Venous Thromboembolism in Women with Cancer with an Additional Focus on Breast and Gynecological Cancers

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Abstract

Cancer-associated venous thromboembolism (VTE) is common in women with cancer. Many clinical practice guidelines provide guidance for prevention and treatment; however, there are no specific recommendations for women. This is unfortunate because the proportion of women with breast- and gynecological cancers is high among patients with cancer-associated VTE. Thromboembolism often heralds cancer progression and poor prognosis and should—besides adequate anticoagulant management—also prompt reassessment and, if necessary, changes in cancer treatment. Recently, the new class of direct-acting oral anticoagulants (DOACs) has started to replace low-molecular-weight heparin as standard thromboprophylaxis and therapy in cancer patients. They are very effective, but they also carry a relevant risk of bleeding. Therefore, despite their ease of use, not every tumor patient qualifies for a DOAC, and this is especially true for gynecological tumor patients. Each prescription must be weighed individually. This review addresses specific aspects of VTE prophylaxis and management in women with cancer. Every physician who treats breast and gynecological cancers should be familiar with prophylaxis, diagnosis, and therapy of cancer-associated VTE. At the same time, patients should be informed by their physician what symptoms to look for and whom to contact if these symptoms occur, even outside of office hours and on weekends.

Keywords

- women with cancer
- venous thromboembolism
- cancer-associated venous thromboembolism

Clinical Case

A 45-year-old woman with a recent diagnosis of cancer to her left breast presents to the emergency room with a 24-hour history of pain and swelling of the right arm. She has a central venous access device (portacath) on the right side of the chest accessing the right subclavian vein. She states that she had chemotherapy 2 weeks ago and is scheduled to receive her third course next week. Duplex ultrasound confirms thrombosis of the right subclavian and axillary vein. She has a history of venous thromboembolism in her 20s, when she was on hormonal contraceptives. What would be the appropriate anticoagulant treatment regimen for this patient?

Introduction

The incidence of cancer is rising. If this trend continues, cancer will soon become the leading cause of death.[1] In parallel to this, the number of cancer-associated venous thromboembolisms (VTEs) also rises.[2–4] One in 12 cancer patients will develop VTE. VTE often heralds cancer progression and indicates a poorer prognosis ("signum malum"). Mortality of cancer patients with VTE is on average two times higher than that of cancer patients without VTE.[5,6] This is particularly true for women with cancer. A study from 2022 shows that the mortality hazard ratio in patients with breast and uterine cancer who develop VTE is 3.9 and 4.8,

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respectively, higher than those for pancreatic or lung cancer patients with VTE.[3] VTEs are the second most common cause of death in ambulatory cancer patients after cancer progression.[7]

The risks of VTE recurrence despite adequate anticoagulation and bleeding events are common in cancer patients.[8] However, there is more to cancer-associated VTEs than just the symptom burden from thromboembolism or potential side effects of anticoagulant therapy. Cancer patients with VTE often experience delays in cancer treatment, which affects treatment efficacy. Patients need additional monitoring and more office visits and sometimes even hospital admissions. Management decisions, particularly for invasive procedures, require close coordination between the specialties involved. All this substantially impacts patients' quality of life. Many cancer patients with VTE report high levels of trauma and anxiety symptoms also referred to as postthrombotic panic syndrome,[9] not to mention that VTE substantially increases health care cost.

Another aspect of cancer-associated VTEs is their impact on the approval of new oncologic therapies. Regulatory authorities nowadays require studies with high numbers of participants for the new and usually high-priced drugs. However, with high participant numbers, complications and side effects in the single-digit range can reach statistical significance. In addition, cancer-associated thrombosis (CAT) is an at least grade 2 and pulmonary embolism (PE) a grade 3 adverse event.[10] Thus, even a small number of cancer-associated VTEs might jeopardize the benefit–risk balance and the market approval of a new drug.

Many clinical practice guidelines provide guidance for prevention and treatment of CAT[11–16]; however, there are no specific recommendations for women with cancer. This article addresses gender-specific aspects of VTE prophylaxis and management in women with cancer in general and with an additional focus on breast cancer and gynecologic cancer.

Incidence of Cancer-Associated VTEs in Women with Cancer

In the 1990s, the prevailing opinion was that only gynecological cancers (cervical, ovarian, uterine, vaginal, and vulvar) are typical causes of VTE, while breast cancer is not. This assessment falls short because it does not count the large number of breast cancer patients. Breast cancer has become the most common cancer in women in Germany with almost 70,000 new patients each year. It is even more common than lung cancer in both sexes combined (57,220 new cases) and colorectal cancer (60,630 new cases).[17] One in eight women will be diagnosed with breast cancer during her lifetime. Although the individual VTE risk of breast cancer patients might not be high, the large number of patients makes breast cancer the fourth most common cancer-causing VTE (►Fig. 1), a recent publication from California even moves

