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REVIEW ARTICLE

Safety and efficacy of primary thromboprophylaxis in cancer patients

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Abstract Cancer is often complicated by venous thromboembolism (VTE), a common and potentially fatal complication associated with poor prognosis in these patients. An increased incidence of VTE is being observed due to the advanced age of cancer patients, the thrombogenic effect of novel drugs and advances in the diagnosis of related complications. In this review, we look at five different risk groups of cancer patients with an increased probability of developing VTE, including hospitalized patients undergoing chemotherapy, patients undergoing a surgical procedure, ambulatory patients undergoing chemotherapy, patients with a central venous access and patients receiving antiangiogenic drugs or anticoagulant therapy due to previous chronic diseases. The aim of this review is to summarize the most important clinical evidence reported to date on the suitability of primary thromboprophylaxis to cancer patients. Recommendations have drawn up for each group based on current evidence and guidelines to facilitate decision-making in clinical practice.

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Introduction

Cancer is often complicated by venous thromboembolism (VTE), which can be clinically observed as deep vein thrombosis (DVT), pulmonary embolism (PE) or both [1]. Cancer patients with VTE have an increased risk of mortality, probably due to the association with PE or to a worse prognosis due to the cancer itself. The incidence of VTE in cancer patients varies between 0.8 and 30 % depending on different studies and several factors related to the patient, the treatment and the tumor type [2]. In recent decades, an increased incidence of thrombosis associated with cancer has been observed due to the advanced age of patients, the thrombogenic effect of novel drugs and advances in the diagnosis of related complications. Fortunately, the advances in the diagnosis and treatment of these complications have allowed an improvement in the management and prognosis of these patients.

There is an increased risk of hemorrhagic complications with the administration of anticoagulant treatment in cancer patients with VTE. To avoid them, it is preferable to focus on the prevention of VTE through effective primary prophylaxis. In this review, we look at five different groups of cancer patients who have an increased risk of developing VTE complications to assess whether it is advisable to give primary thromboprophylaxis. The first risk group includes patients who are admitted in hospital and being treated with chemotherapy. The second risk group includes cancer patients who are being prepared for or have recently undergone a surgical procedure, a large proportion of

whom have the added complication of currently receiving chemotherapy. The third risk group comprises ambulatory cancer patients undergoing chemotherapy. The fourth risk group includes patients with a central venous access, e.g., intravascular catheters including Port-a-cath® or Hickman®. Lastly, the fifth risk group includes other special populations with an increased risk of VTE such as cancer patients being treated with antiangiogenic drugs or cancer patients who have received prior anticoagulant therapy due to pre-existing chronic disease.

The aim of this review is to summarize the most important clinical evidence to date that assesses the suitability of administering primary thromboprophylaxis to cancer patients. We evaluated this evidence according to the five risks groups described above, taking into consideration the principal studies and the recommendations of the principal guidelines actually published. From this evaluation, we have drawn up recommendations for each risk group of cancer patients based on the most recent evidence and guidelines to facilitate decision-making in clinical practice.

Modalities of primary thromboprophylaxis in cancer patients

Existing modalities for the prevention of VTE can be divided into two broad categories: mechanical and pharmacological. As the mechanical approach is generally used in combination with pharmacotherapy, there is little evidence that supports its efficacy either in the broader population of patients at risk for VTE or specifically in cancer patients. The mechanical thromboprophylaxis modalities that are currently available include devices for electrical calf stimulation, intermittent pneumatic compression, graduated compression stockings (GCS), and venous foot pumps [3].

The most important advantage of mechanical thromboprophylaxis is the low risk of potential bleeding complications. Despite the paucity of evidence, these devices are an option for thromboprophylaxis, particularly in patients at high risk of hemorrhagic complications. Mechanical thromboprophylaxis is also used as adjuvant to pharmacological thromboprophylaxis.

Recent data from a randomized controlled trial in hospitalized patients with an acute stroke that compared the efficacy of GCS with routine care in the prevention of DVT showed no benefit with the use of thigh-length GCS [4]. However, it was not specified how many of these patients were also taking aspirin in addition to the mechanical prophylaxis. Hence, it is logical to assume that GCS alone is not an effective option for immobile hospitalized cancer patients.

Primary thromboprophylaxis in hospitalized cancer patients

VTE is the most common preventable cause of death in hospitalized patients, and hence there is much evidence to demonstrate the efficacy of prophylactic strategies to prevent VTE in at-risk hospitalized patients. Thus, international guidelines strongly recommend effective preventive strategies for all hospitalized patients with a moderate- or high-risk of VTE [5].

