly from those in adults [7, 267]. It also means that the risk of complications of anticoagulation therapy, such as the risk of bleeding, may differ from that of adult patients [268–271]. The current standard of care in the treatment of VTE in children includes LMWHs (enoxaparin, nadroparin, dalteparin), UFH and VKAs (warfarin, acenocoumarol), as well as in a selected group of children from birth to 18 years of age – rivaroxaban and dabigatran. The randomized phase III trial EINSTEIN Junior (age 0–17, n = 500) documented that in children with acute VTE, treatment with rivaroxaban resulted in a similarly low risk of recurrent thrombosis (4/335 vs. 1/165, HR 0.40; 95% CI 0.11–1.41) without increased risk of bleeding (major or clinically significant bleeding (10/329 vs. 3/162, HR 1.58; 0.51–6.27) compared with standard anticoagulants (LMWH/VKA). In the EINSTEIN Junior study, 12% (40/335) children with active cancer receiving revaroxaban were compared with 10% (16/165) receiving standard anticoagulant therapy, including the subgroups of patients with hematological malignancies (7%) and with solid tumors (3–4%) [262]. These results proved that rivaroxaban is effective and safe in the treatment of acute VTE in children with cancer. On June 21, 2021, the American Food and Drug Administration (FDA) approved the use of dabigatran in children from 3 months to 12 years of age for secondary VTE prophylaxis based on the phase III DIVERSITY study, in which hematological cancers and cases with central venous access device (CVAD) were 5.5% (11/196) each [263]. Published phase I to IV pediatric studies with DOACs included 1007 children receiving VTE prophylaxis or VTE treatment, and the results of the last three phase III studies, in particular with rivaroxaban and dabigatran, have shown that these agents are at least as effective as traditional anticoagulants [264].

In addition, depending on the standard of care as well as expertise and experience of the center, local thrombolysis and/or thrombectomy may be available and performed.

The most important risk factor for the development of VTE in children with cancer who receive oncological treatment is CVAD, which is necessary due to the limited intravenous access in the pediatric population. Peripherally inserted central catheters have been documented to pose a greater risk than tunnelled catheters [272, 273]. If symptomatic thrombosis occurs and the child who requires CVAD is in good condition, it is suggested, based on the ASH 2021 guidelines for adults, to keep the CVAD (which is in line with the CHEST guidelines) and to start anticoagulant treatment. The CHEST guidelines recommend LMWH or UFH for at least 6 weeks to 3 months as anticoagulant treatment. In the EINSTEIN Junior study, CVAD-related thrombosis was identified and treated in 90/335 (27%) patients in the rivaroxaban arm and 37/165 (22%) patients in the standard anticoagulation arm [274].

When chosing anticoagulation in pediatric cancer patients, the risk of bleeding should be taken into account, including the following factors: recent major bleeding, abnormal renal function, gastrointestinal symptoms that interfere with the absorption of oral medications, tumor location in the genitourinary system or a gynecological cancer, thrombocytopenia ($<100{,}000/\mu$L) and decompensated coagulopathy. A subanalysis of the EINSTEIN Junior study showed a low risk of VTE recurrence and clinically significant bleeding in the pediatric group with cerebral venous sinus thrombosis, including children with active cancer receiving rivaroxaban [7/73 (9.6%)] v. 2/41 (4.9 %) of patients in the standard anticoagulation group] [275].

Many cytostatics can increase the risk of gastrointestinal toxicity, including high-dose alkylating agents (e.g., antimetabolites: cytarabine, methotrexate), programmed death 1 receptor inhibitors (e.g., nivolumab), and antimitotic drugs (e.g., vinblastine, vincristine) (Tab. 10). Anticoagulant drug interactions with anti-cancer therapy and supportive care should also be considered. Oral anticoagulants, both VKAs and DOACs, have potential drug interactions with co-administered drugs affecting the P-glycoprotein transporter (minor inteactions for VKAs but more significant for DOACs) or with inhibitors of CYP3A4 [10, 276, 277].

In the event of significant drug interactions, the use of LMWHs is indicated.

5.2. Prevention of cancer-related venous thromboembolism in children

Clinical question 5B. Is thromboprophylaxis indicated in children with neoplastic disease who are scheduled for surgery?

Recommendation 5.2.1

In all children undergoing oncological treatment, it is always recommended to weigh the benefits and risks of anticoagulant prophylaxis before planned surgery [1A].

Recommendation 5.2.2

In the absence of contraindications, pharmacological antithrombotic prophylaxis is recommended in all children with a history of cancer-related or unrelated DVT undergoing major surgery [1C].

Recommendation 5.2.3

In pediatric oncological patients without a history of VTE, undergoing major surgery, with a low risk of bleeding and coexisting significant risk factors of thrombosis requiring prophylaxis, it is suggested to use pharmacological, not mechanical prophylaxis [2C].

Recommendation 5.2.4

In pediatric oncological patients without a history of VTE, undergoing minor or laparoscopic surgery, with a low risk of bleeding and without coexisting risk factors of thrombosis, it is suggested that antithrombotic prophylaxis be used when justified after an individual assessment of the benefits and risks of such treatment [2C].

Recommendation 5.2.5

LMWH is recommended in children with cancer who are scheduled for surgery and prophylaxis is justified [1B].

Recommendation 5.2.6

If prophylaxis is indicated, it is recommended to initiate treatment before surgery or as soon as possible after surgery, taking into account the risk of bleeding [1B].

Comment

Although in the adult population as much as 20% of all new VTE cases are caused by surgery [278], and the risk of VTE is significantly increased for at least 12 weeks after major surgery, data for the pediatric population, especially children with cancer, are still lacking. Risk factors such as advanced cancer, the presence of a central venous catheter, injury, extensive surgery, and comorbidities may increase the incidence of VTE. When the risk of VTE is high, pharmacological prophylaxis is often initiated, for example with low molecular weight heparin. However, the initiation and duration of VTE prophylaxis depends on the patient's risk factors for thrombosis and contraindications to anticoagulant therapy, such as bleeding. Although many studies have been conducted in recent years to assess the most appropriate type, risk factors and duration of VTE prophylaxis, more studies are needed to develop optimal guidelines for reducing the risk of VTE in children with cancer who are scheduled for surgery.

Chapter 6. Treatment of pulmonary embolism in cancer patients

Treatment of acute pulmonary embolism in patients with coexisting cancer is a difficult clinical challenge due to the fact that it is often performed simultaneously with the treatment of the underlying disease. For the sake of clarity, whenever we mention the term pulmonary embolism (PE), we mean acute pulmonary embolism. The prognosis for cure and deontological issues are also important. There is a high risk of bleeding complications due to a disorder common in these patients – thrombocytopenia – which is especially dangerous in patients with acute PE who are mainly treated with various forms of anticoagulant therapy.

When planning acute PE treatment in this group of patients, the type and biology of cancer (including thrombogenicity), tumor location (e.g., gastrointestinal tract or central nervous system), and the presence of metastases should also be taken into account. Therapeutic decisions are also influenced by the increased incidence of DVT in cancer patients, a higher frequency of recurrences and a high risk of bleeding complications.

The latest European and American guidelines emphasize the importance of creating in-hospital multidisciplinary teams to coordinate the treatment of patients with acute PE (PERT, pulmonary embolism response team) [279–281].

It seems necessary that such a team includes an oncologist who can determine the clinical stage and thrombogenicity of the tumor, anticancer therapy and the risk of bleeding, which will facilitate the optimization of PE treatment. It is worth noting that in the nationwide PERT registry, cancer patients accounted for over 20% of all consulted and treated patients [281, 282].

Before starting treatment, the patient's hemodynamic status must be determined and a clinical evaluation performed using the pulmonary embolism severity index (PESI) or its simplified version (sPESI) [279]. Assessment of right ventricular overload by echocardiography or computed tomography (right ventricle-to-left ventricle diameter ratio) and the levels of cardiac troponin and possibly natriuretic peptide (NT-proBNP) are also important.

Based on these studies, patients are classified as having low, intermediate-low, intermediate-high or high risk PE. This is the basis for the choice of appropriate therapy [279].

6.1. Treatment in the acute phase of pulmonary embolism

Anticoagulation is the treatment of choice in patients with low- and intermediate-risk PE. Earlier clinical

trials demonstrated the advantage of using low-molecular-weight heparins, especially dalteparin, over VKA treatment in oncological patients. LMWHs have become the standard of care for the treatment of VTE, although its use is associated with daily subcutaneous injections.

In recent years, the results of RCTs such as SELECT-D, Hokusai-VTE-Cancer and Caravaggio have been published, which assessed the efficacy and safety of DOACs in patients with cancer and coexisting thromboembolism compared to dalteparin [220, 222, 283]. The SELECT-D study enrolled patients with active cancer who developed symptomatic PE, asymptomatic PE, or symptomatic proximal DVT of the lower limb [220]. Half of the patients were administered dalteparin (200 IU/kg daily for the first month, then 150 IU/kg daily for months 2 to 6) and rivaroxaban in the other arm of the study (15 mg twice daily for 3 weeks, then 20 mg once daily for 6 months in total). Rivaroxaban was as effective in preventing VTE recurrence as dalteparin, but its use was associated with a significantly higher risk of bleeding, especially in patients with gastrointestinal malignancies. Similar results were obtained in the Hokusai-VTE-Cancer study, which assessed edoxaban versus dalteparin [283]. The most recent study with a direct factor Xa inhibitor, which is used in the secondary prevention of thromboembolism in cancer patients, is the CARAVAGGIO study comparing apixaban with dalteparin [222]. There was no increase in the risk of major bleeding, especially in the gastrointestinal tract. The results of the Caravaggio study increase the proportion of cancer-related thrombosis patients eligible for treatment with oral direct anticoagulants, including patients with gastrointestinal cancer. It can be presumed that this study will change the recommendations and apixaban will also be approved for use in the treatment of pulmonary embolism in patients with gastrointestinal cancers.

In patients with high-risk PE, in the absence of contraindications, systemic thrombolysis remains the treatment of choice [279]. In cancer patients, the risk of significant bleeding complications is usually much higher, especially in cancers of the gastrointestinal tract or CNS tumors (including metastatic tumors). Patients are often just after or before major surgery.

All of the above factors make patients more likely to have true or presumed, relative or absolute contraindications to thrombolytic therapy. However, more difficult in these patients is the decision to perform extensive cardiac surgery (surgical embolectomy) in extracorporeal circulation. Therefore, it seems that (invasive) catheter-directed thrombolysis (CDT) should be considered more often in cancer patients with EP [281]. Currently, transcatheter therapy is indicated in high-risk patients, in patients with contraindications to systemic thrombolytic therapy and when surgical embolectomy is impossible; however, in high-risk intermediate patients, this type of therapy may be considered at the time of hemodynamic deterioration as an alternative to thrombolysis or surgical embolectomy [279].

According to recently published Polish recommendations on the functioning of PERTs, CDT should also be considered in high-risk patients, when there is no clinical improvement for a long time despite anticoagulation [279]. Therefore, it seems that CDT may in many cases be a chance for successful thrombus clearance, recanalization of pulmonary arteries, and clinical stabilization of patients with high- or intermediate-high-risk PE. Treatment may include transcatheter mechanical thrombectomy (most commonly aspiration or rheolytic thrombectomy), thrombus fragmentation, or low dose transcatheter thrombolysis [284].

It is also possible to use a combination of mechanical and pharmacological methods, such as mechanical thrombectomy and low-dose thrombolysis (pharmacomechanical treatment) [284, 285].

6.2. Management in the chronic phase of pulmonary embolism

As the risk of another episode of pulmonary embolism in patients with cancer is three times higher than in the general population, the duration of anticoagulant use should be individualized for each patient.

The duration of treatment should take into account the type of cancer (e.g., pancreatic and gastric tumors are more thrombogenic), the risk of bleeding, and the type of anticancer therapy administered (drug interactions). Six months is considered the minimum duration of treatment for a first episode of acute PE, although it is also believed that the patient should be on the anticoagulant for the entire duration of "active neoplastic disease". However, it is often difficult to tell when the cancer is cured.

It should also be remembered that patients receiving DOACs during chemotherapy/radiotherapy should be treated with antiemetics and a temporary switch to low-molecular-weight heparin in the event of vomiting lasting more than 2 days should be considered (Fig. 2). DOACs should not be used when gastrointestinal obstruction is suspected.

A slightly different group of patients are cases of incidental detection of thrombus in the pulmonary arteries during the control CT scan of the chest. According to the ESC guidelines, such patients should be treated in the same way as patients with symptomatic acute PE if the lesions are located in segmental arteries or more proximally, in numerous subsegmental arteries, or if the lesions are accompanied by deep vein thrombosis [279].

Table 16. Initial anticoagulant therapy in patients with pulmonary embolism and concomitant neoplasm

Initial therapy	
Unfractionated heparin	80 IU/kg IV bolus, 18 U/kg/hour IV and adjust a dose based on aPTT
Dalteparin	100 U/kg every 12 hours
	200 U/kg once daily
Enoxaparin	1 mg/kg every 12 hours
	1.5 mg/kg once daily
Fondaparinux	< 50 kg: 5.0 mg once daily
	50–100 kg: 7.5 mg once daily
	> 100 kg: 10 mg once daily
Rivaroxaban	15 mg every 12 hours for 21 days
Apixaban	10 mg every 12 hours for 7 days

aPTT — activated partial thromboplastin time

Table 17. Primary treatment and secondary antithrombotic prevention in patients with pulmonary embolism and coexisting cancer

Primary treatment and secondary prevention	
Dalteparin	200 U/kg once daily for 1 month, then 150 U/kg
Enoxaparin	1.5 mg/kg once daily 1 mg/kg every 12 hours
Warfarin	To maintain INR 2.0–3.0
Rivaroxaban	1 × 20 mg/day (consider 15 mg/day if increased risk of bleeding)
Edoxaban	60 mg/day or 30 mg/day: • < 60 kg • creatinine clearens 30–50 mL/min • in combination with P-glycoprotein inhibitors
Apixaban	5 mg every 12 hours

INR — international normalized ratio

6.3. Recommendations for the treatment of pulmonary embolism in cancer patients

Recommendation 6.3.1

UFH, LMWH, fondaparinux, rivaroxaban or apixaban are recommended in the initial treatment of acute pulmonary embolism in patients with cancer (Table 16) [1A].

Recommendation 6.3.2

LMWH, rivaroxaban, edoxaban, apixaban and VKA are suggested in the primary treatment and prophylaxis of patients with cancer (Table 17) [2B].

Recommendation 6.3.3

It is suggested that the anticoagulant treatment be extended beyond 6 months indefinitely or until the cancer is cured [2B].

