Journal Pre-proof

Venous thromboembolism in cancer patients: ESMO Clinical Practice Guideline[†]

A. Falanga, C. Ay, M. Di Nisio, G. Gerotziafas, F. Langer, R. Lecumberri, M. Mandala, A. Maraveyas, I. Pabinger, L. Jara-Palomares, M. Sinn, K. Syrigos, A. Young, K. Jordan, on behalf of the ESMO Guidelines Committee

Please cite this article as: Falanga A, Ay C, Di Nisio M, Gerotziafas G, Langer F, Lecumberri R, Mandala M, Maraveyas A, Pabinger I, Jara-Palomares L, Sinn M, Syrigos K, Young A, Jordan K, on behalf of the ESMO Guidelines Committee, Venous thromboembolism in cancer patients: ESMO Clinical Practice Guideline[†], *Annals of Oncology* (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.014.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Venous thromboembolism in cancer patients: ESMO Clinical Practice Guideline[†]

A. Falanga[1,2], C. Ay[3], M. Di Nisio[4], G. Gerotziafas[5], F. Langer[6], R. Lecumberri[7,8], M. Mandala[9], A. Maraveyas[10], I. Pabinger[3], L. Jara-Palomares[11,12], M. Sinn[6], K. Syrigos[13], A. Young[14] & K. Jordan[15,16], on behalf of the ESMO Guidelines Committee*

[1]Division Immunohaematology and Transfusion Medicine, Haemostasis and Thrombosis Center, Department of Oncology and Haematology, Hospital Papa Giovanni XXIII, Bergamo; [2]University of Milan Bicocca, Department of Medicine and Surgery, Monza, Italy; [3]Department of Medicine I, Clinical Division of Haematology and Haemostaseology, Comprehensive Cancer Center Vienna, Medical University of Vienna, Vienna, Austria; [4]Department of Medicine and Ageing Sciences, G. d'Annunzio University, Chieti, Italy; [5]Sorbonne University, INSERM UMRS-938, Team "Cancer Vessels, Biology and Therapeutics", Group "Cancer-Hemostasis-Angiogenesis", Institut Universitaire de Cancérologie, Consultation Thrombosis in Oncology (COTHON), Tenon - Saint Antoine Hospital, AP-HP, Paris, France; [6]Centre for Oncology, University Cancer Centre Hamburg (UCCH), II Medical Clinic and Polyclinic, University Medical Centre Eppendorf, Hamburg, Germany; [7]Servicio de Hematología, Clínica Universidad de Navarra, Pamplona (Navarra); [8]CIBER-CV, Instituto de Salud Carlos III, Madrid, Spain; [9]University of Perugia, Unit of Medical Oncology, Santa Maria Misericordia Hospital, Italy; [10]Queen's Centre for Oncology and Haematology, Faculty of Health Sciences, Hull York Medical School and Hull University Teaching Hospitals NHS Trust, Hull, United Kingdom; [11]Respiratory Department, Medical Surgical Unit of Respiratory Diseases, Hospital Virgen del Rocio, Sevilla; [12]Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain; [13]Oncology Unit, 3rd Department of Medicine, School of Medicine, National and Kapodistrian University of Athens, Greece; [14]Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, United Kingdom; [15]Department of Hematology, Oncology and Palliative Medicine, Ernst von Bergmann Hospital, Potsdam; [16]Department of Medicine V, Hematology, Oncology and Rheumatology, University of Heidelberg, Heidelberg, Germany.

Running header: ESMO Clinical practice Guideline for venous thromboembolism in cancer patients

Word count: 11,543 (excluding title page, acknowledgements, funding and disclosure sections); References: 101; Tables: 2; Figures: 5; Supplementary Material: 1.

Key words:

venous thromboembolism (VTE), cancer-associated thrombosis (CAT), thromboprophylaxis/prevention, anticoagulation, catheter-related thrombosis, clinical practice guidelines

Highlights:

- Cancer-associated thrombosis is a major health problem that affects morbidity and mortality of people with cancer.
- Surgical and systemic pharmacological anticancer treatments have a significant impact on the thrombotic risk of patients.
- Primary thromboprophylaxis may be considered in high-risk ambulatory cancer patients using validated risk models.
- Anticoagulant treatment of venous thromboembolism in cancer patients is effective but may be associated with increased bleeding.
- LMWH or DOACs are effective treatments and generally safe options for cancer-associated thrombosis.

INTRODUCTION

Thromboembolism in people with cancer still remains a major health problem and figures as a leading cause of mortality after cancer itself, despite being a largely preventable disease.[1] A hypercoagulable state is the hallmark of cancer. It is induced by specific prothrombotic properties of cancer cells that activate blood clotting, as schematically depicted in **Figure 1**. These properties include the expression and release of procoagulant molecules, the activation of host blood and vascular cells (i.e. platelets, leukocytes and endothelial cells), which enhances their procoagulant potential, and the activation of the endothelium by anti-cancer drugs.[2]

The risk of venous thromboembolism (VTE) is higher in individuals with cancer than in those without cancer across all age categories. Over the last two decades, the risk of VTE in people with cancer has increased 3-fold and is 9-fold higher than in the general population.[3] The mortality rate of people with cancer with VTE is 2- to 3-fold higher compared with those without VTE.[3] In addition, anticoagulant treatment for a VTE event in patients with solid tumours is complicated because these patients have both an increased risk of thrombotic recurrences and bleeding during therapeutic anticoagulation.[4]

The thrombotic risk varies according to the cancer type (patients with pancreatic, gastric or lung cancer or primary brain tumours are among those with the highest risk); the actual burden of cancer-associated thrombosis (CAT) in the community is driven, however, by the common malignancies such as breast, prostate, colorectal and lung cancers, which largely contribute to the overall prevalence of CAT.[5] People with cancer who undergo surgical resection are at significantly higher risk of peri- and post-operative VTE than patients who undergo surgery for non-malignant diseases.[6,7]

Patient-related risk factors including comorbidities—such as presence of cardiovascular disease or cardiovascular risk factors (i.e. diabetes, hypertension, obesity, dyslipidaemia)—contribute to the risk of CAT. More recently, certain single nucleotide polymorphisms in coagulation-related genes have been associated with the risk of CAT (**Supplementary Table S1**). Oncogenic mutations and

3

rearrangements are also associated with a substantial increase of risk for CAT (**Supplementary Table S1**).

CAT complicates the management of anticancer therapies and is associated with substantial increase of expenditure for the healthcare systems.[8] Preventing VTE in people with cancer by pharmacological and non-pharmacological measures is a challenging and crucial issue. It is important to identify patients in the highest risk categories, who can most benefit from primary thromboprophylaxis.

The efficacy and safety of direct oral anticoagulants (DOACs) inhibiting Xa have been recently tested for the treatment of CAT and offer an alternative to low molecular weight heparin (LMWH).[9,10]

The approval status of the agents discussed in this guideline might differ from country to country. With a focus on ease of implementation, this updated ESMO Clinical Practice Guideline (CPG) summarises recommendations for prevention and treatment of VTE in patients with cancer.

DIAGNOSIS OF VTE

VTE includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Clinical manifestations of DVT of the legs include redness, tenderness, swelling, pitting oedema and appearance of collateral superficial veins; while manifestations of PE are dyspnoea, chest pain, cough, tachycardia, cyanosis, dizziness, fainting and excessive sweating.

The diagnosis of VTE, however, cannot rely on the clinical manifestations alone as the signs and symptoms are not specific. Imaging is necessary to confirm the diagnosis. In the general population, diagnostic algorithms consisting of clinical probability assessment and D-dimer testing have been established to guide decisions about who should be referred for compression ultrasonography (CUS) in case of suspected DVT and computed tomography (CT) pulmonary angiography (CTPA) in case of suspected PE.[11] For comparison, the diagnostic algorithm for non-cancer patients is reported in **Supplementary Figure S1**.

Unfortunately, in cancer patients the performance of clinical decision rules and D-dimer testing is poor.[12] As a consequence, in these patients, physicians should consider proceeding to CUS and CTPA directly (**Figure 2**).

Recommendation

- In cancer patients, diagnosis by CUS in case of suspected DVT and diagnosis by CTPA in case of suspected PE, without using clinical prediction rules and D-dimer level, are recommended [I, A].

PRIMARY PREVENTION OF VENOUS THROMBOEMBOLISM

Table 1 shows available pharmacological and mechanical VTE prophylaxis options.

Thromboprophylaxis in the surgical setting

General considerations. Assessment of the risk of thrombosis and bleeding should be carried out before any surgical procedure, including cancer surgery. The following factors are to be considered:

- Patient risk factors [i.e. by risk assessment models (RAMs)], e.g. the Caprini score[13]; see also **Supplementary Material**, **Supplementary Tables S2 and S3** and **Supplementary Figure S2**)

- Type of intervention (minor surgery = open or laparoscopic of <45 minutes duration; or major surgery = open or laparoscopic of >45 minutes duration)

- Contraindications to pharmacological thromboprophylaxis (e.g. active bleeding, acute hepatitis or acquired haemophilic states, uncontrolled hypertension, acute stroke, platelet count <25,000 µl, lumbar puncture or spinal/epidural anaesthesia in the next 12 hours or in the previous 4 hours, ongoing anticoagulant treatment for other indications)

Pharmacological thromboprophylaxis. Pharmacological thromboprophylaxis with LMWH or unfractionated heparin (UFH) is standard of care in surgical patients with a high risk of VTE and a low risk of bleeding. Malignancy is associated with an increased risk for both thromboembolic and haemorrhagic complications. Thus, particular caution is warranted in patients undergoing major cancer surgery, since

the overall risk–benefit ratio of pharmacological thromboprophylaxis may be less clear in cancer versus non-cancer surgical patients.

A recent systematic review and meta-analysis of randomised controlled trials (RCTs) specifically conducted in surgical cancer patients concluded that LMWH, in comparison with no prophylaxis or mechanical prophylaxis, decreased the rates of DVT [relative risk (RR) 0.20, 95% confidence interval (CI) 0.07-0.61] and PE (RR 0.13, 95% CI 0.01-2.25), but potentially increased the risk of major bleeding (RR 2.47, 95% CI 0.08-74.18).[14]

No data support the superiority of any LMWH over the other. Similarly, subcutaneous LMWH once daily (od) and subcutaneous UFH three times daily (tds) have comparable efficacy when used perioperatively in cancer patients.[15] Two meta-analyses have shown no difference between LMWH and UFH regarding mortality, PE and bleeding, but found a lower incidence of wound haematoma with LMWH prophylaxis (RR 0.70, 95% CI 0.54-0.92).[14,16] LMWHs have a lower risk of heparin-induced thrombocytopaenia and a more convenient administration schedule, which makes them an attractive first-choice agent.