Several randomized trials have evaluated the benefit of VTE prophylaxis in hospitalized patients, but none of them specifically in hospitalized cancer patients. In the PREVENT study, comparing dalteparin vs placebo in 3706 patients (5 % with cancer), the incidence of VTE was reduced from 5.0 % in the placebo group to 2.8 % in the dalteparin group ($p = 0.0015$) [6]. In the ARTEMIS study, with 849 patients (15.4 % with cancer), VTE was found in 5.6 % of patients treated with fondaparinux and 10.5 % of patients receiving placebo with a relative risk reduction of 46.7 % (95 % CI 7.7–69.3 %) [7]. The MEDENOX study randomized 1102 patients (14 % with cancer) to receive prophylaxis with enoxaparin (20 or 40 mg) or placebo [8]. The dose of 40 mg of enoxaparin was associated with a lower incidence of DVT and PE than placebo (5.5 vs 14.9 %; $p < 0.001$). In a sub-analysis of this study that focused exclusively on patients with cancer, the incidence of VTE was 19.5 and 9.7 %, respectively, but did not reach statistical significance, probably due to the small number of patients ($n = 72$) [9]. Although data from the general hospital population cannot be directly extrapolated to the cancer patients, in the absence of specific randomized studies for this population, and considering that the cancer patients have additional risk factors that increase the risk of VTE, it can be assumed that there would be a benefit of primary pharmacological prophylaxis in hospitalized cancer patients.

Hence, guidelines of the American Society of Clinical Oncology (ASCO) in 2013 [10, 11], the American College of Chest Physicians (ACCP) in 2012 [12], the European Society of Medical Oncology (ESMO) in 2011 [13], the National Comprehensive Cancer Network (NCCN) in 2015 [14], the International Society on Thrombosis and Hemostasis (ISTH) in 2013 [15] and the Spanish Society of Medical Oncology (SEOM) in 2011 [16] recommend anticoagulant prophylaxis in hospitalized cancer patients with acute disease or who are disabled in the absence of bleeding and other contraindications. Recommended agents are low molecular weight heparins (LMWH), unfractionated heparins (UFH) or fondaparinux. Although UFH and LMWH have also shown efficacy in reducing VTE, UFH is minutely used in prophylaxis due to the

increased complexity of management and the higher rate of side effects. Thromboprophylaxis must be maintained throughout hospitalization and may be continued after discharge depending on individual patient characteristics.

Primary thromboprophylaxis in cancer patients undergoing a surgical procedure

Patients with cancer undergoing surgery have been shown to have a two-fold or greater increased risk for fatal PE compared with similar patients without cancer. Cancer is also an independent predictor of thromboprophylaxis failure. This is due to the prothrombotic state associated with cancer and the complexity and frequent morbidity of oncological surgery. The presence of a malignant disease doubles the risk of VTE, with an incidence of asymptomatic distal venous thrombosis of 40–80 % and proximal vein thrombosis of 10–20 %. The incidence of PE is 4–10 %, and fatal PE of 1–5 %. Thus, VTE becomes the cause of 10 % preoperative early mortality. Surgery also increases the risk of developing VTE. However, several studies, such as ENDORSE, have found that patients often do not receive prophylaxis for VTE [17]. In this study, only 58.5 % of patients at risk received the recommended VTE prophylaxis according to guidelines.

The risk of VTE depends on specific factors of the patient and the tumor, as well as on factors related to the surgical procedure, such as the amount of surgery, the type and duration of the anesthesia, and the need of immobilization [18]. Factors that seem to have more impact on the risk of VTE in cancer patients who undergo surgery are advanced age, residual disease after surgery, obesity, advanced stages of disease, prolonged duration of anesthesia, prolonged immobility (more than three days) and background thromboembolism [19]. According to the ACCP guidelines of 2012, patients who undergo surgery may be split into four risk categories [12]:

- Very low risk (i.e., incidence of VTE <0.5 %)
- Low risk (i.e., incidence of VTE ~1.5 %)
- Moderate risk (i.e., incidence of VTE ~3.0 %)
- High risk (i.e., incidence of VTE ~6.0 %)

The ASCO 2013 guideline, directly and without using any risk scale, recommends that all cancer patients undergoing a surgical procedure should be considered for pharmacological prophylaxis with LMWH or UFH, unless there is a contraindication [10]. Pharmacological prophylaxis should be started preoperatively, and mechanical methods can be added later on. Mechanical methods should not be used as the sole treatment strategy unless there are contraindications for pharmacological prophylaxis (active bleeding or high-risk bleeding). A review of 16 clinical trials of prophylaxis in surgical cancer patients found that the average rate of VTE without prophylaxis was 29 %, corresponding to the subgroup of patients at very high risk [20].

