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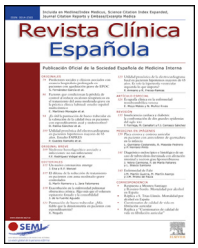

SPECIAL ARTICLE

2024 Spanish Society of Internal Medicine (SEMI) recommendations for the management of cancer-associated venous thromboembolism

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Abstract Vennous thromboembolism (VTE) is a common complication associated to greater mortality in patients with cancer. Its etiology is multifactorial and depends on the characteristics and co-morbidities of the patient, the tumor type and extension, and the oncological treatment. The management of VTE is more complex in patients with cancer due to an increased risk of recurrence and major bleeding complications during anticoagulation compared to the general non-oncological population. The above differences have led to the development of specific clinical trials to assess the efficacy and safety of anticoagulant therapy in patients with cancer. The present clinical guidelines are intended to provide general recommendations on the management of cancer-associated VTE according to updated according to the most recent scientific evidence.

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PALABRAS CLAVE
Trombosis asociada al cáncer;
Trombosis paraneoplásica;
Recomendaciones de consenso para la práctica clínica

Recomendaciones 2024 de la Sociedad Española de Medicina Interna (SEMI) para el manejo de la trombosis venosa asociada al cáncer

Resumen La enfermedad tromboembólica venosa (ETV) es una complicación frecuente y que se asocia a mayor mortalidad en los pacientes con cáncer. Su etiología es multifactorial y depende de las características y comorbilidades del paciente, del tipo y extensión del tumor y del tratamiento oncológico. El manejo de la ETV en los pacientes con cáncer es más complejo debido a un mayor riesgo de recurrencia a pesar del tratamiento anticoagulante y de complicaciones hemorrágicas comparado con la población general. Estas diferencias han llevado al desarrollo de ensayos clínicos específicos para evaluar la eficacia y seguridad del tratamiento anticoagulante en la población oncológica. Estas guías pretenden dar recomendaciones generales sobre el manejo de la ETV asociada al cáncer según la evidencia científica más reciente.

Introduction

Cancer-associated thrombosis (CAT) is a common disease associated with high morbidity and mortality. The most common clinical presentation is as venous thromboembolism (VTE), which encompasses both deep vein thrombosis (DVT), usually of the lower limbs, and pulmonary embolism (PE). Less frequently, CAT manifests as venous thrombosis in atypical locations (in the upper limbs associated or not with a central venous catheter, the splanchnic territory, or the cerebral venous sinuses), arterial thrombosis, thrombotic microangiopathy, marantic endocarditis, or even disseminated intravascular coagulation.[1]

Internal medicine departments play a key role in the diagnosis and treatment of CAT in different clinical scenarios in most hospitals in Spain (Fig. 1). The holistic view of the disease provided by internists allows for creating the backbone of a multidisciplinary intervention with the different specialists involved in the diagnosis and management of patients with cancer: tumor committees, medical and radiation oncologists, surgeons, radiologists, or palliative care teams, among others.

Given the foregoing, the Thromboembolic Disease Group of the Spanish Society of Internal Medicine (SEMI) has prepared this document in order to update recommendations on the management of cancer-associated VTE. These clinical practice guidelines have been developed and agreed upon following a systematic review of the available medical literature (see Appendix updated as of March 4, 2024), taking into consideration the recommendations of the main international scientific societies,[2–5] and include a level of evidence[6] for each of the following sections:

- Epidemiology, risk factors, and particularities in diagnosing CAT.
- Acute and long-term (3–6 months) treatment of CAT.
- Treatment that extends beyond six months.
- Frequent special situations in oncology patients: active bleeding, recurrence of VTE despite anticoagulant therapy, thrombocytopenia, and central venous catheter-associated thrombosis.