There are limited data supporting the efficacy of fondaparinux for VTE prophylaxis in cancer patients undergoing surgery. In a meta-analysis of three RCTs of fondaparinux versus LMWH for perioperative thromboprophylaxis, no statistically significant difference was found, but the certainty of evidence was low.[16] There are no data so far on the efficacy and safety of DOACs in cancer surgery.

Mechanical thromboprophylaxis. Mechanical methods such as intermittent pneumatic compression (IPC) or graduated compression stockings (GCSs) may represent an appealing option for VTE prophylaxis due to their minimal risk of haemorrhage. There is insufficient evidence, however, to support the use of mechanical methods as monotherapy in place of pharmacological VTE prophylaxis in major cancer surgery, unless there are contraindications to anticoagulation. Small RCTs in cancer surgical patients have shown the superiority of LMWH over IPC alone in reducing the occurrence of VTE complications.[17,18]

6

In patients at high risk of VTE (e.g. following surgery, trauma or intensive care unit admission), adding IPC to pharmacological prophylaxis, as compared with pharmacological prophylaxis alone, decreases the incidence of PE [odds ratio (OR) = 0.39, 95% CI 0.23-0.64) and DVT (OR = 0.42, 95% CI 0.18-1.03), without increasing the incidence of major bleeding (OR = 1.21, 95% CI 0.35-4.18).[19] Combined prophylaxis, however, is rarely used in daily clinical practice in oncology patients.

Timing and dosing. The timing of pharmacological thromboprophylaxis initiation varies in clinical practice. In a meta-analysis of 39 studies on pharmacological thromboprophylaxis in cancer patients, 14 reported on DVT events and specified the timing of the first dose (preoperative versus post-operative). Preoperative administration of the first dose significantly reduced the DVT rate (RR 0.38, 95% CI 0.15-0.97), while post-operative administration of the first dose had no significant effect.[14] Two studies indicated a similar risk of bleeding between preoperative and post-operative commencement of pharmacological thromboprophylaxis: one RCT on 376 patients compared pre- versus post-operative UFH in colorectal cancer surgery, and one study compared a prospective cohort of 2058 surgical cancer patients receiving preoperative thromboprophylaxis with a matched historical cohort of patients receiving post-operative thromboprophylaxis.[20,21] LMWH has a longer half-life (4-6 hours) compared with UFH (1-2 hours). To avoid bleeding, the interval between preoperative subcutaneous injection and surgical procedure should be generally longer in patients receiving LMWH, particularly when the highest approved prophylactic dose is used. Some LMWHs may only be licensed for post-operative commencement of VTE prophylaxis.

Where different VTE prophylaxis doses are approved for a given LMWH, the highest dose is recommended to prevent VTE in cancer patients undergoing major surgery. A prospective, randomised, double-blind multicentre trial in patients undergoing surgery demonstrated in the group of cancer patients that prophylaxis with higher-dose dalteparin (5000 IU daily) compared with lower-dose dalteparin (2500 IU daily) reduced DVT rates from 14.9% to 8.5% ($P < 0.001$), without significant increase in bleeding complications.[22] Perioperative prophylaxis with UFH tds is equally effective to LMWH od and superior to UFH twice daily (bd).[16] In a small RCT on 111 cancer

patients undergoing oesophagectomy, the incidence of VTE was lower with nadroparin administered bd compared with od (0% versus 9.1%; *P* = 0.032).[23] Nevertheless, more research is warranted to confirm these findings.

Duration. The duration of post-operative thromboprophylaxis should be at least 10 days.[24,25] The mean time from major surgery to VTE occurrence, however, is reported to be 17 days, and in over one-third of patients VTE occurs later than 21 days after surgery or hospital discharge.[7,26] These data support extended post-operative prophylaxis beyond 10 days in select patients. For example, several meta-analyses show that extended thromboprophylaxis with LMWH after major abdominal or pelvic cancer surgery reduces the risk of VTE compared with conventional duration of 2 weeks or less, without increasing the risk of major bleeding.[14,27] This effect is not limited to open surgery, but also occurs with laparoscopic surgery. In patients undergoing laparoscopic surgery for colorectal cancer, extended pharmacological prophylaxis for 4 weeks reduced VTE risk compared with prophylaxis for 1 week with similar bleeding rates.[28]

Prevention of VTE in non-surgical patients with cancer

Ambulatory patients. The risk of VTE is increased in patients with 'active cancer' (as defined in **Supplementary Table S4**).[29] This risk is, however, very variable depending on individual factors (previous history of thrombosis, immobility, cardiovascular risk factors), the type and stage of cancer, the time since cancer diagnosis (within 6 months after first diagnosis and after progression or recurrence) and the use of systemic anticancer therapy[30]; therefore, primary thromboprophylaxis is not justified in all of these patients. Identifying patients at high risk is of particular interest in this setting. RAMs and material for the calculation of the risk of CAT are provided in the **Supplementary Material**, **Supplementary Tables S2 and S3** and **Supplementary Figure S2**, the latter of which exemplifies the inclusion of a biomarker of hypercoagulability (i.e. D-Dimer) to clinical predictors. Since thrombogenic potential varies depending on the type of cancer or the presence of certain oncogene mutations or rearrangements, the authors endorse the development of cancer-specific RAMs to further refine current risk stratification approaches or to

develop new models that incorporate promising biomarkers. Results of these studies could alter the approach to risk stratification in the future.

A recent meta-analysis and an individual patient-data meta-analysis including 10,431 ambulatory patients with cancer who participated in phase III RCTs, showed that prophylactic doses of heparins reduced symptomatic VTE by about 40% without increasing the bleeding risk as compared with no prophylaxis.[31,32]

Two studies in pancreatic cancer using higher doses of LMWHs (150/IU/kg dalteparin or 1 mg/kg enoxaparin) for 3 months in patients receiving systemic anticancer treatment have shown a 85% and 65% RR reduction of any VTE and the composite of DVT and PE with number needed to treat (NNT) of 5 and 11, respectively.[33]

The recent AVERT and CASSINI studies randomised 574 and 841 patients, respectively, with intermediate-high risk of VTE [estimated thrombosis risk ≥9.6% over 6 months using the Khorana risk score [(KRS) ≥2] to either placebo or a factor Xa inhibitor for 6 months.[34,35] In the AVERT study, apixaban (2.5 mg bd) was associated with a lower rate of VTE [4.2% versus 10.2%; hazard ratio (HR) 0.41, 95% CI 0.26-0.65, NNT = 17] and a higher rate of major bleeding (3.5% versus 1.8%; HR 2.00, 95% CI 1.01-3.95; number needed to harm = 59).[34] In the CASSINI study, rivaroxaban (10 mg od) did not achieve significant VTE risk reduction over placebo (6.0% versus 8.8%; HR 0.66, 95% CI 0.4-1.09) with a major bleeding rate of 2% versus 1% (HR 1.96, 95% CI 0.59-6.49).[35] Neither study included patients with severe thrombocytopaenia (platelet count <50.000/mm^3) or renal dysfunction [creatinine clearance (CrCl) <30 ml/min].

Shared decision making should take into account utility of oral route, renal and hepatic function, drug–drug interactions and risk of bleeding, with caution to be taken in patients with gastrointestinal malignancies, particularly if the primary lesion is luminal and non-resected.

The duration of pharmacological thromboprophylaxis in ambulatory cancer patients cannot be firmly determined. The first three months from diagnosis and anticancer treatment initiation comprise the conventional higher-risk period during which >50%

of VTE episodes occur, and all existing studies have covered at a minimum this period; the two DOAC studies[34,35] had a predetermined, 6-month thromboprophylaxis period and the two pancreatic ductal adenocarcinoma studies[33] explored a maximum of 3 months at a higher dose of LMWH. These patients, however, also have a KRS of ≥2 points and very often progressive disease; hence, prolonging thromboprophylaxis with a DOAC up to 6 months remains evidence-based. For thromboprophylaxis beyond 6 months an individualised approach should be considered.

Patients with cancer hospitalised for an acute medical illness. LMWHs represent the agents of choice for VTE thromboprophylaxis in patients with cancer hospitalised for an acute medical illness. The recommendation of pharmacological thromboprophylaxis to prevent VTE for inpatients with cancer is based on the results from large clinical trials of hospitalised medical patients.[36] Studies suggest that thromboprophylaxis in cancer patients hospitalised for acute medical illness, though frequent, may: i) not be appropriately targeted[37], ii) be based on risk assessment tools (e.g. Padua Score or IMPROVE score) that have limited accuracy in cancer patients[38] (KRS, according to a single retrospective study[39], might have some value in this setting and needs to be further investigated) and iii) not benefit cancer patients as a subgroup.[40]

The use of DOACs in this setting, including extended thromboprophylaxis for 4 weeks after discharge, is currently not recommended since the reduction of VTE compared with standard heparin prophylaxis was offset by an increase in major bleeding.[41]

Dedicated studies to define optimal pharmacological prophylaxis in cancer patients hospitalised for acute medical illness are required.

Patients with multiple myeloma. The incidence of VTE in patients with multiple myeloma (MM) ranges between 8 and 22 per 1000 person-years and about 8%-10% of patients will suffer symptomatic VTE during the course of the disease.[42] The risk of VTE in these patients is influenced by:

10

- The characteristics of MM (e.g. time since diagnosis, levels and type of paraproteinaemia)[43-45]

- The anti-myeloma treatments (e.g. immunomodulatory drugs with high-dose dexamethasone, multi-agent chemotherapy or anthracyclines)[46-50]

- The patient-related intrinsic risk factors (e.g. obesity, cardiovascular disease or cardiovascular risk factors and age)[51]

- Other triggering risk factors [e.g. central venous catheters (CVCs), use of erythropoietin or other colony-stimulating factors, recent hospitalisation for acute medical illness or surgical interventions]

The International Myeloma Working Group (IMWG), the National Comprehensive Cancer Network (NCCN) and the European Myeloma Network (EMN) adopted a simplified algorithm (in practice since 2014), based on the concept that treatment with immunomodulatory imide drugs (IMiDs) is the major determinant of VTE risk in patients with MM. Nevertheless, this algorithm is based on an empirical scoring of the VTE risk and its accuracy is limited.[52-56] The clinical decision tool proposed by the IMWG/NCCN/EMN is shown in **Supplementary Table S5**.