Classically in clinical practice, prophylaxis is continued for at least 7–10 days. Considering that 40 % of VTE events may occur later than 21 days from the surgical intervention, duration of prophylaxis with LMWH after cancer surgery has been prospectively addressed [19]. In a double-blind trial that enrolled patients undergoing curative surgery for abdominal or pelvic cancer, all patients received 40 mg of enoxaparin daily for 6–10 days, then patients were randomized to receive either enoxaparin or placebo for another 21 days [20]. The primary endpoint was the incidence of VTE between days 25 and 31. The final analysis of the trial showed that the incidence of VTE was 4.8 % among patients randomized to additional enoxaparin compared with 12.0 % among those who received placebo ($p = 0.02$). This difference was maintained after 3 months. The rate of bleeding was similar in both groups [21]. Rasmussen et al. reported a systematic review on prolonged prophylaxis for up to 4 weeks in patients undergoing major abdominal or pelvic surgery concluding that prolonged thromboprophylaxis with LMWH significantly reduces the risk of VTE compared to thromboprophylaxis during hospital admittance without increasing bleeding complications [22]. Therefore, considering the actual evidence, patients should receive at least 7–10 days of prophylaxis and patients undergoing major abdominal or pelvic cancer surgery with high-risk features should be considered for extended thromboprophylaxis for 4 weeks (level of evidence: grade 1A).

Primary thromboprophylaxis in ambulatory cancer patients undergoing chemotherapy

Several randomized controlled trials have evaluated the role of LMWH as primary thromboprophylaxis in outpatients receiving chemotherapy (Table 1). It is important to identify patients at high risk of developing VTE for whom prophylaxis may be beneficial. Currently, the only validated assessment tool to analyze the risk of an outpatient undergoing chemotherapy is the Khorana model. This scale considers five clinical variables and three different risk categories (Table 2). Patients with Khorana score ≥3 (high risk score) are at increased risk of VTE [23].

Major limitations of this model include the small number of patients with specific types of cancer thought to be associated with a high risk of thrombosis included, and the good performance status of patients assessed in this cohort. Additionally, only patients who developed symptomatic VTE were included, as there was no routine screening for

Table 1 Trials evaluating the role of low molecular weight heparins (LMWH) as primary thromboprophylaxis in outpatients under chemotherapy

Study	Type of Cancer	Risk of thrombosis	*N*	Treatment
PROTECHT [26]	Mixed	Low–high	779	Nadroparin, 3800 IU/day
			387	Placebo
SAVE-ONCO [29]	Mixed	Moderate-high	1608	Semuloparin, 20 mg/day
			1604	Placebo
CONKO-004 [32]	Pancreatic	High	160	Enoxaparin, 1 mg/kg/day for 3 months → 150 IU/kg/day for 3 months
			152	Observation
FRAGEM [31]	Pancreas	High	60	Dalteparin, 200 IU/kg/day for 4 weeks → 150 IU/kg/day for 8 weeks
			63	Observation
TOPIC I [25]	Breast	Low	174	Certoparin, 3000 IU/day for 6 months
			179	Placebo
TOPIC II [25]	Lung	Moderate	273	Certoparin, 3000 IU/day for 6 months
			274	Placebo
PRODIGE [33]	Malignant glioma	High	99	Dalteparin, 5000 IU/day for 6 months
			87	Placebo

Table 2 Predictive model of chemotherapy-associated venous thromboembolism in the ambulatory setting

	Points
Patient characteristics	
Site of cancer	
Very high risk (stomach, pancreas, primary brain tumor)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular, renal tumors)	1
Pre-chemotherapy platelet count = 350,000/μL	1
Hemoglobin level <10 g/dL or use of red-cell growth factors	1
Pre-chemotherapy leukocyte count <11,000/μL	1
Body mass index = 35 kg/m^2	1
Risk categories	
High risk	≥3
Intermediate risk	1–2
Low risk	0

asymptomatic VTE. Recently, this model has been expanded with the addition of two new laboratory parameters (D-dimer and P-selectin) in the Vienna Cancer and Thrombosis Study [24]. The prediction of VTE was considerably improved with the addition of these biomarkers.