Epidemiology, risk factors, and particularities in diagnosing CAT

Cancer entails a four- to seven-fold increase in the risk of VTE. It is estimated that up to 20% of all initial venous thrombotic events are associated with oncological disease.[1] The incidence of CAT has progressively increased in recent years while remaining stable in the general population. The onset of VTE is more common in the first three months after a cancer diagnosis and is associated with an increased risk of mortality.[1,7] There are multiple risk factors for CAT. They are usually classified into those related to the patient's characteristics and comorbidities, the type and extent of the tumor, and the oncological treatment (Table 1).[1,7]

The clinical manifestations associated with VTE are nonspecific and include edema, pain, and thoracic or cardiovascular symptoms. The differential diagnosis of CAT is particularly complex, as these symptoms can often be attributed to the neoplasm, the toxicity of oncological treatments, or other complications common in this population. Furthermore, in patients with cancer, the performance of the pretest probability scales and D-dimer determination used in the diagnostic process of VTE for the general population are poor.[8,9] Based on the above, an imaging test is recommended when there is clinical suspicion of CAT. The test performed is usually a compression ultrasound for the diagnosis of DVT and/or a computed tomography pulmonary angiogram for the diagnosis of PE.[9,10] A ventilation-perfusion scintigraphy is reserved for patients with an allergy to iodinated contrast media and/or creatinine clearance <30 ml/min. On the other hand, CAT is nowadays very frequently diagnosed incidentally in the imaging tests performed for the diagnosis or follow-up of cancer.

Table 1 Risk factors for venous thromboembolism in patients with cancer.

Patient-related factors		
General	Personal or family history of VTE.	
	Sex. Age.	
	Obesity.	
	Blood group other than O	
	Hospitalization. Immobility.	
	Surgery.	
Venous disease.	Varicose veins. Venous malformations. May-Thurner syndrome. Inferior vena cava agenesis.	
Gestation	Pregnancy, childbirth, and puerperium.	
Concomitant diseases	Inflammatory diseases: acute infections, SARS-CoV-2.	
	Autoimmune diseases: Behçet's disease, antiphospholipid syndrome.	
	Myeloproliferative disorders: polycythemia vera, CML, myelofibrosis.	
	Paroxysmal nocturnal hemoglobinuria.	
Drugs	Antipsychotics. Combined hormone therapy.	
Thrombophilias	Hereditary: prothrombin polymorphisms, factor V Leiden. Protein C, protein S, and antithrombin deficiencies.	
	Acquired: antiphospholipid syndrome.	
Blood test abnormalities.	Anemia. Leukocytosis. Thrombocytosis.	
Tumor-related factors		
Primary tumors and metastases	Primary tumor:	-Very high risk: pancreas, gastric, brain.
		-High risk: lung, gynecological, germline, urothelial.
		-Low risk: prostate and breast.
	Active cancer. Tumor progression.	
	Vascular compression/infiltration.	
	High histological grade.	
	Adenocarcinoma. Mucinous adenocarcinoma.	
	First three months after the cancer diagnosis.	
Molecular genetic profile	-Lung adenocarcinoma with ALK, ROS-1 rearrangement.	
	-KRAS mutation.	
	-JAK-2 mutation.	
Cancer therapy-related factors		
Systemic cancer therapy	**Myeloablative chemotherapy.**	
	Hormone therapy:	-estrogen receptor modulators: tamoxifen, raloxifene.
		-gonadotropin-releasing hormone analog: leuprolide, goserelin acetate.
		-antiandrogens: bicalutamide.
	Immunomodulators:	thalidomide, lenalidomide.
		cetuximab, panitumumab.
	Anti-EGFR: **Antiangiogenics**:	-anti-VEGF: bevacizumab, aflibercept, ramucirumab.
		-anti-TKI: sunitinib, axitinib, regorafenib.
	Immunotherapy:	-PD-1, PD-L1, and CTLA-4 immune checkpoint inhibitors.
		-Chimeric antigen receptor T-cell (CAR-T) therapy.
	Cyclin-dependent kinase inhibitors:	abemaciclib, palbociclib, ribociclib.
Venous catheter	PICC-type catheter greater risk than catheter with a PAC-type reservoir.	
Supportive therapies	High-dose corticosteroids, megestrol acetate.	
	G-CSF. Erythropoietin.	
	Transfusion of blood products.	

