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Special Series: Approach to the Patient with Cancer and Thrombosis

Update on Guidelines for the Management of Cancer-Associated Thrombosis

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Abstract

Cancer-associated thrombosis (CAT) is a major cause of morbidity and mortality in patients with cancer. Over the past 2 decades, enormous advances have been made in the management of CAT. The growing evidence base informing practice has led to the publication of a number of guidelines and guidance documents on the diagnosis and treatment of CAT. The goal of this review is to examine the latest versions of evidence-based guidelines, highlighting the differences and similarities in their methodology, their disease-specific content, and recommendations for management. Our analysis shows that for most clinical topics, the different guidelines provide roughly similar management advice. However, there are a number of important clinical topics in CAT that are not currently covered by the existing guidelines. We think inclusion of these topics in future versions of the guidelines will facilitate ongoing efforts to optimize the care of patients with CAT. ***The Oncologist*** 2021;26:e24–e40

Implications for Practice: Cancer-associated thrombosis (CAT) is a common complication in patients with cancer. This review examines the differences and similarities of the current CAT guidelines methods and recommendations. Current guidelines largely agree on many aspects of CAT management. However, there are a number of topics in CAT that are not currently included in guidelines where evidence-based guidance would be very helpful for clinicians. Coverage of these topics in future guidelines is encouraged to optimize clinical practice.

Introduction

Venous thromboembolism (VTE) is a common cause of morbidity and mortality in patients with cancer [1]. Such patients are at fourfold to sevenfold higher risk for initial VTE than patients without cancer. Furthermore, patients with cancer have a threefold higher risk of recurrent VTE, a twofold higher risk of anticoagulation-associated bleeding, and a 10-fold higher risk of death than patients with VTE who do not have cancer [1]. Consequently, prevention and treatment of VTE in patients with cancer has been the focus of considerable investigation. In 2006, the Italian Association of Medical Oncology and the National Comprehensive Cancer Network (NCCN) published guidelines focused on the prevention and treatment of VTE in patients with cancer [2, 3]. The following year, the American Society of Clinical Oncology (ASCO) published its first guideline [4]. In 2008, the French National Cancer Institute produced guidelines for the prevention and treatment of thrombosis in patients with cancer [5]. Since then, numerous guidelines and guidance documents focusing on cancer-associated thrombosis (CAT) have been published. In this review, we compare and contrast recommendations from the most recent cancer-specific VTE guidelines and their methodology, and we identify clinical topics in CAT where guidance is lacking.

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Methods

Because there are a large number of guidelines focusing on the management of VTE, we chose to concentrate on the most recent versions of select widely recognized international guidelines focusing exclusively on management of CAT. A brief description of the methodology of each guideline is provided below.

The ASCO guidelines committee consists of a multidisciplinary expert panel of hematologists, oncologists, surgeons, and methodologists, as well as a patient representative and an ASCO guidelines staff member with health research methodology expertise [6]. A systematic review was conducted to formulate recommendations for each clinical question. The PubMed and the Cochrane Library search included randomized controlled trials (RCTs) and meta-analyses of RCTs published between August 1, 2014, and December 4, 2018. Publications were included if they assessed the efficacy and safety of anticoagulation in patients with cancer and included at least 50 patients per arm. For the questions on risk assessment, cohort studies were also included. Only English-language studies were included. Standardized ASCO criteria were used to determine the quality of the evidence and the type and strength of each guideline recommendation (Table 1). The guideline recommendations were subject to two 2-week open comment periods. The full guideline was shared with two external reviewers. Comments were taken into consideration during the panel's final revision before submission to the Journal of Clinical Oncology for publication and review by outside experts. The guideline was also reviewed by the ASCO Clinical Practice Guideline Committee prior to publication. Further information on the guideline process can be found in the ASCO Guideline Methodology Manual available at www.asco.org/guideline-methodology [6].

The International Society of Thrombosis and Hemostasis (ISTH) guidance documents are designed to be brief, evidence-based statements of expert opinion drafted by experienced clinicians who are recognized authorities in the designated subject area [7, 8]. The recommendations are based on the authors' review of the relevant literature on the topic at time of the publication [9].

The International Initiative on Thrombosis in Cancer (ITAC) clinical practice guidelines were developed by an international academic multidisciplinary working group as part of an initiative organized by the Group Francophone Thrombose et Cancer, a nonprofit organization based at the Hôpital Saint-Louis in Paris, France. The ITAC clinical practice guidelines were prepared using the Grading of Recommendations Assessment, Development, and Evaluation methodology [10] (Table 1). Additional economic considerations were taken into account during the development and ranking of the recommendations to offer treatment alternatives when possible that address potential economic barriers to treatment. The French National Cancer Institute provided methodological support and conducted a literature search using MEDLINE, EMBASE, and the Cochrane Central Registry of Controlled Trials. An international panel of 15 experts from hematology, oncology, internal medicine, vascular medicine, biology, and epidemiology generated the 2019 ITAC clinical practice guideline update, which was then critically reviewed by an international panel of 86 independent experts in medical and surgical specialties, patient associations, nurses, and patient representatives [10]. The 2019 ITAC clinical practice guidelines addressed new evidence on anticoagulation and the use of direct oral anticoagulants (DOACs) in patients with cancer, as well as risk stratification for primary prophylaxis. The 2019 ITAC clinical practice guidelines are available as a free Web application in English, French, and Spanish at itaccme.com.

NCCN is a nonprofit alliance of 30 of the top cancer centers in the U.S. [11]. To promote high-quality care and continuous quality improvement at member institutions, NCCN has developed over 78 guidelines focusing on different cancer sites and important aspects of supportive care for patients with cancer. NCCN has also developed 12 guidelines for patients that are available in 13 different languages. All the guidelines and related Web applications can be accessed for free at nccn.org. Guidelines are updated annually as new literature is published. Each NCCN guideline committee is composed of a multidisciplinary team of nurses, pharmacists, and physicians who have expertise in the subject area, and each NCCN institution nominates one member to sit on each guideline committee. A patient representative is also present on each guideline panel. The NCCN guideline committees are supported by NCCN staff who conduct literature searches on an ongoing basis in each topic area and forward search results to committee members for review. In addition, committee members can submit articles for review by the committee to supplement the standardized NCCN literature search. Guideline recommendations graded according to criteria developed by the NCCN Guidelines Steering Committee [11] (Table 1).

The Spanish Society of Medical Oncology (SEOM) guidelines were developed by the 10 oncologist members of the Cancer and Thrombosis section of the SEOM. To assess the quality of evidence supporting their recommendations, they used the grading system developed by the Infectious Diseases Society of America–U.S. Public Health Grading System (Table 1). The final text of the guideline was reviewed and approved by each of the authors prior to publication [12].