Recommendation 6.3.4

It is suggested that patients receiving DOACs during chemotherapy/radiotherapy should be treated with antiemetics and a temporary switch to low-molecular-weight heparin in the event of vomiting lasting more than 2 days should be considered [2B].

Recommendation 6.3.5

In high-risk pulmonary embolism, systemic thrombolytic therapy is recommended [1B]. Surgical pulmonary embolectomy is recommended in patients with pulmonary embolism and contraindications to systemic thrombolytic therapy or in the case of its ineffectiveness [1C]. The use of percutaneous catheter-based methods to restore the patency of the pulmonary arteries is suggested in patients with high-risk pulmonary embolism, in whom thrombolytic therapy is contraindicated or ineffective [2A].

In other patients with pulmonary embolism, in whom there are potential indications for systemic or transcatheter treatment, including patients with hemodynamic deterioration during anticoagulation treatment, indications for this type of therapy should be determined individually on the basis of current treatment recommendations included in the relevant guidelines.

Recommendation 6.3.6

Hospital PERTs treating cancer patients with acute PE should include an oncologist [GPS].

Recommendation 6.3.7

In patients with cancer treated with anticoagulants for APE, it is suggested to perform periodic check-ups with an assessment of the risk of bleeding and the potential balance of treatment benefits vs. the risk of bleeding or VTE recurrence, taking into account the degree of tumor progression and the type of anticancer therapy [2C].

Chapter 7. Use of anticoagulants in CAT treatment in patients with chronic kidney disease

Renal failure occurring during neoplastic disease adversely affects the treatment of cancer and the course of the disease itself. Kidney function also worsens with age. There are many causes of kidney disfunction related to cancer or its treatment, including: 1) prerenal: for example due to dehydration (nausea and vomiting, diarrhea); 2) renal: for example during chemotherapy – drug nephrotoxicity, tumor infiltration, kidney involvement in lymphoma; 3) atrophic: for example, tumor infiltration, lympadenopathy. Renal failure may alter the pharmacoki-

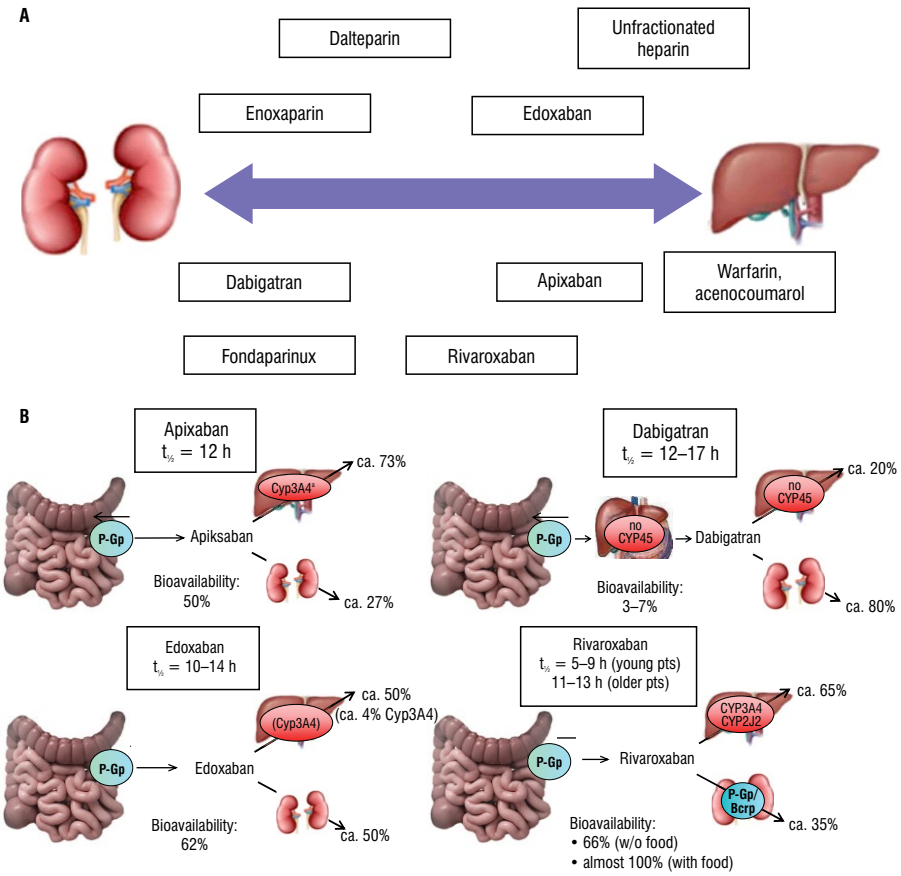

Figure 3. A. Renal and hepatic elimination of anticoagulants, B. Absorption and metabolism of various direct oral anticoagulants. Possible interactions at the level of absorption or first transformation, and at the level of metabolism and elimination, also by CYP1A2, CYP2J2, CYP2C8, CYP2C9 and CYP2C19

netics of many drugs, including anticoagulants, but is also an independent risk factor for bleeding [286].

On the one hand, more than half of cancer patients may have renal insufficiency, and on the other hand – patients with renal insufficiency have an increased risk of developing cancer, estimated at approximately 7% [287–289].

Renal dysfunction is a common complication in cancer patients [288]. Launay-Vacher et al. [287, 290–292] estimated that various degrees of deterioration of renal function, including failure, are found in 50–60% of patients with solid tumors, most often of the lung, breast and prostate cancers.

Renal impairment may lead to the bioaccumulation of certain anticoagulants, resulting in an increased risk of bleeding. Low-molecular-weight heparin should be used with caution in patients with renal failure and cancer, and are often contraindicated, especially when CrCl is ≤ 30 mL/min [293].

Regarding potential bioaccumulation, two of the currently used drug groups should be discussed separately: heparins, especially low-molecular-weight heparins, and DOACs.

The data published so far indicate that not all LMWHs have the same risk of accumulation; in fact, those with higher molecular weight may be less dependent on renal elimination (Figure 3) [294].

Among the available LMWHs, tinzaparin (withdrawn from the US market) has the highest average molecular weight, i.e., 6,500 Da [295]. Low-molecular-weight heparins differ in their molecular weight and anti-Xa/anti-IIa activity (Table 18).

This may be of practical importance. For example, clinically significant bleeding occurred in 22% (13 out of 59) of patients with moderate renal insufficiency (CrCl 30–50 mL/min) who were receiving a therapeutic dose of enoxaparin (1 mg/kg every 12 h or 1.5 mg/kg once daily) for 6 months, and only in 6% of patients (6 out of 105) with normal renal function (OR: 3.9; 95% CI: 0.97–15.6; p = 0.055) [296].

The data published so far indicate that not all LMWHs have the same risk of accumulation; in fact, those with higher molecular weight may be less dependent on renal elimination [292, 293, 295-302]. Figure 4 shows

Table 18. Mean molecular weight and anti-Xa/anti-IIa activities of heparins

Drug	Average/Mean molecular weight (Daltons)	Anti-Xa/anti-IIa activity
Unfractionated heparin	12,000–15,000	1:1
Dalteparin	5,600–6,400	1.9:1 to 3.2:1
Enoxaparin	3,500–5,500	3.3:1 to 5.2:1
Nadroparin	3,600–5,000	2.5:1 to 4.0:1
Tinzaparin	5,600–7,500	1.5:1 to 2.5:1

the mechanism of LMWH excretion depending on the molecular weight.

In a study by Jalal et al. [303] involving 4,684 patients with various types of cancer, more than half (57.4%) of patients had abnormal CrCl (defined as <90 mL/min), whereas in 37.6% of patients CrCl was 60–89 mL/min, in 18.5% of patients CrCl was 30.59, and 1.3% CrCl was <30 mL/min. The clinical implications of such studies suggest that the incidence of renal failure in cancer patients may be underestimated, especially as renal function is assessed in most cases on the basis of serum creatinine (SrCr) levels. A French study by Launay-Vacher et al. [287] in patients with cancer showed that 9.2% of patients had an increased SrCr, while 23% of patients with normal SrCr (<110 μmol/L) had CrCl <80 mL/min and had features of impaired renal function.

In each case, the initial renal impairment may be exacerbated by anticancer treatment, as these therapies may be nephrotoxic, especially when used sequentially or in combination; and in addition, these patients are often dehydrated. Impaired renal function may translate into a deterioration of the clinical effects of treatment in patients treated with anticoagulants, because renal failure may limit elimination of drugs, potentially leading to their bioaccumulation, and thus increasing the risk of bleeding. Anticoagulants are not a homogeneous group of drugs, they have different pharmacokinetic profiles, and the risk of bioaccumulation varies between drug classes as well as between drugs belonging to the same class (e.g., LMWHs).

Unfractionated heparin is cleared from the body at a dose-dependent rate by the reticuloendothelial system of the liver, while LMWHs are excreted through the kidneys [304]. As a result, depending on the dose and duration of treatment, all LMWHs, such as bemiparin, dalteparin, danaparoid, enoxaparin, nadroparin, and tinazaparin, may accumulate more in patients with impaired renal function than in UFH [304,305].

A *post hoc* analysis of the CLOT study and a subanalysis of the CATCH study provided evidence that both dalteparin and tinzaparin, although belonging to a different drug class, have safety profiles similar to VKAs in patients with CAT. In these 2 studies, the incidence of bleeding episodes increased significantly when anticoagulants (LWMH or VKA) were administered to patients with impaired renal function (compared with those with normal renal function), but when LMWH was compared with VKA, there was no increase in bleeding (what to be expected in view of bioaccumulation). Surprisingly, the post hoc analysis of the CLOT study documented a greater and statistically significant reduction in recurrent thrombosis with dalteparin in patients with impaired renal function compared with the results obtained earlier in the entire CLOT study population [306].

A post hoc analysis of the CLOT study assessed the efficacy and safety of long-term treatment with high doses of dalteparin (therapeutic doses of 150–200 IU/kg/day as opposed to prophylactic doses of 2500–5000 IU/day used in primary VTE prophylaxis) compared with VKA in patients with cancer and VTE who at the beginning of the study had normal/slightly impaired

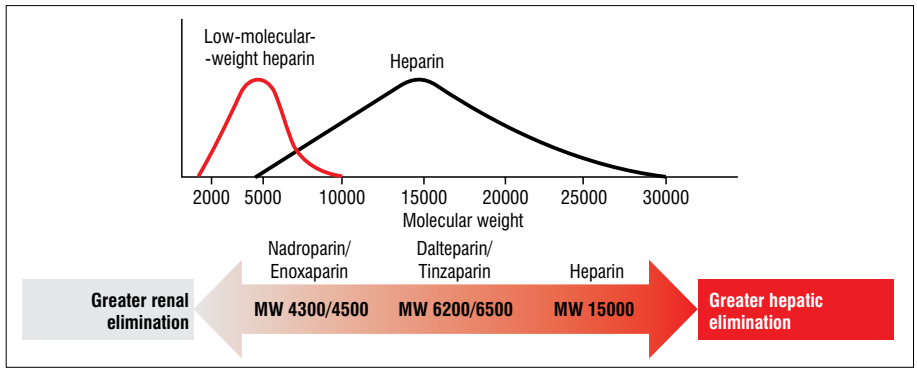

Figure 4. Mechanism of low-molecular-weight-heparin excretion depending on the molecular weight

renal function (CrCl ≥ 60 mL/min), moderate renal impairment (30 ≤ CrCl <60 mL/min) or severe renal impairment (CrCl < 30 mL/min).

The dose distribution of dalteparin in patients with renal insufficiency was similar to that in patients with normal renal function, i.e., no systematic dose reduction was exercised in patients with impaired renal function (including patients with severe kidney failure). Of 74 dalteparin-treated patients with renal failure at baseline, only in one patient the dose was temporarily reduced due to increased anti-Xa levels. In 91/676 (13%) of the CLOT patients who developed renal failure during the study, the dose was reduced in 2/91 (2%) due to increased anti-Xa activity.

In the per-protocol population, the proportion of patients with renal impairment at baseline and at least one bleeding episode was greater in the VKA arm than in the dalteparin arm (24.1% vs. 20.3%, respectively). It is noteworthy that in both arms of the study, the frequency of bleeding episodes increased in line with the deterioration of renal function.

The above-cited efficacy and safety results provide useful and practical information for clinicians on the use of dalteparin in the prophylaxis and treatment of VTE in patients with cancer and renal impairment. There are no comparative analyzes between LMWHs, so it is difficult to extrapolate these results to other LMWHs, as the pharmacokinetic and pharmacodynamic profiles of different LMWHs are clearly different.

This is due to different manufacturing processes and to the differences in the average molecular weight, which is considered to be the factor that determines the degree of renal elimination of individual LMWHs.

A report on the safety of enoxaparin (currently the most widely used LMWH) in secondary prophylaxis in patients with CAT and renal failure was presented at the Congress of the International Society on Thrombosis and Hemostasis. The RIETECAT study compared the long-term efficacy and safety of enoxaparin with those of tinzaparin or dalteparin in the secondary prevention of VTE in adult cancer patients.

This was an observational cohort study using data from the RIETE registry. The study included patients who started treatment with a full dose of enoxaparin, tinzaparin or dalteparin between January 2009 and June 2018 and within 48 hours of the diagnosis of a primary VTE episode. Recurrent VTE and major bleeding were assessed during 6 month after initiation of treatment.

In the population of 4,451 cancer patients with VTE, enoxaparin (n = 3,526), tinzaparin (n = 754) and dalteparin (n = 171) were used. VTE recurrence occurred in 70 patients (2.0%) in the enoxaparin subgroup and 23 patients (2.5%) in the tinzaparin/dalteparin subgroup [OR 0.79, 95% CI: 0.49–1.28, p = 0.343, (p = 0.004 for non-inferiority)]. There was no difference between the subgroups in the rates of DVT recurrences, pulmonary embolism or fatal pulmonary embolism. Major bleeding occurred in 111 patients (3.1%) in the enoxaparin subgroup and 18 patients (1.9%) in the tinzaparin/dalteparin subgroup (OR 1.64, 95% CI 0.99–2.71, p = 0.052). All-cause mortality rates were similar in the treatment subgroups (18.9% vs. 17%, OR 1.14; 95% CI 0.94–1.38, p = 0.182). The Propensity Score Matching analysis showed no differences between the subgroups in the risk of VTE recurrence [adjusted risk ratios (aHR): 0.81, 95% CI 0.48–1.38], major bleeding (aHR 1.41; 95% CI 0.80–2.46, p = 0.235) or death from any cause (aHR 1.07, 95% CI 0.88–1.30, p = 0.476).

The authors conclude that in clinical practice, enoxaparin has a comparable efficacy and safety profile to tinzaparin/dalteparin in CAT cancer patients [307].