ALK: anaplastic lymphoma kinase; CAR-T: chimeric antigen receptor T-cell; EGFR: endothelial growth factor; CTLA-4: cytotoxic T-lymphocyte associated protein 4; VTE: venous thromboembolic disease; EGFR: epidermal growth factor receptor; G-CSF: granulocyte colony-stimulating factor; JAK2: janus kinase 2; CML: chronic myeloid leukemia; PAC: port-a-cath; PD-1: programme death; PD-L1: programmed death ligand; PICC: peripherally inserted central catheter; VTE: venous thromboembolism; TKI: tyrosine kinase inhibitor; CAT: cancer-associated thrombosis; VEGF: vascular endothelial growth factor.

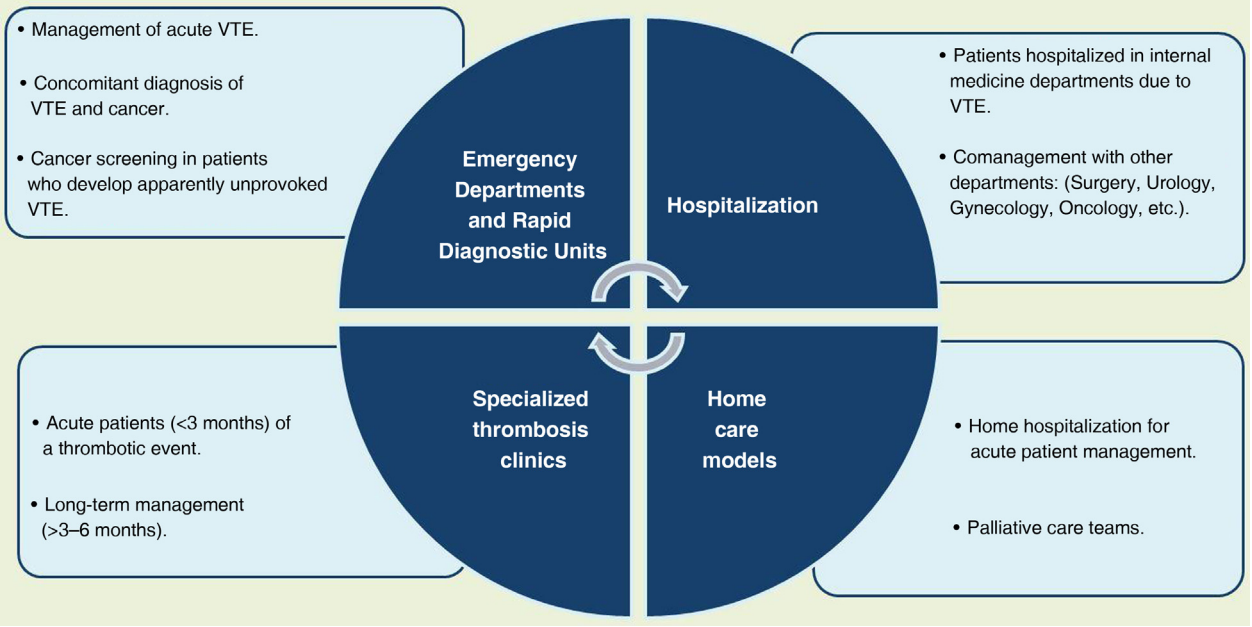

Figure 1 Healthcare settings in which internists are involved in the care of patients with CAT.