The IMPEDE VTE and the SAVED scores have been recently proposed. These scores derived from the retrospective analysis of the Surveillance, Epidemiology and End Results (SEER)–Medicare database (**Supplementary Table S6**).[57,58] Both scores showed borderline accuracy and need independent validation in order to be proposed in clinical practice.

There is a need for prospective derivation and validation of a RAM for VTE in patients with MM. Due to the paucity of specific clinical trials for thromboprophylaxis in patients with MM, the recommendations for thromboprophylaxis stem from those with solid tumours, except for patients receiving IMiDs.[59]

Recommendations

Thromboprophylaxis in the surgical setting

11

- Unless contraindicated due to a high risk of bleeding, pharmacological VTE prophylaxis with LMWH (preferred) or UFH is recommended in patients undergoing major cancer surgery [I, A]. Fondaparinux may be used as an alternative [II, C].

- Mechanical methods such as IPC or GCSs are suggested as an alternative when pharmacological VTE prophylaxis is contraindicated (e.g. in the presence of active bleeding) [II, B]. Mechanical methods may be used in combination with pharmacological VTE prophylaxis in patients at exceedingly high risk of VTE [II, C].

- Depending on the heparin type and dosage, commencement of pharmacological thromboprophylaxis with LMWH or UFH 2-12 hours preoperatively is suggested in cancer surgical patients [II, B].

- Where several prophylactic dosages are approved for a given LMWH, the highest prophylactic LMWH dose od or 5000 IU UFH tds is recommended [II, A].

- Patients undergoing major cancer surgery should receive pharmacological thromboprophylaxis for at least 10 days post-operatively [I, A]. In patients with cancer undergoing open abdominal or pelvic surgery or laparoscopic colorectal cancer surgery, extended post-operative VTE prophylaxis for 4 weeks with LMWH is recommended [I, A].

Prevention of VTE in non-surgical patients with cancer

- Patient education materials on CAT including risk factors, signs and symptoms and information on positive lifestyle factors, should be one component of the information package provided to all ambulatory patients scheduled to receive systemic anti-cancer treatment [III, A].

- Cancer patients should be offered a CAT risk assessment and have an opportunity to discuss their particular risk [III, B].

- VTE risk assessment should be based on validated RAMs such as the KRS, COMPASS-CAT or the Vienna-CATS nomogram score [III, C].

- An estimated risk of VTE >8%-10% at 6 months is suggested as threshold for discussing primary thromboprophylaxis [II, C]. This risk is observed in patients

12

with a KRS ≥2 and can individually be calculated with the Vienna-CATS nomogram score and the COMPASS score.

- For ambulatory pancreatic cancer patients on first-line systemic anticancer treatment , LMWH given at a higher dose (150/IU/kg dalteparin or 1 mg/kg enoxaparin) for a maximum of 3 months may be considered [II, C].

- In ambulatory cancer patients starting systemic anticancer treatment who have a high thrombosis risk, apixaban, rivaroxaban or LMWH may be considered for primary thromboprophylaxis for a maximum of 6 months [I, B].

- In hospitalised cancer patients confined to bed with an acute medical complication, prophylaxis with LMWH, UFH [I, B] or fondaparinux [II, B] is recommended.

- Where concerns of DOAC safety exist and the patient is perceived as having clinically important risk for VTE, LMWH at conventional primary thromboprophylaxis dosing may be administered [II, C].

Patients with multiple myeloma

- All patients with MM should be offered a VTE risk assessment and have the opportunity to discuss their particular risk [III, B].

- Patients with MM scheduled to receive or receiving IMiD treatment should be assessed for VTE risk with the IMWG/NCCN score (**Supplementary Table S5**) [III, B].

- In ambulatory patients with MM receiving IMiD treatment combined with low-dose dexamethasone and without additional risk factors, aspirin (100 mg/day) is recommended [III, B].

- In ambulatory patients with MM classified as high risk for VTE, pharmacological thromboprophylaxis with LMWH for 3-6 months is recommended [II, B].

- Extension of thromboprophylaxis should be considered on a case-by-case basis [IV, B].

- Apixaban 2.5 mg bd or rivaroxaban 10 mg od are potential options in patients with CrCl >30 ml/min who present contraindications or intolerance to LMWH [IV, C].

TREATMENT OF CAT

13

For the treatment of CAT, the agents listed in **Table 2** are available options. Treatment of CAT is usually divided into an acute phase (first 5-10 days after diagnosis), a long-term phase (first 3-6 months) and an extended phase (beyond 6 months) (**Figure 3**).

Acute phase

The evidence on the treatment of CAT during the early phase is largely indirect and based on RCTs conducted in non-cancer patients with acute DVT or PE who were assigned to LMWH versus UFH or LMWH versus fondaparinux. All parenteral agents were administered for about 5-10 days followed by vitamin K antagonists (VKAs) [target international normalised ratio (INR) range between 2.0 and 3.0]. A meta-analysis of these studies suggests that LMWH may reduce mortality and recurrent VTE compared with UFH or fondaparinux with a similar risk of major bleeding.[60] The use of DOACs (rivaroxaban and apixaban) in the acute phase is supported by three prospective RCTs.[61-63] In cancer patients with severe renal impairment, defined as CrCl <30 ml/min, UFH might be preferable over LMWH or fondaparinux, whereas the latter might be considered in patients with CAT and a prior history of heparin-induced thrombocytopaenia.[60]

Long-term phase

LMWH has represented the first-line treatment of CAT for about two decades. A meta-analysis of studies on cancer patients with DVT or PE found a lower rate of recurrent thrombosis and similar risk of bleeding with a 6-month course of LMWH compared with a VKA.[64] The main characteristics of these studies are shown in **Supplementary Table S7**.

LMWH requires daily subcutaneous injections, which may impair the patient's quality of life due to the persistence of anticoagulant therapy.[65]

Five open-label RCTs evaluated the efficacy and safety of direct oral factor Xa inhibitors (i.e. edoxaban, rivaroxaban and apixaban) for the treatment of symptomatic or incidental VTE in patients with active cancer.[61-63,66,67] These trials considered study treatment durations of 6-12 months and all used the same regimen

of dalteparin as the comparator, based on the results of the CLOT study.[68] The main characteristics of these studies are shown in **Supplementary Table S8**.

The Hokusai VTE cancer trial demonstrated that edoxaban was noninferior to dalteparin for the composite outcome of recurrent VTE or major bleeding.[66] The rate of recurrent VTE was lower with edoxaban (7.9% versus 11.3%), but the rates of major bleeding (6.9% versus 4.0%) and clinically relevant non-major bleeding (14.6% versus 11.1%) were higher (**Supplementary Table S8**). The relative excess of major bleeding was observed in patients with gastrointestinal cancer, although the absolute number of severe bleeding events was low and comparable to dalteparin.

In the pilot SELECT-D trial, the 6-month cumulative rate of recurrent VTE was lower with rivaroxaban (4% versus 11%), but the rate of major bleeding was numerically higher (6% versus 4%) and clinically relevant non-major bleeding was significantly increased (13% versus 4%) with rivaroxaban.[61] The incidence of major bleeding was particularly increased in patients with oesophageal and gastro-oesophageal junction cancers (36% versus 11%).

In the ADAM VTE trial, apixaban was associated with significantly lower incidence of recurrent VTE (0.7% versus 6.3%) with no increase in major bleeding (0% versus 1.4%) or clinically relevant non-major bleeding (6.2% versus 4.2%) compared with dalteparin.[62] Patient satisfaction was assessed via monthly surveys, which suggested a lower negative impact on quality of life and a reduced burden with apixaban, resulting in general patient preference for the oral agent over the parenteral treatment.

In the CARAVAGGIO trial, the incidence of recurrent VTE was numerically lower with a 6-month course of apixaban than with dalteparin (5.6% versus 7.9%) with a similar risk of major bleeding (3.8% versus 4.0%) or clinically relevant non-major bleeding (9.0% versus 6.0%).[63] In both the ADAM VTE and CARAVAGGIO trials there was no excess of major gastrointestinal bleeding with apixaban.

The CASTA DIVA trial found a cumulative incidence of recurrent VTE at 3 months of 6.4% and 10.1% in patients that received rivaroxaban and dalteparin, respectively.

The study was stopped prematurely due to slow recruitment, and the total number of patients may have been too low to reach the predefined criteria for noninferiority.[67]

The RCTs on direct oral factor Xa inhibitors were heterogeneous in terms of primary outcomes, study and treatment duration, types of cancer included and proportion of patients with upper gastrointestinal cancer (**Supplementary Table S9**). The lack of head-to-head comparisons further limits any conclusion on whether one agent may perform better than the others. Currently, no study evaluated the use of the direct thrombin inhibitor dabigatran for the treatment of CAT.

Based on these findings, the oral factor Xa inhibitors may represent an acceptable alternative to LMWH for the treatment of CAT.[69] Treatment with edoxaban followed a lead-in period of at least 5 days LMWH, whereas apixaban and rivaroxaban were used from VTE diagnosis, and thus the latter two may be considered as options for the acute treatment phase of CAT. In patients with luminal primary gastrointestinal cancer, LMWH may be first option whereas the decision to use edoxaban or rivaroxaban will need to balance the lower risk of recurrent VTE and patient preferences for an oral anticoagulant treatment with a higher risk of gastrointestinal bleeding.

