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The Saudi Consensus for the Management of Cancer-Associated Thromboembolism: A Modified Delphi-Based Study

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Abstract

Background Cancer is a well-known risk factor of preventable thromboembolic disease. This study aims to provide guidance on the prevention and management of cancer-associated thrombosis (CT) that tailors prophylactic and therapeutic options for medical and surgical oncology patients presenting to health care settings in Saudi Arabia.

Methods The present consensus was developed in concordance with the modified Delphi-based approach, which incorporates a face-to-face meeting between two voting rounds to gain experts' feedback on the proposed statements. All experts were either oncologists, hematologists, or hemato-oncologist with an active clinical and research profile in hemato-oncology.

Results The experts highlighted that the comparatively high incidence of inherited thrombophilia among the Saudi population may account for a higher CT burden in the Kingdom than in other parts of the world. However, due to the lack of literature that assesses CT in Saudi Arabia, primary venous thromboembolism prophylaxis should be tailored according to a valid risk assessment of cancer patients and should be implemented in routine practice. For hospitalized medical oncology patients, the experts agreed that prophylaxis with low-molecular-weight heparin (LMWH) should be offered, regardless of the presence of acute illness. For ambulatory medical oncology patients, LMWH or direct oral anticoagulants (DOACs) prophylaxis should be offered for high-risk patients. Concerning surgical patients, they agreed that all oncology

Keywords
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patients undergoing surgery should be offered thromboprophylaxis. In terms of secondary prophylaxis, the experts recommended continuing a prophylactic dose of anticoagulant (LMWH or DOAC), for an appropriate period depending on the cancer type and stage. Finally, they also provided a set of statements on management of CT in Saudi Arabia.

Conclusion The present modified Delphi-based study combined the best available evidence and clinical experience with the current health care policies and settings in Saudi Arabia to build a consensus statement on the epidemiology, prevention, and management of CT.

Introduction

Venous thromboembolism (VTE) is a major public health concern, with yearly incidence of 100 to 200 per 100,000 and a significantly higher prevalence, morbidity, and mortality rate among cancer patients.[1] The tendency for VTE in cancer patients varies with the type of cancer, being more common in patients with pancreatic and gastrointestinal (GI) tumors, ovarian cancer, primary brain tumors, or lymphomas.[2]

The association between cancer and VTE is due to the effect on at least one component of Virchow's triad.[3] Stasis can be caused by tumor-related compression of vascular beds and increased blood viscosity, both of which are frequent in cancer patients. Local vascular invasion and overexpression of interleukin-1, soluble E-selectin, soluble thrombomodulin, and von Willebrand factor cause abnormalities in blood vessels.[4] Tissue factor production, which increases thrombin generation, may be increased by tumor cells. Finally, a hypercoagulable state is generated by an increase in procoagulant factors like plasminogen activator inhibitor, fibrinogen, and tissue factor and a reduction in antithrombotic factors like tissue plasminogen activator, proteins C and S, and antithrombin.[4]

According to the Saudi Cancer Registry, there were 15,807 new cancer patients in Saudi Arabia in 2014.[5] In 2018, the World Health Organization reported 24,485 new cancer cases in Saudi Arabia.[6] According to data from the Middle East and North Africa, the 5-year cancer prevalence is predicted to be around 82,500 people in Saudi Arabia.[7] Despite that cancer-associated VTE (CT) poses a substantial burden on cancer patients and the health care system, the published literature is scarce concerning the burden of CT and the management algorithm in Saudi Arabia. Therefore, a group of Saudi experts developed a consensus statement to provide guidance on the prophylaxis and management of CT that tailors prophylactic and therapeutic options according to patients' profiles. This consensus document utilized the modified Delphi method approach to gather experts' insights and recommendations for medical and surgical oncology patients presenting to health care settings in Saudi Arabia.

Methodology

Study Design and Panel Recruitment

The present consensus was developed in concordance with the modified Delphi-based approach, as described by Gustafson et al,[8] and conducted from August 2021 to October 2021.

Eight experts were recruited through a nonprobability purposive sampling technique from the following institutions in Saudi Arabia: King Faisal Specialist Hospital and Research Center, King Saud bin Abdulaziz University for Health Sciences, College of Medicine at King Saud University, and Umm Al-Qura University. Experts were composed of a multidisciplinary background including oncologists, hematologists, or hemato-oncologists with an active clinical and research profile in the field of hemato-oncology.

Survey Development and Voting Rounds

Three experts were selected to develop the survey. They conducted a systematic literature search on Medline via PubMed, Scopus, and EMBASE at the end of August 2021, using several combinations of the following queries: ((((venous thrombosis [MeSH Terms]) OR (deep venous thrombosis [MeSH Terms])) OR (deep vein thromboses [MeSH Terms])) AND (cancer [MeSH Terms])). Relevant statements were extracted from retrieved studies that cover one of the following clinical domains: epidemiology and risk factors, diagnosis, prophylaxis, treatment, assessment, medications, and unmet medical needs for CT. A manual search of the references of retrieved publications was also conducted. The statements were primarily extracted from studies with level 1 quality of evidence, as classified by Wright et al.[9] Additional statements were retrieved from studies with lower quality of evidence whenever deemed required by the panel. A total of 58 statements were developed.

All retrieved statements were mailed to the eight experts via Alchemer platform to complete the first round of anonymous voting. A consensus was reached if a statement achieved an agreement level of $\geq$ 75%.[10] This round of voting was followed by a virtual meeting to gather the experts' feedback and recommendations concerning the statements that did not reach a consensus. In the second round of voting, the list of modified statements was emailed to experts for voting and followed the same voting process of step one.