Acute phase and long-term (3–6 months) treatment of CAT

Anticoagulation is the cornerstone of CAT treatment. It has a twofold objective: to halt thrombus progression and prevent recurrence. Some real-life studies have demonstrated that patients with CAT have greater difficulty in maintaining adequate follow-up INR levels[11] and a higher risk of recurrence and major bleeding with the use of vitamin K antagonists (VKA) compared to patients without cancer.[11,12] These data led to the development of new treatment strategies for the population with cancer that involve prolonged treatment with low-molecular-weight heparin (LMWH). Five clinical trials have evaluated the efficacy and safety of initial and long-term (3–6 months) treatment with LMWH *versus* the classic treatment regimen of LMWH followed by VKA: the CANTHANOX[13] and ONCENOX[14] studies with enoxaparin, the CLOT[15] study with dalteparin, and the LITE[16] and CATCH[17] studies with tinzaparin. Of these, the CLOT study[15] stands out. In it, 336 patients were randomized into the standard treatment arm with LMWH followed by VKA and 336 patients into the experimental arm with dalteparin at full doses for the first month and a 25% reduction in the dose from the second month until completing six months of treatment. The outcomes of the CLOT study[15] and the meta-analysis with data from the five trials mentioned above confirmed the greater efficacy of treatment with LMWH *versus* VKA, with a 40% reduction in the risk of VTE recurrence (RR: 0.60; 95% CI: 0.45—0.79)[18] with no differences observed in the incidence of major bleeding or mortality. These results led to a change in the standard of initial and long-term treatment with LMWH in patients with cancer.

There are no prospective studies to compare the efficacy and safety of direct oral anticoagulants (DOACs) *versus* VKAs in patients with CAT. The *ad hoc* analysis of the population with cancer (which represented only 6% of the total) included in the phase III clinical trials evaluating DOACs *versus* VKAs in the general population showed no differences in efficacy and safety in the subanalysis of the population with cancer.[19] These favorable data led to the conduct of phase 3 clinical trials in patients with CAT to compare DOACs with anti-Xa activity (edoxaban, rivaroxaban, apixaban) *versus* standard LMWH therapy: the Hokusai-VTE-Cancer (N = 1046 patients) study with edoxaban,[20] the SELECT-D (N = 406 patients)[21] and CASTA-DIVA (N = 158 patients)[22] studies with rivaroxaban, the ADAM-VTE (N = 287 patients)[23] and Caravaggio (N = 1155 patients)[24] studies with apixaban, and finally the CANVAS study (N = 638 patients)[25] with various anti-Xa DOACs. Except for the CANVAS[25] study, in which the use of any LMWH and even the transition with VKA was allowed, dalteparin was used in the rest of the trials as a comparator according to the CLOT trial regimen. Subsequently, up to 17 meta-analyses have been published with data from the above clinical trials. The meta-analysis by Mulder et at.[26] included data from 2607 patients from the four main studies.[20,24] It found no significant differences in efficacy, safety, or mortality, including in the subanalysis of a subgroup of 774 patients with incidentally diagnosed CAT. More recently, the meta-analysis by Frere et al.,[27] with data from 3690 patients from the six trials,[20,25] has demonstrated the greater efficacy of DOACs with a significant reduction in recurrences (RR: 0.67; 95% CI: 0.52–0.85; $p = 0.001$) at the expense of a higher incidence of clinically relevant non-major bleeding (CRNMB) (RR: 1.66, 95% CI: 1.31–2.09; $p < 0.0001$), although without significant differences in major bleeding or mortality compared to LMWH. Major bleeding was more frequent in patients with gastrointestinal tumors not operated on in the case of treatment with edoxaban[20,27] and rivaroxaban.[21,27] Even in the SELECT-D study, the recruitment of patients with esophageal or gastroesophageal junction cancer was discontinued after the first safety analysis. This increased frequency of major

Table 2 2024 recommendations for acute phase and long-term (first 3–6 months) management of CAT.

Acute phase and long-term (3–6 months) treatment of CAT	
-**LMWH and anti-factor Xa DOACs** (apixaban, edoxaban, rivaroxaban) **are the first choice** for most patients with CAT with a high level of evidence: 1A.[6]	
-The **choice between LMWH or DOACs** will depend on different factors:	
Factors favoring the use of **LMWH**:	Factors favoring the use of **DOACs**:
• Oral route not available.	• **Oral** route preserved.
• Risk of **drug interactions.**[29,30]	• Little risk of drug interactions.[29,30] Check at least 2 updated databases[a] and periodically review changes in medication.
• Tumor type: first choice in unresected intraluminal digestive and genitourinary tumors.	• **Low bleeding risk** (see Table 3).
• **High bleeding risk** (see Table 3).	• **Heparin-induced thrombocytopenia**.
• Thrombocytopenia.	• Other forms of **hypersensitivity or intolerance to LMWH administration**.
• Liver failure.	• Healthcare coverage.
• Kidney failure.	• Patient preference.
• Healthcare coverage.	
• Patient preference.	