For enoxaparin, dose reduction to 50% of the usual dose is recommended in patients with CrCl <30 mL/min. There are no specific recommendations for the remaining LMWHs [286].

DOACs may accumulate in patients with acute and chronic kidney disease (Figure 3). They are eliminated by the kidneys in different amounts: dabigatran in 80%; rivaroxaban, 1/3 of the unchanged active molecule is excreted in the urine and 2/3 of the remainder is also excreted through the kidneys; apixaban and edoxaban are excreted in the urine in 25% and 35%, respectively [308]. Oral direct anticoagulants are as effective as VKAs, with less bleeding in patients with stage 3 chronic kidney disease. There are reports that as renal function worsens, the advantage of DOACs over VKAs becomes less pronounced. Patients with eGFR below 30 mL/min should not be treated with dabiagatran, and rivaroxaban and apixaban can be considered in patients with CrCL of 15–29 mL/min, especially in secondary prevention, at doses of 15 mg/day or 2.5 mg every 12 h, respectively, with regular assessment of risk and renal function, like in non-oncological patients [14, 225].

In conclusion, in patients with renal failure, a few basic rules should be followed when using anticoagulants, which are listed below:

1. Assess renal function at the start of anticoagulant therapy and reassess at regular intervals.
2. Assess the risk of bleeding on the basis of the patient's medical history, clinical condition, medications used, planned diagnostic tests and treatment
3. In patients with renal impairment, use only LMWHs and DOACs with known pharmacokinetic and clinical data (e.g., enoxaparin). Set the dose according to the summary of product characteristics. In patients with chronic renal failure, minor dose adjustments are usually needed and most patients do not require routine monitoring of anti-Xa activity.

4. Sub-threshold doses of anticoagulants should not be used to prevent bleeding complications.
5. Regular monitoring of peak anti-Xa levels in patients with severe renal insufficiency is indicated. The frequency of check-ups should depend on renal function in patients receiving LMWHs or oral direct factor Xa inhibitors.
6. Two treatment regimens are recommended for the treatment of patients with kidney disease and VTE who have severe (end-stage) renal failure:
   a) UFH and treatment continuation with VKA [309, 310].
   b) UFH and treatment continuation with LMWH; anti-Xa activity monitoring required [311, 312].

References

1. Levitan N, Dowlati A, Remick SC, et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. Medicine (Baltimore). 1999; 78(5): 285–291, doi: 10.1097/00005792-199909000-00001, indexed in Pubmed: 10499070.
2. Chew HK, Wun T, Harvey D, et al. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med. 2006; 166(4): 458–464, doi: 10.1001/archinte.166.4.458, indexed in Pubmed: 16505267.
3. Khorana AA, Francis CW, Culakova E, et al. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost. 2007; 5(3): 632–634, doi: 10.1111/j.1538-7836.2007.02374.x, indexed in Pubmed: 17319909.
4. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. J Thromb Thrombolysis. 2016; 41(1): 3–14, doi: 10.1007/s11239-015-1311-6, indexed in Pubmed: 26780736.
5. Urbanek T, Krasiński Z, Kostrubiec M, et al. Venous thromboembolism prophylaxis in cancer patients — guidelines focus on surgical patients. Acta Angiologica. 2017; 22(3): 71–102, doi: 10.5603/aa.2016.0011.
6. http://www.g-i-n.net.
7. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv. 2020; 4(19): 4693–4738, doi: 10.1182/bloodadvances.2020001830, indexed in Pubmed: 33007077.
8. Anderson DR, Morgano GP, Bennett C, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Adv. 2019; 3(23): 3898–3944, doi: 10.1182/bloodadvances.2019000975, indexed in Pubmed: 31794602.
9. Kakkos SK, Gohel M, Baekgaard N, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis. Eur J Vasc Endovasc Surg. 2021; 61(1): 9–82, doi: 10.1016/j.ejvs.2020.09.023, indexed in Pubmed: 33334670.
10. 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(5): 496–520, doi: 10.1200/JCO.19.01461, indexed in Pubmed: 31381464.
11. Farge D, Frere C, Connors J, et al. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. The Lancet Oncology. 2019; 20(10): e566–e581, doi: 10.1016/s1470-2045(19)30336-5.
12. Shojania KG, Sampson M, Ansari MT, et al. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med. 2007; 147(4): 224–233, doi: 10.7326/0003-4819-147-4-200708210-00179, indexed in Pubmed: 17638714.
13. Wittens C, Davies AH, Bækgaard N, et al. Editor's Choice – Management of Chronic Venous Disease. European Journal of Vascular and Endovascular Surgery. 2015; 49(6): 678–737, doi: 10.1016/j.ejvs.2015.02.007.
14. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016; 149(2): 315–352, doi: 10.1016/j.chest.2015.11.026, indexed in Pubmed: 26867832.
15. Rabe E, Partsch H, Hafner J, et al. Indications for medical compression stockings in venous and lymphatic disorders: An evidence-based consensus statement. Phlebology. 2018; 33(3): 163–184, doi: 10.1177/0268355516689631, indexed in Pubmed: 28549402.
16. Kahn SR, Comerota AJ, Cushman M, et al. American Heart Association Council on Peripheral Vascular Disease, Council on Clinical Cardiology, and Council on Cardiovascular and Stroke Nursing. The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. Circulation. 2014; 130(18): 1636–1661, doi: 10.1161/CIR.0000000000000130, indexed in Pubmed: 25246013.
17. Guyatt G, Oxman A, Kunz R, et al. Going from evidence to recommendations. BMJ. 2008; 336(7652): 1049–1051, doi: 10.1136/bmj.39493.646875.ae.
18. Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008; 336(7650): 924–926, doi: 10.1136/bmj.39489.470347.AD, indexed in Pubmed: 18436948.
19. Guyatt GH, Norris SL, Schulman S, et al. Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2 Suppl): 53S–70S, doi: 10.1378/chest.11-2288, indexed in Pubmed: 22315256.
20. Elyamany G, Alzahrani AM, Bukhary E. Cancer-associated thrombosis: an overview. Clin Med Insights Oncol. 2014; 8: 129–137, doi: 10.4137/CMO.S18991, indexed in Pubmed: 25520567.
21. Farge D, Bounameaux H, Brenner B, et al. International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. J Thromb Haemost. 2013; 11(1): 56–70, doi: 10.1111/jth.12070, indexed in Pubmed: 23217107.
22. Lyman GH, Bohlke K, Falanga A, et al. American Society of Clinical Oncology. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Oncol Pract. 2015; 11(3): e442–e444, doi: 10.1200/JOP.2015.004473, indexed in Pubmed: 25873061.
23. Mandalà M, Falanga A, Roila F, et al. ESMO Guidelines Working Group. Management of venous thromboembolism (VTE) in

cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2011; 22 Suppl 6: vi85–vi92, doi: 10.1093/annonc/mdr392, indexed in Pubmed: 21908511.
24. Gould MK, Garcia DA, Wren SM, et al. Approach to outcome measurement in the prevention of thrombosis in surgical and medical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2 Suppl): e185S–e194S, doi: 10.1378/chest.11-2289, indexed in Pubmed: 22315260.
25. Zawilska K, Bała M, Błędowski P, et al. Polish guidelines for the prevention and treatment of venous thromboembolism. 2012 update. Polish Archives of Internal Medicine. 2012; 122(Suppl. 2): 1–76, doi: 10.20452/pamw.1566.
26. Akl EA, Muti P, Schünemann HJ. Anticoagulation in patients with cancer: an overview of reviews. Pol Arch Med Wewn. 2008; 118(4): 183–193, indexed in Pubmed: 18575417.
27. Kakkar VV, Howe CT, Nicolaides AN, et al. Deep vein thrombosis of the leg. The American Journal of Surgery. 1970; 120(4): 527–530, doi: 10.1016/s0002-9610(70)80023-x.
28. Rickles FR, Levine M, Edwards RL. Hemostatic alterations in cancer patients. Cancer Metastasis Rev. 1992; 11(3-4): 237––248, doi: 10.1007/BF01307180, indexed in Pubmed: 1423816.
29. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015; 12(8): 464–474, doi: 10.1038/nrcardio.2015.83, indexed in Pubmed: 26076949.
30. Cushman M. Epidemiology and risk factors for venous thrombosis. Semin Hematol. 2007; 44(2): 62–69, doi: 10.1053/j.seminhematol.2007.02.004, indexed in Pubmed: 17433897.
31. Wun T, White RH, Ku GH, et al. Venous thromboembolism in patients with acute leukemia: incidence, risk factors, and effect on survival. Blood. 2009; 113(17): 3911–3917, doi: 10.1182/blood-2008-08-175745, indexed in Pubmed: 19088376.
32. Pellino G, Sciaudone G, Candilio G, et al. Predictors of Venous Thromboembolism after Colorectal Surgery in a Single Unit. Acta Chir Belg. 2015; 115(4): 288–292, doi: 10.1080/00015458.2015.11681114, indexed in Pubmed: 26324031.
33. Kucher N, Spirk D, Baumgartner I, et al. Lack of prophylaxis before the onset of acute venous thromboembolism among hospitalized cancer patients: the SWIss Venous ThromboEmbolism Registry (SWIVTER). Ann Oncol. 2010; 21(5): 931–935, doi: 10.1093/annonc/mdp406, indexed in Pubmed: 19828560.
34. Lyman GH. Thromboprophylaxis with low-molecular--weight heparin in medical patients with cancer. Cancer. 2009; 115: 5637.
35. Agnelli G, Caprini JA. The prophylaxis of venous thrombosis in patients with cancer undergoing major abdominal surgery: emerging options. J Surg Oncol. 2007; 96(3): 265–272, doi: 10.1002/jso.20808, indexed in Pubmed: 17474075.
36. Heit JA, Silverstein MD, Mohr DN. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med. 2000; 160(6): 809–815, doi: 10.1001/archinte.160.6.809, indexed in Pubmed: 10737280.
37. Nijziel MR, van Oerle R, Hillen HFP, et al. From Trousseau to angiogenesis: the link between the haemostatic system and cancer. Neth J Med. 2006; 64(11): 403–410, indexed in Pubmed: 17179570.
38. Easaw JC, Shea-Budgell MA, Wu CMJ, et al. Canadian consensus recommendations on the management of venous thromboembolism in patients with cancer. Part 1: prophylaxis. Curr Oncol. 2015; 22(2): 133–143, doi: 10.3747/co.22.2586, indexed in Pubmed: 25908912.
39. Caprini JA, Arcelus JI, Hasty JH, et al. Clinical assessment of venous thromboembolic risk in surgical patients. Semin Thromb Hemost. 1991; 17 Suppl 3: 304–312, indexed in Pubmed: 1754886.
40. Caprini JA. Thrombosis risk assessment as a guide to quality patient care. Dis Mon. 2005; 51(2-3): 70–78, doi: 10.1016/j.disamonth.2005.02.003, indexed in Pubmed: 15900257.
41. Ay C, Pabinger I. VTE risk assessment in cancer. Who needs prophylaxis and who does not? Hamostaseologie. 2015; 35(4): 319–324, doi: 10.5482/HAMO-14-11-0066, indexed in Pubmed: 25740182.
42. Bouras G, Burns EM, Howell AM, et al. Risk of Post-Discharge Venous Thromboembolism and Associated Mortality in General Surgery: A Population-Based Cohort Study Using Linked Hospital and Primary Care Data in England. PLoS One. 2015; 10(12): e0145759, doi: 10.1371/journal.pone.0145759, indexed in Pubmed: 26713434.
43. NICE guidance: Venous thromboembolism: reducing the risk: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital [CG92]. https://www.nice.org.uk/guidance/cg92..
44. Törngren S, Rieger A. Prophylaxis of deep venous thrombosis in colorectal surgery. Dis Colon Rectum. 1982; 25(6): 563–566, doi: 10.1007/BF02564166, indexed in Pubmed: 7117060.
45. Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004; 126(3 Suppl): 338S–400S, doi: 10.1378/chest.126.3_suppl.338S, indexed in Pubmed: 15383478.
46. Merkow RP, Bilimoria KY, McCarter MD, et al. Post-discharge venous thromboembolism after cancer surgery: extending the case for extended prophylaxis. Ann Surg. 2011; 254(1): 131–137, doi: 10.1097/SLA.0b013e31821b98da, indexed in Pubmed: 21527843.
47. Alsubaie H, Leggett C, Lambert P, et al. Diagnosis of VTE postdischarge for major abdominal and pelvic oncologic surgery: implications for a change in practice. Can J Surg. 2015; 58(5): 305–311, doi: 10.1503/cjs.012314, indexed in Pubmed: 26204144.
48. Larsen AC, Frøkjær JB, Fisker RV, et al. Treatment-related frequency of venous thrombosis in lower esophageal, gastro-esophageal and gastric cancer--a clinical prospective study of outcome and prognostic factors. Thromb Res. 2015; 135(5): 802–808, doi: 10.1016/j.thromres.2015.01.021, indexed in Pubmed: 25743885.
49. Lodders JN, Parmar S, Stienen NLM, et al. Incidence of symptomatic venous thromboembolism in oncological oral and maxillofacial operations: retrospective analysis. Br J Oral Maxillofac Surg. 2015; 53(3): 244–250, doi: 10.1016/j.bjoms.2014.12.001, indexed in Pubmed: 25640701.
50. Chiesa Estomba C, Rivera Schmitz T, Ossa Echeverri CC, et al. The risk of venous thromboembolism in ENT and head & neck surgery. Otolaryngol Pol. 2015; 69(3): 31–36, doi: 10.5604/00306657.1156336, indexed in Pubmed: 26388248.
51. Kakei Y, Akashi M, Hasegawa T, et al. Incidence of Venous Thromboembolism After Oral Oncologic Surgery With Simultaneous Reconstruction. J Oral Maxillofac Surg. 2016; 74(1): 212–217, doi: 10.1016/j.joms.2015.08.006, indexed in Pubmed: 26342948.