Results and Discussion

Epidemiology

Patients with active cancer have a substantially greater relative risk (RR) of VTE than the general population.[11–13]

In one large population-based study, nearly 20% of all new VTE cases were linked to malignancy.[14] In a prospective study, the incidence of VTE after 1 year of developing malignancy was 8%.[15] The incidence rate of VTE in all malignancies was 13.9 per 1,000 person-years in another research from the United Kingdom.[11] The overall incidence rate among high-risk patients (including those with metastatic cancer) was 68 per 1,000 person-years.[16] Connolly et al estimated the incidence at 10 per 100 person-years,[17] but Chew et al estimated it at 1 per 100 person-years.[13]

Between 1995 and 2012, Lyman et al demonstrated that among 3,146,388 American patients with cancer, the CT annual incidence substantially rose from 3.5 to $>$ 6.5%.[18] In China, 2,214 new VTE patients were evaluated, and active malignant tumors were determined to be the major cause of VTE, which grew from 34.8 to 60.9% between 2005 and 2014.[19] The survival rate and prognostic factors of VTE patients are negatively influenced by cancer. According to Uppuluri et al, patients with CT had a three to eight times greater mortality risk when compared with noncancer patients.[20] Furthermore, thrombosis places a significant financial burden on cancer patients. When compared with cancer patients without VTE, CT had nearly doubled the medical costs.[18]

The risk of VTE is highest in the first 12 months after cancer diagnosis.[11,12,21] The largest incidence of VTE was seen in the first 3 months after cancer diagnosis (odds ratio [OR]: 53.5; 95% confidence interval [CI]: 8–334.4).[12] Alcalay et al investigated VTE incidence rates in colorectal cancer patients using the California Cancer Registry. In the first 6 months following a cancer diagnosis, the incidence was 5 per 100 person/years versus 0.6 per 100 person/years after 1 year.[21] CT was found to be common (27%) among women who died within 3 months of their diagnosis, compared with 10.7% in those who died 1 year later,[22] suggesting a significant link between CT and cancer aggressiveness. The overall rate of CT has risen steadily over time.[23,24] This might be attributable to various variables, including improved identification by serial imaging for staging purposes, changes in medications that may be more thrombogenic, and prolonged survival of cancer patients, increasing their risk of VTE.[25]

Clinical evidence on VTE in cancer patients from Saudi Arabia is very limited. VTE was detected in 6.7% of 701 patients with solid tumors or lymphoma treated at a tertiary care institution in Riyadh from 2004 to 2009. In addition, 79% of VTE patients have advanced cancer stages.[26] However, this prevalence of CT seems to be underestimated for many reasons; (1) the retrospective nature of the study, (2) several individuals who had confirmed thrombosis and were highly suspected of having an underlying malignancy died before the diagnosis could be confirmed, and (3) the lack of objective diagnosis and absence of autopsy studies due to religious and cultural beliefs. As a result, it is reasonable to assume that the actual prevalence of CT in Saudi patients is significantly greater than what is observed.

Consensus Statement

The experts agreed on the scarcity of published literature that assesses the incidence of CT in Saudi Arabia. They confirmed that many of the CT cases in Saudi Arabia are diagnosed incidentally, which highlights the increased awareness among the health care providers of CT and its associated risk factors. Nonetheless, the experts emphasized that the current figures underestimate the actual incidence of CT in Saudi Arabia due to the variations in the management protocols across different centers and regions. The experts also agreed that the majority of CT occur during the first year of a cancer diagnosis (►**Table 1**).

Table 1 Consensus statements concerning the epidemiology and risk factors of CT in Saudi Arabia

Statements	Level of agreement
1. There are not enough data or a national registry to reflect the exact incidence of CT in Saudi Arabia	100%
2. Many of CT cases in Saudi Arabia are diagnosed incidentally	75%
3. The majority of CT occur during the first year of a cancer diagnosis	83%
4. The Center for Arab Genomic Studies highlight that the Saudi population has a higher incidence of inherited thrombophilia which may reflect on the higher incidence of CT	100%
5. In Saudi Arabia, patients with gastrointestinal/colorectal and breast cancers have a higher prevalence of CT, especially DVT, than other types of cancer	100%
6. Patients with metastatic cancers have an increased risk of developing VTE	100%
7. Patient-related factors associated with VTE in cancer patients include: a- Gender b- Advanced age (65 $\geq$) c- Obesity d- Medical comorbidities e- The occurrence of varicose veins and prior VTE	100%

Abbreviations: CT, cancer-associated thrombosis; DVT, deep vein thrombosis; VTE, venous thromboembolism.

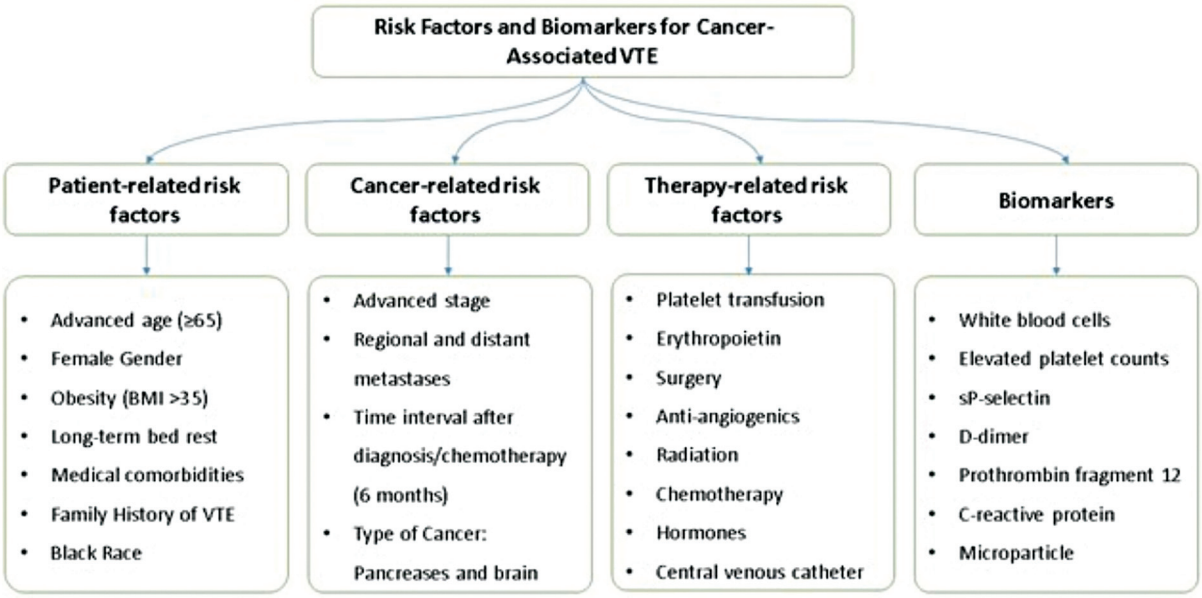

Fig. 1 Risk factors of cancer-associated thrombosis (CT).

Risk Factors

The risk factors for developing CT are classified into patient-related factors, tumor-related factors, treatment-related factors, and biomarkers. Understanding clinical risk factors and biomarkers can aid in evaluating and managing such cases (►**Fig. 1**).