DOAC: direct acting oral anticoagulant; CVC: central venous catheter; VTE: venous thromboembolism; LMWH: low-molecular-weight heparin; CNS: central nervous system; PE: pulmonary embolism; DVT: deep vein thrombosis.
[a] Lexicomp® http://www.wolterskluwer.com/en/solutions/lexicomp; Medscape https://reference.medscape.com/drug-interactionchecker; ONCO/ACOD https://oncoacod.es; Drugs.com https://www.drugs.com/drug_interactions.html; ONCOassist: https://oncoassist.com/drug-interaction-checker.

bleeding was not found in the case of treatment with apixaban.[23,24,27] As for CRNMB, it was more frequent with the three DOACs.[27] There are no clinical trials on dabigatran in patients with cancer, so its use would not be indicated in this population.

Based on the above, this group recommends the use of LMWH or anti-Xa DOACs as the first choice for treatment in the acute phase and in the long term (first 3–6 months) for most patients with CAT (Table 2) with a high level of evidence (1A).[6]

The choice between LMWH or DOACs should be carefully individualized, taking several aspects into consideration:[2–5,26–28] (i) available oral or parenteral route of administration; (ii) type and location of the tumor; (iii) bleeding risk; (iv) possible drug interactions (DI), in particular the potential interaction of DOACs with potent CYP3A4 and/or P-glycoprotein modulating drugs,[29,30] given the multiple cancer and supportive treatments (antiemetics, anticonvulsants, corticosteroids, etc.) that these patients frequently receive; (v) access to medications (cost, health coverage, etc.); and (vi) the patient's values and preferences.

At present, the use of VKAs for patients with CAT should be reserved for very select cases that cannot be treated with DOACs or LMWH. Similarly, despite the lack of quality evidence, the use of fondaparinux can be considered in patients with hypersensitivity to LMWH who cannot be treated with DOACs or VKA (see Appendix).

The assessment of bleeding risk is a challenge in clinical practice, given that there is no validated predictive model for patients anticoagulated due to CAT.[31–34] Caution should be exercised and a clinical estimation of risk should be made based on variables associated with bleeding risk that are common in the general population with VTE,[31] bleeding scales developed for other clinical scenarios,[33,34] tumor characteristics, the presence of other comorbidities, and the specific clinical circumstances of each patient that are listed in Table 3.[28,31–34] As an added layer of complexity in decision making, some variables (age, sex, body mass index, PE as the index event, cardiovascular comorbidity, location and extent of cancer, and the use of chemotherapy) have been associated with both increased risk of bleeding and recurrence of VTE.[33]

Finally, it should be taken into account that it is common in clinical practice to find particularly fragile oncology patients who have been excluded from clinical trials.[13–17,20–25] In these cases, treatment should be individualized based on the best clinical judgment, taking into account real-world data, an interdisciplinary assessment, and taking into consideration the patient's values and preferences. Furthermore, these patients should be monitored more closely and education should be given on alarm symptoms for this profile of frail patients.[3–5,28,32]

Extended-phase anticoagulant treatment after six months of therapy

Most clinical trials[13–17,20–25] for the treatment of CAT ended the observation period at six months. Therefore, the level of evidence available on what should be the optimal duration of anticoagulant therapy and with which drug and dosage (full or reduced doses) after completing the first six months of treatment is limited and of low quality.