LMWH offers the possibility of frequent dose adjustments and may be the preferable approach in patients with active mucosal abnormalities such as gastroduodenal ulcers, patients with hepatic impairment, severe thrombocytopaenia, triple-positive antiphospholipid syndrome, vomiting and nausea. LMWHs are virtually devoid of drug–drug interactions and may be preferred for patients with CAT in whom the concomitant use of strong inhibitors or inducers of the CYP3A4 and P-glycoprotein may affect the pharmacokinetics of direct factor Xa inhibitors. All direct factor Xa inhibitors may be affected by drugs that have an effect on the P-glycoprotein transporter, while concentrations of rivaroxaban and apixaban, and to a lesser extent edoxaban, may also be influenced by CYP3A4 metabolism. While the clinical relevance of these drug–drug interactions remain uncertain, preliminary data suggest that anticancer agents can be concomitantly administered to DOAC-treated patients with VTE.[10]

Extended phase

The optimal duration of treatment for CAT is unclear. Two prospective studies evaluated extended anticoagulation for CAT and suggested that the risk of thrombotic complications may remain significant beyond 6 months.[70,71] Extending anticoagulation beyond 6 months may be considered in patients with active cancer receiving cancer treatment in whom the risk of recurrence may outweigh that of bleeding complications.[72] Periodic assessment of the risk–benefit profile and patient preferences remain crucial to evaluate the need for anticoagulation or dose adjustments. The absence of residual vein thrombosis in patients with cancer and index DVT identifies a population at low risk for recurrent thrombotic events.[73,74] High levels of D-dimer or C-reactive protein 3 weeks after interruption of anticoagulant therapy may identify a group of patients with CAT who are at risk of recurrent thrombosis [73,75]; whether patients with residual vein thrombosis and high levels of D-dimer and C-reactive protein may benefit from longer treatment duration requires validation in prospective management studies.

In the recent 12-month SELECT-D trial, 92 patients who had received 6 months of anticoagulant treatment and had residual DVT or index PE were randomly assigned to 6 months of rivaroxaban or placebo.[74] The 6-month cumulative rate of recurrent VTE was lower with rivaroxaban (4% versus 14%), but the risks of major and clinically relevant non-major bleeding were higher (5% versus 0% and 4% versus 0%, respectively).

In a post-hoc analysis of the Hokusai VTE Cancer study (n = 566), the incidences of recurrent VTE and major bleeding between 6-12 months were low and similar between patients receiving edoxaban or dalteparin (0.7% versus 1.1% for recurrent VTE and 1.7% versus 1.1% for major bleeding, respectively).

Patients with cancer were excluded from trials evaluating reduced doses of rivaroxaban or apixaban for the treatment of VTE after 6 months of anticoagulation, therefore the efficacy and safety of these regimens in patients with cancer require further evaluation (NCT03692065, NCT03080883). **Figure 4** shows a proposed management for CAT treatment.

17

Incidental CAT

In patients with cancer, VTE is diagnosed incidentally in about one-half of cases on routine imaging scans requested for cancer staging or evaluation of cancer treatment response.[76] While incidentally-detected VTE is associated with a non-negligible risk of recurrent thrombosis, a recent meta-analysis of patients with CAT reported that incidental VTE was associated with a lower rate of VTE recurrence at 6 months compared with symptomatic VTE (RR 0.6, 95% CI 0.4-0.9), with a trend for increased major bleeding (RR 1.47, 95% CI 0.99-2.2).[77] The 12-month incidence of recurrent VTE appeared to be similar in patients with subsegmental PE and those with more proximal PE (6.4% versus 6.0%).[75] For that reason, anticoagulant therapy is suggested for most patients with subsegmental PE, although a watchful approach or a shorter course of anticoagulation may be considered when there is high risk of bleeding or involvement of a single subsegmental artery without concomitant DVT, provided that there is adequate cardiopulmonary reserve.

Special populations

Data in this setting largely derive from retrospective trials in the non-cancer population (**Figure 5**). This topic has been extensively reviewed elsewhere.[9]

Renal impairment. Patients with VTE and concomitant renal impairment are at higher risk of major bleeding and recurrent VTE during anticoagulant treatment compared with patients with normal renal function. Post-hoc and subgroup analyses suggest that in patients with CAT and moderate renal impairment (CrCl 30-60 ml/min), the efficacy and safety of LMWH and DOACs are generally consistent with those of cancer patients without renal impairment. Patients with CAT and severe renal impairment (CrCl <30 ml/min) were excluded from the pivotal trials on the treatment of CAT. In these patients, two options may be considered: UFH followed by VKAs or LMWH with the dose adjusted to anti-Xa activity level for the treatment of CAT. Data on the dosing and safety of DOACs in patients with CAT and severe renal impairment are lacking.

Obese patients. Based on limited data from observational and retrospective studies, it is suggested that in patients with extreme body weight (>120 kg or body mass index >40 kg/m^2) the dose of LMWH should be calculated based on a person's

actual body weight without capping at a maximum dose. Although subgroup analyses have not shown any significant reduction in efficacy and safety of DOACs in obese patients, DOACs should be used cautiously in patients weighing >120 kg.[78]

Patients with thrombocytopaenia. In patients with persistent, severe thrombocytopaenia (<50,000/μL), two management strategies have been proposed based on the underlying risk of thrombosis recurrence or extension.[79] In patients with acute VTE who are at high risk of thrombus progression (i.e. first 30 days from thromboembolic event, segmental or more proximal PE, proximal DVT or a history of recurrent thrombosis), full-dose anticoagulation may be considered in combination with platelet transfusion support aiming at platelet count >40-50,000/μL. If the risk of thrombosis progression is deemed to be low (i.e. >30 days from thromboembolic event, distal DVT, isolated subsegmental PE), intermediate to prophylactic dose LMWH may be considered with temporary discontinuation of anticoagulation if the platelet count falls below 25,000/μL. In patients with platelet count >50,000/μL, full therapeutic dose anticoagulation should be considered. Data on the use of DOACs for the treatment of CAT in the presence of severe thrombocytopaenia are lacking.

Vena cava filters in CAT

The efficacy and safety of vena cava filters for acute CAT have not been evaluated in RCTs. In the general population, the use of vena cava filters in addition to anticoagulant treatment may reduce the incidence of PE, but increases the risk of DVT and has no survival benefits over anticoagulation alone.[80] Inferior vena cava filters may be indicated in the acute phase of VTE when there is a contraindication to anticoagulant treatment. The potential value of vena cava filters is likely reduced after the acute phase when the risk of thrombosis recurrence or extension diminishes significantly.

Recommendations

- In patients with CAT, LMWH, UFH, fondaparinux, apixaban or rivaroxaban are recommended treatments for the acute phase [I, A]. LMWH is preferred over UFH or fondaparinux [V, A]. UFH may be considered in patients with CAT and severe renal impairment (defined as CrCl <30 ml/min) [IV, C].

- Long-term anticoagulation for at least 6 months includes LMWH, apixaban, edoxaban or rivaroxaban which are preferred over VKAs [I, A]. VKAs may be used if LMWH or direct factor Xa inhibitors are not accessible [IV, C].

- In patients with luminal gastrointestinal cancer, LMWH is preferred for treating CAT [II, B]. Similar considerations potentially apply to patients with urothelial cancer [II, B]. The use of oral factor Xa inhibitors should consider patient preferences [IV, C].

- In patients at high risk for gastrointestinal bleeding, such as those with active gastroduodenal ulcers or patients receiving strong inhibitors or inducers of P-glycoprotein and CYP3A, LMWH is preferred [IV, B]. The author panel acknowledges that only limited evidence is available on drug–drug interactions between direct factor Xa inhibitors and systemic antineoplastic therapy.

- Extended anticoagulation beyond the initial 6 months with LMWH, apixaban, edoxaban, rivaroxaban or VKAs should be considered for patients with active cancer in whom the risk of recurrent thrombosis is higher and may outweigh that of bleeding [III, B]. The risk–benefit profile of anticoagulant therapy should be regularly assessed to ensure a favourable balance [IV, C].

- For incidentally detected VTE, the same treatment as for symptomatic VTE is recommended [II, A].

- Anticoagulant therapy is suggested for most of patients with subsegmental PE [II, A].

- In patients with high risk of bleeding or single incidental subsegmental PE without concomitant DVT, provided that there is adequate cardiopulmonary reserve, a watchful approach or a shorter course of anticoagulation may be considered [V, C].

- The insertion of vena cava filters is suggested in patients with acute and life-threatening VTEs who have absolute contraindications to anticoagulant therapy [III, B] or as an adjunct to anticoagulation in patients with recurrent VTE or extension of thrombosis despite optimal anticoagulant therapy [IV, C].

PREVENTION AND MANAGEMENT OF CATHETER-RELATED VENOUS THROMBOSIS IN ADULTS WITH CANCER

CVCs are commonly used for patients with cancer receiving intravenous chemotherapy or other systemic anticancer medications or supportive care. Upper extremity deep vein thrombosis (UEDVT) is a common complication of having a CVC. Most catheter-related thromboses (CRTs) are asymptomatic [81] and may go undetected. The overall rate of CRT is estimated to be 14%-18% with approximately 5% becoming symptomatic.[82] In a recent systematic review of 80 studies (39,148 cancer patients with CVCs), implantable ports had a decreased risk of thrombosis compared with peripherally inserted central catheters (PICCs) (OR 0.20, 95% CI 0.09-0.43).[83,84]

Pharmacological prophylaxis of CRT

A Cochrane review and meta-analysis of people with cancer and CVCs[85] found that LMWH decreased the incidence of symptomatic CRT up to 3-month follow-up in comparison with no LMWH (RR 0.43, 95% CI 0.22-0.31), although the certainty of evidence was moderate due to serious risk of bias (**Supplementary Figure S3**). This review concluded that, compared with no prophylaxis, LMWH may reduce CRT without increasing the risk of bleeding (**Supplementary Figure S4)**, whereas VKAs may lower the risk of CRT, but potentially increase the risk of bleeding. Nevertheless, the absolute effect is low (LMWH: 38 fewer events per 1000, VKA: 31 fewer events per 1000). There is no improvement in mortality due to anticoagulation (**Supplementary Figure S5)** and the burden of injecting daily LMWH or intake of VKA is considerable.

Treatment of established catheter-related VTE

Previous recommendations for the treatment of CRT were mainly based on the extrapolation of the results from clinical trials evaluating the treatment of lower-limb DVT and two prospective and one retrospective cohort that had evaluated the efficacy and safety of LMWH plus VKA.[86-88] The evidence remains scant.

In one retrospective and two prospective studies rivaroxaban was used to treat CRT.[89,90,91] These three studies are small and may be unreliable. Properly powered randomised trials are needed to evaluate the safety and efficacy of DOACs for the treatment of CRT.