Patient-Related Factors

Advanced age ($\geq$ 65), infection, obesity, long-term bed rest, and the presence of medical comorbidities are all patient-related variables linked to VTE in cancer patients.[11,21,23,27–29] While not all studies have found a relationship between advanced age or obesity and an increased risk of VTE in cancer patients,[13,21,30–32] the presence of more than three medical comorbidities have consistently been linked to CT.[13,21,27,28,30] The prevalence of VTE was 2.3% in patients without comorbidities, while it was $>$ 11% in patients with $>$ 3 comorbidities, according to Lyman et al.[18] VTE has also been linked to the presence of varicose veins and previous VTE in cancer patients.[31,33,34] A family history of VTE was found to be a significant risk factor for CT in several cancers such as gastric cancer, colorectal cancer, breast cancer, and testicular cancer in a large registry investigation.[35,36] Overall, emerging data demonstrate that inherited thrombophilia is a significant risk factor for CT. In addition, a significant association between factor V Leiden and CT was observed.[37] Individuals with cancer and mutation of factor V Leiden had a two times higher risk of CT than those without factor V Leiden mutation.[38] Likewise, patients who developed CT were considerably more likely to have a factor V Leiden mutation than others.[39]

In terms of race and ethnicity, Brunson et al have found that African American patients have the highest risk of CT (1.5 to 2 times), even for cancers with a low overall risk of VTE, such as prostate cancer.[29] White et al reported that Hispanics and Asian patients had a substantially lower risk of VTE and case–fatality rate than African Americans.[14] In the study of Khorana et al, that included 1,015,598 cancer patients, 4.1% had VTE. They found that VTE was most common in black patients (5.1%), followed by white and Hispanic patients (4%), and Asians/Pacific Islanders (3.3%) ($p < 0.0001$). They also found that females had a significantly ($p < 0.001$) higher risk of developing CT compared with males.[23]

Tumor-Related Factors

The cancer stage, grade, primary site, and duration since diagnosis are all tumor-related factors. Gastric and pancreatic cancers are the most common tumors linked to VTE in general.[11–13,27,28,40,41] Brain, gynecological, lung, renal, bladder, bone, and hematological cancers are among the tumors linked to a greater incidence of VTE.[11–13,27,28,40,41] A meta-analysis showed that patients with pancreatic and brain cancer had a high incidence of CT (110/1,000 and 80/1,000 patient-years) compared with breast and prostate cancer (10/1,000 patient-years for both).[16] In a cohort study based on the U.K. national health registry, thyroid and melanoma cancers have significantly lower CT rates (3/1,000 and 4/1,000 patient-years) than pancreatic cancer patients (98/1,000 patient-years).[11] According to the study of Svendsen and Karwinski, stomach, extrahepatic bile duct system, and ovarian cancers had the highest prevalence (15.2, 31.7, and 34.5%, respectively).[41] Chew et al discovered that patients with cancers involving kidney, bladder, uterus, lung, stomach, and metastatic pancreas cancers had the highest incidence of concurrently diagnosed VTE.[13] This shows that various cancers may have their unique thrombogenic mechanisms. If such mechanisms can be discovered, they may be useful for targeted thrombus treatment and prevention.

Individuals with localized cancer have a substantially lower risk of VTE than patients with metastatic cancer.[13,21,28,42,43] After 6 months, the prevalence of CT with regional, distant, and local stage cancer was 6.5, 6, and 2.1%, respectively, in the Cancer and Thrombosis Study. This study indicated that distant stage and regional cancers had similar risk; however, local stage cancer was associated with a relatively lower CT rate.[44] Histological grading is another key risk indicator. After controlling for cofactors such as distant metastases, sex, and age, the risk of VTE in patients with high-grade tumors was nearly twice as high as in those with low-grade tumors (hazard ratio [HR] = 2.0, 95% CI: 1.1–3.5; $p = 0.015$).[45] VTE and cancer have also been linked in a time-dependent manner, with the majority of VTE incidents happening during the first 3 to 6 months after a cancer diagnosis.[11,13,21,27,30,42]

Treatment-Related Factors

Surgery, chemotherapy, radiation therapy, erythropoietin anti-angiogenetic medicines (such as thalidomide and bevacizumab), hormonal therapy, platelet transfusion, and central venous catheter, are all treatment-related variables that significantly increase the risk of CT.[46–48] The risk of thrombosis is extremely significant during chemotherapy since patients might have many risk factors at the same time. According to a case–control study, chemotherapy was associated with a substantially higher risk of CT (6.5 times), exceeding the risk associated with the illness itself.[49] Patients receiving cisplatin or bevacizumab therapy had a substantially greater risk of VTE than patients receiving non-cisplatin or non-bevacizumab therapy (RR = 1.67 [1.25–2.23] and 1.33 [1.13–1.56], respectively) in meta-analyses of clinical studies.[50,51]

Biomarkers

White blood cells (WBCs) count was proposed to be linked to CT. In the Pabinger and Posch study, the risk of CT elevated by 7% for every 1×10^9/L rise in the WBCs count of cancer patients.[52] Aggregation of platelet is a crucial step in the thrombosis and hemostasis pathways. Elevated platelet counts have been reported as a predictor of VTE in several investigations. Patients with platelet counts of 443×10^9/L had a 3.5-fold greater risk of CT (HR = 3.50, 95% CI: 1.52–8.06, $p = 0.0032$).[53] Furthermore, according to Ay et al, CT incidence was 11.9% in patients with a high level of soluble P (sP)-selectin, whereas it was 3.7% in patients with a low level of sP-selectin. Another study reported sP-selectin level as a predictor of CT ($p = 0.003$).[47] Grossly elevated D-dimer level and prothrombin fragment 12 (F12), which represent intravascular thrombosis or hyperfibrinolysis, are also important predictors of CT.[46] The predictive value of these biomarkers was not established owing to the impact of the detection technique and the ethnicity of the participants. Using these biomarkers alone to estimate VTE risk is not suggested at this time. C-reactive protein, a biomarker of systemic inflammation, has also been linked to an elevated risk of CT.[34] However, this link has not been repeated in other investigations.

Consensus Statement

Concerning the risk factors, the experts highlighted that the comparatively high incidence of inherited thrombophilia among the Saudi population may account for a higher CT burden in the Kingdom than in other parts of the world. They agreed that advanced age, presence of comorbidities, history of VTE, certain types of malignancy, and advanced stage significantly increase the risk of CT, especially deep vein thrombosis (►**Table 1**).