52. Tran BH, Nguyen TJ, Hwang BH, et al. Risk factors associated with venous thromboembolism in 49,028 mastectomy patients. Breast. 2013; 22(4): 444–448, doi: 10.1016/j.breast.2013.04.018, indexed in Pubmed: 23692931.
53. De Martino RR, Goodney PP, Spangler EL, et al. Variation in thromboembolic complications among patients undergoing commonly performed cancer operations. J Vasc Surg. 2012; 55(4): 1035–1040.e4, doi: 10.1016/j.jvs.2011.10.129, indexed in Pubmed: 22409858.
54. Lovely JK, Nehring SA, Boughey JC, et al. Balancing venous thromboembolism and hematoma after breast surgery. Ann Surg Oncol. 2012; 19(10): 3230–3235, doi: 10.1245/s10434-012-2524-y, indexed in Pubmed: 22820939.
55. Clagett GP, Reisch JS. Prevention of venous thromboembolism in general surgical patients. Results of meta-analysis. Ann Surg. 1988; 208(2): 227–240, doi: 10.1097/00000658-198808000-00016, indexed in Pubmed: 2456748.
56. Wille-Jorgensen P. Prophylaxis of postoperative deep venous thrombosis. JAMA: The Journal of the American Medical Association. 1985; 253(8): 1120b-1120, doi: 10.1001/jama.253.8.1120b.
57. Bergqvist D, Burmark US, Frisell J, et al. Low molecular weight heparin once daily compared with conventional low-dose heparin twice daily. A prospective double-blind multicentre trial on prevention of postoperative thrombosis. Br J Surg. 1986; 73(3): 204–208, doi: 10.1002/bjs.1800730316, indexed in Pubmed: 3512031.
58. Bergqvist D, Mätzsch T, Burmark US, et al. Low molecular weight heparin given the evening before surgery compared with conventional low-dose heparin in prevention of thrombosis. Br J Surg. 1988; 75(9): 888–891, doi: 10.1002/bjs.1800750920, indexed in Pubmed: 2846113.
59. Samama M, Bernard P, Bonnardot JP, et al. Low molecular weight heparin compared with unfractionated heparin in prevention of postoperative thrombosis. Br J Surg. 1988; 75(2): 128–131, doi: 10.1002/bjs.1800750213, indexed in Pubmed: 2832030.
60. Leizorovicz A, Picolet H, Peyrieux JC, et al. Prevention of postoperative deep vein thrombosis in general surgery: a multicenter double-blind study comparing two doses of logiparin and standard heparin. Br J Surg. 1991; 78: 412–416.
61. Boneu B. An international multicentre study: Clivarin in the prevention of venous thromboembolism in patients undergoing general surgery. Report of the International Clivarin Assessment Group. Blood Coagul Fibrinolysis. 1993; 4 Suppl 1: S21–S22, indexed in Pubmed: 8180325.
62. ENOXACAN Study Group (1997) Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a double-blind randomi¬zed multicentre trial with venographic assessment. Br J Surg; 84: 1099–1103.
63. Kakkar VV, Cohen AT, Edmonson RA, et al. Low molecular weight versus standard heparin for prevention of venous thromboembolism after major abdominal surgery. The Thromboprophylaxis Collaborative Group. Lancet. 1993; 341(8840): 259–265, doi: 10.1016/0140-6736(93)92614-y, indexed in Pubmed: 8093915.
64. The European Fraxiparin Study (EFS) Group (1988) Compari¬son of a low molecular weight heparin and unfractionated heparin for the prevention of deep vein thrombosis in patients undergoing abdominal surgery. Br J Surg; 75: 1058–1063.
65. Baykal C, Al A, Demirtaş E, et al. Comparison of enoxaparin and standard heparin in gynaecologic oncologic surgery: a randomised prospective double-blind clinical study. Eur J Gynaecol Oncol. 2001; 22(2): 127–130, indexed in Pubmed: 11446476.
66. Akl EA, Kahale L, Sperati F, et al. Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer. Cochrane Database Syst Rev. 2014(6): CD009447, doi: 10.1002/14651858.CD009447.pub2, indexed in Pubmed: 24966161.
67. Bergqvist D, Burmark US, Flordal PA, et al. Low molecular weight heparin started before surgery as prophylaxis against deep vein thrombosis: 2500 versus 5000 Xal units in 2070 patients. British Journal of Surgery. 2005; 82(4): 496–501, doi: 10.1002/bjs.1800820421.
68. Kakkar AK, Agnelli G, George D et al. The ultra-low-molecular-weight heparin semuloparin for prevention of venous thromboembolism in patients undergoing major abdominal surgery. Presented at the 53rd Annual Meeting of the American Society of Hematology, San Diego, CA, 2011, December 10–13.
69. Simonneau G, Laporte S, Mismetti P, et al. FX140 Study Investigators. A randomized study comparing the efficacy and safety of nadroparin 2850 IU (0.3 mL) vs. enoxaparin 4000 IU (40 mg) in the prevention of venous thromboembolism after colorectal surgery for cancer. J Thromb Haemost. 2006; 4(8): 1693–1700, doi: 10.1111/j.1538-7836.2006.02083.x, indexed in Pubmed: 16796710.
70. Agnelli G, Bergqvist D, Cohen AT, et al. PEGASUS investigators. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. Br J Surg. 2005; 92(10): 1212–1220, doi: 10.1002/bjs.5154, indexed in Pubmed: 16175516.
71. Yamaoka Y, Ikeda M, Ikenaga M, et al. Safety and efficacy of fondaparinux for prophylaxis of venous thromboembolism after colorectal cancer resection: a propensity score matched analysis. Dig Surg. 2015; 32(3): 190–195, doi: 10.1159/000381034, indexed in Pubmed: 25871913.
72. Yasui M, Ikeda M, Miyake M, et al. Clinical Study Group of Osaka University (CSGO), Colorectal Group. Comparison of bleeding risks related to venous thromboembolism prophylaxis in laparoscopic vs open colorectal cancer surgery: a multicenter study in Japanese patients. Am J Surg. 2017; 213(1): 43–49, doi: 10.1016/j.amjsurg.2015.10.019, indexed in Pubmed: 26772140.
73. Kimura Y, Oki E, Ando K, et al. Incidence of Venous Thromboembolism Following Laparoscopic Surgery for Gastrointestinal Cancer: A Single-Center, Prospective Cohort Study. World J Surg. 2016; 40(2): 309–314, doi: 10.1007/s00268-015-3234-y, indexed in Pubmed: 26316113.
74. Xie YZ, Fang K, Ma WL, et al. Risk of postoperative deep venous thrombosis in patients with colorectal cancer treated with open or laparoscopic colorectal surgery: a meta-analysis. Indian J Cancer. 2015; 51 Suppl 2: e42–e44, doi: 10.4103/0019-509X.151992, indexed in Pubmed: 25712842.
75. Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Guidelines Committee. Guidelines for deep venous thrombosis prophylaxis during laparoscopic surgery. Surg Endosc. 2007; 21(6): 1007–1009, doi: 10.1007/s00464-007-9340-7, indexed in Pubmed: 17410400.
76. Vedovati MC, Becattini C, Rondelli F, et al. A randomized study on 1-week versus 4-week prophylaxis for venous thromboembolism after laparoscopic surgery for colorectal cancer. Ann Surg. 2014; 259(4): 665–669, doi: 10.1097/SLA.0000000000000340, indexed in Pubmed: 24253138.

77. Fagarasanu A, Alotaibi GS, Hrimiuc R, et al. Role of Extended Thromboprophylaxis After Abdominal and Pelvic Surgery in Cancer Patients: A Systematic Review and Meta-Analysis. Ann Surg Oncol. 2016; 23(5): 1422–1430, doi: 10.1245/s10434-016-5127-1, indexed in Pubmed: 26887853.
78. Felder S, Rasmussen MS, King R, et al. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. Cochrane Database Syst Rev. 2018; 11: CD004318, doi: 10.1002/14651858.CD004318.pub3, indexed in Pubmed: 30481366.
79. Bustos Merlo AB, Arcelus Mart ınez JI, Turi o Luque JD, et al. Form of presentation, natural history and course of postoperative venous thromboembolism in patients operated on for pelvic and abdominal cancer. Analysis of the RIETE registry. Cir Esp 95: 328-334, 2017.
80. Guo Q, Huang B, Zhao J, et al. Perioperative Pharmacological Thromboprophylaxis in Patients With Cancer: A Systematic Review and Meta-analysis. Ann Surg. 2017; 265(6): 1087–1093, doi: 10.1097/SLA.0000000000002074, indexed in Pubmed: 27849664.
81. Carrier M, Altman AD, Blais N, et al. Extended thromboprophylaxis with low-molecular weight heparin (LMWH) following abdominopelvic cancer surgery. Am J Surg. 2019; 218(3): 537–550, doi: 10.1016/j.amjsurg.2018.11.046, indexed in Pubmed: 30595331.
82. Schomburg J, Krishna S, Soubra A, et al. Extended outpatient chemoprophylaxis reduces venous thromboembolism after radical cystectomy. Urol Oncol. 2018; 36(2): 77.e9–77.e13, doi: 10.1016/j.urolonc.2017.09.029, indexed in Pubmed: 29097086.
83. Pariser JJ, Pearce SM, Anderson BB, et al. Extended Duration Enoxaparin Decreases the Rate of Venous Thromboembolic Events after Radical Cystectomy Compared to Inpatient Only Subcutaneous Heparin. J Urol. 2017; 197(2): 302–307, doi: 10.1016/j.juro.2016.08.090, indexed in Pubmed: 27569434.
84. Kim BJ, Day RW, Davis CH, et al. Extended pharmacologic thromboprophylaxis in oncologic liver surgery is safe and effective. J Thromb Haemost. 2017; 15(11): 2158–2164, doi: 10.1111/jth.13814, indexed in Pubmed: 28846822.
85. Bergqvist D, Agnelli G, Cohen AT, et al. ENOXACAN II Investigators. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med. 2002; 346(13): 975–980, doi: 10.1056/NEJMoa012385, indexed in Pubmed: 11919306.
86. Rasmussen MS, Jorgensen LN, Wille-Jørgensen P, et al. FAME Investigators. Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicenter randomized open-label study. J Thromb Haemost. 2006; 4(11): 2384–2390, doi: 10.1111/j.1538-7836.2006.02153.x, indexed in Pubmed: 16881934.
87. Sakon M, Kobayashi T, Shimazui T. Efficacy and safety of enoxaparin in Japanese patients undergoing curative abdominal or pelvic cancer surgery: results from a multicenter, randomized, open-label study. Thromb Res. 2010; 125(3): e65–e70, doi: 10.1016/j.thromres.2009.09.009, indexed in Pubmed: 19919878.
88. Nagata C, Tanabe H, Takakura S, et al. Randomized controlled trial of enoxaparin versus intermittent pneumatic compression for venous thromboembolism prevention in Japanese surgical patients with gynecologic malignancy. J Obstet Gynaecol Res. 2015; 41(9): 1440–1448, doi: 10.1111/jog.12740, indexed in Pubmed: 26111609.
89. Song KY, Yoo HMo, Kim EY, et al. Optimal prophylactic method of venous thromboembolism for gastrectomy in Korean patients: an interim analysis of prospective randomized trial. Ann Surg Oncol. 2014; 21(13): 4232–4238, doi: 10.1245/s10434-014-3893-1, indexed in Pubmed: 25012265.
90. Wang Jp, Lin Yd, Wang L, et al. [Effect of intermittent pneumatic compression on coagulation function and deep venous hemodynamics of lower limbs after rectal cancer resection]. Zhonghua Wei Chang Wai Ke Za Zhi. 2013; 16(8): 739–743, indexed in Pubmed: 23980044.
91. Ramirez JI, Vassiliu P, Gonzalez-Ruiz C, et al. Sequential compression devices as prophylaxis for venous thromboembolism in high-risk colorectal surgery patients: reconsidering American Society of Colorectal Surgeons parameters. Am Surg. 2003; 69(11): 941–945, indexed in Pubmed: 14627252.
92. Zareba P, Wu C, Agzarian J, et al. Meta-analysis of randomized trials comparing combined compression and anticoagulation with either modality alone for prevention of venous thromboembolism after surgery. Br J Surg. 2014; 101(9): 1053–1062, doi: 10.1002/bjs.9527, indexed in Pubmed: 24916118.
93. Jung YJu, Seo HoS, Park CH, et al. Venous Thromboembolism Incidence and Prophylaxis Use After Gastrectomy Among Korean Patients With Gastric Adenocarcinoma: The PROTECTOR Randomized Clinical Trial. JAMA Surg. 2018; 153(10): 939–946, doi: 10.1001/jamasurg.2018.2081, indexed in Pubmed: 30027281.
94. Nagata C, Tanabe H, Takakura S, et al. Randomized controlled trial of enoxaparin versus intermittent pneumatic compression for venous thromboembolism prevention in Japanese surgical patients with gynecologic malignancy. J Obstet Gynaecol Res. 2015; 41(9): 1440–1448, doi: 10.1111/jog.12740, indexed in Pubmed: 26111609.
95. Dong J, Wang J, Feng Y, et al. Effect of low molecular weight heparin on venous thromboembolism disease in thoracotomy patients with cancer. J Thorac Dis. 2018; 10(3): 1850–1856, doi: 10.21037/jtd.2018.03.13, indexed in Pubmed: 29707339.
96. Khorana AA, Francis CW, Culakova E, et al. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. Cancer. 2007; 110(10): 2339–2346, doi: 10.1002/cncr.23062, indexed in Pubmed: 17918266.
97. Vitale C, D'Amato M, Calabrò P, et al. Venous thromboembolism and lung cancer: a review. Multidiscip Respir Med. 2015; 10(1): 28, doi: 10.1186/s40248-015-0021-4, indexed in Pubmed: 26380084.
98. Zhang Y, Yang Y, Chen W, et al. China Venous Thromboembolism VTE Study Group, China Venous Thromboembolism (VTE) Study Group. Prevalence and associations of VTE in patients with newly diagnosed lung cancer. Chest. 2014; 146(3): 650–658, doi: 10.1378/chest.13-2379, indexed in Pubmed: 24676401.
99. Steuer CE, Behera M, Kim S, et al. Predictors and outcomes of venous thromboembolism in hospitalized lung cancer patients: A Nationwide Inpatient Sample database analysis. Lung Cancer. 2015; 88(1): 80–84, doi: 10.1016/j.lungcan.2015.01.022, indexed in Pubmed: 25726042.
100. Yu Y, Lv Q, Zhang B, et al. Adjuvant therapy with heparin in patients with lung cancer without indication for anticoagulants: A systematic review of the literature with meta-analysis. J Cancer Res Ther. 2016; 12(Supplement): 37–42, doi: 10.4103/0973-1482.191627, indexed in Pubmed: 27721250.
101. Fuentes HE, Oramas DM, Paz LH, et al. Meta-analysis on anticoagulation and prevention of thrombosis and mortality among patients with lung cancer. Thromb Res. 2017; 154: 28–34, doi: 10.1016/j.thromres.2017.03.024, indexed in Pubmed: 28402864.