Guideline Recommendations for VTE Prophylaxis in Hospitalized Medical Oncology Patients

RCTs focusing on outcomes associated with VTE prophylaxis in hospitalized medical oncology patients have not been conducted. A meta-analysis of three RCTs of VTE prophylaxis in hospitalized medically ill patients included 307 patients with cancer and found that pharmacologic VTE prophylaxis did not reduce VTE risk (pooled relative risk, 0.91; 95% confidence interval, 0.21–4.0; I^2 = 68%). Major bleeding was not reported for the cancer subpopulation [13]. Therefore, there are limited data available to inform evidence-based recommendations for VTE prophylaxis in hospitalized medical oncology patients. Hospitalization (odds ratio, 2.34) has been associated with VTE in patients with cancer, although it is unclear if hospital admission for chemotherapy alone represents a risk factor for VTE [14]. Patients receiving bone

Table 1. Approach of guidelines to grading recommendations

Guideline	Approach
American Society of Clinical Oncology	
Type of recommendation	Evidence based: Sufficient evidence to inform clinical practice (based upon assessment of aggregate risk of bias, consistency of results, directness of evidence, and precision of results). Formal consensus: Insufficient evidence to inform a recommendation. Panel used a formal consensus process to reach the recommendation that represents best current guidance for practice. Informal consensus: Insufficient evidence to inform a recommendation. The recommendation represents best practice based upon an informal consensus of the panel. No recommendation: Insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice.
Rating the strength of recommendation	Strong: High degree of confidence that the recommendation reflects best practice based upon (a) strong evidence for true net effect, (b) consistent results, (c) minor or no concerns about study quality, (d) the extent of panelists' agreement. Moderate: Moderate confidence that the recommendation represents best practice based upon (a) good evidence for true net effect, (b) consistent results, (c) minor or few concerns about study quality, (d) extent of panelists' agreement. Weak: Some confidence that the recommendation offers best current guidance for practice based upon (a) limited evidence, (b) consistent results but important exceptions, (c) concerns about study quality, (d) panelists' agreement.
International Initiative on Thrombosis and Cancer	
Levels of evidence	High: Further research very unlikely to change our confidence in the estimate of effect. Moderate: Further research is further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low: Any estimate of effect is very uncertain.
Levels of recommendation	Strong: The panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects. Weak: The panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects but is not confident. Best clinical practice (guidance): In the absence of any clear scientific evidence and because of the undetermined balance between desirable and undesirable effects, judgment was based on the professional experience and consensus of the international experts within the working group.
National Comprehensive Cancer Network: Strength of recommendations	Category 1: Based upon high-level evidence (multiple adequately powered randomized controlled trials with consistent results) and uniform consensus (≥85% agreement) of the guideline committee that the intervention is appropriate. Category 2A: Based upon lower-level evidence and uniform National Comprehensive Cancer Network consensus (≥85% agreement) that the intervention is appropriate. Category 2B: Based upon lower-level evidence and less than uniform consensus (>50% but <85% of the panel vote) that the intervention is appropriate. Category 3: Based upon any level of evidence with major disagreement (<50% of panel) that the intervention is appropriate.
Spanish Society of Medical Oncology	
Strength of recommendation	A: Good evidence to support a recommendation for use. B: Moderate evidence to support a recommendation for use. C: Poor evidence to support a recommendation for use. D: Moderate evidence to support a recommendation against use. E: Good evidence to support a recommendation against use.
Quality of evidence	I: Evidence from at least one properly randomized controlled trial. II: Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from more than one center); from multiple time series; or from dramatic results from uncontrolled experiments. III: Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

marrow transplant are a unique inpatient population with a relatively low frequency of lower-extremity deep vein thrombosis and pulmonary embolism (1.3%) that is offset by a much higher risk of clinically significant bleeding (15.2%) [15]. As outlined below, differing guideline recommendations reflect the ongoing uncertainty around the risks and benefits of thromboprophylaxis in hospitalized patients with cancer [6–8, 10–12] (See Table 2).

Table 2. Guideline recommendations for venous thromboembolism prevention in hospitalized medical oncology patients

Guideline	Recommendation(s)
American Society of Clinical Oncology 2020	Patients with acute medical illness or reduced mobility **should be** offered pharmacological thromboprophylaxis in the absence of bleeding or other contraindications. (Recommendation type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate.) Patients without additional risk factors **may be offered** pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications. (Recommendation type: evidence-based; evidence quality: low; strength of recommendation: moderate.) Routine pharmacologic thromboprophylaxis **should not be offered** to patients admitted for the sole purpose of minor procedures or chemotherapy infusion, nor to patients undergoing stem cell/bone marrow transplantation. (Recommendation type: informal consensus; evidence quality: insufficient; strength of recommendation: moderate.)
International Society of Thrombosis and Hemostasis 2014	**Recommend** prophylaxis for patients admitted with acute medical illness in the absence of contraindications. **Suggest** use of LMWH over UFH. **Recommend** against use of DOACs. **Suggest** PCD for patients with contraindications. **Recommend** initiation of pharmacologic prophylaxis for patients when contraindication resolves. **Suggest** against prophylaxis for patients admitted for minor procedures or chemotherapy. **Recommend** pharmacologic thromboprophylaxis for patients with platelets ≥50,000/μL. **Suggest** individualized approach to patients with platelets 25,000–49,000/μL. **Recommend** against pharmacologic thromboprophylaxis in patients with platelets <25,000/μL.
International Initiative on Thrombosis in Cancer 2019	**Recommend** LMWH or fondaparinux (when CrCl is ≥30 mL/min) or UFH recommended in hospitalized patients with cancer and reduced mobility (grade 1B). DOACs **not recommended** routinely in this setting (guidance).
National Comprehensive Cancer Network 2020	**Recommend** LMWH, UFH, or fondaparinux with or without PCD for patients with no contraindication to anticoagulation (grade 2A). **Recommend** PCD if pharmacologic thromboprophylaxis is contraindicated (grade 2A).
Spanish Society of Medical Oncology 2018	Anticoagulant prophylaxis **should be considered** for hospitalized patients with cancer with acute medical illness in the absence of contraindications. LMWHs are the preferred agents (grade 1B).

Abbreviations: CrCl, creatinine clearance; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; PCD, pneumatic compression device; UFH, unfractionated heparin.

ASCO recommends prophylaxis for hospitalized medically ill medical oncology patients with additional risk factors for VTE. It does not recommend thromboprophylaxis in patients admitted for chemotherapy or stem cell transplantation. Prophylaxis may be offered to hospitalized medical oncology patients without risk factors [6].

The ISTH guidance document has similar recommendations, although it does not specifically recommend against prophylaxis in patients receiving stem cell transplant. However, ISTH does provide recommendations for patients with thrombocytopenia—an important risk factor for bleeding in patients receiving stem cell transplant [7, 8].

ITAC recommends low-molecular-weight heparin (LMWH) or fondaparinux for hospitalized patients with cancer and reduced mobility in the presence of adequate renal function (creatinine clearance [CrCl] ≥30 mL/min). Unfractionated heparin (UFH) is recommended for patients with reduced renal function. The guideline further recommends that medication cost and patient values and preferences be taken into account when choosing prophylaxis [10].

NCCN recommends pharmacologic VTE prophylaxis in all hospitalized patients without a contraindication. Presence of renal failure, cost, U.S. Food and Drug Administration approval status, ease of administration, monitoring, and reversal should be taken into consideration [11].

SEOM recommends that anticoagulant prophylaxis should be considered for medical oncology patients hospitalized with an acute medical illness. LMWH is the recommended agent [12].

VTE Prophylaxis in Ambulatory Medical Oncology Patients

Ambulatory medical oncology patients receiving chemotherapy are at increased risk for VTE [16]. LMWH and semuloparin have been demonstrated to reduce the incidence of VTE compared with placebo in unselected populations of ambulatory patients with cancer receiving chemotherapy. However, the absolute event rates in these studies were low, such that thromboprophylaxis was not widely adopted or recommended by guidelines [17, 18].