VTE Prophylaxis among Cancer Patients

Risk Assessment

Several investigations have developed risk-stratified CT models based on the above risk variables to select the patients who may benefit from prophylaxis. The most extensively utilized VTE risk stratification tool is the Khorana score, which is aimed to help clinicians decide if preventive anticoagulation is necessary.[54] In addition to the common risk assessment models for VTE such as Caprini and Padua risk assessment models.[55] The following factors are included in the score: erythropoietin administration, hemoglobin level of < 10 g/dL, cancer location, platelet count of $\geq 350 \times 10^9$/L, body mass index (BMI) of ≥ 35 kg/m^2, and WBCs $> 11 \times 10^9$/L. Each component is given one point, except for the cancer type. Patients are classified as low-risk (0 points), intermediate-risk (1–2 points), or high-risk (> 2 points) based on their total score. The risk score showed an excellent negative predictive value (NPV) of 98.5% in patients with low risk but somewhat weak positive predictive value (PPV) of 7.1% in patients with high risk.[54] The Khorana score's prediction accuracy is mostly dependent on the cancer type (►**Table 2**). The influence of chemotherapy on blood cell counts was not considered; therefore, it can only be utilized when chemotherapy is started, limiting its predictive role. As a result, newer techniques are needed to improve risk assessment for specific cancer patients.

Recent research has continued to improve risk prediction methods in cancer patients.[61,62] Several new or updated risk assessment techniques, including biomarkers, have been proposed. However, many of them have yet to be verified, and none have been employed as inclusion criteria in thromboprophylaxis studies.[46,56,57,63] D-dimer and sP-selectin levels have been added to the Vienna score. In this tool, patients with the lowest risk levels had NPV of 99.0%, whereas cancer patients with the highest risk scores had a PPV of 42.9%.[46] The disadvantage of this approach is that sP-selectin tests are not widely available in ordinary clinical practice. Similarly, Pabinger et al added D-dimer level and removed all other variables except cancer site.[61] The PROTECHT tool removed the BMI from the Khorana tool and added the administration of chemotherapy.[56] Besides, the ONKOTEV tool has added metastatic disease, prior VTE, and compression to the original

Table 2 Risk assessment models for lung cancer-associated VTE

Risk assessment tool	Factors
Khorana Score[54]	• Site of cancer • Platelet count • Hemoglobin level • Leukocyte count • Body mass index
Vienna (CATS) Score[46]	• Site of cancer • Platelet count • Hemoglobin level • Leukocyte count • Body mass index • D-dimer level • Soluble P-selectin
PROTECHT Score[56]	• Site of cancer • Platelet count • Hemoglobin level • Leukocyte count • Body mass index • Cisplatin/carboplatin-based chemotherapy or gemcitabine
ONKOTEV Score[57]	• Khorana score >2 • Personal history of VTE • Metastatic disease • Vascular/lymphatic macroscopic compression
COMPASS-CT Score[58]	• Anthracycline/antihormonal therapy • Time since cancer diagnosis • Central venous catheter • Stage of cancer • Presence of cardiovascular risk • Platelet count • Recent hospitalization for acute medical illness • Personal history of VTE
Tic-ONCO Score[59]	• Site of cancer • Genetic risk score • Hemoglobin level • Leukocyte count • Body mass index • Platelet count
SAVED	• Dexamethasone dose • Age $\geq$ 80 years • VTE history • Prior surgery • Asian race
IMPEDE[60]	• Immunomodulatory agent • Body mass index $\geq 25\,kg/m^2$ • Pelvic, hip, or femur fracture • Erythropoietic-stimulating agent • Dexamethasone/Doxorubicin • Asian ethnicity/Race • VTE history • Tunneled line/central venous catheter • Existing thromboprophylaxis
Pabinger et al (2018)[61]	• Site of cancer • D-dimer level

Abbreviations: CATS, Cancer and Thrombosis Study; CT, cancer-associated thrombosis; VTE, venous thromboembolism.

Khorana tool.[57] However, low prediction ability and poor usability restrict the success of these models. As a result, finding a simple, practical, and effective risk model for various tumor populations is critical and difficult.

Primary Prevention

Surgical Setting

Without prophylaxis, the incidence of VTE in cancer patients having general, urologic, or gynecologic surgery is believed to be three times higher than noncancer patients undergoing the same procedures.[64] The precise risk varies depending on the type of operation, although anticoagulants often lower it by 50 to 80%.[65] Strong evidence and international and national consensus recommendations support the frequent use of postoperative thromboprophylaxis in cancer patients.[66–70] Low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) effectively prevent VTE and have similar bleeding risks.[71,72] According to a recent study, VTE risk was decreased by 91% in cancer patients who underwent major abdominal surgery and continued anticoagulation for 4 weeks following surgery.[73] In patients with a Khorana score of 3 or less, a recent individual patient data meta-analysis of numerous randomized trials examined the effectiveness and safety of LMWH. Compared with placebo, LMWH reduced VTE incidence by 64% in these high-risk patients (OR = 0.36; 95% CI: 0.22–0.58).[74] Likewise, several trials have supported the efficacy and tolerability of direct oral anticoagulants (DOACs) in reducing the risk of VTE in high-risk cancer patients; it was found that DOACs significantly reduce the incidence of VTE by 59%, compared with no prophylaxis.[75]

In individuals with additional risk factors for VTE, extended prophylaxis should be carefully considered. Mechanical approaches are acceptable alternatives for anticoagulation in people who have contraindications. In gynecologic malignancy, Clarke-Pearson et al showed that the application of intra- and postoperative intermittent pneumatic compression effectively reduced VTE risk in the experimental group compared with the control group (12.7% vs. 34.6%, $p < 0.005$).[76]

Medical Setting

Hospitalized patients: Although inpatient thromboprophylaxis is commonly advocated by guidelines and is used by regulatory authorities as a quality parameter, there is no evidence to back it up. A meta-analysis found no significant effect in hospitalized patients with cancer receiving standard dosages of thromboprophylaxis.[77] Despite standard dosages of inpatient LMWH prophylaxis, a recent phase II randomized study found a substantial cumulative incidence of VTE at day 17.[78] Many guidelines recommended the administration of LMWH, fondaparinux, warfarin, or UFH in hospitalized patients with cancer to prevent the risk of VTE, including the National Comprehensive Cancer Network (NCCN), International Society on Thrombosis and Haemostasis (ISTH), and European Society of Medical Oncology (ESMO).[32,66,67,69,79] The American Society of Clinical

Oncology (ASCO) recommends prophylaxis for hospitalized patients with cancer who have additional risk factors for VTE. Hospitalized cancer patients with no identified risk factors may be administered prophylaxis; however, for hospitalized patients admitted for the sole purpose of undergoing chemotherapy or for those undergoing stem cell transplantation, routine pharmacologic thromboprophylaxis should not be offered (see ref. 68 and Lyman GH, Kuderer NM. Clinical practice guidelines for the treatment and prevention of cancer-associated thrombosis. Thromb Res 2020;191 (Suppl 1):S79–S84).[32] Similar advice may be found in the ISTH guidance statement, though it does not particularly advise against prophylaxis in stem cell transplant patients.[67] In all hospitalized patients who do not have a contraindication, the NCCN recommends pharmacologic VTE prevention.[79] Anticoagulant prophylaxis, particularly LMWH, should be considered for hospitalized patients with an acute medical disease, according to the Spanish Society of Medical Oncology (SEOM).[80] No major randomized trials show whether hospital thromboprophylaxis is beneficial or harmful to cancer patients, and studies imply that inpatient prophylaxis is used inconsistently across risk categories.[81] Therefore, randomized clinical studies are needed to determine the real benefit and danger of inpatient thromboprophylaxis.