The Hokusai VTE Cancer[20] clinical trial is the only trial that optionally allowed anticoagulant treatment to be

Table 3 Risk factors for bleeding in patients anticoagulated due to CAT.[31–34]

General factors common to the general population	Risk of falls
	Alcohol use
	Concomitant use of antiplatelet medications
	Kidney failure
	Liver failure
	Anemia
	Gastritis
	Corticosteroid therapy
Tumor characteristics	History of tumor bleeding
	Hypervascular tumors
	Unresected intraluminal tumors of the upper gastrointestinal or urinary tract
	Primary and secondary CNS tumors
	Vascular infiltration by the tumor
	Histology: squamous tumors are greater risk than adenocarcinoma
	Thrombocytopenia due to bone marrow infiltration
Cancer treatment	Thrombocytopenia due to chemotherapy
	Antiangiogenic therapy
Other frequent factors in oncology patients	Invasive examinations: biopsies, lumbar puncture, CVC placement
	Invasive treatments: surgery
	Coagulopathy associated with sepsis, hepatic tumor infiltration

CVC: central venous catheter; CNS: central nervous system.

extended to 12 months, which occurred in approximately half of patients. There were no differences in efficacy, safety, or mortality in the treatment arm with full-dose edoxaban *versus* dalteparin. In the initial design of the SELECT-D[21] study, a second randomization was planned after six months of treatment in patients with residual venous thrombosis (RVT) that could not be completed due to low recruitment.

The Cancer-DACUS study[35] evaluated the role of RVT in 347 oncology patients with DVT after completing six months of anticoagulation. Three arms were compared: RVT treated with LMWH until completing 12 months, RVT without a treatment extension, and patients without RVT. The study concluded that patients without RVT have a lower risk of recurrence. In patients with RVT, the incidence of recurrence was similar in the arm with extended LMWH treatment for 12 months *versus* the observation arm without extended anticoagulation therapy. The study's results should be interpreted with caution in terms of their practical application because of the small sample size; the low proportion of patients with metastatic cancer; and insufficient relevant information, such as cancer progression or successive cancer treatments during follow-up.

The ONCO DVT[36] clinical trial evaluated treatment with edoxaban at full doses for three or 12 months in 604 oncology patients with isolated distal DVT. It found positive results in regard to efficacy (recurrence rate of 7.2% *vs*. 1% for three and 12 months, respectively; OR 0.13; 95%CI, 0.03—0.44) and no difference in the incidence of major bleeding (7.2% *vs*. 9.5% for three and 12 months, respectively; OR 1.34; 95%CI, 0.75–2.41).

A recent systematic review of patients with CAT treated for up to 12 months[37] included data on 3019 patients from three previously mentioned studies;[20,21,35] from the DALTECAN[38] and TiCAT[39] studies with a single treatment arm with dalteparin and tinzaparin, respectively; and from six other observational studies. VTE recurrence rates ranged from 1% to 12% and major bleeding rates were generally lower, ranging from 2% to 5%, considering that most patients received uninterrupted anticoagulation therapy. In regard to the risk of CAT recurrence after discontinuation of anticoagulant therapy, in another meta-analysis with 14 observational studies and a total of 1922 patients,[40] the cumulative rate of recurrent VTE was 28.3% (95% CI: 15.6%–39.6%) per year and up to 35% (95% CI: 16.8%–47.4%) at five years of follow-up.

There is no predictive model that allows for accurately estimating the risk of CAT recurrence. Variables that have been associated with a higher risk of recurrence in different cohort studies, and in particular during the first six months of treatment, are (see Appendix)[32,40]: those included in the Ottawa score (previous VTE, female sex, lung *versus* breast cancer, and disseminated *versus* localized cancer), age younger than 65 years, recent cancer diagnosis (<3 months), and adenocarcinoma compared to other histologies. In a Danish study of 34,072 patients,[41] the risk of recurrence during the first six months was 4%–6% for most tumors, with a higher incidence for advanced tumor stages but no differences according to sex. In another recent study of more than 14,000 patients with CAT from the RIETE registry[42] who were discontinued from anticoagulation after a period of at least three months, the risk of recurrence at one year of follow-up was 10.2% (95% CI: 9.1–11.5). The following factors were associated with increased risk of recurrence: tumors with a high thrombotic risk (lung, pancreas, kidney, carcinoma of unknown origin); tumor progression; chronic kidney disease; and the presence of metastases, RVT, inferior vena cava filter, and residual pulmonary vascular obstruction. In

Table 4 2024 recommendations for the indication of extended anticoagulant therapy beyond six months in patients with CAT.