Nevertheless, the advantage of the Khorana score is that all parameters of this risk model are routinely determined in cancer patients at diagnosis or at the beginning of chemotherapy and are easily available, whereas P-selectin is not widely available in clinical practice, and the expanded risk assessment model (Vienna score) has not been validated yet. In the near future, new biomarkers (e.g., tissue factor, C-reactive protein, factor VIII) may enhance the VTE prediction in this setting.

The clinical benefit of thromboprophylaxis in patients with advanced cancer under chemotherapy was initially evaluated in two randomized placebo-controlled studies [25]. Ambulatory patients with metastatic breast carcinoma (study TOPIC-1) or non-small-cell lung carcinoma (study TOPIC-2) were randomized to certoparin or placebo for 6 months. VTE occurrence was not difference between the treatment groups in TOPIC-1 (4 % in both groups), but certoparin significantly reduced VTE in stage IV lung carcinoma compared with placebo (3.5 vs 10.2 %; $p = 0.032$).

The largest studies of thromboprophylaxis (PROTECHT and SAVE-ONCO) have been conducted in patients with a variety of solid tumors [26–28]. The PROTECHT trial randomly assigned 1150 patients receiving chemotherapy for advanced solid tumors to be treated with either nadroparin (3800 IU once a day) or placebo in a 2:1 ratio [26]. Study treatment was started on the same day as

chemotherapy and was given for the duration of chemotherapy up to a maximum of 4 months. The incidence of symptomatic VTE was 2.0 % in the group treated with nadroparin and 3.9 % in patients receiving placebo (primary efficacy outcome), but no effect on patient survival was observed. The incidence of minor bleeding and serious adverse events was comparable in both groups. The number of patients needed to (NNT) treat with nadroparin to prevent a symptomatic VTE was 53. A subsequent analysis assessed the effect of nadroparin for VTE prophylaxis according to the Khorana score [28]. The rate of VTE in patients identified as 'at high risk' according to the Khorana score was 4.5 % in the nadroparin group, and 11.1 % in the placebo group (NNT = 15, compared with NNT = 77 for patients with Khorana score 0–2). A post hoc survival analysis of the trial was recently presented and suggests a benefit in survival for patients receiving nadroparin, although this benefit was limited to patients responding to chemotherapy [28].

The SAVE-ONCO study was a randomized, double-blind, placebo-controlled trial that included 3212 patients receiving chemotherapy for locally advanced or metastatic solid tumors (lung, pancreas, colon, rectum, bladder or ovary) [29]. Eligible patients were randomly assigned to receive semuloparin (20 mg, once daily) or placebo, until there was a change of the chemotherapy regimen. Prophylaxis with semuloparin reduced the incidence of VTE events from 3.4 to 1.2 % [hazard ratio (HR) 0.36; 95 % CI 0.21–0.60; $p < 0.001$] with no differences in the incidence of major bleeding. Baseline VTE risk was assessed by the Khorana risk score. In a per-protocol subgroup analysis, patients with Khorana score ≥ 3 (550 patients, 17.4 %) had an incidence of VTE of 1.5 % with semuloparin vs 5.4 % with placebo [30].

The incidence of VTE varies considerably among the different malignancies, suggesting that the risk–benefit ratio of thromboprophylaxis cannot be generalized from one tumor type to another. Studies including selected populations at higher risk for thromboembolic events may show a greater benefit for thromboprophylaxis. In this context, FRAGEM and CONKO-004 trials have evaluated the role of LMWH in patients with advanced pancreatic cancer receiving chemotherapy [31, 32]. The FRAGEM study randomized 123 patients to receive gemcitabine with or without weight-adjusted dalteparin for 12 weeks [31]. LMWH treatment reduced the incidence of thromboembolic events from 23 to 3 % [risk ratio (RR) 0.15; 95 % CI 0.04–0.61; $p = 0.002$] at the end of treatment period (12 weeks), and from 28 to 12 % at the end of follow-up (RR 0.42; 95 % CI 0.19–0.94; $p = 0.039$). The incidence of severe hemorrhagic complications was low in both groups (3.4 % for dalteparin vs 3.2 % for observation group). In the CONKO-004 study, 312 patients with pancreatic cancer were randomized to receive enoxaparin (1 mg/kg daily for 3 months, then 40 mg daily) or standard care, starting in parallel to palliative systemic chemotherapy [32]. LMWH demonstrated a significant reduction in the cumulative incidence rate of symptomatic thromboembolic events from 15.1 to 6.4 % (HR 0.40; 95 % CI 0.19–0.83; $p = 0.01$), with no differences in major bleeding events. The PRODIGE trial focused on malignant brain tumors. Patients with malignant glioma were randomized to dalteparin (5000 IU once daily for 6 months) or placebo [33]. Only 186 patients (of the 434 patients initially planned) were recruited. A reduction in thromboembolic events was observed in patients receiving dalteparin (9 vs 15 %), but the statistical power of the study was too low to detect statistically significant differences.