102. Hachey KJ, Hewes PD, Porter LP, et al. Caprini venous thromboembolism risk assessment permits selection for postdischarge prophylactic anticoagulation in patients with resectable lung cancer. J Thorac Cardiovasc Surg. 2016; 151(1): 37–44.e1, doi: 10.1016/j.jtcvs.2015.08.039, indexed in Pubmed: 26386868.
103. Sterbling HM, Rosen AK, Hachey KJ, et al. Caprini Risk Model Decreases Venous Thromboembolism Rates in Thoracic Surgery Cancer Patients. Ann Thorac Surg. 2018; 105(3): 879–885, doi: 10.1016/j.athoracsur.2017.10.013, indexed in Pubmed: 29397103.
104. Tun NM, Guevara E, Oo TH. Benefit and risk of primary thromboprophylaxis in ambulatory patients with advanced pancreatic cancer receiving chemotherapy: a systematic review and meta-analysis of randomized controlled trials. Blood Coagul Fibrinolysis. 2016; 27(3): 270–274, doi: 10.1097/MBC.0000000000000413, indexed in Pubmed: 26963028.
105. Salmaggi A, Simonetti G, Trevisan E, et al. Perioperative thromboprophylaxis in patients with craniotomy for brain tumours: a systematic review. J Neurooncol. 2013; 113(2): 293–303, doi: 10.1007/s11060-013-1115-5, indexed in Pubmed: 23543244.
106. Collen JF, Jackson JL, Shorr AF, et al. Prevention of venous thromboembolism in neurosurgery: a metaanalysis. Chest. 2008; 134(2): 237–249, doi: 10.1378/chest.08-0023, indexed in Pubmed: 18641095.
107. Hamilton MG, Yee WH, Hull RD, et al. Venous thromboembolism prophylaxis in patients undergoing cranial neurosurgery: a systematic review and meta-analysis. Neurosurgery. 2011; 68(3): 571–581, doi: 10.1227/NEU.0b013e3182093145, indexed in Pubmed: 21311292.
108. Brandes AA, Scelzi E, Salmistraro G, et al. Incidence of risk of thromboembolism during treatment high-grade gliomas: a prospective study. Eur J Cancer. 1997; 33(10): 1592–1596, doi: 10.1016/s0959-8049(97)00167-6, indexed in Pubmed: 9389920.
109. Marras LC, Geerts WH, Perry JR. The risk of venous thromboembolism is increased throughout the course of malignant glioma: an evidence-based review. Cancer. 2000; 89(3): 640–646, doi: 10.1002/1097-0142(20000801)89:3<640::aid-cncr20>3.0.co;2-e, indexed in Pubmed: 10931464.
110. Ruff RL, Posner JB. Incidence and treatment of peripheral venous thrombosis in patients with glioma. Ann Neurol. 1983; 13(3): 334–336, doi: 10.1002/ana.410130320, indexed in Pubmed: 6303201.
111. Walsh DC, Kakkar AK. Thromboembolism in brain tumors. Curr Opin Pulm Med. 2001; 7(5): 326–331, doi: 10.1097/00063198-200109000-00013, indexed in Pubmed: 11584184.
112. Semrad TJ, O'Donnell R, Wun T, et al. Epidemiology of venous thromboembolism in 9489 patients with malignant glioma. J Neurosurg. 2007; 106(4): 601–608, doi: 10.3171/jns.2007.106.4.601, indexed in Pubmed: 17432710.
113. Jenkins EO, Schiff D, Mackman N, et al. Venous thromboembolism in malignant gliomas. J Thromb Haemost. 2010; 8(2): 221–227, doi: 10.1111/j.1538-7836.2009.03690.x, indexed in Pubmed: 19912518.
114. Yust-Katz S, Mandel JJ, Wu J, et al. Venous thromboembolism (VTE) and glioblastoma. J Neurooncol. 2015; 124(1): 87–94, doi: 10.1007/s11060-015-1805-2, indexed in Pubmed: 25985958.
115. Chan AT, Atiemo A, Diran LK, et al. Venous thromboembolism occurs frequently in patients undergoing brain tumor surgery despite prophylaxis. J Thromb Thrombolysis. 1999; 8(2): 139–142, doi: 10.1023/a:1008915202859, indexed in Pubmed: 10436144.
116. Kimmell KT, Walter KA. Risk factors for venous thromboembolism in patients undergoing craniotomy for neoplastic disease. J Neurooncol. 2014; 120(3): 567–573, doi: 10.1007/s11060-014-1587-y, indexed in Pubmed: 25149164.
117. Turpie AG, Gallus A, Beattie WS, et al. Prevention of venous thrombosis in patients with intracranial disease by intermittent pneumatic compression of the calf. Neurology. 1977; 27(5): 435––438, doi: 10.1212/wnl.27.5.435, indexed in Pubmed: 558547.
118. Skillman JJ, Collins RE, Coe NP, et al. Prevention of deep vein thrombosis in neurosurgical patients: a controlled, randomized trial of external pneumatic compression boots. Surgery. 1978; 83(3): 354–358, indexed in Pubmed: 628896.
119. Bucci M, Papadopoulos S, Chen J, et al. Mechanical prophylaxis of venous thrombosis in patients undergoing craniotomy: A randomized trial. Surgical Neurology. 1989; 32(4): 285–288, doi: 10.1016/0090-3019(89)90231-0.
120. Agnelli G, Piovella F, Buoncristiani P, et al. Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. N Engl J Med. 1998; 339(2): 80–85, doi: 10.1056/NEJM199807093390204, indexed in Pubmed: 9654538.
121. Turpie AG, Hirsh J, Gent M, et al. Prevention of deep vein thrombosis in potential neurosurgical patients. A randomized trial comparing graduated compression stockings alone or graduated compression stockings plus intermittent pneumatic compression with control. Arch Intern Med. 1989; 149(3): 679–681, indexed in Pubmed: 2645846.
122. Wautrecht JC, Macquaire V, Vandesteene A et al (1996) Prevention of deep vein thrombosis in neurosurgical patients withbrain tumors: a controlled, randomized study comparing graded compression stockings alone and with intermittent sequential compression: correlation with pre- and post-operative fibrinolysis; preliminary results. Int Angiol; 15 (suppl 1): 5–10.
123. Sobieraj-Teague M, Hirsh J, Yip G, et al. Randomized controlled trial of a new portable calf compression device (Venowave) for prevention of venous thrombosis in high-risk neurosurgical patients. J Thromb Haemost. 2012; 10(2): 229–235, doi: 10.1111/j.1538-7836.2011.04598.x, indexed in Pubmed: 22188037.
124. Iorio A, Agnelli G. Low-molecular-weight and unfractionated heparin for prevention of venous thromboembolism in neurosurgery: a meta-analysis. Arch Intern Med. 2000; 160(15): 2327–2332, doi: 10.1001/archinte.160.15.2327, indexed in Pubmed: 10927730.
125. Khaldi A, Helo N, Schneck MJ, et al. Venous thromboembolism: deep venous thrombosis and pulmonary embolism in a neurosurgical population. J Neurosurg. 2011; 114(1): 40–46, doi: 10.3171/2010.8.JNS10332, indexed in Pubmed: 20815694.
126. Dickinson LD, Miller LD, Patel CP, et al. Enoxaparin increases the incidence of postoperative intracranial hemorrhage when initiated preoperatively for deep venous thrombosis prophylaxis in patients with brain tumors. Neurosurgery. 1998; 43(5): 1074–1081, doi: 10.1097/00006123-199811000-00039, indexed in Pubmed: 9802851.
127. Nurmohamed MT, van Riel AM, Henkens CM, et al. Low molecular weight heparin and compression stockings in the prevention of venous thromboembolism in neurosurgery. Thromb Haemost. 1996; 75(2): 233–238, indexed in Pubmed: 8815566.
128. Cerrato D, Ariano C, Fiacchino F. Deep vein thrombosis and low-dose heparin prophylaxis in neurosurgical patients. J Neu-

rosurg. 1978; 49(3): 378–381, doi: 10.3171/jns.1978.49.3.0378, indexed in Pubmed: 681999.
129. Constantini S, Kanner A, Friedman A, et al. Safety of perioperative minidose heparin in patients undergoing brain tumor surgery: a prospective, randomized, double-blind study. J Neurosurg. 2001; 94(6): 918–921, doi: 10.3171/jns.2001.94.6.0918, indexed in Pubmed: 11409520.
130. Goldhaber SZ, Dunn K, Gerhard-Herman M, et al. Low rate of venous thromboembolism after craniotomy for brain tumor using multimodality prophylaxis. Chest. 2002; 122(6): 1933–1937, doi: 10.1378/chest.122.6.1933, indexed in Pubmed: 12475829.
131. Macdonald RL, Amidei C, Baron J, et al. Randomized, pilot study of intermittent pneumatic compression devices plus dalteparin versus intermittent pneumatic compression devices plus heparin for prevention of venous thromboembolism in patients undergoing craniotomy. Surg Neurol. 2003; 59(5): 363–72; discussion 372, doi: 10.1016/s0090-3019(03)00111-3, indexed in Pubmed: 12765806.
132. Glotzbecker MP, Bono CM, Wood KB, et al. Thromboembolic disease in spinal surgery: a systematic review. Spine (Phila Pa 1976). 2009; 34(3): 291–303, doi: 10.1097/BRS.0b013e318195601d, indexed in Pubmed: 19179925.
133. Samama CM, Albaladejo P, Benhamou D, et al. Committee for Good Practice Standards of the French Society for Anaesthesiology and Intensive Care (SFAR). Venous thromboembolism prevention in surgery and obstetrics: clinical practice guidelines. Eur J Anaesthesiol. 2006; 23(2): 95–116, doi: 10.1017/S0265021505002164, indexed in Pubmed: 16438749.
134. Nicolaides AN, Fareed J, Kakkar AK, et al. Cardiovascular Disease Educational and Research Trust and the International Union of Angiology. Prevention of venous thromboembolism. International Consensus Statement. Guidelines compiled in accordance with the scientific evidence. Int Angiol. 2001; 20(1): 1–37, indexed in Pubmed: 11342993.
135. Streiff MB, Holmstrom B, Ashrani A, et al. Cancer-Associated Venous Thromboembolic Disease, Version 1.2015. J Natl Compr Canc Netw. 2015; 13(9): 1079–1095, doi: 10.6004/jnccn.2015.0133, indexed in Pubmed: 26358792.
136. Forrest JB, Clemens JQ, Finamore P, et al. American Urological Association. AUA Best Practice Statement for the prevention of deep vein thrombosis in patients undergoing urologic surgery. J Urol. 2009; 181(3): 1170–1177, doi: 10.1016/j.juro.2008.12.027, indexed in Pubmed: 19152926.
137. Colby FH. The prevention of fatal pulmonary emboli after prostatectomy. J Urol. 1948; 59(5): 920–4; Disc., 925, doi: 10.1016/s0022-5347(17)69460-6, indexed in Pubmed: 18913855.
138. Gordon-Smith IC, Hickman JA, el-Masri SH. The efect of the fibrinolytic inhibitor epsilonaminocaproic amid on the incidence of deep-vein thrombosis after prostatectomy. Br J Surg. 1972; 59: 599.
139. Nicolaides AN, Field ES, Kakkar VV, et al. Prostatectomy and deep-vein thrombosis. Br J Surg. 1972; 59(6): 487–488, doi: 10.1002/bjs.1800590620, indexed in Pubmed: 5031195.
140. Thomas PJ, Nurse DE, Deliveliotis C, et al. Cystoprostatectomy and substitution cystoplasty for locally invasive bladder cancer. Br J Urol. 1992; 70(1): 40–42, doi: 10.1111/j.1464-410x.1992.tb15661.x, indexed in Pubmed: 1638373.
141. Alberts BD, Woldu SL, Weinberg AC, et al. Venous thromboembolism after major urologic oncology surgery: a focus on the incidence and timing of thromboembolic events after 27,455 operations. Urology. 2014; 84(4): 799–806, doi: 10.1016/j.urology.2014.05.055, indexed in Pubmed: 25156513.
142. Potretzke AM, Wong KS, Shi F, et al. Highest risk of symptomatic venous thromboembolic events after radical cystectomy occurs in patients with obesity or nonurothelial cancers. Urol Ann. 2015; 7(3): 355–360, doi: 10.4103/0974-7796.152050, indexed in Pubmed: 26229325.
143. VanDlac AA, Cowan NG, Chen Y, et al. Timing, incidence and risk factors for venous thromboembolism in patients undergoing radical cystectomy for malignancy: a case for extended duration pharmacological prophylaxis. J Urol. 2014; 191(4): 943–947, doi: 10.1016/j.juro.2013.10.096, indexed in Pubmed: 24184368.
144. Rosario DJ, Becker M, Anderson JB. The changing pattern of mortality and morbidity from radical cystectomy. BJU Int. 2000; 85(4): 427–430, doi: 10.1046/j.1464-410x.2000.00454.x, indexed in Pubmed: 10691819.
145. James AC, Holt SK, Wright JL, et al. Burden and timing of venothrombolic events in patients younger than 65 years undergoing radical cystectomy for bladder cancer. Urol Oncol. 2014; 32(6): 815–819, doi: 10.1016/j.urolonc.2014.02.016, indexed in Pubmed: 24837010.
146. White RH, Zhou H, Gage BF, et al. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. Thromb Haemost. 2003; 90(3): 446–455, doi: 10.1160/TH03-03-0152, indexed in Pubmed: 12958614.
147. Heinzer H, Hammerer P, Graefen M, et al. Thromboembolic complication rate after radical retropubic prostatectomy. Impact of routine ultrasonography for the detection of pelvic lymphoceles and hematomas. Eur Urol. 1998; 33(1): 86–90, doi: 10.1159/000019516, indexed in Pubmed: 9471046.
148. Leibovitch I, Foster R, Wass J, et al. Color Doppler Flow Imaging For Deep Venous Thrombosis Screening in Patients Undergoing Pelvic Lymphadenectomy and Radical Retropubic Prostatectomy for Prostatic Carcinoma. The Journal of Urology. 1995: 1866–1869, doi: 10.1097/00005392-199506000-00034.
149. Hautmann RE, Sauter TW, Wenderoth UK. Radical retropubic prostatectomy: Morbidity and urinary continence in 418 consecutive cases. Urology. 1994; 43: 47–51, doi: 10.1016/0090-4295(94)90218-6.
150. Leandri P, Rossignol G, Gautier JR, et al. Radical retropubic prostatectomy: morbidity and quality of life. Experience with 620 consecutive cases. J Urol. 1992; 147(3 Pt 2): 883–887, doi: 10.1016/s0022-5347(17)37412-8, indexed in Pubmed: 1538489.
151. Pedersen K, Herder A. Radical Retropubic Prostatectomy for Localised Prostatic Carcinoma: A Clinical and Pathological Study of 201 Cases. Scand J Urol Nephrol. 1993; 27(2): 219–224, doi: 10.3109/00365599309181253.
152. Shekarriz B, Upadhyay J, Wood DP. Intraoperative, perioperative, and long-term complications of radical prostatectomy. Urol Clin North Am. 2001; 28(3): 639–643, doi: 10.1016/s0094-0143(05)70168-3, indexed in Pubmed: 11590819.
153. Andriole GL, Smith DS, Rao G, et al. Early complications of contemporary anatomical radical retropubic prostatectomy. J Urol. 1994; 152(5 Pt 2): 1858–1860, doi: 10.1016/s0022-5347(17)32400-x, indexed in Pubmed: 7933241.
154. Dillioglugil O, Leibman BD, Leibman NS, et al. Risk factors for complications and morbidity after radical retropubic prostatectomy. J Urol. 1997; 157(5): 1760–1767, indexed in Pubmed: 9112522.
155. Lerner SE, Blute ML, Lieber MM, et al. Morbidity of contemporary radical retropubic prostatectomy for localized prostate