Anticoagulation versus catheter removal. In a retrospective study, 112 cancer patients with CRT underwent a variety of therapeutic interventions that included anticoagulation, CVC removal or a combination of both. No patient developed a PE or compromise of the limb. Only four patients required delayed catheter removal due to persistence of their symptoms.[92] In another prospective study, 74 cancer patients with CRT were treated with anticoagulants for 3 months. No recurrent DVT events were reported, and no catheter was removed due to malfunction or thrombosis extension.[87] In a recent retrospective study including 83 patients with PICC-associated thrombosis, 62 were managed with catheter removal alone, while 21 underwent PICC removal followed by therapeutic anticoagulation. No patient in the anticoagulation group developed progressive thrombosis compared with 6.4% of patients treated with catheter removal alone, although major bleeding was higher in the anticoagulation group (28.5% versus 4.8%).[93]

Duration of anticoagulant therapy. A systematic review including 23 studies (no RCTs) evaluated the efficacy and safety of different durations of anticoagulant treatment for CRT.[94] Duration of anticoagulation in most studies was between 3 and 6 months. The heterogeneity of study designs, populations and outcome definitions does not allow firm conclusions to be drawn on the optimal duration of anticoagulant therapy. Data extrapolated from studies of patients with provoked lower limb DVT are frequently used in the setting of CRT. For this reason, if the CVC is maintained after completion of 3 months of anticoagulation, the scenario would be comparable to that of a DVT related with a persistent risk factor. Extended secondary prophylaxis beyond 3 months may be considered.

Recommendations

- Routine pharmacological prophylaxis of CRT is not recommended [II, D].
- For the treatment of symptomatic CRT in cancer patients, anticoagulant treatment is recommended for a minimum of 3 months [III, A]. LMWH is suggested, although, in the absence of direct comparisons between anticoagulants in this setting, VKA or DOAC may be considered alternative options [IV, C].

22

- It is recommended to remove the catheter if it is not needed or is infected, anticoagulant treatment is contraindicated or there is clinical deterioration due to thrombus extension despite treatment [III, B].
- In patients with CRT, who have completed 3 months of anticoagulant treatment, extended anticoagulation until catheter removal is suggested, if the patient´s bleeding risk is low [IV, C].

METHODOLOGY

This CPG was developed in accordance with the ESMO standard operating procedures for CPG development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors.

Assessment prioritised recent literature [01 January 2020-manuscript resubmission (December 2022)] and its evaluation in the context of existing systematic reviews that focus on earlier knowledge. The lead author (AF) assigned co-authors to subgroups for evaluating topics, questions and literature based on their expertise (FL, KS and MS: thromboprophylaxis in the surgical setting; AM, CA, GG and IP: prevention of VTE in non-surgical patients; LJP, MDN and MM: treatment of CAT; RL, AY and IP: prevention and management of CRT). Further literature searching and validation was conducted by the ESMO Guidelines Committee Subject Editor (KJ). Each co-author subgroup drafted manuscript text and recommendation statements. The full manuscript was compiled and revised by AF and KJ. Recommendation statements were finalised through nominal group technique. All authors reviewed and approved the finalised text. For future updates to this CPG, including eUpdates and Living Guidelines, please see the ESMO Guidelines website: https://www.esmo.org/guidelines/guidelines-by-topic/supportive-and-palliative-care/venous-thromboembolism-in-cancer-patients. Levels of evidence and grades of recommendation have been applied using the system shown in **Supplementary Table S10**.[95,96] Statements without grading were considered justified standard clinical practice by the authors.

ACKNOWLEDGMENTS

FUNDING

DISCLOSURE

AF reports personal fees as an invited speaker from LEO Pharma, Pfizer, Rovi, Sanofi, Stago and Werfen.

CA reports personal fees as an invited speaker from Bayer, Bristol-Myers Squibb (BMS)/Pfizer, Daiichi Sankyo and Sanofi; and personal fees for advisory board membership from Bayer, BMS/Pfizer and Sanofi.

MDN reports personal fees as an invited speaker from Bayer, Daiichi Sankyo and Viatris; personal fees for advisory board membership from LEO Pharma and Pfizer; and institutional funding from LEO Pharma.

GG reports no conflicts of interest.

FL reports personal fees as an invited speaker from Bayer, BMS, Janssen-Cilag, LEO Pharma, Mitsubishi Tanabe Pharma and Pfizer; personal fees for advisory board membership from Alexion, Aspen, BioMarin, Chugai, CSL Behring, Daiichi Sankyo, GSK, Mylan (Viatris), Roche, SOBI, Takeda and Werfen and institutional funding from Bayer, CSL Behring, Intersero, Novo Nordisk and SOBI.

RL reports personal fees as an invited speaker from BMS, Daiichi Sankyo, Janssen, Laboratorios Rovi, LEO Pharma and Sanofi; personal fees for advisory board membership from Janssen, LEO Pharma and Sanofi; institutional funding from Laboratorios Rovi and complimentary product samples from Laboratorios Rovi.

MM reports personal fees as an invited speaker from Sun Pharma; personal fees for advisory board membership from BMS, Merck Sharp & Dohme (MSD), Novartis, Pierre Fabre and Sanofi.

AM reports personal fees as an invited speaker from Bayer, BMS, LEO Pharma, Pfizer and Sanofi; personal fees for advisory board membership from Bayer, BMS, LEO Pharma and Pfizer and personal fees for a writing engagement from BMS and LEO Pharma.

IP reports personal fees as an invited speaker from Bayer, BMS, Pfizer and Sanofi and personal fees for advisory board membership from Bayer, BMS, Daiichi Sankyo and Pfizer.

LJP reports personal fees as an invited speaker from Actelion, Daiichi Sankyo, LEO Pharma, MSD, Pfizer and Rovi and institutional funding from LEO Pharma and MSD.

MS reports personal fees as an invited speaker from art tempi American Society of Clinical Oncology (ASCO) Direct, BMS, Esanum, MSD, Pfizer and Pierre Faber; personal fees for advisory board membership from Amgen, AstraZeneca, Sanofi and Servier; expert testimony for Incyte and institutional funding as local principal investigator (PI) from Amgen, AstraZeneca, BeiGene, BMS and GSK; non-remunerated membership to Association of Scientific Medical Societies in Germany Guidelines Pancreatic and Liver Cancer and a non-remunerated leadership role at Arbeitsgemeinschaft Internistische Onkologie in der Deutschen Krebsgesellschaft e.V (AIO) Leitgruppe Pancreatic Cancer.

KS reports personal fees for advisory board membership from Amgen and BMS and institutional funding from MSD.

AY reports personal fees as an invited speaker from LEO Pharma and personal fees for advisory board membership from BMS/Pfizer Alliance.

KJ reports personal fees as an invited speaker from Amgen, art tempi, Helsinn, Hexal, med update GmbH, MSD, Mundipharma, onkowissen, Riemser, Roche, Shire (Takeda) and Vifor; personal fees for advisory board membership from Amgen, AstraZeneca, BD Solutions, Hexal, Karyopharm and Voluntis; royalties from Elsevier

REFERENCES

1   Khorana AA, Francis CW, Culakova E et al. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. Journal of thrombosis and haemostasis : JTH 2007; 5 (3): 632-634.

2   Falanga A, Schieppati F, Russo L. Pathophysiology 1. Mechanisms of Thrombosis in Cancer Patients. Cancer Treat Res 2019; 179: 11-36.

3   Mulder FI, Horváth-Puhó E, van Es N et al. Venous thromboembolism in cancer patients: a population-based cohort study. Blood 2021; 137 (14): 1959-1969.

4   Ay C, Beyer-Westendorf J, Pabinger I. Treatment of cancer-associated venous thromboembolism in the age of direct oral anticoagulants. Ann Oncol 2019; 30 (6): 897-907.

5   Cohen AT, Katholing A, Rietbrock S et al. Epidemiology of first and recurrent venous thromboembolism in patients with active cancer. A population-based cohort study. Thrombosis and haemostasis 2017; 117 (1): 57-65.

6   Kakkar AK, Haas S, Wolf H et al. Evaluation of perioperative fatal pulmonary embolism and death in cancer surgical patients. Thrombosis and haemostasis 2005; 94 (10): 867-871.

7   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.

8   Lyman GH, Culakova E, Poniewierski MS et al. Morbidity, mortality and costs associated with venous thromboembolism in hospitalized patients with cancer. Thrombosis research 2018; 164 Suppl 1: S112-S118.

9   Becattini C, Di Nisio M, Franco L et al. Treatment of venous thromboembolism in cancer patients: The dark side of the moon. Cancer treatment reviews 2021; 96: 102190.

10   Verso M, Munoz A, Bauersachs R et al. Effects of concomitant administration of anticancer agents and apixaban or dalteparin on recurrence and bleeding in patients with cancer-associated venous thromboembolism. Eur J Cancer 2021; 148: 371-381.

11   Di Nisio M, van Es N, Büller HR. Deep vein thrombosis and pulmonary embolism. Lancet 2016; 388 (10063): 3060-3073.

12   Geersing GJ, Zuithoff NP, Kearon C et al. Exclusion of deep vein thrombosis using the Wells rule in clinically important subgroups: individual patient data meta-analysis. BMJ 2014; 348: g1340.

13   Sterbling HM, Rosen AK, Hachey KJ et al. Caprini Risk Model Decreases Venous Thromboembolism Rates in Thoracic Surgery Cancer Patients. The Annals of Thoracic Surgery 2018; 105 (3): 879-885.

14   Guo Q, Huang B, Zhao J et al. Perioperative Pharmacological Thromboprophylaxis in Patients With Cancer: A Systematic Review and Meta-analysis. Annals of Surgery 2017; 265 (6): 1087-1093.

15   Akl EA, Kahale LA, Sperati F et al. Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer. Cochrane Database of Systematic Reviews 2014 (6).

16   Matar CF, Kahale LA, Hakoum MB et al. Anticoagulation for perioperative thromboprophylaxis in people with cancer. Cochrane Database Syst Rev 2018; 7: CD009447.

17   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.

18   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. Thrombosis research 2010; 125 (3): e65-e70.

19   Kakkos SK, Caprini JA, Geroulakos G et al. Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism. Cochrane Database Syst Rev 2016; 9 (9): Cd005258.

20   Zaghiyan KN, Sax HC, Miraflor E et al. Timing of Chemical Thromboprophylaxis and Deep Vein Thrombosis in Major Colorectal Surgery: A Randomized Clinical Trial. Annals of Surgery 2016; 264 (4): 632-639.