Ambulatory medical oncology patients: Regarding outpatient thromboprophylaxis, Levine et al conducted a randomized controlled trial (RCT) to evaluate the efficacy of warfarin in patients receiving outpatient chemotherapy. For the first 6 weeks, warfarin was administered at a dose of 1 mg daily, and subsequently, the dose was increased to keep the international normalized ratio between 1.3 and 1.9. The incidence of VTE in the control group was 4.4% compared with 0.65% of the warfarin group ($p = 0.03$). However, the risk of major bleeding was comparable in both groups ($p = 0.4$).[82] In patients receiving chemotherapy, the ASCO highly recommended LMWH for patients with solid tumors and aspirin or LMWH for patients with multiple myeloma (MM),[32,83] which is also supported by the ISTH.[67] Moreover, NCCN and ESMO recommended LMWH and warfarin for patients with MM receiving thalidomide plus dexamethasone.[69,79] On the other hand, the Saudi Expert Panel did not recommend routine thromboprophylaxis with heparin for outpatients due to the risk of major bleeding. Similarly, they voted against the use of oral anticoagulants at all in outpatients with cancer.[84]

Secondary Prevention

No randomized studies assess different treatment durations in cancer patients; hence, the ideal treatment period for CT is unknown. Nevertheless, the current evidence suggests that cancer patients undergoing treatment need at least 3 months of treatment according to the NCCN,[79] and 6 months as recommended by the ASCO,[68] International Initiative on Cancer and Thrombosis (ITAC),[66] and SEOM.[80] However, all guidelines agreed that the length of therapy should be evaluated frequently as suitable for the patient's clinical status, considering the risks and benefits of therapy and patient preferences. The ASCO, NCCN, and SEOM recommendations cover incidental VTE management,[68,79,80] and the ITAC, NCCN, and SEOM guidelines cover recurrent thromboembolism care.[66,79,80] In general, all of the recently released guidelines offer consistent treatment recommendations for CT.

Consensus Statement

The experts agreed that the primary VTE prophylaxis should be tailored according to the risk assessment of the patient. They highlighted that the risk assessment should be implemented in routine practice and stated that some risk assessment tools, such as Caprini and Khorana risk scores, are being used in some Saudi centers. However, this practice is not standardized, and there is a need for establishing a comprehensive risk assessment score. On the other hand, the experts emphasized upon the importance of developing CT-specific prophylactic protocols in Saudi institutions of ambulatory patients by a multidisciplinary team involving both hematologists and oncologists. For hospitalized medical oncology patients, the experts agreed that prophylaxis with LMWH should be offered, regardless of the presence of acute illness. In case of contraindications to LMWH, pneumatic compression devices can be provided. Patients admitted for minor procedures should not be offered prophylactic measures. For ambulatory medical oncology patients, LMWH prophylaxis should be offered for high-risk patients. For patients who cannot take LMWH, DOACs for 6 months can be offered. Concerning surgical patients, the experts agreed that all oncology patients undergoing surgery should be offered thromboprophylaxis; the prophylaxis should be continued for 4 weeks postoperatively. In terms of secondary prophylaxis, the experts recommended continuing a prophylactic dose of anticoagulant (LMWH or DOAC), depending on the cancer type and stage. They stated that monitoring D-dimer levels can be useful; however, it is not an effective decision-making tool (►**Table 3**).

Management

The purpose of anticoagulant therapy for CT is the same as in other groups of patients at higher risk of VTE. All of the therapy options for VTE primary prevention and acute treatment are potentially accessible for CT.

Vitamin K Antagonist

Vitamin K antagonist (VKA) medication is linked to a higher risk of recurrence and bleeding in cancer patients than in noncancer patients.[2,85,86] VKA-treated cancer patients had a threefold increased risk of VTE recurrence and a two- to sixfold increased risk of bleeding.[2,85] Moreover, a systematic review and meta-analysis of five RCTs showed that LMWH was associated with a lower recurrence rate than VKA (RR = 0.53, 95% CI: 0.36–0.76). On the other hand, both treatments were comparable in terms of major bleeding (RR = 0.98, 95% CI: 0.49–1.93) and all-cause mortality (RR = 0.94, 95% CI: 0.80–1.11).[87]

Table 3 Consensus statements concerning the prophylaxis of CT in Saudi Arabia

Statements	Level of agreement
Risk assessment	
1. Primary VTE prophylaxis among cancer patients should be individualized on a case-by-case basis based on risk assessment	100%
2. VTE risk assessments should be implemented in chemotherapy protocols to adequately prescribe prophylactic treatment and reduce the incidence of thrombosis in cancer patients	100%
3. In Saudi Arabia, VTE risk assessment is performed in some centers using the Caprini and Khorana risk scores. However, this practice is not standardized	100%
4. Although many Saudi institutes have protocols and risk assessment tools regards the anticoagulation and prophylaxis of hospitalized patients, there is a need to develop protocols for the prophylactic treatment of ambulatory patients by a multidisciplinary team involving both hematologists and oncologists	100%
5. There is a need to validate and apply a comprehensive risk assessment score to generate local data and guide prophylaxis use	100%
Primary prophylaxis	
A: Hospitalized medical oncology patients	
6. For hospitalized medical oncology patients with acute medical illness, primary prophylaxis with LMWH should be offered for patients admitted in the absence of contraindications	100%
7. For hospitalized medical oncology patients without additional risk factors, primary pharmacological prophylaxis can be offered in the absence of bleeding or other contraindications	83%
8. LMWH is the pharmacological option of choice for the primary prophylaxis of CT and remained predominately used in an inpatient and outpatient setting in Saudi Arabia unless contraindicated	83%
9. Prophylaxis should not be offered for patients admitted for minor procedures or patients with platelets less than 25,000/uL	100%
10. Pneumatic compression devices can be offered for patients with contraindications for anticoagulants until the contraindications are resolved	100%
B: Ambulatory patients	
11. For ambulatory patients, treatment decisions should be based on the risk of VTE and bleeding, as well as patient preferences/values	100%
12. Ambulatory low-risk patients should not be offered primary pharmacological prophylaxis	100%
13. High-risk ambulatory patients should be offered thromboprophylaxis. In Saudi Arabia, DOACs and LMWH is commonly used in this setting unless contraindicated	75%
14. DOACs can be offered for up to 6 months for primary prophylaxis in high-risk ambulatory cancer patients (KRS $\geq$ 2) if no contraindications and they cannot take LMWH DOACs are relatively inexpensive and readily available, which allows their use for primary prophylaxis in high-risk patients	100%
15. 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)	100%
C: Surgical patients	
16. All patients undergoing major surgery should be offered pharmacological, preoperative. prophylaxis with UFH or LMWH, unless contraindicated, and should be continued for at least 7–10 days	100%
17. 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	100%
18. Combined pharmacologic/mechanical prophylaxis may improve efficacy, especially in highest-risk patients. However, mechanical prophylaxis should not be used as monotherapy unless pharmacologic prophylaxis is contraindicated	100%
Secondary prophylaxis	
19. D-dimer levels can be used to assist during patient follow-up but do not constitute a decision-making tool, as opposed to the presence of active cancer, thrombophilia, and CT risk factors	100%