The Khorana risk score (KRS) is a validated risk stratification tool that can identify ambulatory patients with cancer receiving chemotherapy who are at increased risk for VTE [19]. The AVERT and CASSINI studies demonstrated that apixaban and rivaroxaban reduced the incidence of VTE in high-risk ambulatory patients with cancer (KRS ≥2) initiating a new chemotherapy regimen [20, 21]. Based on these data, all guidelines have incorporated the option of

Table 3. Guideline recommendations for VTE prevention in ambulatory medical oncology patients

Guideline	Recommendations
American Society of Clinical Oncology 2020	Routine pharmacological thromboprophylaxis **should not be offered** to all outpatients with cancer. (Recommendation type: evidence-based; evidence quality: intermediate to high; strength of recommendation: strong.) High-risk outpatients with cancer (KRS ≥2) prior to starting a new systemic chemotherapy regimen **may be offered** thromboprophylaxis with apixaban, rivaroxaban, or LMWH if no significant risk factors for bleeding and no drug interactions. Provider **should discuss** with patient the benefits and harms, drug cost, and duration of prophylaxis. (Recommendation type: evidence-based; evidence quality: intermediate to high for apixaban and rivaroxaban, intermediate for LMWH; strength of recommendation: moderate.) Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone **should be offered** thromboprophylaxis with either aspirin or LMWH (lower-risk patients) or LMWH (higher-risk patients). (Recommendation type: evidence-based; evidence quality: intermediate; strength of recommendation: strong.)
International Society of Thrombosis and Hemostasis 2019	**Suggest** apixaban or rivaroxaban for primary thromboprophylaxis in high-risk ambulatory patients (KRS ≥2) starting chemotherapy if no contraindications or drug-drug interactions for up to 6 months. Treatment decision should be made after considering the risk of VTE and bleeding as well as patient preferences/values. **Suggest** LMWH be considered for high-risk patients with contraindications to apixaban or rivaroxaban.
International Initiative on Thrombosis and Cancer 2019	Primary prophylaxis with LMWH, VKAs, or DOACs is **not recommended routinely** in ambulatory patients on systemic anticancer therapy (grade 1B). Primary prophylaxis with LMWH **is indicated** in ambulatory patients with locally advanced or metastatic pancreatic cancer on systemic anticancer therapy who have a low risk of bleeding (grade 1B). Primary prophylaxis with LMWH is **not recommended** outside a clinical trial for patients with locally advanced or metastatic lung cancer on systemic anticancer therapy (guidance). Primary prophylaxis with DOAC (apixaban or rivaroxaban) is **recommended** in ambulatory patients on systemic anticancer therapy at intermediate-to-high VTE risk, identified by cancer type (i.e., pancreatic) or by a validated risk assessment model (i.e., KRS ≥2), and not actively bleeding or at a high risk of bleeding (grade 1B). In patients treated with immunomodulatory drugs combined with steroids or other systemic cancer therapies, primary prophylaxis is **recommended** (grade 1A). In this setting, VKAs at low or therapeutic doses, LMWH at prophylactic doses, and low-dose aspirin have been effective (grade 2C).
National Comprehensive Cancer Network 2020	**Consider** apixaban or rivaroxaban for up to 6 months in high-risk patients with cancer (KRS ≥2) starting a new chemotherapy regimen (grade 2A). **Recommend** LMWH or VKA (INR 2–3) for high-risk patients with myeloma (IMPEDE-VTE score >3 points or SAVED score ≥2 points) (grade 2A). **Recommend** aspirin (81–325 mg daily) or no prophylaxis for low-risk patients with myeloma (IMPEDE-VTE score ≤3 points or SAVED <2 points) (grade 2A).
Spanish Society of Medical Oncology 2018	A validated risk assessment model **should be used** to assess VTE risk at the initiation of systemic therapy and during the evolution of treatment and disease (grade 2C). Routine thromboprophylaxis **is not recommended** in ambulatory patients with cancer (grade 1B). Thromboprophylaxis with LMWH or DOACs **may be considered in** high-risk ambulatory patients with cancer such as those with advanced pancreatic cancer, NSCLC with ROS-1 and ALK rearrangements, patients with KRS ≥2, or high-risk according to another validated risk model initiating systemic therapy and no contraindications and low risk of bleeding. No consensus on dose or duration of thromboprophylaxis, but at least 12 weeks is suggested. If DOAC thromboprophylaxis is planned, must assess drug-drug interactions. **Recommend** discussing the indication for thromboprophylaxis and the risks and benefits. Patients should be closely monitored (grade 1B). **Recommend** educating patients about risk factors and symptoms of VTE (grade 2A).

Abbreviations: ALK, anaplastic lymphoma kinase; DOAC, direct oral anticoagulant; INR, international normalized ratio; KRS, Khorana risk score; LMWH, low-molecular-weight heparin; NSCLC, non-small cell lung cancer; ROS-1, c-ros oncogene; VKA, vitamin K antagonist; VTE, venous thromboembolism.

thromboprophylaxis for ambulatory, at-risk patients with cancer [6–8, 10–12] (Table 3).

Patients with multiple myeloma undergoing therapy with immunomodulatory drugs in combination with corticosteroids or chemotherapy are at increased risk for VTE [22]. ASCO recommends that thromboprophylaxis should be offered with aspirin or LMWH in low-risk patients and LMWH in higher-risk patients with myeloma receiving thalidomide or lenalidomide in conjunction with corticosteroids or chemotherapy [6]. ITAC recommends thromboprophylaxis in patients with myeloma treated with immunomodulatory imide drugs (IMiDs) combined with corticosteroids or systemic chemotherapy. Low- or therapeutic-dose vitamin K antagonists (VKAs), prophylactic-dose LMWH, or aspirin are

Table 4. Guideline recommendations for thromboprophylaxis in patients undergoing cancer surgery

Guideline	Recommendations
American Society of Clinical Oncology 2020	All patients undergoing major surgery **should be offered** pharmacological prophylaxis with UFH or LMWH unless contraindicated. (Recommendation type: evidence-based; evidence quality: high; strength of recommendation: strong.) Prophylaxis **should be commenced** preoperatively. (Recommendation type: evidence based; evidence quality: intermediate; strength of evidence: moderate.) Mechanical prophylaxis **should not be used** as monotherapy unless pharmacologic prophylaxis contraindicated. (Recommendation type: evidence based; evidence quality: intermediate; strength of recommendation: strong.) Combined pharmacologic/mechanical prophylaxis **may improve** efficacy, especially in highest-risk patients. (Recommendation type: evidence based; evidence quality: intermediate; strength of recommendation: moderate.) Pharmacologic prophylaxis **should be continued** for **at least 7–10 days**. Extended prophylaxis with LMWH for **up to 4 weeks** postoperatively **is recommended** for patients undergoing major open or laparoscopic abdominal or pelvic cancer surgery with high-risk features (restricted mobility, obesity, history of VTE, or additional risk factors). In lower-risk surgical settings, the decision on appropriate duration of thromboprophylaxis should be made on a case-by-case basis. (Recommendation type: evidence based; evidence quality: high; strength of recommendation: moderate to strong.)
International Initiative on Thrombosis and Cancer 2019	LMWH (if CrCl ≥30 mL/min) once daily or low-dose UFH three times a day **is recommended**. Pharmacologic prophylaxis **should be started 2–12 hours** preoperatively and continued for **at least 7–10 days**. No data to suggest one LMWH superior to another (grade 1A). Values and preferences: Once-daily LMWH more convenient. Insufficient evidence to support fondaparinux as an alternative to LMWH (grade 2C). Values and preferences: Same as above. Use of highest prophylactic dose of LMWH **is recommended** (grade 1A). Values and preferences: Same as above. Extended prophylaxis (**4 weeks**) with LMWH to prevent postoperative VTE after major laparotomy (grade 1A) and laparoscopic surgery (grade 2C) **is indicated** in patients with a high VTE risk and low bleeding risk. Values and preferences: Daily injections for longer duration. Costs: The price of LMWH may influence choice. Mechanical thromboprophylaxis **is not recommended** as monotherapy, except when pharmacologic prophylaxis is contraindicated (grade 2B). Values and preferences: No injections. IVC filters are **not recommended** for routine prophylaxis (grade 1A).
National Comprehensive Cancer Network 2020	Prophylactic dose LMWH, UFH, or fondaparinux with or without PCD **is recommended** (category 1). **Consider** preoperative dosing with UFH or LMWH for high-risk surgery patients with or without PCD (category 2A). If anticoagulant prophylaxis is contraindicated, mechanical prophylaxis **is recommended** (category 2A). Out-of-hospital VTE prophylaxis **is recommended** for **up to 4 weeks** postsurgery for high-risk patients with abdominal or pelvic cancer (category 2A).
Spanish Society of Medical Oncology 2018	In the absence of contraindications, all patients undergoing major surgery **should receive** pharmacologic thromboprophylaxis (grade 1A). LMWH are the preferred agents. Prophylaxis **should be initiated** preoperatively or as soon as possible postoperatively. Mechanical prophylaxis **can be added** to pharmacologic prophylaxis in high-risk patients but **should not be used** as monotherapy unless pharmacologic prophylaxis is contraindicated (grade 2C). Patients **should receive at least 7–10 days** of prophylaxis, and high-risk patients undergoing major abdominal or pelvic cancer surgery **should be considered** for extended thromboprophylaxis for 4 weeks (grade 1A). We **suggest** the same recommendation for laparoscopic surgery; risk factors and the duration and type of procedure must be assessed (grade 2C).