21   Selby LV, Sovel M, Sjoberg DD et al. Preoperative Chemoprophylaxis Is Safe in Major Oncology Operations and Effective at Preventing Venous Thromboembolism. J Am Coll Surg 2016; 222 (2): 129-137.

22   Bergqvist D, Burmark US, Flordal PA et al. Low molecular weight heparin started before surgery as prophylaxis against deep vein thrombosis: 2500 versus 5000 XaI units in 2070 patients. BJS (British Journal of Surgery) 1995; 82 (4): 496-501.

23   Song J-Q, Xuan L-Z, Wu W et al. Low molecular weight heparin once versus twice for thromboprophylaxis following esophagectomy: a randomised, double-blind and placebo-controlled trial. J Thorac Dis 2015; 7 (7): 1158-1164.

24   Bergqvist D, Agnelli G, Cohen AT et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med 2002; 346 (13): 975-980.

25   Rasmussen MS, Jorgensen LN, Wille-Jørgensen P et al. Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicenter randomized open-label study. Journal of thrombosis and haemostasis : JTH 2006; 4 (11): 2384-2390.

26   Agnelli G, Bolis G, Capussotti L et al. A Clinical Outcome-Based Prospective Study on Venous Thromboembolism After Cancer Surgery: The @RISTOS Project. Annals of Surgery 2006; 243 (1): 89-95.

27   Carrier M, Altman AD, Blais N et al. Extended thromboprophylaxis with low-molecular weight heparin (LMWH) following abdominopelvic cancer surgery. The American Journal of Surgery 2019; 218 (3): 537-550.

28   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. Annals of Surgery 2014; 259 (4): 665-669.

29   Khorana AA, Noble S, Lee AYY et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. Journal of thrombosis and haemostasis : JTH 2018; 16 (9): 1891-1894.

30   Falanga A, Russo L, Milesi V et al. Mechanisms and risk factors of thrombosis in cancer. Critical reviews in oncology/hematology 2017; 118: 79-83.

31   Rutjes AW, Porreca E, Candeloro M et al. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. Cochrane Database Syst Rev 2020; 12 (12): Cd008500.

32   Schünemann HJ, Ventresca M, Crowther M et al. Evaluating prophylactic heparin in ambulatory patients with solid tumours: a systematic review and individual participant data meta-analysis. Lancet Haematol 2020; 7 (10): e746-e755.

33   Maraveyas A. Latest advances in preventing thromboembolic disease in the ambulatory oncology patient. Thrombosis research 2020; 191 Suppl 1: S91-S98.

34   Carrier M, Abou-Nassar K, Mallick R et al. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. N Engl J Med 2019; 380 (8): 711-719.

35   Khorana AA, Soff GA, Kakkar AK et al. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. N Engl J Med 2019; 380 (8): 720-728.

36   Samama MM, Kleber FX. An update on prevention of venous thromboembolism in hospitalized acutely ill medical patients. Thrombosis journal 2006; 4: 8.

37   Zwicker JI, Rojan A, Campigotto F et al. Pattern of frequent but nontargeted pharmacologic thromboprophylaxis for hospitalized patients with cancer at academic medical centers: a prospective, cross-sectional, multicenter study. J Clin Oncol 2014; 32 (17): 1792-1796.

38   Barbar S, Noventa F, Rossetto V et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. Journal of thrombosis and haemostasis : JTH 2010; 8 (11): 2450-2457.

39   Patell R, Rybicki L, McCrae KR et al. Predicting risk of venous thromboembolism in hospitalized cancer patients: Utility of a risk assessment tool. Am J Hematol 2017; 92 (6): 501-507.

40   Carrier M, Khorana AA, Moretto P et al. Lack of evidence to support thromboprophylaxis in hospitalized medical patients with cancer. The American journal of medicine 2014; 127 (1): 82-86.e81.

41   Cohen AT, Spiro TE, Spyropoulos AC. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. N Engl J Med 2013; 368 (20): 1945-1946.

42   Brown JD, Adams VR. Incidence and Risk Factors of Thromboembolism with Multiple Myeloma in the Presence of Death as a Competing Risk: An Empirical Comparison of Statistical Methodologies. Healthcare (Basel, Switzerland) 2016; 4 (1).

43   Fotiou D, Gavriatopoulou M, Ntanasis-Stathopoulos I et al. Updates on thrombotic events associated with multiple myeloma. Expert review of hematology 2019; 12 (5): 355-365.

44   Brown JD, Adams VR, Moga DC. Impact of Time-Varying Treatment Exposures on the Risk of Venous Thromboembolism in Multiple Myeloma. Healthcare (Basel, Switzerland) 2016; 4 (4).

45   Huang H, Li H, Li D. Effect of serum monoclonal protein concentration on haemostasis in patients with multiple myeloma. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis 2015; 26 (5): 555-559.

46   Zamagni E, Brioli A, Tacchetti P et al. Multiple myeloma, venous thromboembolism, and treatment-related risk of thrombosis. Seminars in thrombosis and hemostasis 2011; 37 (3): 209-219.

47   Palumbo A, Palladino C. Venous and arterial thrombotic risks with thalidomide: evidence and practical guidance. Therapeutic advances in drug safety 2012; 3 (5): 255-266.

48   Cini M, Zamagni E, Valdré L et al. Thalidomide-dexamethasone as up-front therapy for patients with newly diagnosed multiple myeloma: thrombophilic alterations, thrombotic complications, and thromboprophylaxis with low-dose warfarin. European journal of haematology 2010; 84 (6): 484-492.

49   Fouquet G, Tardy S, Demarquette H et al. Efficacy and safety profile of long-term exposure to lenalidomide in patients with recurrent multiple myeloma. Cancer 2013; 119 (20): 3680-3686.

50   Zonder JA, Crowley J, Hussein MA et al. Lenalidomide and high-dose dexamethasone compared with dexamethasone as initial therapy for multiple myeloma: a randomized Southwest Oncology Group trial (S0232). Blood 2010; 116 (26): 5838-5841.

51   Elice F, Fink L, Tricot G et al. Acquired resistance to activated protein C (aAPCR) in multiple myeloma is a transitory abnormality associated with an increased risk of venous thromboembolism. British journal of haematology 2006; 134 (4): 399-405.

52   Baker HA, Brown AR, Mahnken JD et al. Application of risk factors for venous thromboembolism in patients with multiple myeloma starting chemotherapy, a real-world evaluation. Cancer Med 2019; 8 (1): 455-462.

53   Paludo J, Mikhael JR, LaPlant BR et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed lenalidomide-refractory multiple myeloma. Blood 2017; 130 (10): 1198-1204.

54   Leleu X, Rodon P, Hulin C et al. MELISSE, a large multicentric observational study to determine risk factors of venous thromboembolism in patients with multiple myeloma treated with immunomodulatory drugs. Thrombosis and haemostasis 2013; 110 (4): 844-851.

55   Fotiou D, Sergentanis TN, Papageorgiou L et al. Longer procoagulant phospholipid-dependent clotting time, lower endogenous thrombin potential and higher tissue factor pathway inhibitor concentrations are associated with increased VTE occurrence in patients with newly diagnosed multiple myeloma: results of the prospective ROADMAP-MM-CAT study. Blood cancer journal 2018; 8 (11): 102.

56   Bradbury CA, Craig Z, Cook G et al. Thrombosis in patients with myeloma treated in the Myeloma IX and Myeloma XI phase 3 randomized controlled trials. Blood 2020; 136 (9): 1091-1104.

57   Sanfilippo KM, Luo S, Wang TF et al. Predicting venous thromboembolism in multiple myeloma: development and validation of the IMPEDE VTE score. Am J Hematol 2019; 94 (11): 1176-1184.

58   Li A, Wu Q, Luo S et al. Derivation and Validation of a Risk Assessment Model for Immunomodulatory Drug-Associated Thrombosis Among Patients With Multiple Myeloma. J Natl Compr Canc Netw 2019; 17 (7): 840-847.

59   Carrier M, Le Gal G, Tay J et al. Rates of venous thromboembolism in multiple myeloma patients undergoing immunomodulatory therapy with thalidomide or lenalidomide: a systematic review and meta-analysis. Journal of thrombosis and haemostasis : JTH 2011; 9 (4): 653-663.

60   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 (1): CD006649.

61   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.

62   McBane RD, 2nd, Wysokinski WE, Le-Rademacher JG et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. Journal of thrombosis and haemostasis : JTH 2020; 18 (2): 411-421.

63   Agnelli G, Becattini C, Meyer G et al. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. N Engl J Med 2020; 382 (17): 1599-1607.

64   Kahale LA, Hakoum MB, Tsolakian IG et al. Anticoagulation for the long-term treatment of venous thromboembolism in people with cancer. Cochrane Database Syst Rev 2018; 6 (6): CD006650.

65   Khorana AA, McCrae KR, Milentijevic D et al. Current practice patterns and patient persistence with anticoagulant treatments for cancer-associated thrombosis. Research and practice in thrombosis and haemostasis 2017; 1 (1): 14-22.

66   Raskob GE, van Es N, Verhamme P et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. N Engl J Med 2018; 378 (7): 615-624.

67   Planquette B, Bertoletti L, Charles-Nelson A et al. Rivaroxaban vs Dalteparin in Cancer-Associated Thromboembolism: A Randomized Trial. Chest 2022; 161 (3): 781-790.

68   Lee AY, Levine MN, Baker RI et al. 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.

69   Mulder FI, Bosch FTM, Young AM et al. Direct oral anticoagulants for cancer-associated venous thromboembolism: a systematic review and meta-analysis. Blood 2020; 136 (12): 1433-1441.

70   Jara-Palomares L, Solier-Lopez A, Elias-Hernandez T et al. Tinzaparin in cancer associated thrombosis beyond 6months: TiCAT study. Thrombosis research 2017; 157: 90-96.

71   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. Journal of thrombosis and haemostasis : JTH 2015; 13 (6): 1028-1035.

72   Moik F, Colling M, Mahé I et al. Extended anticoagulation treatment for cancer-associated thrombosis-Rates of recurrence and bleeding beyond 6 months: A systematic review. Journal of thrombosis and haemostasis : JTH 2021.

73   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. J Clin Oncol 2014; 32 (32): 3607-3612.