cancer. Oncology (Williston Park). 1995; 9(5): 379–82; discussion 382, 385, indexed in Pubmed: 7547200.
156. Catalona WJ, Carvalhal GF, Mager DE, et al. Potency, continence and complication rates in 1,870 consecutive radical retropubic prostatectomies. J Urol. 1999; 162(2): 433–438, indexed in Pubmed: 10411052.
157. Hammond J, Kozma C, Hart JC, et al. Rates of venous thromboembolism among patients with major surgery for cancer. Ann Surg Oncol. 2011; 18(12): 3240–3247, doi: 10.1245/s10434-011-1723-2, indexed in Pubmed: 21584837.
158. Beyer J, Wessela S, Hakenberg OW, et al. Incidence, risk profile and morphological pattern of venous thromboembolism after prostate cancer surgery. J Thromb Haemost. 2009; 7(4): 597–604, doi: 10.1111/j.1538-7836.2009.03275.x, indexed in Pubmed: 19143928.
159. Chan SYS, Leung VFY, Yee CH, et al. Incidence of postoperative deep vein thrombosis after robotic-assisted laparoscopic prostatectomy: a prospective study in Chinese patients. Int Urol Nephrol. 2014; 46(11): 2139–2142, doi: 10.1007/s11255-014-0781-3, indexed in Pubmed: 25011633.
160. Streiff MB, Bockenstedt PL, Cataland SR, et al. National comprehensive cancer network. Venous thromboembolic disease. J Natl Compr Canc Netw. 2013; 11(11): 1402–1429, doi: 10.6004/jnccn.2013.0163, indexed in Pubmed: 24225973.
161. Pettus JA, Eggener SE, Shabsigh A, et al. Perioperative clinical thromboembolic events after radical or partial nephrectomy. Urology. 2006; 68(5): 988–992, doi: 10.1016/j.urology.2006.06.026, indexed in Pubmed: 17113889.
162. Smith AB, Horvath-Puhó E, Nielsen ME, et al. Effect of comorbidity on risk of venous thromboembolism in patients with renal cell carcinoma. Urol Oncol. 2014; 32(4): 466–472, doi: 10.1016/j.urolonc.2013.07.008, indexed in Pubmed: 24767684.
163. Ihaddadene R, Yokom DW, Le Gal G, et al. The risk of venous thromboembolism in renal cell carcinoma patients with residual tumor thrombus. J Thromb Haemost. 2014; 12(6): 855–859, doi: 10.1111/jth.12580, indexed in Pubmed: 24702743.
164. Yokom DW, Ihaddadene R, Moretto P, et al. Increased risk of preoperative venous thromboembolism in patients with renal cell carcinoma and tumor thrombus. J Thromb Haemost. 2014; 12(2): 169–171, doi: 10.1111/jth.12459, indexed in Pubmed: 24283651.
165. Kavoussi L, Sosa E, Chandhoke P, et al. Complications of Laparoscopic Pelvic Lymph Node Dissection. Journal of Urology. 1993; 149(2): 322–325, doi: 10.1016/s0022-5347(17)36069-x.
166. Caddedu JA, Wolf JS, Nakada S. Complications of laparoscopic procedures after concentrated training in urological laparoscopy. J Urol. 2001; 166: 2109–2111.
167. Fahlenkamp D, Rassweiler J, Fornara P, et al. Complications of laparoscopic procedures in urology: experience with 2,407 procedures at 4 German centers. J Urol. 1999; 162(3 Pt 1): 765–70; discussion 770, doi: 10.1097/00005392-199909010-00038, indexed in Pubmed: 10458362.
168. Rassweiler JJ, Seemann O, Frede T, et al. Retroperitoneoscopy: experience with 200 cases. J Urol. 1998; 160(4): 1265–1269, doi: 10.1016/s0022-5347(01)62512-6, indexed in Pubmed: 9751332.
169. Trabulsi EJ, Guillonneau B, Touijer K, et al. Laparoscopic radical prostatectomy: a review of techniques and results worldwide. Minerva Urol Nefrol. 2003; 55(4): 239–250, indexed in Pubmed: 14765016.
170. Montgomery JS, Wolf JS. Venous thrombosis prophylaxis for urological laparoscopy: fractionated heparin versus sequential compression devices. J Urol. 2005; 173(5): 1623–1626, doi: 10.1097/01.ju.0000154635.22551.23, indexed in Pubmed: 15821517.
171. Permpongkosol S, Link RE, Su LM, et al. Complications of 2,775 urological laparoscopic procedures: 1993 to 2005. J Urol. 2007; 177(2): 580–585, doi: 10.1016/j.juro.2006.09.031, indexed in Pubmed: 17222637.
172. Secin FP, Jiborn T, Bjartell AS, et al. Multi-institutional study of symptomatic deep venous thrombosis and pulmonary embolism in prostate cancer patients undergoing laparoscopic or robot-assisted laparoscopic radical prostatectomy. Eur Urol. 2008; 53(1): 134–145, doi: 10.1016/j.eururo.2007.05.028, indexed in Pubmed: 17597288.
173. Chalmers D, Scarpato K, Staff I, et al. Does Heparin Prophylaxis Reduce the Risk of Venous Thromboembolism in Patients Undergoing Robot-Assisted Prostatectomy? Journal of Endourology. 2013; 27(6): 800–803, doi: 10.1089/end.2012.0532.
174. Patel T, Kirby W, Hruby G, et al. Heparin prophylaxis and the risk of venous thromboembolism after robotic-assisted laparoscopic prostatectomy. BJU Int. 2011; 108(5): 729–732, doi: 10.1111/j.1464-410X.2010.09910.x, indexed in Pubmed: 21231988.
175. Abel EJ, Wong K, Sado M, et al. Surgical operative time increases the risk of deep venous thrombosis and pulmonary embolism in robotic prostatectomy. JSLS. 2014; 18(2): 282–287, doi: 10.4293/108680813X13693422518551, indexed in Pubmed: 24960494.
176. Donat R, Mancey-Jones B. Incidence of thromboembolism after transurethral resection of the prostate (TURP)--a study on TED stocking prophylaxis and literature review. Scand J Urol Nephrol. 2002; 36(2): 119–123, doi: 10.1080/003655902753679409, indexed in Pubmed: 12028685.
177. Kibel A, Loughlin K. Pathogenesis and Prophylaxis of Postoperative Thromboembolic Disease in Urological Pelvic Surgery. The Journal of Urology. 1995: 1763–1774, doi: 10.1097/00005392-199506000-00003.
178. Tikkinen KAO, Agarwal A, Craigie S, et al. Systematic reviews of observational studies of risk of thrombosis and bleeding in urological surgery (ROTBUS): introduction and methodology. Syst Rev. 2014; 3: 150, doi: 10.1186/2046-4053-3-150, indexed in Pubmed: 25540016.
179. Kutnowski M, Vandendris M, Steinberger R, et al. Prevention of postoperative deep-vein thrombosis by low-dose heparin in urological surgery. A double-blind, randomised study. Urol Res. 1977; 5(3): 123–125, doi: 10.1007/BF00256865, indexed in Pubmed: 919112.
180. Sebeseri O, Kummer H, Zingg E. Controlled prevention of post-operative thrombosis in urological diseases with depot heparin. Eur Urol. 1975; 1(5): 229–230, indexed in Pubmed: 1233188.
181. Bigg SW, Catalona WJ. Prophylactic mini-dose heparin in patients undergoing radical retropubic prostatectomy. A prospective trial. Urology. 1992; 39(4): 309–313, doi: 10.1016/0090-4295(92)90203-9, indexed in Pubmed: 1557840.
182. Vandendris M, Kutnowski M, Futeral B, et al. Prevention of postoperative deep-vein thrombosis by low-dose heparin in open prostatectomy. Urol Res. 1980; 8(4): 219–221, doi: 10.1007/BF00256997, indexed in Pubmed: 7013228.
183. Collins R, Scrimgeour A, Yusuf S, et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic sur-

gery. N Engl J Med. 1988; 318(18): 1162–1173, doi: 10.1056/NEJM198805053181805, indexed in Pubmed: 3283548.
184. Nakamura K, Kasraeian A, Yacoub S, et al. The use of enoxaparin to prevent venous thromboembolism in patients undergoing radical retropubic prostatectomy: feasibility and utility. Int Braz J Urol. 2007; 33(3): 347–52; discussion 352, doi: 10.1590/s1677-55382007000300007, indexed in Pubmed: 17626651.
185. Grasso M, Confalonieri S, Blanco S, et al. Preoperative blood donation program and postoperative low molecular weight heparine (LMWH) prophylaxis in patients undergoing radical prostatectomy. Arch Esp Urol. 2009; 62(2): 161–166, doi: 10.4321/s0004-06142009000200017, indexed in Pubmed: 19459250.
186. Donat R, Mancey-Jones B. Incidence of thromboembolism after transurethral resection of the prostate (TURP)--a study on TED stocking prophylaxis and literature review. Scand J Urol Nephrol. 2002; 36(2): 119–123, doi: 10.1080/003655902753679409, indexed in Pubmed: 12028685.
187. Scarpa RM, Carrieri G, Gussoni G, et al. @RISTOS Study Group. Clinically overt venous thromboembolism after urologic cancer surgery: results from the @RISTOS Study. Eur Urol. 2007; 51(1): 130–5; discussion 136, doi: 10.1016/j.eururo.2006.07.014, indexed in Pubmed: 16942832.
188. Cerruto MA, D'Elia C, Piccoli M, et al. Association between postoperative thromboembolism prophylaxis and complications following urological surgery. Exp Ther Med. 2016; 11(1): 157–163, doi: 10.3892/etm.2015.2845, indexed in Pubmed: 26889233.
189. Coe NP, Collins RE, Klein LA, et al. Prevention of deep vein thrombosis in urological patients: a controlled, randomized trial of low-dose heparin and external pneumatic compression boots. Surgery. 1978; 83(2): 230–234, indexed in Pubmed: 622696.
190. Koya MP, Manoharan M, Kim SS, et al. Venous thromboembolism in radical prostatectomy: is heparinoid prophylaxis warranted? BJU Int. 2005; 96(7): 1019–1021, doi: 10.1111/j.1464-410X.2005.05783.x, indexed in Pubmed: 16225520.
191. Cisek LJ, Walsh PC. Thromboembolic complications following radical retropubic prostatectomy. Influence of external sequential pneumatic compression devices. Urology. 1993; 42(4): 406–408, doi: 10.1016/0090-4295(93)90369-l, indexed in Pubmed: 8212439.
192. Prandoni P. How I treat venous thromboembolism in patients with cancer. Blood. 2005; 106(13): 4027–4033, doi: 10.1182/blood-2005-04-1508, indexed in Pubmed: 16076870.
193. Prandoni P, Lensing AWA, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood. 2002; 100(10): 3484–3488, doi: 10.1182/blood-2002-01-0108, indexed in Pubmed: 12393647.
194. Wojtukiewicz MZ, Sierko E, Tomkowski W. Guidelines for the prevention and treatment of venous thromboembolism in patients with cancers treated conservatively. Oncol Clin Pract. 2016; 12: 67–91.
195. Kearon C. A conceptual framework for two phases of anticoagulant treatment of venous thromboembolism. J Thromb Haemost. 2012; 10(4): 507–511, doi: 10.1111/j.1538-7836.2012.04629.x, indexed in Pubmed: 22497864.
196. Streiff MB, Agnelli G, Connors JM, et al. Guidance for the treatment of deep vein thrombosis and pulmonary embolism. J Thromb Thrombolysis. 2016; 41(1): 32–67, doi: 10.1007/s11239-015-1317-0, indexed in Pubmed: 26780738.
197. Lee AYY, Levine MN, Baker RI, et al. Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003; 349(2): 146–153, doi: 10.1056/NEJMoa025313, indexed in Pubmed: 12853587.
198. Deitcher SR, Kessler CM, Merli G, et al. ONCENOX Investigators. Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. Clin Appl Thromb Hemost. 2006; 12(4): 389–396, doi: 10.1177/1076029606293692, indexed in Pubmed: 17000884.
199. Lee AYY, Kamphuisen PW, Meyer G, et al. CATCH Investigators. Tinzaparin vs Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer: A Randomized Clinical Trial. JAMA. 2015; 314(7): 677–686, doi: 10.1001/jama.2015.9243, indexed in Pubmed: 26284719.
200. Agnelli G, Verso M, Ageno W, et al. MASTER investigators. The MASTER registry on venous thromboembolism: description of the study cohort. Thromb Res. 2008; 121(5): 605–610, doi: 10.1016/j.thromres.2007.06.009, indexed in Pubmed: 17692901.
201. Hull RD, Pineo GF, Brant RF, et al. LITE Trial Investigators. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. Am J Med. 2006; 119(12): 1062–1072, doi: 10.1016/j.amjmed.2006.02.022, indexed in Pubmed: 17145251.
202. Meyer G, Marjanovic Z, Valcke J, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Arch Intern Med. 2002; 162(15): 1729–1735, doi: 10.1001/archinte.162.15.1729, indexed in Pubmed: 12153376.
203. Romera A, Cairols MA, Vila-Coll R, et al. A Randomised Open-Label Trial Comparing Long-term Sub-Cutaneous Low-Molecular-weight Heparin Compared with Oral-Anticoagulant Therapy in the Treatment of Deep Venous Thrombosis. Journal of Vascular Surgery. 2009; 49(3): 815, doi: 10.1016/j.jvs.2009.01.054.
204. Laporte S, Bertoletti L, Romera A, et al. Long-term treatment of venous thromboembolism with tinzaparin compared to vitamin K antagonists: a meta-analysis of 5 randomized trials in non-cancer and cancer patients. Thromb Res. 2012; 130(6): 853–858, doi: 10.1016/j.thromres.2012.08.290, indexed in Pubmed: 22939430.
205. Francis CW, Kessler CM, Goldhaber SZ, et al. Treatment of venous thromboembolism in cancer patients with dalteparin for up to 12 months: the DALTECAN Study. J Thromb Haemost. 2015; 13(6): 1028–1035, doi: 10.1111/jth.12923, indexed in Pubmed: 25827941.
206. Krasiński Z, Krasińska B. Commentary on the DALTECAN study. Pol Arch Med Wewn. 2016; 126(3): 204–206, doi: 10.20452/pamw.3306, indexed in Pubmed: 26907606.
207. Pini M, Aiello S, Manotti C, et al. Low Molecular Weight Heparin versus Warfarin in the Prevention of Recurrences after Deep Vein Thrombosis. Thrombosis and Haemostasis. 2018; 72(02): 191–197, doi: 10.1055/s-0038-1648837.
208. López-Beret P, Orgaz A, Fontcuberta J, et al. Low molecular weight heparin versus oral anticoagulants in the long-term