Abbreviations: CrCl, creatinine clearance; IVC, inferior vena cava; LMWH, low-molecular-weight heparin; PCD, pneumatic compression device; UFH, unfractionated heparin; VTE, venous thromboembolism.

recommended thromboprophylaxis [10]. The SAVED and IMPEDE VTE scores are recently published evidence-based risk assessment models for VTE in patients with myeloma who are starting therapy [23, 24]. NCCN recommends risk stratification of patients with myeloma using either the SAVED or IMPEDE VTE scores depending on their treatment regimen. (SAVED only applies to IMiD-based regimens.) High-risk patients should receive prophylactic-dose LMWH or VKA (international normalized ratio, 2–3), whereas low-risk patients should receive aspirin or no prophylaxis [11].

VTE Prophylaxis in Surgical Patients with Cancer

Patients with cancer undergoing major surgery are at particularly high risk for VTE. Several RCTs support the efficacy and safety of anticoagulant thromboprophylaxis in patients with cancer undergoing surgery [25–27]. ITAC, NCCN, and SEOM recommend thromboprophylaxis for patients undergoing cancer surgery, whereas ASCO recommends that thromboprophylaxis should be offered to such patients [6, 10–12]. All the guidelines recommend that thromboprophylaxis be started preoperatively, with ITAC

Table 5. Guideline recommendations for treatment of cancer-associated VTE

Guideline	Recommendations
American Society of Clinical Oncology 2020	Initial anticoagulation may involve LMWH, UFH, fondaparinux, or rivaroxaban. Among parenteral agents, LMWH preferred over UFH in the absence of severe renal impairment (CrCl <30 mL/min). (Recommendation type: evidence based; evidence quality: high; strength of recommendation: strong.) For long-term anticoagulation, LMWH, edoxaban, or rivaroxaban for at least 6 months is preferred over VKA. VKAs are inferior but may be used if LMWH or DOACs are not accessible. DOACs are associated with increased major bleeding in GI and potentially GU malignancies. Caution with DOACs is warranted in other settings with high risk for mucosal bleeding. Drug-drug interactions should be checked before use of DOACs. (Recommendation type: evidence based; evidence quality: high; strength of recommendation: strong.) Anticoagulation beyond the initial 6 months should be offered to select patients with active cancer—including metastatic disease or those receiving chemotherapy—and needs to be reassessed on an intermittent basis to ensure a continued favorable risk-benefit profile. (Recommendation type: informal consensus; evidence quality: low; Strength of recommendation: weak to moderate.) The insertion of an IVC filter should not be offered to patients with established or chronic thrombosis (VTE diagnosis >4 weeks) or to patients with a temporary contraindication to anticoagulation. There is no role for IVC filters for primary prevention of VTE, but they may be offered to patients with absolute contraindications to anticoagulation in the acute setting if thrombus burden is considered life-threatening. (Recommendation type: informal consensus; evidence quality: low to intermediate; strength of recommendation: moderate.) An IVC filter may be offered as an adjunct to anticoagulation in patients with progressive thrombosis despite optimal anticoagulation. (Recommendation type: informal consensus; evidence quality: low to intermediate; strength of recommendation: weak.) For patients with primary or metastatic CNS malignancies and VTE, anticoagulation should be offered, although uncertainty remains as to choice of agent and the type of patients most likely to benefit. (Recommendation type: informal consensus; evidence quality: low; strength of recommendation: moderate.) Incidental VTE should be treated in the same manner as symptomatic VTE. (Recommendation type: informal consensus; evidence quality: low; strength of recommendation: moderate.) Treatment of isolated subsegmental PE or splanchnic or visceral vein thrombi should be offered on a case-by-case basis considering the potential benefits and risks. (Recommendation type: informal consensus; evidence quality: insufficient; strength of recommendation: moderate.)
International Society of Thrombosis and Hemostasis 2018	Recommend individualized treatment regimens after shared decision making with patients. Suggest edoxaban and rivaroxaban for patients with cancer with acute VTE, a low risk of bleeding, and no drug-drug interactions. LMWHs are an acceptable alternative. Suggest LMWH for patients with acute VTE at high risk for bleeding, including those with luminal GI malignancy with intact primaries, GU malignancies, nephrostomy tubes, or GI mucosal abnormalities. Edoxaban and rivaroxaban are acceptable alternatives if no drug-drug interactions.
International Initiative on Thrombosis and Cancer 2019	LMWH is recommended over UFH for initial treatment unless CrCl <30 mL/min (grade 1B). Values and preferences: LMWH is easier to use than UFH. A once-daily LMWH regimen is recommended unless patient characteristics (fragile patients at increased bleeding risk) require a twice-daily regimen. Rivaroxaban or edoxaban (after initial LMWH/UFH for 5 days) can be used for initial treatment if CrCl ≥30 mL/min and patient is not at high risk of GI or GU bleeding (grade 1B). UFH can be used for initial treatment when LMWH or DOACs are contraindicated or not available (grade 2C). Fondaparinux can also be used for initial treatment if CrCl ≥30 mL/min (grade 2D). Values and preferences: Fondaparinux is easier to use than UFH. Thrombolysis can only be considered on a case-by-case basis with specific attention paid to contraindications, especially bleeding. (Guidance based on evidence of very low quality and high bleeding risk.) Values and preferences: Expert opinion is recommended prior to thrombolysis, and it should only be done in centers with the appropriate expertise. IVC filters may be considered for initial treatment when anticoagulation is contraindicated or when PE occurs despite optimal anticoagulation. Periodic reassessment of contraindications to anticoagulation is recommended and anticoagulation should be resumed when safe. (Guidance based on evidence of very low quality and unknown balance of risk and benefits.) LMWH favored over VKA for early maintenance and long-term therapy if CrCl ≥30 mL/min (grade 1A). Values and preferences: Daily injections can be a burden to patients. Rivaroxaban and edoxaban recommended for patients with CrCl ≥30 mL/min if no impairment in GI absorption or strong drug-drug interactions (grade 1A). Use caution in patients with GI malignancies. LMWH or DOACs should be continued for at least 6 months (grade 1A). After 6 months, continuation of therapy should be based on individual assessment of benefit-risk ratio, tolerability, drug availability, patient preference, and cancer activity. (Guidance in the absence of data.) In the event of recurrent VTE, three options can be considered: (a) increase LMWH by 20%–25% or switch to DOAC; (b) for DOACs, switch to LMWH; and (c) for VKAs, switch to LMWH or DOAC.