74   Marshall A, Levine M, Hill C et al. Treatment of cancer-associated venous thromboembolism: 12-month outcomes of the placebo versus rivaroxaban randomization of the SELECT-D Trial (SELECT-D: 12m). Journal of thrombosis and haemostasis : JTH 2020; 18 (4): 905-915.

75   Jara-Palomares L, Solier-Lopez A, Elias-Hernandez T et al. D-dimer and high-sensitivity C-reactive protein levels to predict venous thromboembolism recurrence after discontinuation of anticoagulation for cancer-associated thrombosis. Br J Cancer 2018; 119 (8): 915-921.

76   Di Nisio M, Carrier M. Incidental venous thromboembolism: is anticoagulation indicated? Hematology American Society of Hematology Education Program 2017; 2017 (1): 121-127.

77   Caiano L, Carrier M, Marshall A et al. Outcomes among patients with cancer and incidental or symptomatic venous thromboembolism: A systematic review and meta-analysis. Journal of thrombosis and haemostasis : JTH 2021; 19 (10): 2468-2479.

78   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.

79   Leader A, Ten Cate H, Spectre G et al. Antithrombotic medication in cancer-associated thrombocytopenia: Current evidence and knowledge gaps. Critical reviews in oncology/hematology 2018; 132: 76-88.

80   PREPIC Study Group. Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism: the PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) randomized study. Circulation 2005; 112 (3): 416-422.

81   Boddi M, Villa G, Chiostri M et al. Incidence of ultrasound-detected asymptomatic long-term central vein catheter-related thrombosis and fibrin sheath in cancer patients. European journal of haematology 2015; 95 (5): 472-479.

82   Kamphuisen PW, Lee AY. Catheter-related thrombosis: lifeline or a pain in the neck? Hematology American Society of Hematology Education Program 2012; 2012: 638-644.

83   Jiang M, Li CL, Pan CQ et al. Risk of venous thromboembolism associated with totally implantable venous access ports in cancer patients: A systematic review and meta-analysis. Journal of thrombosis and haemostasis : JTH 2020; 18 (9): 2253-2273.

84   Moss JG, Wu O, Bodenham AR et al. Central venous access devices for the delivery of systemic anticancer therapy (CAVA): a randomised controlled trial. Lancet 2021; 398 (10298): 403-415.

85   Kahale LA, Tsolakian IG, Hakoum MB et al. Anticoagulation for people with cancer and central venous catheters. Cochrane Database Syst Rev 2018; 6 (6): CD006468-CD006468.

86   Savage KJ, Wells PS, Schulz V et al. Outpatient use of low molecular weight heparin (Dalteparin) for the treatment of deep vein thrombosis of the upper extremity. Thrombosis and haemostasis 1999; 82 (3): 1008-1010.

87   Kovacs MJ, Kahn SR, Rodger M et al. A pilot study of central venous catheter survival in cancer patients using low-molecular-weight heparin (dalteparin) and warfarin without catheter removal for the treatment of upper extremity deep vein thrombosis (The Catheter Study). Journal of thrombosis and haemostasis : JTH 2007; 5 (8): 1650-1653.

88   Tran H, Arellano M, Chamsuddin A et al. Deep venous thromboses in patients with hematological malignancies after peripherally inserted central venous catheters. Leuk Lymphoma 2010; 51 (8): 1473-1477.

89   Laube ES, Mantha S, Samedy P et al. Treatment of central venous catheter-associated deep venous thrombosis in cancer patients with rivaroxaban. Am J Hematol 2017; 92 (1): E9-e10.

90   Fan F, Zou Y, Zhang S et al. Rivaroxaban in the Treatment of PICC-associated Upper Extremity Venous Thrombosis. Clin Ther 2017; 39 (9): 1882-1888.

91   Davies GA, Lazo-Langner A, Gandara E et al. A prospective study of Rivaroxaban for central venous catheter associated upper extremity deep vein thrombosis in cancer patients (Catheter 2). Thrombosis research 2018; 162: 88-92.

92   Frank DA, Meuse J, Hirsch D et al. The treatment and outcome of cancer patients with thromboses on central venous catheters. J Thromb Thrombolysis 2000; 10 (3): 271-275.

93   Shatzel JJ, Mart D, Bien JY et al. The efficacy and safety of a catheter removal only strategy for the treatment of PICC line thrombosis versus standard of care anticoagulation: a retrospective review. J Thromb Thrombolysis 2019; 47 (4): 585-589.

94   Baumann Kreuziger L, Jaffray J, Carrier M. Epidemiology, diagnosis, prevention and treatment of catheter-related thrombosis in children and adults. Thrombosis research 2017; 157: 64-71.

95   Gross PA, Barrett TL, Dellinger EP et al. Purpose of Quality Standards for Infectious Diseases. Clin Infect Dis 1994; 18 (3): 421-421.

96   Dykewicz CA. Summary of the Guidelines for Preventing Opportunistic Infections among Hematopoietic Stem Cell Transplant Recipients. Clin Infect Dis 2001; 33 (2): 139-144.

97   Marchetti M, Diani E, ten Cate H et al. Characterization of the thrombin generation potential of leukemic and solid tumor cells by calibrated automated thrombography. Haematologica 2012; 97 (8): 1173-1180.

98   Sasano T, Gonzalez-Delgado R, Munoz NM et al. Podoplanin promotes tumor growth, platelet aggregation, and venous thrombosis in murine models of

ovarian cancer. Journal of thrombosis and haemostasis : JTH 2022; 20 (1): 104-114.

99 DuPre SA, Hunter KW, Jr. Murine mammary carcinoma 4T1 induces a leukemoid reaction with splenomegaly: association with tumor-derived growth factors. Exp Mol Pathol 2007; 82 (1): 12-24.

100 Hisada Y, Mackman N. Update from the laboratory: mechanistic studies of pathways of cancer-associated venous thrombosis using mouse models. Hematology American Society of Hematology Education Program 2019; 2019 (1): 182-186.

101 Riedl J, Preusser M, Nazari PM et al. Podoplanin expression in primary brain tumors induces platelet aggregation and increases risk of venous thromboembolism. Blood 2017; 129 (13): 1831-1839.
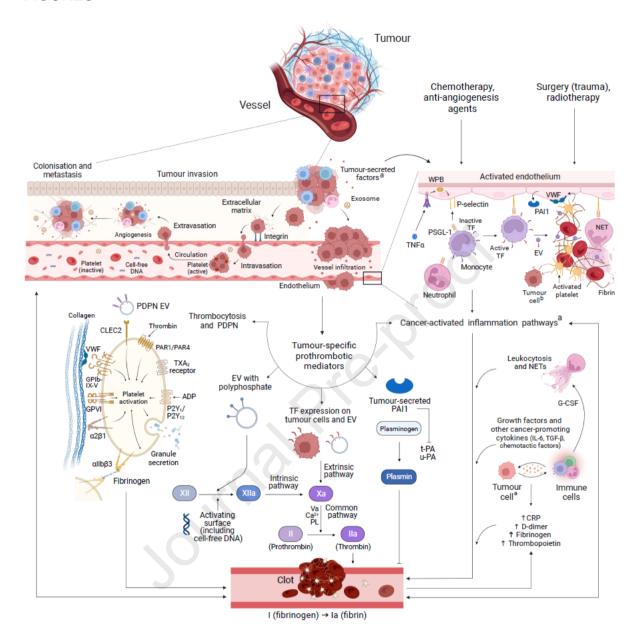
FIGURES

Figure 1. Cancer-associated hypercoagulability and thrombosis.

Cancer-associated thrombosis is associated with worsened survival, morbidity, need for hospitalisation and potential delay or interruption of systemic cancer therapy. VTE rates vary according to several factors. Besides well-known patient-related risk factors, such as age, comorbidities, history of previous VTE, central venous catheters, immobility and hospitalisation, a number of cancer-related aspects have been increasingly recognised as potentially thrombogenic. Some cancer types pose by definition an increased risk of thrombosis, e.g. pancreatic, stomach and primary

brain tumours. Multiple cancer-specific mechanisms of VTE have been identified.[97] For example, high levels of platelets and high levels of leukocytes have been described as thrombogenic in ovarian and lung cancer, respectively.[98-100] The release into the circulation of procoagulant proteins that directly activate the coagulation cascade or platelets has been described, such as TF and PDPN in pancreatic and brain cancer, respectively.[98,100,101]

I, coagulation factor I; Ia, activated coagulation factor I; II, coagulation factor II; IIa, activated coagulation factor II; Va, activated coagulation factor V; Xa, activated coagulation factor X; XII, coagulation factor XII; XIIa, activated coagulation factor XII; CLEC2, C-type lectin-like receptor 2; CRP, C-reactive protein; EV, extracellular vesicle; G-CSF, granulocyte colony-stimulating factor; GP, glycoprotein; IL-6, interleukin 6; NET, neutrophil extracellular trap; P2Y1/P2Y12, adenosine diphosphate receptor; PAI1, plasminogen activator inhibitor-1; PAR1/PAR4, protease-activated receptor 1/4; PDPN, podoplanin; PL, phospholipid; PSGL-1, P-selectin glycoprotein ligand-1; t-PA, tissue plasminogen activator; TF, tissue factor; TGF-β, transforming growth factor beta; TNFα, tumour necrosis factor alpha; TXA2, thromboxane A2; u-PA, urokinase-type plasminogen activator; VTE, venous thromboembolism; VWF, Von Willebrand factor; WPB, Weibel–Palade bodies.

Created with BioRender.com.

[a] Cancer cells cause the release of chemotactic, angiogenic and pro-inflammatory mediators that attract circulating monocytes and activate neutrophils and endothelial cells.