treatment of deep venous thrombosis. J Vasc Surg. 2001; 33(1): 77–90, doi: 10.1067/mva.2001.109336, indexed in Pubmed: 11137927.
209. Lensing AW, Prins MH, Davidson BL, Hirsh J. Treatment of deep venous thrombosis with low-molecular-weight heparins, a metaanalysis. Arch Intern Med 1995; 155: 601–607.
210. Siragusa S, Cosmi B, Piovella F, et al. Low-molecular-weight heparins and unfractionated heparin in the treatment of patients with acute venous thromboembolism: results of a meta-analysis. Am J Med. 1996; 100(3): 269–277, doi: 10.1016/S0002-9343(97)89484-3, indexed in Pubmed: 8629671.
211. Hettiarachchi R, Prins M, Lensing A, Buller HR. Low molecular weight heparin versus unfractionated heparin in the initial treatment of venous thromboembolism. Curr Opin Pulm Med 1998; 4: 220–225.
212. Gould MK, Dembitzer AD, Doyle RL, et al. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A meta-analysis of randomized, controlled trials. Ann Intern Med. 1999; 130(10): 800–809, doi: 10.7326/0003-4819-130-10-199905180-00003, indexed in Pubmed: 10366369.
213. Dolovich LR, Ginsberg JS, Douketis JD, et al. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. Arch Intern Med. 2000; 160(2): 181–188, doi: 10.1001/archinte.160.2.181, indexed in Pubmed: 10647756.
214. Rocha E, Martínez-González MA, Montes R, et al. Do the low molecular weight heparins improve efficacy and safety of the treatment of deep venous thrombosis? A meta-analysis. Haematologica. 2000; 85(9): 935–942, indexed in Pubmed: 10980632.
215. Quinlan DJ, McQuillan A, Eikelboom JW. Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: a meta-analysis of randomized, controlled trials. Ann Intern Med. 2004; 140(3): 175–183, doi: 10.7326/0003-4819-140-3-200402030-00008, indexed in Pubmed: 14757615.
216. Büller HR, Davidson BL, Decousus H, et al. Matisse Investigators. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. Ann Intern Med. 2004; 140(11): 867–873, doi: 10.7326/0003-4819-140-11-200406010-00007, indexed in Pubmed: 15172900.
217. Hakoum MB, Kahale LA, Tsolakian IG, et al. Anticoagulation for the initial treatment of venous thromboembolism in people with cancer. Cochrane Database Syst Rev. 2018; 1: CD006649, doi: 10.1002/14651858.CD006649.pub7, indexed in Pubmed: 29363105.
218. Carrier M, Cameron C, Delluc A, et al. Efficacy and safety of anticoagulant therapy for the treatment of acute cancer-associated thrombosis: a systematic review and meta-analysis. Thromb Res. 2014; 134(6): 1214–1219, doi: 10.1016/j.thromres.2014.09.039, indexed in Pubmed: 25457583.
219. Raskob GE, van Es N, Verhamme P. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med. 2018; 378(7): 615–624.
220. 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, indexed in Pubmed: 29746227.
221. McBane RD, Wysokinski WE, Le-Rademacher JG, et al. Apixaban and dalteparin in active malignancy associated venous thromboembolism. The ADAM VTE Trial. Thromb Haemost. 2017; 117(10): 1952–1961, doi: 10.1160/TH17-03-0193, indexed in Pubmed: 28837207.
222. Agnelli G, Becattini C, Bauersachs R, et al. Caravaggio Study Investigators. Apixaban versus Dalteparin for the Treatment of Acute Venous Thromboembolism in Patients with Cancer: The Caravaggio Study. Thromb Haemost. 2018; 118(9): 1668–1678, doi: 10.1055/s-0038-1668523, indexed in Pubmed: 30103252.
223. Bellesoeur A, Thomas-Schoemann A, Allard M, et al: Pharmacokinetic variability of anticoagulants in patients with cancer-associated thrombosis: Clinical consequences. Crit Rev Oncol Hematol 2018; 129: 102–112.
224. Momin W, Goble J, Thotakura S, et al. 5742 Increased bleeding events in patients co-administered rivaroxaban and either cyp3A4 or p-gp inhibitors. Eur Heart J. 2017; 38(suppl_1), doi: 10.1093/eurheartj/ehx493.5742.
225. Steffel J, Collins R, Antz M. et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace. 2021: euab065. doi: 10.1093/europace/euab065. Epub ahead of print. Erratum in: Europace. 2021 Jun 28;: PMID: 33895845).
226. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2017; 35(28): 3240–3261, doi: 10.1200/JCO.2017.74.4789, indexed in Pubmed: 28759346.
227. Riess H, Ay C, Bauersachs R et al. Use of Direct Oral Anticoagulants in Patients with Cancer: Practical Considerations for the Management of Patients with Nausea or Vomiting. Oncologist. 2018; 23(7): 822-839. doi:10.1634/theoncologist.2017-0473.
228. Mantha S, Laube E, Miao Y, et al. Safe and effective use of rivaroxaban for treatment of cancer-associated venous thromboembolic disease: a prospective cohort study. J Thromb Thrombolysis. 2017; 43(2): 166–171, doi: 10.1007/s11239-016-1429-1, indexed in Pubmed: 27696084.
229. Enden T, Haig Y, Kløw NE, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. The Lancet. 2012; 379(9810): 31–38, doi: 10.1016/s0140-6736(11)61753-4.
230. Kim HS, Preece SR, Black JH, et al. Safety of catheter-directed thrombolysis for deep venous thrombosis in cancer patients. J Vasc Surg. 2008; 47(2): 388–394, doi: 10.1016/j.jvs.2007.10.033, indexed in Pubmed: 18241762.
231. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. JAMA. 2014; 311(23): 2414–2421, doi: 10.1001/jama.2014.5990, indexed in Pubmed: 24938564.
232. Mismetti P, Laporte S, Pellerin O. Effect of a Retrievable Inferior Vena Cava Filter Plus Anticoagulation vs Anticoagulation Alone on Risk of Recurrent Pulmonary Embolism: A Randomized Clinical Trial. Journal of Vascular Surgery. 2016; 63(1): 280, doi: 10.1016/j.jvs.2015.11.006.
233. 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(7): CD006650, doi: 10.1002/14651858.CD006650.pub4, indexed in Pubmed: 25004410.
234. Louzada ML, Majeed H, Wells PS. Efficacy of low- molecular-weight- heparin versus vitamin K antagonists for long term treatment of cancer-associated venous thromboembolism in adults: a systematic review of randomized controlled trials. Thromb Res. 2009; 123(6): 837–844, doi: 10.1016/j.thromres.2008.09.002, indexed in Pubmed: 18977517.
235. Ferretti G, Bria E, Giannarelli D, et al. Is recurrent venous thromboembolism after therapy reduced by low-molecular-weight heparin compared with oral anticoagulants? Chest. 2006; 130(6): 1808–1816, doi: 10.1378/chest.130.6.1808, indexed in Pubmed: 17167001.
236. Brunetti ND, Gesuete E, De Gennaro L, et al. Direct oral anti-coagulants compared with vitamin-K inhibitors and low-molecular-weight-heparin for the prevention of venous thromboembolism in patients with cancer: A meta-analysis study. Int J Cardiol. 2017; 230: 214–221, doi: 10.1016/j.ijcard.2016.12.168, indexed in Pubmed: 28062137.
237. Posch F, Königsbrügge O, Zielinski C, et al. Treatment of venous thromboembolism in patients with cancer: A network meta-analysis comparing efficacy and safety of anticoagulants. Thromb Res. 2015; 136(3): 582–589, doi: 10.1016/j.thromres.2015.07.011, indexed in Pubmed: 26210891.
238. Gómez-Outes A, Terleira-Fernández AI, Lecumberri R, et al. Direct oral anticoagulants in the treatment of acute venous thromboembolism: a systematic review and meta-analysis. Thromb Res. 2014; 134(4): 774–782, doi: 10.1016/j.thromres.2014.06.020, indexed in Pubmed: 25037495.
239. Kahale LA, Hakoum MB, Tsolakian IG. Non-vitamin K antagonist oral anticoagulants and the treatment of venous thromboembolism in cancer patients: a semi systematic review and meta-analysis of safety and efficacy outcomes. Cochrane Database Syst Rev. 2018; 6: CD006650.
240. Larsen TB, Nielsen PB, Skjøth F, et al. Non-vitamin K antagonist oral anticoagulants and the treatment of venous thromboembolism in cancer patients: a semi systematic review and meta-analysis of safety and efficacy outcomes. PLoS One. 2014; 9(12): e114445, doi: 10.1371/journal.pone.0114445, indexed in Pubmed: 25479007.
241. Prins MH, Lensing AWA, Brighton TA, et al. Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials. Lancet Haematol. 2014; 1(1): e37–e46, doi: 10.1016/S2352-3026(14)70018-3, indexed in Pubmed: 27030066.
242. 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(12): 1968–1975, doi: 10.1182/blood-2014-04-571232, indexed in Pubmed: 24963045.
243. Vedovati MC, Germini F, Agnelli G, et al. Direct oral anticoagulants in patients with VTE and cancer: a systematic review and meta-analysis. Chest. 2015; 147(2): 475–483, doi: 10.1378/chest.14-0402, indexed in Pubmed: 25211264.
244. Napolitano M, Saccullo G, Malato A, et al. Optimal Duration of Low Molecular Weight Heparin for the Treatment of Cancer-Related Deep Vein Thrombosis: The Cancer-DACUS Study. Journal of Clinical Oncology. 2014; 32(32): 3607–3612, doi: 10.1200/jco.2013.51.7433.
245. Farge D, Trujillo-Santos J, Debourdeau P, et al. RIETE Investigators.. Fatal Events in Cancer Patients Receiving Anticoagulant Therapy for Venous Thromboembolism. Medicine (Baltimore). 2015; 94(32): e1235, doi: 10.1097/MD.0000000000001235, indexed in Pubmed: 26266353.
246. Schulman S, Zondag M, Linkins L, et al. Recurrent venous thromboembolism in anticoagulated patients with cancer: management and short-term prognosis. J Thromb Haemost. 2015; 13(6): 1010–1018, doi: 10.1111/jth.12955, indexed in Pubmed: 25851122.
247. Jara-Palomares L, Solier-Lopez A, Elias-Hernandez T, et al. Tinzaparin in cancer associated thrombosis beyond 6months: TiCAT study. Thromb Res. 2017; 157: 90–96, doi: 10.1016/j.thromres.2017.07.004, indexed in Pubmed: 28719850.
248. Brighton TA, Eikelboom JW, Mann K, et al. ASPIRE Investigators. Low-dose aspirin for preventing recurrent venous thromboembolism. N Engl J Med. 2012; 367(21): 1979–1987, doi: 10.1056/NEJMoa1210384, indexed in Pubmed: 23121403.
249. Becattini C, Agnelli G, Schenone A, et al. WARFASA Investigators. Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med. 2012; 366(21): 1959–1967, doi: 10.1056/NEJMoa1114238, indexed in Pubmed: 22621626.
250. Gervaso L, Dave H, Khorana A. Venous and Arterial Thromboembolism in Patients With Cancer. JACC: CardioOncology. 2021, doi: 10.1016/j.jaccao.2021.03.001.
251. Bikdeli B, Chatterjee S, Kirtane AJ, et al. Sulodexide versus Control and the Risk of Thrombotic and Hemorrhagic Events: Meta-Analysis of Randomized Trials. Semin Thromb Hemost. 2020; 46(8): 908–918, doi: 10.1055/s-0040-1716874, indexed in Pubmed: 33086402.
252. Mannello F, Medda V, Ligi D, et al. Glycosaminoglycan sulodexide inhibition of MMP-9 gelatinase secretion and activity: possible pharmacological role against collagen degradation in vascular chronic diseases. Curr Vasc Pharmacol. 2013; 11(3): 354–365, doi: 10.2174/15701611113110300010, indexed in Pubmed: 22724470.
253. Mannello F, Raffetto JD. Matrix metalloproteinase activity and glycosaminoglycans in chronic venous disease: the linkage among cell biology, pathology and translational research. Am J Transl Res. 2011; 3(2): 149–158, indexed in Pubmed: 21416057.
254. Mattana P, Mannello F, Ferrari P, et al. Vascular pathologies and inflamma-tion: The anti-inflammatory properties of sulodexide. Italian Journal of Vascular and Endovascular Surgery. 2012; 19: 1–7.
255. Połubińska A, Staniszewski R, Baum E, et al. Sulodexide modifies intravascular homeostasis what affects function of the endothelium. Adv Med Sci. 2013; 58(2): 304–310, doi: 10.2478/ams-2013-0016, indexed in Pubmed: 24421218.
256. Sosińska P, Baum E, Maćkowiak B, et al. Sulodexide Reduces the Proinflammatory Effect of Serum from Patients with Peripheral Artery Disease in Human Arterial Endothelial Cells. Cell Physiol Biochem. 2016; 40(5): 1005–1012, doi: 10.1159/000453157, indexed in Pubmed: 27941341.
257. Suminska-Jasinska K, Polubinska A, Ciszewicz M, et al. Sulodexide reduces senescence-related changes in human endothelial cells. Med Sci Monit. 2011; 17(4): CR222–CR226, doi: 10.12659/msm.881719, indexed in Pubmed: 21455109.
258. Bręborowicz A. Sulodexide — mixture of glycosaminoglycans with the pro-tective effect towards the vascular endothelium. Acta Angiologica. 2014; 20(3): 112–8.
259. Konstantinides SV, Meyer G, Becattini C, et al. The Task Force for the diagnosis and management of acute pulmonary embo-