Two systematic reviews identified randomized trials comparing LMWH prophylaxis with placebo or with no prophylaxis in the outpatient setting. A meta-analysis by the Cochrane Collaboration group published in 2012, which included 9 studies and 3538 patients, evaluated primary thromboprophylaxis in cancer outpatients undergoing chemotherapy [34]. LMWH, when compared with the observation, significantly reduced the incidence of symptomatic VTE (RR 0.61; 95 % CI 0.41–0.93), with no differences in mortality in 1 year. The NNT to prevent a symptomatic VTE was 60. No significant increased risk of major bleeding was seen with LMWH (RR 1.57; 95 % CI 0.69–3.60). Another meta-analysis carried out after the publication of SAVE-ONCO study, which included more than 6000 patients, demonstrated a reduced risk of symptomatic VTE (RR 0.57; 95 % CI 0.40–0.81) with no significant differences in bleeding complications [35].

Current guidelines from ASCO [10, 36], ESMO [13], NCCN [37] and ACCP [38] do not recommend routine thromboprophylaxis in ambulatory patients with cancer (level of evidence: grade 1B). However, based on data from the above-mentioned studies, several of these guidelines suggest that LMWH prophylaxis may be considered in high-risk ambulatory cancer patients, such as patients with advanced pancreatic cancer or with a Khorana score ≥ 3, and low bleeding risk [10, 37]. The administration of such therapy should be discussed in advance with the patient along with the benefits and risks expected. Nevertheless, there is no consensus on the type of LMWH, dosage or duration of thromboprophylaxis.

Recent guidelines from ISTH recommend against routine thromboprophylaxis in cancer outpatients, but suggest that the cancer patients with solid tumors and a Khorana score ≥ 3 or patients with advanced pancreatic cancer starting chemotherapy should receive thromboprophylaxis, except for those with contraindications to anticoagulation or a diagnosis of primary brain tumor [15, 39]. The authors suggest that LMWH should be used at routine prophylaxis

doses for a period of 12 weeks after the initiation of a new chemotherapy regimen in patients with solid tumors. However, they recommend higher doses in patients with advanced pancreatic cancer, such as those included in the FRAGEM or CONKO-004 trials [31, 32].

Primary thromboprophylaxis in cancer outpatients with central venous catheter

The use of central venous catheters is increasingly common in cancer patients. The placement of a central venous catheter is associated with an increased incidence of VTE located in upper limbs. The incidence reported varies widely depending on the study design, population (symptomatic or asymptomatic), the diagnostic methods used for detection (Doppler, venography) and even the definition of the thromboembolic event. The incidence of symptomatic thrombotic events ranged from 0.3 to 28 % [40–43], while the incidence of thrombotic events assessed systematically by venography ranged from 27 to 66 % [43], most of them being asymptomatic. The risk for the development of thrombosis in relation to central venous catheters will depend on the factors related to the catheter, tumor, treatments given and patient risk (Table 3).

Most studies with warfarin have not shown efficacy in the prevention of thrombosis when compared with placebo [44]. The WARP study evaluated the incidence of thrombosis in patients treated with fixed-dose warfarin (1 mg/day) and warfarin adjusted to international normalized ratio [INR] 1.5–2 dose. INR-adjusted warfarin was associated with a significant reduction of thrombotic events (2.7 vs 7.2 %, respectively; OR 0.38; 95 % CI 0.20–0.71), but with an increase in major bleeding (3.4 vs 1.5 %, respectively; $p = 0.04$) [45]. De Cicco et al. reported that warfarin reduced the incidence of asymptomatic partial thrombosis, but not the symptomatic occlusive forms of thrombosis [46]. In a single study that used UFH administered as a continuous infusion in hematological patients undergoing bone marrow transplant, the incidence of symptomatic and asymptomatic thrombosis detected by venography was reduced [47]. The study could not, however, take into consideration the clinical reality of the difficulties of continuous administration. Studies with a large number of patients have evaluated the role of prophylactic LMWH. The use of dalteparin, nadroparin and enoxaparin did not show a decrease in the incidence of mortality or symptomatic DVT, but it did show an increased risk of hemorrhage [43, 48, 49].