[b] Platelets interact with tumour cells through different receptors expressed on the platelet surface (e.g. collagen receptor GPVI, P-selectin, integrins α6β1 or αIIbβ3 and GPIIb/IIIa).
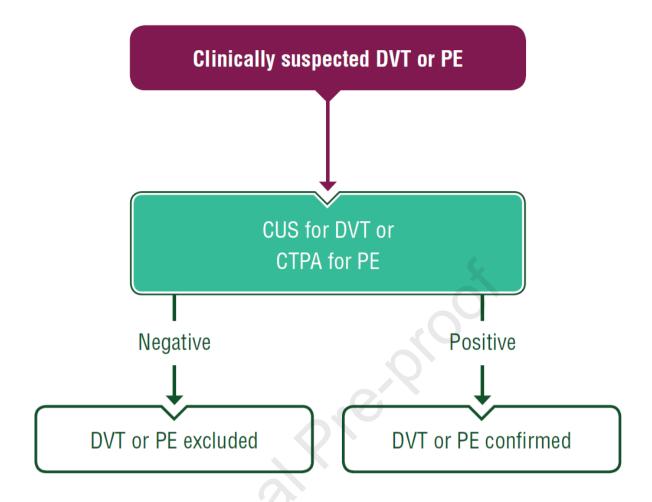
Figure 2. Diagnostic algorithm for suspected DVT and PE in cancer patients.

Purple: general categories or stratification; white: other aspects of management; turquoise: combination of treatments or other systemic treatments.

CUS, compression ultrasonography; CTPA, computed tomography pulmonary angiography; DVT, deep vein thrombosis; PE, pulmonary embolism.
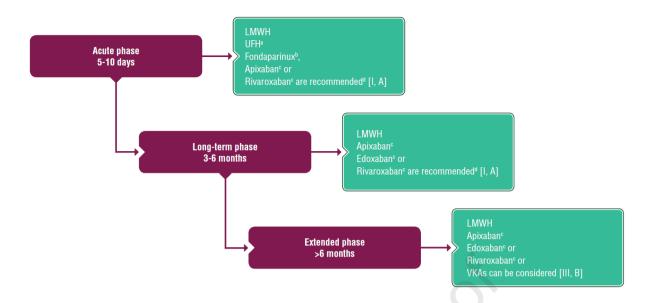
Figure 3. Treatment of CAT.

Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments.

CAT, cancer-associated thrombosis; DVT, deep vein thrombosis; GI, gastrointestinal; HIT, heparin-induced thrombocytopaenia; LMWH, low molecular weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonist.

[a] UFH to consider in patients with creatinine <30 mg/ml.

[b] Fondaparinux if previous HIT.

[c] Caution in patients receiving potent inhibitors of P-glycoprotein and CYP3A4 or with luminal GI cancers.

[d] There are some clinical situations in which these are contraindicated: triple positive antiphospholipid syndrome, renal failure with creatinine clearance <15 ml/min, pregnancy and lactation. Limited clinical experience in patients with thrombosis of unusual location (upper limb DVT, catheter-associated thrombosis, venous sinus thrombosis or splanchnic thrombosis). In patients with brain metastases LMWH should be used.

Figure 4. Algorithm on CAT treatment, shared decision-making in the ambulatory patient.

Purple: general categories or stratification; white: other aspects of management; turquoise: combination of treatments or other systemic treatments.

CAT, cancer-associated thrombosis; GI, gastrointestinal; LMWH, low molecular weight heparin.

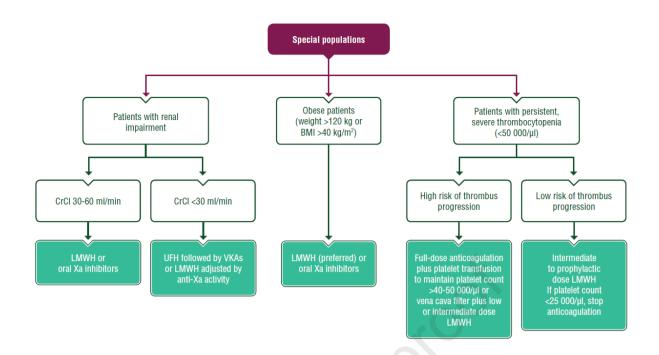**Figure 5. Algorithms of CAT in special populations.**

Purple: general categories or stratification; white: other aspects of management; turquoise: combination of treatments or other systemic treatments.

BMI, body mass index; CAT, cancer-associated thrombosis; CrCl, creatinine clearance; LMWH, low molecular weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonist.

Table 1. VTE prophylaxis options in cancer patients

Options	Hospitalised patients	Surgical patients	Ambulatory patients
Heparins[a]			
UFH	5000 IU every 8 hours	5000 IU 2-4 hours preoperatively and every 8 hours thereafter	-
Bemiparin	3500 anti-Xa IU od	3500 anti-Xa IU starting 2 hours preoperatively or 6 hours post-operatively and 3500 anti-Xa IU od thereafter	3500 anti-Xa IU od[b]
Dalteparin	5000 anti-Xa IU od	5000 anti-Xa IU 12 hours preoperatively and 5000 anti-Xa IU od thereafter	5000 anti-Xa IU od[b,c]
Enoxaparin	4000 anti-Xa IU od	4000 anti-Xa IU 12 hours preoperatively and 4000 anti-Xa IU od thereafter	4000 anti-Xa IU od[b]
Nadroparin	3800 anti-Xa IU od (if weight >70 kg 5700 anti-Xa IU/kg od)	2850 anti-Xa IU 2-4 hours preoperatively and 2850 anti-Xa IU od thereafter	3800 anti-Xa IU od (if weight >70 kg 5700 anti-Xa IU od)[b]
Tinzaparin	4500 anti-Xa IU od	4500 anti-Xa IU od, beginning 12 hours post-operatively	4500 anti-Xa IU od[b]

Selective parenteral indirect factor Xa inhibitor			
Fondaparinux	2.5 mg od	2.5 mg od beginning 6-8 hours post-operatively	Not studied in the outpatient prophylaxis setting
DOACs			
Apixaban	Not recommended	Not recommended	2.5 mg orally bd[b]
Rivaroxaban	Not recommended	Not recommended	10 mg orally od[b]
Mechanical prophylaxis			
IPC	If pharmacological VTE prophylaxis is contraindicated[d]	If pharmacological VTE prophylaxis is contraindicated[d]	Not recommended
Venous foot pump	If pharmacological VTE prophylaxis is contraindicated[d]	If pharmacological VTE prophylaxis is contraindicated[d]	Not recommended
GCSs	If pharmacological VTE prophylaxis is contraindicated[d]	If pharmacological VTE prophylaxis is contraindicated[d]	Not recommended

bd, twice daily; DOAC, direct oral anticoagulant; GCS, graduated compression stocking; IPC, intermittent pneumatic compression; od, once daily; UFH, unfractionated heparin; VTE, venous thromboembolism

[a] Approved indications and dosages of anticoagulants may vary across different countries.

[b] Lack of a specific indication for cancer outpatients in the package inserts.

[c] In pancreatic cancer, higher doses have been used in clinical trials in this setting.

[d] Some patients may also have a contraindication for mechanical prophylaxis (e.g. patients with peripheral limb ischaemia).

Table 2. Treatment options of VTE in cancer patients

Drug	Initial treatment of established VTE (5-10 days)	Early maintenance (up to 6 months) and long-term maintenance (beyond 6 months)
Heparins (LMWH)		
Dalteparin	100 anti-Xa IU/kg every 12 hours, or 200 anti-Xa IU/kg daily for the first 30 days	150 anti-Xa IU/kg daily after day 30
Enoxaparin	100 anti-Xa IU/kg every 12 hours, or 150 anti-Xa IU/kg od	100 anti-Xa IU/kg every 12 hours, or 150 anti-Xa IU/kg od
Tinzaparin	175 anti-Xa IU/kg od	175 anti-Xa IU/kg od
Nadroparin	86 anti-Xa IU/kg every 12 hours, or 171 anti-Xa IU/kg od	86 anti-Xa IU/kg every 12 hours, or 171 anti-Xa IU/kg od
Bemiparin	115 anti-Xa IU/kg od	115 anti-Xa IU/kg od
Heparins (UFH)		
UFH	80 IU/kg i.v. bolus, then 18 U/kg/h i.v.; adjust dose based on aPTT	-

DOACs		
Edoxaban		60 mg, od 30 mg, od if: 1) creatinine clearance <50 ml/min, 2) ≤60 kg or 3) patients receiving inhibitors of P-glycoprotein
Rivaroxaban	15 mg every 12 hours for 3 weeks	20 mg od
Apixaban	10 mg every 12 hours for 7 days	5 mg every 12 hours
Vitamin K antagonists		
Acenocoumarol		Adjust dose to maintain INR 2-3
Phenprocoumon		Adjust dose to maintain INR 2-3
Warfarin	-	Adjust dose to maintain INR 2-3

aPTT, activated partial thromboplastin time; DOAC, direct oral anticoagulant;
INR, international normalised ratio; i.v., intravenous; LMWH, low molecular weight
heparin; od, once daily; UFH, unfractionated heparin;
VTE, venous thromboembolism.

Clinically suspected DVT or PE

CUS for DVT or
CTPA for PE

Negative

Positive

DVT or PE excluded

DVT or PE confirmed

**Acute phase
5-10 days**

LMWH
UFH[a]
Fondaparinux[b],
Apixaban[c] or
Rivaroxaban[c] are recommended[d] [I, A]

**Long-term phase
3-6 months**

LMWH
Apixaban[c]
Edoxaban[c] or
Rivaroxaban[c] are recommended[d] [I, A]

**Extended phase
>6 months**

LMWH
Apixaban[c]
Edoxaban[c] or
Rivaroxaban[c] or
VKAs can be considered [III, B]

CAT

- Unresected upper GI or urothelial cancer
- Risk of bleeding:
  - Moderate/severe GI toxicity (i.e. mucositis)
  - Recent and/or life-threatening bleeding
- CYP3A4 or P-glycoprotein strong inhibitors or inducers
- Other CAT patients

LMWH

LMWH or oral Xa inhibitors

Beyond 6 months of anticoagulant treatment

Consider extending anticoagulation if active cancer (i.e. metastatic or unresectable, locally-advanced disease)

Special populations

Patients with renal impairment

Obese patients (weight >120 kg or BMI >40 kg/m^2)

Patients with persistent, severe thrombocytopenia (<50 000/µl)

CrCl 30-60 ml/min

CrCl <30 ml/min

High risk of thrombus progression

Low risk of thrombus progression

LMWH or oral Xa inhibitors

UFH followed by VKAs or LMWH adjusted by anti-Xa activity

LMWH (preferred) or oral Xa inhibitors

Full-dose anticoagulation plus platelet transfusion to maintain platelet count >40-50 000/µl or vena cava filter plus low or intermediate dose LMWH

Intermediate to prophylactic dose LMWH If platelet count <25 000/µl, stop anticoagulation