lism of the European Society of Cardiology (ESC). 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J. 2019; 54(3), doi: 10.1183/13993003.01647-2019, indexed in Pubmed: 31473594.
260. Tomkowski W, Kuca P, Urbanek T, et al. Żylna choroba zakrzepowo-zatorowa — wytyczne profilaktyki, diagnostyki i terapii. Konsensus Polski 2017. Acta Angiologica. 2017; 23(2): 73–113.
261. Andreozzi GM, Bignamini AA, Davi G. Sulodexide for the Prevention of Recurrent Venous Thromboembolism: The Sulodexide in Secondary Prevention of Recurrent Deep Vein Thrombosis (SURVET) Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2016; 4(4): 536, doi: 10.1016/j.jvsv.2016.06.012.
262. Male C, Lensing A, Palumbo J, et al. Rivaroxaban compared with standard anticoagulants for the treatment of acute ve-nous thromboembolism in children: a randomised, controlled, phase 3 trial. Lancet Haematol. 2020; 7(1): e18–e27.
263. Brandão L, Albisetti M, Halton J, et al. Safety of dabigatran etexilate for the secondary prevention of venous thromboembolism in children. Blood. 2020; 135(7): 491–504, doi: 10.1182/blood.2019000998.
264. Branstetter JW, Kiskaddon AL, King MA, et al. Efficacy and Safety of Non-Vitamin K Antagonist Oral Anticoagulants in Pediatric Venous Thromboembolism Treatment and Thromboprophylaxis: A Systematic Review of the Literature. Semin Thromb Hemost. 2021 [Epub ahead of print], doi: 10.1055/s-0041-1725944, indexed in Pubmed: 33971679.
265. https://www.ema.europa.eu/en/documents/product-information/xarelto-epar-product-information_en.pdf.
266. https://www.ema.europa.eu/en/documents/product-information/pradaxa-epar-product-information_en.pdf.
267. Cortelazzo S, Marchetti M, Orlando E, et al. Aspirin increases the bleeding side effects in essential thrombocythemia independent of the cyclooxygenase pathway: role of the lipoxygenase pathway. Am J Hematol. 1998; 57(4): 277–282, doi: 10.1002/(sici)1096-8652(199804)57:4<277::aid-ajh2>3.0.co;2-r, indexed in Pubmed: 9544970.
268. Witmer C, Raffini L. Treatment of venous thromboembolism in pediatric patients. Blood. 2020; 135(5): 335–343.
269. Bosch A, Albisetti M. Management of Venous Thromboembolism in Chil-dren: Current Recommendations and Therapeutic Options. Ther Clin Risk Manag. 2020; 16(673): 679.
270. Monagle P, Chan AKC, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2 Suppl): e737S–e801S, doi: 10.1378/chest.11-2308, indexed in Pubmed: 22315277.
271. Monagle P, Cuello CA, Augustine C, et al. American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. Blood Adv. 2018; 2(22): 3292–3316, doi: 10.1182/bloodadvances.2018024786, indexed in Pubmed: 30482766.
272. Smitherman AB, Alexander T, Connelly M, et al. The incidence of catheter-associated venous thrombosis in noncritically ill children. Hosp Pediatr. 2015; 5(2): 59–66, doi: 10.1542/hpeds.2014-0041, indexed in Pubmed: 25646197.
273. Kanin M, Young G. Incidence of thrombosis in children with tunneled central venous access devices versus peripherally inserted central catheters (PICCs). Thromb Res. 2013; 132(5): 527–530, doi: 10.1016/j.thromres.2013.08.018, indexed in Pubmed: 24055175.
274. International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med. 1993; 329(14): 987–994, doi: 10.1056/NEJM199309303291402, indexed in Pubmed: 8141877.
275. Connor P, Sánchez van Kammen M, Lensing AWA, et al. Safety and efficacy of rivaroxaban in pediatric cerebral venous thrombosis (EINSTEIN-Jr CVT). Blood Adv. 2020; 4(24): 6250–6258, doi: 10.1182/bloodadvances.2020003244, indexed in Pubmed: 33351120.
276. Carrier M, Wang TF. Direct oral anticoagulants and cancer-associated VTE: good for all, or just some? Blood. 2020; 136(6): 669–673, doi: 10.1182/blood.2019004177, indexed in Pubmed: 32575112.
277. Vazquez SR. Drug-drug interactions in an era of multiple anticoagulants: a focus on clinically relevant drug interactions. Hematology Am Soc Hematol Educ Program. 2018; 2018(1): 339–347, doi: 10.1182/asheducation-2018.1.339, indexed in Pubmed: 30504330.
278. Naess IA, Christiansen SC, Romundstad P, et al. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost. 2007; 5(4): 692–699, doi: 10.1111/j.1538-7836.2007.02450.x, indexed in Pubmed: 17367492.
279. Konstantinides SV, Meyer G. The 2019 ESC Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism. Eur Heart J. 2019; 40(3453): 3455.
280. Rivera-Lebron B, McDaniel M, Ahrar K, et al. PERT Consortium. Diagnosis, Treatment and Follow Up of Acute Pulmonary Embolism: Consensus Practice from the PERT Consortium. Clin Appl Thromb Hemost. 2019; 25: 1076029619853037, doi: 10.1177/1076029619853037, indexed in Pubmed: 31185730.
281. Araszkiewicz A, Kurzyna M, Kopeć G, et al. Expert opinion on the creating and operating of the regional Pulmonary Embolism Response Teams (PERT). Polish PERT Initiative. Cardiol J. 2019; 26(6): 623–632, doi: 10.5603/CJ.2019.0127, indexed in Pubmed: 31970735.
282. Sławek-Szmyt S, Jankiewicz S, Smukowska-Gorynia A, et al. Implementation of a regional multidisciplinary pulmonary embolism response team: PERT-POZ initial 1-year experience. Kardiol Pol. 2020; 78(4): 300–310, doi: 10.33963/KP.15230, indexed in Pubmed: 32165606.
283. Raskob GE, van Es N, Segers A, et al. Hokusai-VTE investigators. Edoxaban for venous thromboembolism in patients with cancer: results from a non-inferiority subgroup analysis of the Hokusai-VTE randomised, double-blind, double-dummy trial. Lancet Haematol. 2016; 3(8): e379–e387, doi: 10.1016/S2352-3026(16)30057-6, indexed in Pubmed: 27476789.
284. Giri J, Sista AK, Weinberg I, et al. Interventional Therapies for Acute Pulmonary Embolism: Current Status and Principles for the Development of Novel Evidence: A Scientific Statement From the American Heart Association. Circulation. 2019; 140(20): e774–e801, doi: 10.1161/CIR.0000000000000707, indexed in Pubmed: 31585051.
285. De Gregorio MA, Guirola JA, Kuo WT, et al. Catheter-directed aspiration thrombectomy and low-dose thrombolysis for patients with acute unstable pulmonary embolism: Prospective outcomes from a PE registry. Int J Cardiol. 2019; 287: 106–110, doi: 10.1016/j.ijcard.2019.02.061, indexed in Pubmed: 30846255.
286. Schmid P, Fischer AG, Wuillemin WA. Low-molecularweight heparin in patients with renal insufficiency. Swiss Med Wkly. 2009; 139: 438–452.

287. Launay-Vacher V, Oudard S, Janus N, et al. Renal Insufficiency and Cancer Medications (IRMA) Study Group. Prevalence of Renal Insufficiency in cancer patients and implications for anticancer drug management: the renal insufficiency and anticancer medications (IRMA) study. Cancer. 2007; 110(6): 1376–1384, doi: 10.1002/cncr.22904, indexed in Pubmed: 17634949.
288. Givens ML, Wethern J. Renal complications in oncologic patients. Emerg Med Clin North Am. 2009; 27(2): 283–291, doi: 10.1016/j.emc.2009.01.001, indexed in Pubmed: 19447312.
289. Cengiz K. Increased incidence of neoplasia in chronic renal failure (20-year experience). Int Urol Nephrol. 2002; 33(1): 121–126, doi: 10.1023/a:1014489911153, indexed in Pubmed: 12090317.
290. Launay-Vacher V, Etessami R, Janus N, et al. Renal Insufficiency Anticancer Medications (IRMA) Study Group. Lung cancer and renal insufficiency: prevalence and anticancer drug issues. Lung. 2009; 187(1): 69–74, doi: 10.1007/s00408-008-9123-5, indexed in Pubmed: 18941834.
291. Launay-Vacher V, Gligorov J, Le Tourneau C, et al. Renal Insufficiency and Anticancer Medications (IRMA) Study Group. Prevalence of renal insufficiency in breast cancer patients and related pharmacological issues. Breast Cancer Res Treat. 2010; 124(3): 745–753, doi: 10.1007/s10549-008-0131-1, indexed in Pubmed: 18704681.
292. Launay-Vacher V, Ayllon J, Janus N. Drug management of prostate cancer: prevalence and consequences of renal insufficiency. Clin Genitourin Cancer. 2009; 7(3): E83–E89, doi: 10.3816/CGC.2009.n.029, indexed in Pubmed: 19815487.
293. Akl EA, Vasireddi SR, Gunukula S, et al. Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer. Cochrane Database Syst Rev. 2011(4): CD006649, doi: 10.1002/14651858.CD006649.pub4, indexed in Pubmed: 21491395.
294. Shea-Budgell MA, Wu CMJ, Easaw JC. Evidence-based guidance on venous thromboembolism in patients with solid tumours. Curr Oncol. 2014; 21(3): e504–e514, doi: 10.3747/co.21.1938, indexed in Pubmed: 24940110.
295. Johansen KB, Balchen T. Tinzaparin and other low-molecular-weight heparins: what is the evidence for differential dependence on renal clearance? Exp Hematol Oncol. 2013; 2: 21, doi: 10.1186/2162-3619-2-21, indexed in Pubmed: 23927414.
296. DeCarolis DD, Thorson JG, Clairmont MA, et al. Enoxaparin outcomes in patients with moderate renal impairment. Arch Intern Med. 2012; 172(22): 1713–1718, doi: 10.1001/2013.jamainternmed.369, indexed in Pubmed: 23128835.
297. Cardiovascular Disease Educational and Research Trust, Cyprus Cardiovascular Disease Educational and Research Trust, European Venous Forum, International Surgical Thrombosis Forum, International Union of Angiology, Union Internationale de Phlébologie. Prevention and treatment of venous thromboembolism. International Consensus Statement (guidelines according to scientific evidence). Int Angiol. 2006; 25(2): 101–161, indexed in Pubmed: 16763532.
298. Mahé I, Aghassarian M, Drouet L, et al. Tinzaparin and enoxaparin given at prophylactic dose for eight days in medical elderly patients with impaired renal function: a comparative pharmacokinetic study. Thromb Haemost. 2007; 97(4): 581–586, indexed in Pubmed: 17393021.
299. Siguret V, Gouin-Thibault I, Pautas E, et al. No accumulation of the peak anti-factor Xa activity of tinzaparin in elderly patients with moderate-to-severe renal impairment: the IRIS substudy. J Thromb Haemost. 2011; 9(10): 1966–1972, doi: 10.1111/j.1538-7836.2011.04458.x, indexed in Pubmed: 21819539.
300. Siguret V, Gouin-Thibault I, Pautas E, et al. No accumulation of the peak anti-factor Xa activity of tinzaparin in elderly patients with moderate-to-severe renal impairment: the IRIS substudy. J Thromb Haemost. 2011; 9(10): 1966–1972, doi: 10.1111/j.1538-7836.2011.04458.x, indexed in Pubmed: 21819539.
301. Warkentin T, Greinacher A, Koster A, et al. Treatment and Prevention of Heparin-Induced Thrombocytopenia. Chest. 2008; 133(6), doi: 10.1378/chest.08-0677.
302. Siguret V, Pautas E, Février M. Elderly patients treated with tinzaparin (Innohep) administered once daily (175 anti-xa IU/kg): anti-xa and anti-iia activities over 10 days. Thromb Haemost. 2000; 84: 58–60.
303. Jalal DI, Chonchol M, Targher G. Disorders of hemostasis associated with chronic kidney disease. Semin Thromb Hemost. 2010; 36(1): 34–40, doi: 10.1055/s-0030-1248722, indexed in Pubmed: 20391294.
304. Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest. 2001; 119(1 Suppl): 64S–94S, doi: 10.1378/chest.119.1_suppl.64s, indexed in Pubmed: 11157643.
305. Garcia DA, Baglin TP, Weitz JI, et al. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2 Suppl): e24S–e43S, doi: 10.1378/chest.11-2291, indexed in Pubmed: 22315264.
306. Woodruff S, Feugère G, Abreu P, et al. A post hoc analysis of dalteparin versus oral anticoagulant (VKA) therapy for the prevention of recurrent venous thromboembolism (rVTE) in patients with cancer and renal impairment. J Thromb Thrombolysis. 2016; 42(4): 494–504, doi: 10.1007/s11239-016-1386-8, indexed in Pubmed: 27344439.
307. Monreal M, Trujillo-Santos J, Farge-Bancel D, Pedrajas JM, Gómez-Cuervo C, Ballaz A, Braester A, Mahé I. Comparison of Real-world Effectiveness and Safety of Enoxaparin versus Tinzaparin or Dalteparin in Cancer Patients with Venous Thromboembolism. The RIETECAT Cohort Study [abstract]. Res Pract Thromb Haemost. 2021; 5 (Suppl 1). https://abstracts.isth.org/abstract/comparison-of-real-world-effectiveness-and-safety-of-enoxaparin-versus-tinzaparin-or-dalteparin-in-cancer-patients-with-venous thromboembolism-the-rietecat-cohort-study/ (12.08.2021).
308. Krasiński Z, Stępak H, Jawień A, et al. Safety of New Oral Anticoagulants for Patients with Chronic Kidney Disease. Curr Pharm Des. 2018; 24(38): 4505–4510, doi: 10.2174/1381612825666190130144051, indexed in Pubmed: 30706805.
309. Farge D, Durant C, Villiers S, et al. Groupe Francophone Thrombose et Cancer (GFTC). Lessons from French National Guidelines on the treatment of venous thrombosis and central venous catheter thrombosis in cancer patients. Thromb Res. 2010; 125 Suppl 2: S108–S116, doi: 10.1016/S0049-3848(10)70027-X, indexed in Pubmed: 20433988.
310. Venous thromboembolic disease NCCN guidelines V2.2009. http://www.nccn.org/professionals/physician_gls/PDF/vte.pdf.
311. Mandalà M, Falanga A, Piccioli A, et al. working group AIOM. Venous thromboembolism and cancer: guidelines of the Italian Association of Medical Oncology (AIOM). Crit Rev Oncol Hematol. 2006; 59(3): 194–204, doi: 10.1016/j.critrevonc.2006.05.001, indexed in Pubmed: 16837209.
312. Mandalà M, Falanga A, Roila F, et al. ESMO Guidelines Working Group, ESMO Guidelines Working Group. Management of venous thromboembolism in cancer patients: ESMO clinical recommendations. Ann Oncol. 2008; 19 Suppl 2: ii126–ii127, doi: 10.1093/annonc/mdn110, indexed in Pubmed: 18456750.