A recently published Cochrane meta-analysis included 10 studies with data collected from 2564 adult patients [50]. Prophylactic doses of LMWH were associated with a significant reduction in symptomatic VTE compared with no treatment (RR 0.48; 95 % CI 0.27–0.86) with no impact on mortality (RR 0.82; 95 % CI 0.53–1.26) or major bleeding (RR 0.49; 95 % CI 0.03–7.84). Low doses of vitamin K antagonists compared with no treatment was associated with a reduction of asymptomatic VTE (RR 0.43; 95 % CI 0.30–0.62), but without any difference in mortality (RR 1.04; 95 % CI 0.89–1.22), symptomatic forms (RR 0.51; 95 % CI 0.21–1.22) or major bleeding (RR 7.60; 95 % CI 0.94–61.49). When LMWH was compared with vitamin K antagonists, a significant increase in thrombocytopenia (RR 3.73; 95 % CI 2.26–6.16) and asymptomatic forms of VTE (RR 1.74; 95 % CI 1.20–2.52) were observed without affecting mortality or bleeding.

A prospective study randomized 407 patients to no prophylaxis, prophylaxis with warfarin (fixed doses of 1 mg/day) and LMWH prophylaxis [51]. Anticoagulation significantly reduced the incidence of catheter-related thrombosis (RR 0.55; 95 % CI 0.31–0.96) and non catheter-related thrombosis (RR 0.14; 95 % CI 0.03–0.67), and found no differences between warfarin and LMWH. Other three studies examined the preventive role of urokinase. In two, patients treated with urokinase had less occlusive thrombosis (23 vs 31 %; $p = 0.02$ and 4 vs 16 %; $p < 0.05$) [52, 53], while in the third study no benefit was shown though with similar thrombosis incidence (16 vs 19 %) [54].

Since the rate of complications without prophylaxis is low, it is important to identify the risk factors that are associated with an increased risk of thrombosis in patients with central venous catheters. In a series of studies by Lee et al. [42], the overall group of patients had 4.3 % of symptomatic complications. They identified risk factors as the presence of ovarian cancer, more than one venous access and a history of prior central venous catheters.

Several studies have analyzed the influence of the type of catheter, the position and the insertion method in the incidence of thrombosis. In a meta-analysis conducted in 5636 adult patients, a greater frequency of thrombosis was observed when the central venous catheters were peripherally inserted, when the insertion was done through the subclavian vein (compared with the jugular vein), and when the catheter tip was located above the junction between the superior vena cava and the right atrium [55].

The latest guidelines of the main scientific societies (ASCO, ESMO, NCCN and ACCP) do not recommend routine thromboprophylaxis in cancer patients with central venous catheters (level of evidence: grade 1B) [10, 13–15, 37, 56]. The ISTH published, in addition to the General Guidelines for thrombosis in oncological patients [15], specific guidance focused on cancer patients with central venous catheters [56]. Again, the guideline does not support the use of systemic pharmacological prophylaxis, but

Table 3 Risk factors associated with the development of thrombosis related to central venous catheters

Factors and risks
Material used
Higher incidence with the use of polyvinyl and polyethylene
Lower incidence with the use of silicone and second or third generation polyurethane
Placement technique
Possible tissue damage during catheter insertion
Vascular occlusion according to the relation between catheter and vessel sizes
Right location of the catheter tip (the atrio cava junction is considered the optimum location)
More than one venipuncture attempt
Location
Higher incidence in the left side
Higher incidence in the upper half of the superior cava vein than in the innominate or lower cava vein
Type of catheter
Higher incidence with three-way catheter (probably due to the higher vessel occlusion it provokes)
Previous history of central venous catheterization
Catheter infection
Neoplasia
Higher incidence in thoracic or mediastinal tumors
Treatment received
Radiotherapy
Parenteral nutrition
Other risk factors not related with the type of catheter
Type of cancer
Type of chemotherapy
Use of antiangiogenic therapy
Use of hormonal therapy

gives some recommendations regarding the implementation of the central venous catheters such as the placement of the catheter in the right side in the jugular vein rather than in the subclavian vein, and the convenience of locating the tip at the junction of the vena cava and right atrium.