(continued)

Table 5. (continued)

Guideline	Recommendations
	(Guidance based on evidence of very low quality and unknown balance of desirable and undesirable effects.) Effect of therapy should be monitored for symptomatic improvement.
National Comprehensive Cancer Network 2020	Apixaban (category 1), edoxaban after at least 5 days of parenteral anticoagulation (category 1), or rivaroxaban (category 2A) preferred over LMWH for patients without GI malignancies. LMWH (dalteparin category 1) preferred over DOACs in patients with GI malignancies. Dabigatran after at least 5 days of parenteral anticoagulation (alternative to apixaban, edoxaban, rivaroxaban, or LMWH if not appropriate or unavailable) (category 2A). UFH is an alternative to LMWH for initial therapy (category 2B) and is preferred for patients with CrCl <30 mL/min. Fondaparinux is contraindicated in patients with CrCl <30 mL/min and should be used with caution with CrCl 30–50 mL/min. Dabigatran, edoxaban, and rivaroxaban are contraindicated with CrCl <30 mL/min. Apixaban is contraindicated if CrCl <25 mL/min. Apixaban and edoxaban are contraindicated in patients with clinically significant liver disease (total bilirubin >1.5 × ULN or transaminases >2 × ULN). Dabigatran and rivaroxaban are contraindicated if transaminases >3 × ULN. Apixaban and rivaroxaban should not be used in conjunction with strong inducers/inhibitors of CYP3A4 and P-glycoprotein. Dabigatran and edoxaban should not be used in conjunction with strong inducers/inhibitors of P-glycoprotein. Choice of anticoagulation regimen should be based on individual risk of thrombosis and bleeding, renal and hepatic function, inpatient/outpatient status, FDA approval status, ease of administration, cost, burden of laboratory monitoring, agent reversibility, and patient preferences. Consider catheter-directed pharmacomechanical thrombolysis for DVT in patients at low risk for bleeding but at risk for limb loss or severe persistent symptoms despite anticoagulation (category 2A). Consider systemic or catheter-directed thrombolysis (category 2A) or embolectomy (category 2B) for patients with hemodynamically unstable PE at low risk for bleeding. Consider IVC filter (retrievable preferred) if anticoagulation is contraindicated for acute VTE (within 1 month of diagnosis). Recommend filter retrieval once patient is tolerating anticoagulation (category 2A). Incidental PE should be treated similarly to symptomatic PE (category 2A). Recommended duration of anticoagulation therapy is for as long as the patient's cancer is active or under treatment. Providers should continue to discuss the risks and benefits (category 2A). For recurrent VTE on UFH, recommend considering HIT, antiphospholipid syndrome (check UFH anti-Xa level), increase dose of UFH, or switch to LMWH or DOAC (category 2B). For recurrent VTE on LMWH, recommend considering HIT, switch to twice-daily injections or increase dose or switch to fondaparinux or DOAC (category 2B). For recurrent VTE on fondaparinux, recommend considering HIT or switching to UFH, LMWH, or DOAC (category 2B). For recurrent VTE on warfarin, recommend switching to LMWH, UFH, fondaparinux, or DOAC (category 2B). For recurrent VTE on DOAC, recommend switching to LMWH or fondaparinux (category 2B).
Spanish Society of Medical Oncology 2018	LMWH is the drug of choice for initial treatment of VTE (grade 1B). Rivaroxaban can be used if bleeding risk is low and no significant drug-drug interactions (grade 1B). UFH and fondaparinux can be considered as alternative agents for initial treatment (grade 1B). LMWH and DOACs for 6 months are drugs of choice for long-term treatment of VTE. DOACs must be used in patients with low bleeding risk and no significant drug-drug interactions (grade 1A). Extended-duration treatment should be considered in high-risk patients such as those with active cancer and those receiving systemic therapy. Patients should be reevaluated frequently to assess risk-benefit ratio of continued anticoagulation (grade 2C). Incidental VTE should be treated similarly to symptomatic VTE (grade 1B). Treatment of isolated incidental subsegmental PE or superficial vein thrombosis should be individualized. It is suggested to consider anticoagulation (grade 2C). Therapeutic LMWH should be used for recurrent VTE in patients on VKA or prophylactic or intermediate doses of LMWH (grade 2B). For recurrent VTE on therapeutic LMWH, increase LMWH dose 25% or switch to DOAC (grade 2B). For recurrent VTE on DOAC, switch to LMWH or increase DOAC dose to therapeutic dose if subtherapeutic doses were being used (grade 3C). IVC filter insertion may be considered if anticoagulation contraindicated or recurrent events occur despite appropriate anticoagulation. A retrievable filter is preferred, and anticoagulation should be resumed as soon as possible (grade 2B).

Abbreviations: CNS, central nervous system; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; GU, genitourinary; HIT, heparin-induced thrombocytopenia; IVC, inferior vena cava; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin; ULN, upper limit of normal range; VKA, vitamin K antagonist; VTE, venous thromboembolism.

specifying precise timing for prophylaxis initiation [10]. ASCO, ITAC, and SEOM recommend that thromboprophylaxis be continued for at least 7–10 days and recommend against mechanical prophylaxis alone unless pharmacologic thromboprophylaxis is contraindicated [6, 10, 12]. All guidelines recommend extended-duration thromboprophylaxis for up to 4 weeks in patients undergoing high-risk abdominal and/or pelvic cancer surgery [6, 10–12]. ASCO characterizes high-risk patients as those with restricted mobility, obesity, previous VTE, or additional risk factors [6], whereas NCCN and SEOM identify high-risk patients as those with an anesthesia time >2 hours, gastrointestinal (GI) malignancies, previous VTE, advanced-stage disease, bed rest of ≥4 days, or age >60 years [11, 12]. ITAC recommends against the use of inferior vena cava (IVC) filters for thromboprophylaxis [10] (Table 4).

Guideline Recommendations for Cancer-Associated Treatment in Medical Oncology Patients

Four RCTs comparing LMWH (dalteparin) with DOACs for the treatment of CAT have been completed, including HOKUSAI VTE Cancer (edoxaban), SELECT-D (rivaroxaban), and ADAM VTE and Caravaggio (apixaban) [28–31]. In each study, patients were followed for at least 6 months. DOACs were shown to be noninferior to dalteparin for recurrent VTE and major bleeding. Bleeding was more common in patients with GI malignancies taking edoxaban and rivaroxaban compared with dalteparin [28, 29]. In contrast, apixaban was not associated with an increased risk of bleeding compared with dalteparin in the ADAM and Caravaggio trials [30, 31]. All the guidelines have incorporated DOACs into their treatment recommendations [6, 10–12, 32] (Table 5). In general, DOACs are recommended for patients at low risk for bleeding who do not have GI or genitourinary (GU) malignancies, who have adequate renal (and hepatic function in the NCCN guidelines), and who have no significant drug-drug interactions. LMWH is preferred for patients with GI or GU malignancies or significant drug-drug interactions. Although apixaban appears to be associated with a similar risk of bleeding compared with dalteparin, guidelines thus far have been cautious about recommending apixaban in patients with GI and GU malignancies until more experience is accrued.

Initial anticoagulation may involve LMWH, UFH, fondaparinux, apixaban, or rivaroxaban. Among parenteral agents, ASCO recommends LMWH over UFH in the absence of severe renal impairment (CrCl <30 mL/min) [6]. ITAC and NCCN recommend LMWH in patients with cancer who have CrCl ≥30 mL/min [10, 11]. SEOM prefers LMWH as well [12]. For long-term therapy, LMWH and DOACs are favored over VKA. Fondaparinux is an alternative if LMWH or DOACs are not available.