Abbreviations: CT, cancer-associated thrombosis; DOAC, direct oral anticoagulants; DVT, deep vein thrombosis; KRS, Khorana Risk Score; LMWH, low molecular weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism.

LMWH

Treatment guidelines, including from the ASCO, BCSH, ESMO, and NCCN, recommend LMWH for the short- and long-term management of CT. In the absence of significant renal impairment (creatinine clearance [CrCl] 30 mL/min), ASCO recommends LMWH over UFH among parenteral agents.[68] ITAC and NCCN suggest LMWH for cancer patients with a CrCl of less than 30 mL/min.[66,79] LMWH is also preferred by SEOM.[80]

DOACs

The DOACs represent an attractive alternative for the historically standard of care of CT patients, with the advantages of being easy to use and having an acceptable risk profile.[88] DOACs can be administered orally in fixed doses with no routine monitoring. A cumulative body of evidence supported the consistent efficacy and safety of DOACs for treatment of VTE in cancer patients.[89] The Caravaggio, ADAM VTE, SELECT-D, and HOKUSAI VTE trials compared LMWH with DOACs for the treatment of CT[90–93] (►**Table 4**). Patients were followed for at least 6 months in each trial. For recurrent VTE and severe bleeding, DOACs were found to be noninferior to dalteparin. Compared with dalteparin, edoxaban and rivaroxaban caused greater bleeding in individuals with GI cancers.[90,91] In the ADAM and Caravaggio studies, apixaban was not linked to an increased risk of bleeding compared with dalteparin.[92,93]

DOACs are suggested for patients with a low risk of bleeding who do not have GI or genitourinary (GU) malignancies, according to the NCCN recommendations.[79] For patients with GI or GU cancers or significant drug–drug interactions, LMWH is preferable. Even though apixaban appears to have a RR of bleeding as dalteparin, recommendations have been cautious about suggesting it in patients with GI and GU malignancies until further data are obtained.[94] Apixaban, rivaroxaban, LMWH, UFH, or fondaparinux may be used as initial anticoagulants.

Wysokinski et al compared the apixaban to rivaroxaban and enoxaparin in CT. Their findings showed comparable major bleeding and VTE recurrence rates in apixaban, rivaroxaban, and enoxaparin groups. Compared with apixaban and enoxaparin, rivaroxaban was related to greater clinically relevant safety outcomes and clinically relevant nonmajor bleeding (CRNMB) but reduced mortality.[95]

A recent meta-analysis demonstrated that the risk of recurrent VTE was comparable in both DOACs and LMWH. Additionally, the risks of CRNMB and mortality were similar in both groups.[89] These findings indicated that DOACs are not inferior to LMWH and should be used in cases of CT, with monitoring of the risk of bleeding. Another meta-analysis showed that DOACs were linked with a significant reduction in VTE recurrence but with an incremental risk of CRNM.[96]

Bemiparin

Bemiparin is an anti-factor Xa/anti-factor IIa with LMWH that was investigated to prevent CT in abdominal or pelvic surgery patients. In the CANBESURE trial, 703 cancer patients were randomly assigned to receive 3,500 IU of bemiparin subcutaneously daily for 8 days after surgery. In the bemiparin group, the incidental VTE was significantly lower than in the placebo group ($p = 0.010$). The researchers determined that using bemiparin for 4 weeks significantly decreased the likelihood of serious VTE without increasing the risk of bleeding in cancer patients having surgery.[97]

Semuloparin

Semuloparin is a factor Xa inhibitor with residual factor IIa activity that is administered subcutaneously. The TREK trial demonstrated that the efficacy of semuloparin in terms of VTE incidence was dose dependent. For significant bleeding episodes, a comparable dose–response impact was seen ($p = 0.0231$). A dosage of 20 to 40 mg per day was shown to have an appropriate benefit-to-risk profile.[98] Semuloparin was also studied for thromboprophylaxis in cancer patients following chemotherapy by Agnelli et al.[99]

Direct Oral Thrombin Inhibitors

Ximelagatran was the first oral direct thrombin inhibitor to undergo clinical trials; however, it was shelved due to the possibility of severe hepatotoxicity. It has been demonstrated to be noninferior to LMWH in lowering the risk of significant VTE in orthopaedic surgery patients in randomized, double-blind studies.[100]

Treatment in Special Population

Anticoagulation for the prevention or treatment of VTE in cancer patients does not need to be adjusted differently in individuals with modest renal insufficiency, an overweight BMI, or mild obesity.[107] More severe renal impairment, extremes in BMI or body weight, and individuals who have had proximal GI surgery that may alter medication absorption should all be considered. In individuals with possibly aberrant proximal GI absorption, injectable anticoagulants, for example, have been favored, at least theoretically.[68] DOACs and LMWH may be used in extremes of body weight, although weight adjustments should be made when appropriate, especially for people with low body weight. In the case of low body weight, most DOACs' package inserts and prescription advice/urge dosage decrease.[79,80] The selection and administration of DOACs in individuals with an elevated BMI and body weight are more difficult. Patients with BMIs of 40 to 50 kg/m^2 and $> 50\ kg/m^2$ are less likely to be comfortable with DOACs usage for VTE therapy, owing to concerns that sufficient anticoagulation may not be attained during the acute treatment phase.[90–93] The ASCO recommendations advocate recording peak and trough values when DOACs are utilized in patients at extremes of body weight.[68] In pregnancy, the use of standard doses of LMWH was recommended. In patients with thrombocytopenia, anticoagulation administration is based on the platelets count and the risk of bleeding. The reported cutoff point was 50,000/μL; if less than this number, the administration of anticoagulants is not indicated. In cases of hepatic dysfunction, DOACs should be avoided if clinically significant liver disease.[94]