Extended anticoagulant therapy of CAT beyond six months		
-Maintain anticoagulant therapy when there is **active cancer or while continuing cancer treatment** (chemotherapy, radiotherapy, immunotherapy, hormone therapy) with a low level of evidence: 2C. -The **balance between thrombotic/bleeding risk factors** should be **reassessed periodically** to promote information and shared decision making with the patient:		
In favor of maintaining anticoagulation.	Factor	In favor of suspending anticoagulation.
Active cancer. Presence of metastases. Cancer progression Tumors with high thrombotic risk: pancreas, stomach, lung, glioma, etc.	**Cancer assessment**	Cancer in remission
Active cancer treatment: in particular tamoxifen, chemotherapy	**Cancer treatment**	**No systemic anti-cancer treatment**
Presence of CVC (in cases of CVC-associated DVT in the upper limb) Use of erythropoiesis-stimulating agents		**End-of-life scenario**
Severity of the index event: -Life-threatening symptomatic acute PE -Residual DVT -Recurrent VTE during anticoagulation	**Index thrombotic event**	**Non-threatening:** Asymptomatic incidental PE; recanalized DVT; VTE that occurred in the context of reversible risk factors (surgery, hospital admission...)
Low (see Table 3)	**Bleeding risk**	**High** (see Table 3) Prior history of severe bleeding Thrombocytopenia Bleeding during initial anticoagulant treatment
Age <65 years. Previous VTE	**Other comorbidities and psychosocial risk factors**	Risk of falls
Previous venous disease: varicose veins, varicocelectomy Other thrombophilia factors Obesity Immobility Easy access and autonomy for self-administration of treatment		Kidney failure Liver failure Difficulty accessing and self-administering medications
Main concern: recurrence of VTE	**The patient's values and preferences**	Main concern: bleeding

DOAC: direct oral anticoagulant; CVC: central venous catheter; VTE: venous thromboembolism; LMWH: low-molecular-weight heparin; PE: pulmonary embolism; DVT: deep vein thrombosis.

contrast, surgery during the two months prior to VTE was identified as a protective factor for thrombosis recurrence.

In the AMPLIFY-EXT[43] clinical trial, which was designed to compare extended treatment with apixaban, the population with cancer was clearly underrepresented (<2% of the cohort), so conclusions cannot be drawn for this subgroup of patients. At present, the results of two clinical trials (EVE (NCT030808883) and API-CAT (NCT03692065)) (see Appendix) are pending. These trials are designed to evaluate the efficacy and safety of extended treatment with apixaban at full doses (5 mg every 12 h) *versus* reduced doses (2.5 mg every 12 h) in patients with CAT.

In summary, based on the above and in agreement with most authors,[2–5,7,28,32] this working group recommends continuing with extended treatment after six months in patients with active cancer and/or those receiving systemic anticancer therapy with the established doses (not reduced) of LMWH or DOACs and following the criteria for choice similar to those used in the acute phase, with a low level of evidence (2C)[6] (Table 4). Also in line with other authors,[2–5,28,31] in order to individualize the indication for extended treatment, other factors such as the severity of the index thrombotic event (life-threatening *versus* incidental detection in asymptomatic patients); the resolution of other

Table 5 Recommendations for the management of common special situations in patients with CAT, all with a low level of evidence: 2C.[6]