The optimal duration of therapy for CAT remains unclear, as there are no randomized studies testing different durations of therapy in patients with cancer. However, the available data support the conclusion that patients with active cancer—and particularly metastatic cancer—undergoing therapy are at high risk for recurrent thromboembolism. ASCO, ITAC, and SEOM recommend at least 6 months of therapy [6, 10, 12]. NCCN recommends at least 3 months of therapy or for as long as cancer is active or undergoing treatment, whichever is longer [11]. Each of the guidelines recommends that the duration of therapy should be reassessed on a regular basis as appropriate for the patient's clinical situation, taking into account the risks and benefits of therapy and patient preferences. Guidance regarding systemic and catheter-directed thrombolytic therapy and embolectomy are discussed in the ITAC, NCCN, and SEOM guidelines [10–12]. ASCO, ITAC, NCCN, and SEOM also provide guidance for the use of IVC filters in the treatment of CAT [6, 10–12]. Management of incidental VTE is featured in the ASCO, NCCN, and SEOM guidelines, and management of recurrent thromboembolism is reviewed in the ITAC, NCCN, and SEOM guidelines [6, 10–12]. In general, all the recently published guidelines provide consistent advice on the treatment of CAT.

Anticoagulant Therapy in Special Populations with CAT

Patients with CAT represent a rapidly growing population requiring anticoagulant therapy. In patients without cancer, the DOACs have supplanted VKAs as the preferred anticoagulants for VTE [33]. Since the approval of dabigatran over a decade ago, growing clinical experience, pharmacological and observational studies, and large population data analyses have provided key insights into the safety and efficacy of DOACs in special patient populations, such as those with increased body mass index (BMI) or body weight, impaired renal function, and history of proximal GI surgery (e.g., gastric bypass) [34–36]. As a growing body of literature also supports the use of DOACs in the setting of CAT, guidance on the clinical use of DOACs in patients with cancer with these comorbidities is critical [6, 10–12] (Table 6).

In general, anticoagulation for prevention or treatment of VTE in patients with cancer does not require specific adjustment in patients with mild renal insufficiency, overweight BMI, or mild obesity. However, more severe renal impairment, extremes of either BMI or body weight, and patients with proximal GI surgery that can affect drug absorption warrant special consideration. For example, injectable anticoagulants have been at least theoretically preferred in patients with potentially abnormal proximal GI absorption.

Data regarding the safety and efficacy of DOACs for prevention and treatment of VTE in patients with cancer are accumulating at a rapid pace; however, there are very limited population data for those with severe renal impairment, extremes of weight, and prior proximal GI surgery. Accordingly, the growing enthusiasm for DOACs in VTE prevention and treatment in patients with cancer has been tempered in these special populations, who are at risk for both thrombotic and hemorrhagic complications. One particular clinical challenge is the prevention and treatment of VTE in patients were severe renal dysfunction because LMWHs and DOACs depend on at least some degree of renal clearance [37, 38]. DOAC selection in the setting of severe renal impairment should focus on agents with limited renal clearance and requires shared decision making

Table 6. Guideline recommendations for management of cancer-associated VTE in special patient populations

Patient Population	American Society of Clinical Oncology 2020	International Initiative on Thrombosis and Cancer 2019	International Society of Thrombosis and Hemostasis 2018	National Comprehensive Cancer Network 2020	Spanish Society of Medical Oncology 2020
Extremes of weight	Treatment: LMWH: Use actual body weight. DOACs: Use caution with weight >120 kg, BMI >40 kg/m^2. LMWH is preferred. If DOAC must be used, then check drug-specific peak and trough levels.	No specific recommendations.	No specific recommendations.	Treatment: LMWH: Follow package insert for dosing; consider LMWH anti-Xa levels. Fondaparinux: Use caution with weight <50 kg. DOACs: No specific recommendations. Prophylaxis: For BMI ≥40, use dalteparin 7,500 units s.c. daily, enoxaparin 40 mg s.c. twice daily, fondaparinux 5 mg s.c. daily, or UFH 7,500 units s.c. three times daily. Use aspirin 81–325 mg daily or VKA (INR 2–3) only for patients with myeloma. For weight <50 kg, consider checking LMWH anti-Xa levels.	No specific recommendations.
Renal impairment	Treatment: LMWH: Anti-Xa measurement is recommended in patients with moderate-to-severe renal impairment. If this is unavailable, UFH and VKA are safer options for initial and long-term treatment, respectively. DOACs: Refer to package inserts for guidance.	Treatment: LMWH: Suggest use of UFH followed by VKA for CrCl <30 mL/min or LMWH adjusted to LMWH anti-Xa levels (guidance). Prophylaxis: For CrCl <30 mL/min, mechanical prophylaxis can be used and UFH can be considered on case-by-case basis (guidance).	No specific recommendations.	Treatment: For CrCl 20–30 mL/min, use enoxaparin 1 mg/kg daily; consider LMWH anti-Xa levels for dalteparin. For fondaparinux, use caution with CrCl 30–50 mL/min; avoid with CrCl <30 mL/min. DOACs: Avoid with CrCl <30 mL/min. For initial therapy, consider UFH and for chronic therapy, consider VKA. Prophylaxis: Consider UFH. For enoxaparin, reduce dose to 30 mg daily or use UFH or dalteparin. Avoid DOACs with CrCl <30 mL/min. No dose adjustment for aspirin or VKA.	No specific recommendations.
Hepatic dysfunction	Treatment: DOACs: Refer to package inserts for guidance.	No specific recommendations.	No specific recommendations.	DOACs: Avoid if clinically significant liver disease. Apixaban and edoxaban: Avoid if total bilirubin (not due to Gilbert's syndrome) >1.5 × ULN or transaminases >2 × ULN Dabigatran or rivaroxaban: Avoid if transaminases >3 × ULN.	No specific recommendations.
Proximal GI surgery	No specific recommendations.	No specific recommendations.	No specific recommendations.	No specific recommendations.	No specific recommendations.
Thrombocytopenia	No specific recommendations.	Treatment: Anticoagulation can be used with platelets >50,000/μL and no bleeding; if platelets <50,000/μL, decisions on dose and treatment should be made on case-by-case basis (guidance). Prophylaxis: Anticoagulation might be used if platelets >80,000/μL; if platelets <80,000/μL, anticoagulation should only be considered on case-by-case basis with utmost caution (guidance).	Treatment: For acute proximal DVT or PE or recurrent VTE (within 30 days) and platelets <50,000/μL, consider platelet transfusions to maintain platelets 40,000–50,000/μL, and continue therapy. For acute distal DVT or incidental subsegmental PE and platelets 25,000–50,000/μL, consider half-dose (50%) or prophylactic-dose LMWH.	Treatment: LMWH: If platelets >50,000/μL, use full-dose therapy enoxaparin 1 mg/kg every 12 hours. If platelets 25,000–50,000/μL, suggest enoxaparin 0.5 mg/kg every 12 hours or transfuse platelets to maintain >50,000/μL or IVC filter. If platelets <25,000/μL, hold LMWH or consider platelet transfusion to continue therapy or IVC filter. DOAC: If platelets >50,000/μL, hold until platelet recovery or transfuse platelets or IVC filter. Prophylaxis: If platelets >50,000/μL, use standard doses.	No specific recommendations.