Table 4 Published trials regarding the management of CT with LMWH and DOACs

	Low-molecular-weight heparin trials					Direct oral anticoagulants			
	CLOT[101]	Meyer et al[102]	ONCENOX[103]	LITE[104]	CATCH[105]	Hokusai VTE Cancer[91]	SELECT-D[90]	ADAM VTE[92]	Caravaggio[106]
Number	676	146	101	200	900	1,050	406	300	1,170
Treatments	Dalteparin, 338	Enoxaparin, 71	Enoxaparin, 67	Tinzaparin, 100	Tinzaparin, 449	Edoxaban, 522	Rivaroxaban, 203	Apixaban, 145	Apixaban, 576
Comparator drug, n	Warfarin, 338	Warfarin, 75	Warfarin, 34	Warfarin, 100	Warfarin, 451	Dalteparin, 524	Dalteparin, 203	Dalteparin, 142	Dalteparin, 579
Duration	6 mo	3 mo	6 mo	3, 12 mo	6 mo	6–12 mo	6 mo	6 mo	6 mo
DVT only, *n* (%)									
• Total	465 (68.78)	44 (30.1)	84 (83.2)	186 (93)	511 (56.8)	389 (32.7)	110 (27.1)	106 (36.9)	517 (44.7)
• Study arm	235 (69.52)	19 (26.8)	53 (79.1)	92 (92)	252 (56.1)	194 (37.2)	53 (26.1)	54 (36.7)	272 (47.2)
• Comparator arm	230 (68.04)	25 (33.3)	31 (91.2)	94 (94)	259 (57.4)	195 (37.2)	57 (28.1)	52 (35.1)	245 (42.3)
PE with or without DVT, *n* (%)									
• Total	211 (31.21)	102 (69.8)	74 (73.2)	42 (21)	366 (40.1)	657 (62.8)	295 (72.6)	156 (54.3) 81 (55.9) 75 (52.8)	638 (55.2) 304 (52.8) 334 (57.7)
• Study arm	103 (30.47)	52 (73.2)	46 (68.6)	21 (21)	189 (42.1)	328 (62.8)	150 (73.9)		
• Comparator arm	108 (31.95)	50 (66.7)	28 (82.3)	21 (21)	177 (39.2)	329 (62.8)	145 (71.4)		
Incidental thrombosis, *n* (%)									
• Total • Study arm • Comparator arm	NR	NR	NR	39 (19.5) 13 (13) 26 (26)	2 (0.22) 0 (0) 2 (0.44)	340 (32.5) 167 (32.0) 173 (33.0)	213 (52.5) 108 (53.2) 105 (51.7)	NR	230 (19.9) 116 (20.1) 114 (19.7)
Metastatic disease, *n* (%)									
• Total • Study arm • Comparator arm	455 (67.30) 223 (65.97) 232 (68.63)	77 (52.7) 38 (53.5) 39 (52.0)	59 (58.4) 41 (61.1) 18 (52.9)	83 (41.5) 47 (47) 36 (36)	492 (54.6) 247 (55.0) 245 (54.3)	554 (53.0) 274 (52.5) 280 (53.4)	236 (58.1) 118 (58.1) 118 (58.1)	193 (67.2) 96 (65.3) 97 (66.0)	785 (68.0) 389 (67.5) 396 (68.4)
VTE recurrence, *n* (%)									
• Total • Study arm • Comparator arm	80 (11.90) 27 (8.03) 53 (15.77)	NR	4 (4.4) 2 (2.98) 2 (6.7)	NR	76 (8.44) 31 (6.9) 45 (10.0)	100 (9.6) 41 (7.9) 59 (11.3)	36 (8.9) 8 (3.9) 18 (8.9)	10 (3.5) 1 (0.7) 9 (6.3)	78 (6.8) 32 (5.6) 46 (7.9)
Major bleeding, *n* (%)									
• Total	34 (5.0)	17 (11.6)	7 (6.9)	14 (7.0)	23 (2.55)	57 (5.4)	17 (4.2)	2 (0.7)	45 (3.9)
• Study arm	20 (6.0)	5 (7.0)	6 (8.9)	7 (7.0)	12 (2.7)	36 (6.9)	11 (5.4)	0 (0)	22 (3.8)
• Comparator arm	14 (4.0)	12 (16)	1 (2.9)	7 (7.0)	11 (2.4)	21 (4.0)	6 (3.0)	2 (1.4)	23 (4.0)

(*Continued*)

Table 4 (*Continued*)

	Low-molecular-weight heparin trials					Direct oral anticoagulants			
	CLOT[101]	Meyer et al[102]	ONCENOX[103]	LITE[104]	CATCH[105]	Hokusai VTE Cancer[91]	SELECT-D[90]	ADAM VTE[92]	Caravaggio[106]
CRNMB, *n* (%)									
• Total • Study arm • Comparator arm	NR	NR	NR	NR	118 (13.1) 49 (10.9) 69 (15.3)	134 (12.8) 76 (14.6) 58 (11.1)	32 (7.9) 25 (12.3) 7 (3.4)	16 (5.6) 9 (6.2) 7 (4.2)	87 (7.5) 52 (9.0) 35 (6.0)
Deaths (any cause), *n* (%)									
• Total	271 (40.08)	25 (17.1)	33 (32.7)	133 (66.5)	288 (32.0)	399 (38.1)	104 (25.6)	38 (13.2)	288 (24.9)
• Study arm	132 (39.05)	8 (11.3)	22 (32.8)	67 (67)	150 (33.4)	206 (39.5)	48 (23.6)	23 (16)	135 (23.4)
• Comparator arm	139 (41.12)	17 (22.7)	11 (32.4)	66 (66)	138 (30.6)	193 (36.6)	56 (27.6)	15 (11)	153 (26.4)

Abbreviations: CRNMB, clinically relevant nonmajor bleeding; CT, cancer-associated thrombosis; DOAC, direct oral anticoagulants; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; NR, not reported; PE, pulmonary embolism; VTE, venous thromboembolism.

Consensus statement: The experts' consensus on the management of CT in Saudi Arabia is present in ►**Table 5**.