CAT and active bleeding	-Identify and **control the sources of bleeding**.
	-Maintain anticoagulation with **close clinical follow-up in patients with** intermittent **minor bleeding** or with high risk factors for bleeding (see Table 3).
	-Consider insertion of a **retrievable inferior vena cava filter in very select cases** with an absolute contraindication to anticoagulation, recent CAT (<1 month), and an interdisciplinary consensus that the potential benefit outweighs the risk.
Recurrent CAT despite anti-coagulation	-**Confirm recurrence** of VTE (rule out post-thrombotic syndrome and other causes for symptoms).
	-Confirm that the patient is receiving **adequate anticoagulation**: treatment adherence, dosage.
	-**Exclude heparin-induced thrombocytopenia**.
	-Rule out **cancer progression** and optimize cancer therapy.
	-**Consider modifying anticoagulant therapy**:
	•Patients treated with VKA: switch to LMWH or DOAC.
	•Patients treated with LMWH: increase the LMWH dose by 25% or switch to DOAC.
	•Patients treated with DOAC: switch to LMWH.
Thrombocytopenia	-In all cases, **close clinical and analytical follow-up**.
	-Adjust anticoagulation **according to the number of platelets per mm^3 and the stage of VTE progression**:
	•≥50000: maintain anticoagulation at full doses.
	•20,000–50,000 and acute phase (<1 month) of the index event: consider transfusing platelets to maintain therapeutic anticoagulation doses.
	•20,000–50,000 and subacute phase (>1 month) of the index event: consider intermediate anticoagulation doses.
	•<20000: discontinue anticoagulation.
CVC-related thrombosis	-**Attempt to preserve the CVC** if necessary, there is no suspicion of infection and it is patent.
	-Anticoagulate (preferably with LMWH) for a **minimum of three months** and while maintaining the CVC and systemic treatment.
	-The **duration and intensity of treatment after three months of anticoagulation in patients who maintain the CVC should be individualized** according to each patient's characteristics (balance of thrombotic and hemorrhagic risk factors, the degree of vascular repermeabilization, and the type of oncological treatment through the CVC).
	-Consider **invasive measures** (fibrinolysis, thrombectomy) in very select severe cases that are a threat to life or limb integrity (*e.g.* superior vena cava syndrome due to thrombosis, phlegmasia cerulea dolens).

DOAC: direct oral anticoagulant; CVC: central venous catheter; LMWH: low molecular weight heparin; VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis.

prothrombotic risk factors in the index event (*e.g.*, previous surgery); and, again, the patient's values and preferences should be considered. Finally, we recommend periodically reassessing and correcting potentially reversible risk factors for both bleeding (Table 3) and VTE recurrence.

Management of frequent special situations in oncology patients

Most clinical trials only included patients with CAT in the form of DVT of the lower limbs associated or not with PE.[13–17,20–25] Table 5 includes some brief recommendations for four of the clinical situations that, although considered special, are very common and characteristic of patients with cancer: active bleeding, recurrence of VTE despite anticoagulant treatment, thrombocytopenia, and central venous catheter-associated thrombosis.

The consensus recommendations of our group are in line with the guidelines accepted by most authors,[2–5,28,31,32] although they are based on a low level of evidence (2C).[6] The clinical heterogeneity of the real-world cases in healthcare practice together with the limited scientific evidence available makes it necessary to individualize management with the utmost caution and considering an adequate multidisciplinary evaluation of these complex scenarios.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.rceng.2024.10.007.

Conflicts of interest

Aurora Villalobos has received speaker's fees from the following pharmaceutical companies: Leo Pharma, Pfizer, ROVI, Sanofi, and Techdow and has participated in an advisory role for Pfizer. Pablo Demelo-Rodríguez has received speaker's fees from the following pharmaceutical companies: Bayer, Bristol-Myers, Daiichi Sankyo, Leo Pharma, Menarini, Pfizer, ROVI, Sanofi, and Techdow and has participated in an advisory role for Leo Pharma, Pfizer, and Techdow. Carme Font has received speaker's fees from the following pharmaceutical companies: Daiichi Sankyo, Leo Pharma, Pfizer, ROVI, Sanofi, and Techdow and has participated in an advisory role for Leo Pharma and Pfizer.

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