(continued)

Table 6. (continued)

Patient Population	American Society of Clinical Oncology 2020	International Initiative on Thrombosis and Cancer 2019	International Society of Thrombosis and Hemostasis 2018	National Comprehensive Cancer Network 2020	Spanish Society of Medical Oncology 2020
			For platelets <25,000/μL, hold anticoagulation. For chronic VTE (beyond 30 days), consider half-dose or prophylactic-dose LMWH. For DOACs, hold if platelets <50,000/μL or transfuse platelets. Consider retrievable IVC filter on case-by-case basis if acute VTE with platelets <50,000/μL refractory to transfusional support. Prophylaxis: No specific recommendations.	If platelets <30,000–50,000/μL, hold or use clinical judgment.	
Pregnancy	No specific recommendations.	Use standard doses of LMWH for treatment and prophylaxis (guidance).	No specific recommendations.	No specific recommendations.	No specific recommendations.
Primary or metastatic brain tumors	Treatment: Anticoagulation should be offered as it is for other patients with cancer, although uncertainty remains as to choice of agent and patients most likely to benefit. (Recommendation type: informal consensus; evidence quality: low; strength of recommendation: moderate.) Preliminary data suggest that DOACs may be associated with a lower risk of intracranial hemorrhage than LMWH in patients with metastatic brain tumors.	Prevention: Recommend use of LMWH or UFH postoperatively for VTE prevention in neurosurgery patients (grade 1A). Primary pharmacological prophylaxis of VTE is not recommended in patients with a brain tumor who are not undergoing neurosurgery (grade 1B). Treatment: LMWH or DOACs can be used for anticoagulation in patients with a brain tumor and VTE (grade 2B).	No specific recommendations.	No specific recommendations.	Treatment: In the absence of contraindications, patients with primary or metastatic brain tumors should be managed similarly to other solid tumors (grade 2B). For patients with brain metastases from melanoma or kidney cancer, a 25%–50% dose reduction in LMWH dose maybe considered (grade 2C). For patients with brainstem glioma, a 25%–50% dose reduction in LMWH dose is suggested (grade 2C).

Abbreviations: BMI, body mass index; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; GI, gastrointestinal; INR, international normalized ratio; IVC, inferior vena cava; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin; ULN, upper limit of normal range; VTE, venous thromboembolism.

Table 7. Guideline recommendations on treatment of unusual sites of cancer-associated venous thromboembolism

Unusual site thrombosis	American Society of Clinical Oncology 2020	International Initiative on Thrombosis and Cancer 2019	International Society of Thrombosis and Hemostasis 2018	National Comprehensive Cancer Network 2020	Spanish Society of Medical Oncology 2020
CVC thrombosis	Prophylaxis: No specific recommendations. Treatment: No specific recommendations.	Prophylaxis: Use of routine pharmacologic prophylaxis for CVC thrombosis is not recommended (grade 1A). CVC should be inserted on the right side, in the jugular vein, and the distal catheter tip should be located at the junction of the superior vena cava and the right atrium (grade 1B). In patients requiring CVC, we suggest the use of implanted ports over peripherally inserted CVC (guidance). Treatment: For the treatment of symptomatic CVC thrombosis, anticoagulation is recommended for a minimum of 3 months and as long as the CVC is in place; LMWHs are suggested. Direct comparisons between LMWHs, DOACs, and VKA have not been made (guidance). In patients with CVC thrombosis, the CVC can be kept in place if it is functional, well positioned, and not infected, with resolution of symptoms during anticoagulation. No standard duration of therapy is established (guidance).	Prevention: No specific recommendation. Treatment: Suggest (weak guidance) anticoagulation with LMWH without CVC removal if functional and required for ongoing therapy. Recommend (strong guidance) removal of a nonfunctional, infected, or incorrectly positioned catheter and suggest anticoagulation with LMWH. Suggest (weak guidance) a short duration of anticoagulation (3 to 5 days), if clinically practical, prior to removal of a CVC. Suggest (weak guidance) removal of CVC without anticoagulation if therapeutic anticoagulation cannot be safely administered because of the active risk of hemorrhage. Suggest (weak guidance) anticoagulation over no anticoagulation for an incidental CVC DVT. Alternative strategies such as serial ultrasound and/or catheter removal can be considered. Recommend (strong guidance) anticoagulation over thrombolysis for acute CVC thrombosis. Consideration of clot-directed thrombolysis should be reserved for cases of massive clot burden and/or refractory thrombosis. In cases of thrombocytopenia without bleeding, the decision to use or withhold anticoagulation should be made on an individual basis. Suggest (weak guidance) 3 to 6 months of anticoagulation for a symptomatic, CVC upper-extremity DVT. Suggest (weak guidance) LMWH over warfarin in patients with cancer. Suggest (weak guidance) anticoagulation for the duration the catheter remains in place for individuals with ongoing risk factors, such as persistent CVC.	Prevention: The panel does not recommend prophylactic anticoagulation for CVC. Treatment: If CVC is still needed, anticoagulation alone is recommended for CVC DVT. If CVC is no longer required, anticoagulation for 5–7 days is recommended before CVC removal, if feasible. If CVC is infected or symptoms of thrombosis fail to resolve, then CVC should be removed. If anticoagulation is contraindicated, CVC should be removed after consideration of thrombus burden and potential for embolization as well as feasibility of short course of anticoagulation prior to CVC removal. Anticoagulation for CVC DVT should be continued for at least 3 months or the life of the CVC should it remain in place.	Treatment: Recommend LMWH for 3–6 months or indefinitely if CVC is not removed (grade 2B). DOAC could be considered as a treatment option (grade 2C). Recommend against CVC removal unless it is no longer needed, infected, anticoagulation is contraindicated, or anticoagulation failure (grade 2B). Removal should be done after 5–7 days of anticoagulation.

(continued)

Table 7. (continued)

Unusual site thrombosis	American Society of Clinical Oncology 2020	International Initiative on Thrombosis and Cancer 2019	International Society of Thrombosis and Hemostasis 2018	National Comprehensive Cancer Network 2020	Spanish Society of Medical Oncology 2020
Superficial vein thrombosis	No specific recommendations.	No specific recommendations.	No specific recommendations.	Prevention: No recommendations. Treatment: Distal upper extremity: Initial symptomatic treatment (warm compresses, elevation, NSAIDs) and remove catheter if present. If progression, consider anticoagulation. Proximal upper extremity: Same as above except consider initial anticoagulation if clot is within 3 cm of deep vein. Distal leg: Initial symptomatic treatment and remove catheter if present. If progression or clot within 3 cm of deep vein, consider anticoagulation. Proximal leg: Initial anticoagulation for at least 6 weeks. Remove catheter if present. At 6 weeks if persistent symptoms or risk factors for progression (advanced cancer, active cancer treatment, non–catheter-related clots), consider longer course of therapy. Fondaparinux 2.5 mg daily and rivaroxaban 10 mg daily have been shown to be effective in studies with limited number of patients with cancer. Therapeutic anticoagulation at clinician discretion.	No specific recommendations.
Hepatic vein thrombosis	No specific recommendations.	No specific recommendations.	No specific recommendations.	Acute (symptoms/signs ≤8 weeks): If no contraindication, recommend anticoagulation. Hepatology evaluation. Consider catheter-directed pharmacomechanical thrombolysis. If anticoagulation contraindicated, consider TIPS or surgical shunt. Hepatology evaluation. Reassess contraindication to anticoagulation regularly. Chronic (symptoms/signs >8 weeks): Hepatology evaluation. Consider TIPS or surgical shunt. Consider anticoagulation. Duration of anticoagulation at least 6 months for provoked hepatic vein thrombosis, indefinite for unprovoked event or persistent risk factor (i.e., cancer, thrombophilia).	No specific recommendations.