Unmet Clinical Needs with Current Practice/Therapeutic Options

The increased incidence of CT in cancer patients, as well as the higher mortality rate, demonstrated that primary and secondary prevention of VTE is a significant unmet need. The current risk assessment tools are heterogeneous and need proper external validation; therefore, an urgent need to create realistic and practical risk assessment techniques that can classify cancer patients into low-, intermediate-, and high-risk primary and recurrent VTE groups that can be treated with tailored thromboprophylaxis.[108] Over the last decade, thromboprophylaxis in hospitalized cancer patients has improved significantly, but prevention of VTE in medical patients remains a large unmet need when compared with VTE prevention and care in surgical patients.[109]

Major bleeding and recurrent VTE are two crucial aspects of CT management. Recurrent VTE is prevalent despite the wide use of anticoagulants. Patients-, tumor-, or treatment-related variables significantly increase the recurrence rate.[110] Recent research suggests that stopping periprocedural anticoagulation increases the recurrence rate of VTE and serious bleeding after surgery.[111] The treatment of recurrent VTE is debatable, although physicians may consider switching to a different anticoagulant, increasing the dosage of LMWH, or adding a vena cava filter to LMWH.[111,112]

In general, anticoagulation administration increases the risk of bleeding in cancer patients compared with noncancer patients. In addition, recurrent VTE and major bleeding events are linked to considerable morbidity and a reduction in quality of life in cancer patients; therefore, it is critical to balance the risks and advantages of various anticoagulants when determining which one to take.[113,114] Furthermore, therapy should be tailored to the patient's specific needs, considering the toxicity, drug–drug interactions, bleeding risk, and most importantly, the patient's preferences.

In summary, there are many limitations in CT risk assessment tools, patient stratification methodologies for prophylaxis, and suboptimal use of anticoagulants for primary and secondary prophylaxis and treatment.

Consensus statement: The experts' stated several unmet medical needs concerning the management of CT in Saudi Arabia is present in ►**Table 5**.

Conclusion

Overall, the development of CT is associated with an increased risk of morbidity, mortality, and financial burden. Nonetheless, the incidence of CT varies due to patient-related factors, tumor-related factors, and treatment-related factors. There are several available risk assessment tools; however, all of them need major modifications and external validation. Because VKAs are less effective in cancer patients, LWMH monotherapy is the standard of care for CT. The present Delphi-based study combined the best

Table 5 Consensus statements concerning the management of CT in Saudi Arabia

Statements	Level of agreement
Management	
1. The 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, the burden of laboratory monitoring, agent reversibility, and patient preferences	100%
2. DOACs, LMWH, UFH, or fondaparinux, can be used as initial anticoagulants. Among parenteral agents, LMWH is preferred over UFH in the absence of severe renal impairment	100%
3. LMWH is preferred for patients with acute VTE at high risk for bleeding or with GI malignancy	83.3%
4. For long-term anticoagulation, DOACs or LMWH for at least 6 months is preferred over VKA. VKAs are less effective but may be used if DOACs or LMWH are not accessible	100%
5. For hospitalized medical oncology patients with acute medical illness, primary prophylaxis with LMWH should be offered for patients admitted in the absence of contraindications	100%
6. Catheter-directed pharmacomechanical thrombolysis can be considered for DVT in patients at low risk for bleeding but at risk for limb loss or severe persistent symptoms despite anticoagulation	100%
7. IVC filters may be offered to patients with absolute contraindications to anticoagulation in the acute setting independent of thrombosis burden	100%
8. Incidental VTE should be treated in the same manner as symptomatic VTE	100%
9. 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	100%
Unmet needs	
10. There are no available registries in Saudi Arabia for thrombosis in cancer patients. Thus, the published incidence of CT is not reflective of the actual number of CT in Saudi Arabia	100%
11. The available evidence from Saudi Arabia was generated from retrospective studies, which often leads to the underestimation of CT prevalence	100%
12. There is a need for the validation of CT models in Saudi Arabian patient populations as it would also shed insights into CT risk factors to further understand the landscape of this disease in Saudi Arabia	87%
13. Multicenter studies are needed in Saudi Arabia to establish the incidence, risk factors, mortality, and optimal treatment strategies for CT patients	100%
14. The establishment of a thrombosis registry should incorporate patient data across different medical institutions to provide a comprehensive overview of CT in Saudi Arabia considering the involvement of different medical specialties in the treatment of CT to avoid duplication of data	100%
15. Practitioners from Saudi Arabia need further information related to the current practice including the pattern of treatment, type of anticoagulation used, and the prognosis	100%
16. There is a need for the validation of CT models in Saudi Arabian patient populations as it would also shed insights into CT risk factors to further understand the landscape of this disease in Saudi Arabia	87%
17. There is a need for national and institutional guidelines for patient referral between oncology, hematology, and thrombosis clinics in Saudi Arabia to ensure optimal patient management Also, there is a need for standardized multidisciplinary CT management and unified treatment protocol in Saudi Arabia	100%
18. The use of novel DOACs in patients with other medical conditions such as hemodialysis or valvular atrial fibrillation is still ambiguous and requires further evidence	100%

Abbreviations: CT, cancer-associated thrombosis; DOAC, direct oral anticoagulants; DVT, deep vein thrombosis; FDA, Food and Drug Administration; LMWH, low molecular weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

available evidence and clinical experience with the current health care policies and settings in Saudi Arabia to build a consensus statement on the epidemiology, prevention, and management of CT. The experts developed several statements and clinical pathway algorithm to aid physicians for diagnosis and management of CT presenting to the health care settings in Saudi Arabia. Further studies are required to improve the risk assessment tools, highlight the suboptimal usage of LMWH and DOACs, and improve the primary and secondary preventive methods.

What is known about this topic?

- Venous thromboembolism (VTE) is a major public health concern with significantly higher prevalence, morbidity, and mortality rate among patients with cancer.
- Cancer-associated thrombosis (CT) is one of the leading causes of cancer and thrombosis and is three times more fatal for cancer patients compared with people without cancer.
- CT manifests as either deep vein thrombosis or pulmonary embolism.

What does this paper add?

- Management and prevention guidelines for CT are available internationally, however, no local Saudi-based management procedure and recommendation are available.
- This consensus provides best available evidence and clinical experience with the current health care policies and settings in Saudi Arabia.

Disclosures

The data in this manuscript was based on the outcomes of a series of advisory boards. All authors made a significant contribution to the work reported, whether that is in the conception, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. This work was supported by Pfizer Emerging Markets. Pfizer (Saudi Arabia) provided funding for the advisory board meetings and editorial assistance in the development of the manuscript. Neither honoraria nor payments were made for authorship.

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Conflict of Interest

The authors declare no conflicts of interest.

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