Primary thromboprophylaxis in other special cancer populations

Aside from the four main risks groups of cancer patients considered previously, there are other groups of patients with special considerations worth noting.

Cancer patients receiving antiangiogenic agents

To date, several antiangiogenic agents have been approved for clinical use, such as thalidomide, bevacizumab, sorafenib, sunitinib and pazopanib. These antiangiogenic agents appear to increase the VTE risk associated with chemotherapy.

Treatment with bevacizumab, a humanized monoclonal antibody that targets the vascular endothelial growth factor (VEGF), is associated with a moderate, but significant increase in arterial thromboembolic events (ATE) [57]. This risk increases with age and with a previous history of such events. However, the effect of bevacizumab on VTE remains controversial. A meta-analysis that included 7956 patients with a variety of advanced solid tumors from 15 randomized controlled trials reported an increased risk of VTE with bevacizumab (RR 1.33; 95 % CI 1.13–1.56; $p < 0.001$) [58]. However, there are conflicting data on this subject [57, 59]. Pooled analysis of data from 5 randomized trials, involving 1745 patients with metastatic cancer, showed that the addition of bevacizumab to chemotherapy was associated with an increased risk of ATE (HR 2.0; 95 % CI 1.05–3.75; $p = 0.031$), but not with an increased risk of VTE (HR 0.89, 95 % CI 0.66–1.20; $p = 0.44$) [57]. A recent analysis, using patient-specific data from 6055 patients from 10 randomized studies, showed an unadjusted incidence of all grade VTEs of 10.9 % in the bevacizumab group and 9.8 % in the control group [odds ratio (OR) 1.14; 95 % CI 0.96–1.35; $p = 0.13$] [59]. The use of low-dose acetylsalicylic acid (ASA) as prophylaxis of ATE is controversial and it is not generally recommended. Routine use of LMWH is also not recommended for prophylaxis of VTE in patients receiving bevacizumab. The association between increased risk of bleeding and most antiangiogenics drugs requires a strict control of anticoagulant medication.

Patients with multiple myeloma (MM)

Ambulatory patients with MM have an increased risk of VTE [60]. The introduction of the immunomodulatory drugs such as thalidomide and lenalidomide has improved outcomes in these patients, but they have also increased the rate of thromboembolic complications observed, especially in combination with chemotherapy and high dose corticosteroids [61–63].

The majority of the studies related to MM and VTE reported a higher incidence at the time of diagnosis than after relapse, but they are retrospective or not designed to evaluate the risk of VTE. For patients receiving treatment with thalidomide or lenalidomide, the risk of VTE ranges from 10 to 28 % [64–67]. Thalidomide alone does not seem to increase the risk of VTE when used on newly diagnosed patients or in refractory/relapse disease. However, the risk is increased when thalidomide is given in combination with the alkylating agents anthracyclines, dexamethasone or multiagent chemotherapy combinations [64, 67, 68]. Studies on maintenance treatment have not found a higher risk of VTE, probably due to low tumor burden. Again, the group of patients treated with lenalidomide as single agent treatment in newly diagnosed patients or in refractory/relapsed patients did not show an increased risk of VTE [69]. Different results were obtained with lenalidomide in association with dexamethasone or cyclophosphamide, with a significant increase in the risk of VTE [70, 71]. Comparing both treatment strategies, there were no differences in the incidence of VTE observed in patients treated with thalidomide and dexamethasone compared with patients treated with lenalidomide and dexamethasone [72].

Other therapies such as bortezomib have not been related with an increased risk of VTE, even when associated with other chemotherapies [73]. A probable protective role for bortezomib in the development of VTE should be taken into consideration for future clinical trials. Finally, other complementary treatments, such as erythropoietin or varying doses of dexamethasone, have been related to an increased risk of VTE in ambulatory MM patients [74, 75].