(continued)

Table 7. (continued)

Unusual site thrombosis	American Society of Clinical Oncology 2020	International Initiative on Thrombosis and Cancer 2019	International Society of Thrombosis and Hemostasis 2018	National Comprehensive Cancer Network 2020	Spanish Society of Medical Oncology 2020
Portal, mesenteric, or splenic veins thrombosis	No specific recommendations.	No specific recommendations.	No specific recommendations.	Acute (symptoms/signs ≤8 weeks): If no contraindication, recommend anticoagulation. Surgery if bowel infarction present. Consider catheter-directed pharmacomechanical thrombolysis. If anticoagulation contraindicated, GI and surgery evaluation. Surgery if bowel infarction. Reassess contraindication to anticoagulation regularly. Chronic (symptoms/signs >8 weeks): GI evaluation, beta blockade. Consider variceal banding; consider anticoagulation if no contraindication. Duration of anticoagulation at least 6 months for provoked hepatic vein thrombosis, indefinite for unprovoked event or persistent risk factor (i.e., cancer, thrombophilia).	No specific recommendations.

Abbreviations: CVC, central venous catheter; DVT, deep vein thrombosis; DOAC, direct oral anticoagulant; GI, gastrointestinal; LMWH, low-molecular-weight heparin; NSAID, nonsteroidal anti-inflammatory drug; TIPS, transjugular intrahepatic portosystemic shunt; VKA, vitamin K antagonist.

Table 8. Arterial thromboembolic disease (mainly CHD and CVD) in cancer

Study (study duration)	*n*	Study design	Inclusion criteria	Source of information	ATE rate	Comment(s)
Khorana et al. [41] (1995–2002)	66,106	Multicenter retrospective (115 hospitals)	Hospitalized and chemotherapy-related neutropenia	Discharge database	1.5%	Arterial events, including CHD (0.8%), CVD (0.5%), and arterial embolism (0.2%) In-hospital mortality was significantly greater with ATE (OR, 5.04; 95% CI, 4.38–5.79) A 124% increase in arterial events ($p < .0001$ for trend) over the 8 years of study
Di Nisio et al. [39] (2003–2009)	1,934	Multicenter retrospective	Ambulatory patients with cancer on chemotherapy Patients with a history of CHD/CVD were excluded	Medical records	0.27%	Median age of patients was 61 years All except one event was cardiac Medication-induced cardiac events highlighted
Zoller et al. [42, 43] (1987–2008)	820,491	Nationwide retrospective	Diagnosis of cancer	National registries	N/A	CHD: 1.7% at first 6 months of diagnosis Ischemic stroke: 1.6% at first 6 months of diagnosis Hemorrhagic stroke: 2.2% at first 6 months of diagnosis Highest risk of CHD/CVD in first 6 months of diagnosis and metastatic disease
Navi et al. [37] (2002–2011)	279,719	Retrospective matched	Age >65 (older adults) Breast, lung, prostate, gastric, pancreatic colorectal, bladder, NHL	SEER Medicare data	N/A	The 6-month cumulative incidence of CHD was 2.0% in patients with cancer compared with 0.7% in control patients (HR, 2.9; 95% CI, 2.8–3.1) The 6-month cumulative incidence of ischemic stroke was 3.0% in patients with cancer compared with 1.6% in control patients (HR, 1.9; 95% CI, 1.8–2.0)
Brenner et al. [40] (2009–2014)	5,717	Multicenter prospective	Active cancer with previous diagnosis of venous thrombosis	RIETE Registry	1.10%	Arterial ischemic events and major bleeding appeared early after VTE in patients with active cancer and were among frequent causes of their deaths 6.1% had major bleeding with 30-day mortality of 41%
Grilz et al. [38] (2003–2013)	1,880	Single-center prospective	Age >18 years with active cancer diagnosis No indication for long-term anticoagulation	CATS database	1.7% at 12 months	The cumulative 3-, 6-, 12-, and 24-month risks of ATE were 0.9%, 1.1%, 1.7%, and 2.6%, respectively Occurrence of ATE was associated with a 3.2-fold increased risk of all-cause mortality (HR, 3.2; 95% CI, 2.2–4.8; $p < .001$)

Abbreviations: ATE, arterial thromboembolism; CATS, Vienna Cancer and Thrombosis Study; CHD, coronary heart disease; CI, confidence interval; CVD, Cerebrovascular disease; HR, hazard ratio; N/A, not assessed; NHL, non-Hodgkin lymphoma; OR, odds ratio; RIETE, Registro Informatizado de Enfermedad TromboEmbólica; SEER, Surveillance, Epidemiology, and End Results; VTE, venous thromboembolism.
Source: Adopted from De Stefano V, Arterial thrombosis and cancer: The neglected side of the coin of Trousseau syndrome. Haematologica 2018;103:1419–1421.

between the prescriber, patient, and entire health care team.

LMWHs and DOACs may be considered in extremes of body weight, but adjustments based on weight should be made when applicable, especially for those with low body weight. The package inserts and prescribing guidance for most of the DOACs provide recommendations for dose reduction in the setting of low body weight. More challenging is the selection and dosing of DOACs in patients with increased BMI and body weight. RCTs of DOACs for VTE therapy in patients without cancer (EINSTEIN VTE, EINSTEIN PE, RE-COVER, RE-COVER II, HOKUSAI, AMPLIFY) and patients with cancer (HOKUSAI VTE Cancer, Caravaggio, ADAM VTE, SELECT-D) included enough patients with BMIs between 30 and 40 kg/m^2 that most clinicians are comfortable with these agents in such a setting [28–31, 39–44]. Much more modest study populations of patients with BMIs of 40–50 kg/m^2 and >50 kg/m^2 preclude a high level

of comfort with DOAC use for VTE treatment, primarily because of concern that adequate anticoagulation may not be achieved in the acute treatment phase. The ASCO guidelines recommend measuring peak and trough levels when DOACs are used in patients at extremes of body weight (Table 6). However, there are limited data correlating DOAC drug levels with clinical outcomes and adjusting drug doses based on levels. Therefore, the clinical utility of this approach to management approach remains unclear.

Also challenged by limited RCT data, DOAC use in patients with cancer, VTE, and a history of proximal GI surgery, either for tumor resection or weight reduction, remains a subject of much debate. Providers often rely on LMWH in such a setting to assure adequate levels of anticoagulation when GI absorption may be suspect.

Thrombocytopenia is a common adverse effect of chemotherapy that complicates the management of anticoagulation in patients with cancer. Each of the guideline organizations have provided recommendations for managing this common and difficult dilemma [6, 10–12, 45].

Cancer-Associated Thrombosis in Unusual Site(s)

Venous thrombosis at unusual sites in the presence of malignancy encompasses a substantial part of hematology consultative service. Several important consensus statements exist that successfully assist practitioners with guidance for prevention and treatment of CAT [6–8, 10–12, 32, 45]. However, only a few cancer-specific guidelines provide advice on management of central venous catheter thrombosis, superficial vein thrombosis, hepatic vein thrombosis, and splanchnic vein thrombosis [6, 10–12] (Table 7). There is no available guidance specific to patients with cancer on prevention and treatment of thrombosis in other unusual sites, such as cerebral and dural sinus vein, retinal vein, renal vein, or ovarian and testicular veins; this paucity of evidence leads to unnecessary heterogeneity in clinical practice (Table 7). Furthermore, none of the existing cancer-specific guidelines provide advice on management of arterial thromboembolism in patients with cancer (Table 7). Many retrospective and a few prospective studies have shown higher-than-baseline risk of arterial thrombosis in patients with cancer [46–52] (Table 8). Understandably, this finding is primarily due to a lack of high-quality data. Nevertheless, practitioners are compelled to use their best judgment to make clinical decisions based on anecdotal and retrospective data.

Conclusion

Our review of current cancer-specific guidelines has identified many gaps that warrant further investigation. We hope this review will serve as a catalyst for further research, preferably through international collaborative efforts to investigate optimal diagnostic, preventive, and management strategies for CAT and provide comprehensive advice on these topics for the busy practitioner.

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