When considering the indications for thromboprophylaxis in ambulatory patients with MM, there are not many randomized studies to answer this question. In the first prospective multicenter phase III trial, Palumbo et al. randomized 991 newly diagnosed MM patients to receive different regimens of bortezomib, melphalan, thalidomide, dexamethasone and prednisone [76]. In a subsequent substudy, patients treated with thalidomide were randomized to receive enoxaparin 30 mg/day ($n = 223$), ASA 100 mg/day ($n = 227$) or warfarin 1.25 mg/day ($n = 223$) using the group of patients treated without thalidomide as control arm [76]. No difference was observed between groups. In another study, 402 patients received 4 cycles of lenalidomide-dexamethasone as induction treatment and were randomized to melphalan-prednisone-lenalidomide or tandem autologous stem cell transplantation with ASA or enoxaparin as thromboprophylaxis [77]. The incidence of VTE was again similar in both groups (2 vs 1 %, $p = 0.42$).

In a prospective trial, Larocca et al. reported that thromboprophylaxis with low dose ASA was very effective in previously untreated MM patients with low thromboembolic risk receiving lenalidomide and low-dose dexamethasone for 4 cycles, followed by the consolidation with melphalan-lenalidomide-prednisone or melphalan 200 mg/m^2 and autologous hematopoietic stem cell transplantation [78]. Patients were randomized to either low-dose ASA (100 mg/day) or enoxaparin (40 mg/day). The frequency of VTE was 2.27 vs 1.2 % comparing ASA vs enoxaparin. However, all cases of PE and superficial thrombophlebitis occurred in the ASA group.

According to this evidence and other retrospective studies [79–82], and considering risk-assessment models such as the one published by the International Myeloma Working group [83], the experts panel make recommendations about the prophylaxis of MM patients receiving thalidomide and lenalidomide [14]. Prophylaxis with either LMWH or warfarin dose-adjusted to INR 2–3 is recommended in patients with two or more individuals or disease-related risk factors. ASA prophylaxis (81–325 mg/day) is an option for patients receiving treatment with one or fewer individuals or MM specific risk factors.

Patients with anticoagulation treatment secondary to chronic diseases

The frequent diversity of co-morbidities and drug interactions observed in cancer patients is considered more relevant. There are few studies that evaluate the optimal anticoagulant treatment associated with chronic diseases in cancer patients. Arrhythmias and heart valve diseases represent the highest group of patients. The high rate of complications and the difficulties in assessing the optimal INR ratio in those patients treated with oral warfarin is of special importance. In most cases, they are secondary to drug interactions, vomiting, malnutrition, hepatic dysfunction, and other important co-morbidities that affected the tolerability and the absorption of anticoagulant therapy [84].

Meanwhile, LMWH is associated with a lower rate of side effects and a more predictable anticoagulant effect [85]. Some studies have evaluated the risk of bleeding associated with the use of warfarin and LMWH in patients with and without chemotherapy, especially of major bleeding [86, 87]. The results confirm the feasibility and safety of low-dose heparins compared with warfarin in cancer patients. The same recommendations should be made considering interactions with other treatments

frequently used in these patients. A great number of interactions are related to other common drugs not directly indicated for cancer [88–90]. All these factors make the recommendation to select the correct anticoagulant treatment in these patients even more important, which should be LMVH in the first setting.

Conclusions

Primary thromboprophylaxis is of great importance in cancer patients and should be considered according to the risk of developing VTE. Prophylactic anticoagulation should be considered for hospitalized cancer patients with acute medical illness in the absence of contraindications. In the same way, in the absence of contraindications, all patients undergoing major surgical intervention should receive pharmacologic thromboprophylaxis. The preferred agents are LMWH, and prophylaxis should be started before surgery or as soon as possible in the post-operative period. Mechanical methods may be added to pharmacologic prophylaxis in high-risk patients, but should not be used as monotherapy unless pharmacologic prophylaxis is contraindicated. In ambulatory patients receiving chemotherapy, routine thromboprophylaxis is not recommended, although it may be considered in high-risk cancer patients such as those with advanced pancreatic cancer or with a Khorana score ≥ 3, and low bleeding risk. In cancer patients with CVC, routine thromboprophylaxis is not recommended. To reduce the incidence of VTE, CVC should be placed on the right side in the jugular vein, and the catheter tip should be positioned at the right atrium/superior vena cava junction. Finally, thromboprophylaxis is recommended in patients diagnosed with MM receiving treatment with thalidomide or lenalidomide plus chemotherapy or dexamethasone. LMWH is recommended for high-risk patients and ASA for low-risk patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they do not have any conflicts of interest that may inappropriately influence this work.

Ethical statement The study has been performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments. This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent statement Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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