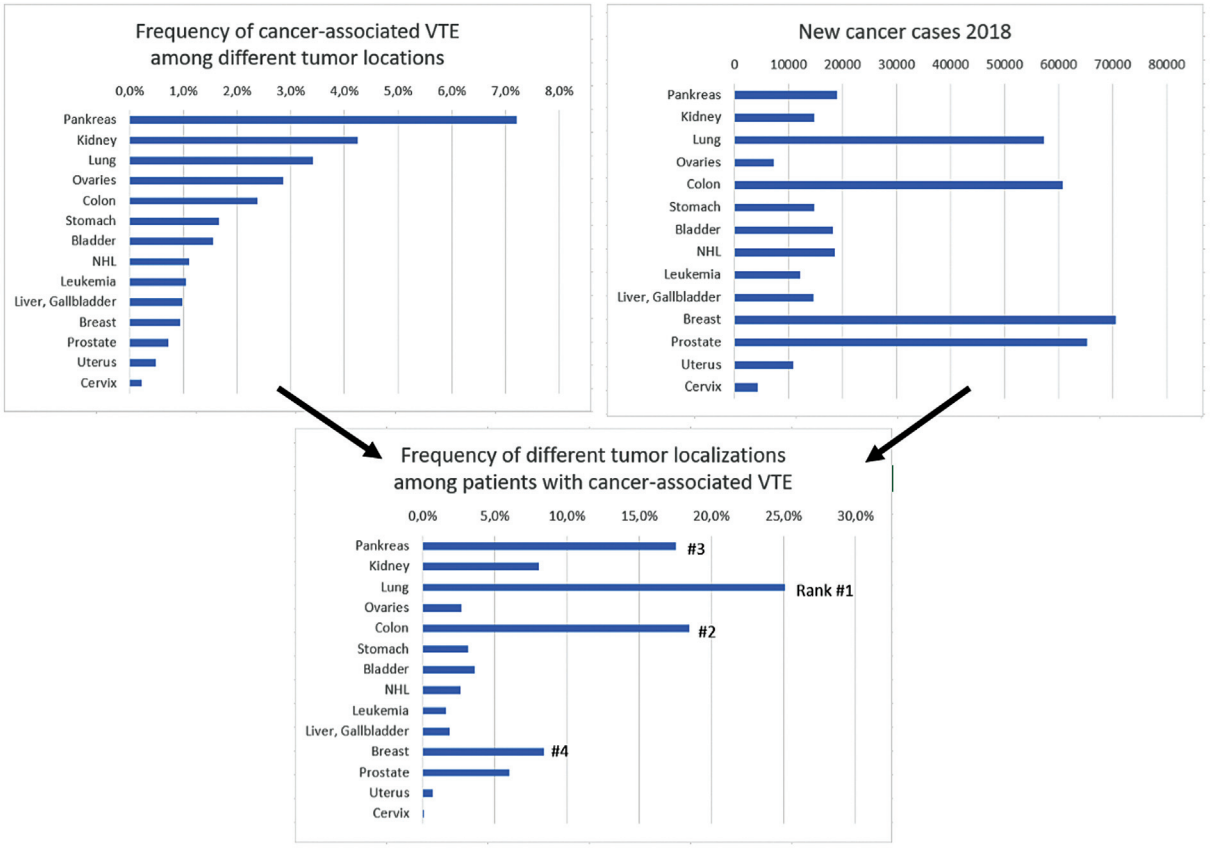

Fig. 1 Graphical representation of how a low VTE risk together with a high incidence of a tumor leads to a high proportion of patients with this tumor among VTE patients.[2,17] VTE, venous thromboembolism.

Table 1 Cancer locations and proportion of malignancies among cancer-associated VTEs[17–19,90]

	Proportion among all cancer patients	Proportion among cancer deaths	Proportion among patients with cancer-associated VTE
Cancers in men and women			
Colorectal	11.5%	10.8%	11.0–17.4%
Lung	9.4%	15.8%	10.2–14.5%
Melanoma	4.7%	1.1%	0.9%
Pancreas	3.9%	8.7%	3.6–3.8%
Women's cancers only			
Breast	30%	17.7%	10.6–15.5%
Uterus	4.7%	2.5%	3.4–5.7%
Ovaries	3.1%	5.1%	2.2–4.6%
Cervix	1.9%	1.5%	Not given
Vulva	1.4%	0.9%	Not given

Abbreviation: VTE, venous thromboembolism.
Note: Weitz only gives a combined proportion of 10.3% for all gynecologic tumors among cancer-associated VTEs.[18]

it to rank 3.[3] Uterine and ovarian cancers are much less common. This is supported by real-world data from the recent GARFIELD-VTE study and from the UK Clinical Practice Research Datalink.[18,19] They both show that breast and gynecologic cancers are among the most common cancers in VTE patients (►**Table 1**). This has consequences for the specialists taking care of these patients, in Germany these are commonly gynecologists. Although anticoagulation and VTE management are not at the heart of their daily practice, they should all be familiar with diagnosis and management of this common complication in their patients.

VTE Prophylaxis in Women with Cancer

Studies in the 1990s and early 2000s established thromboprophylaxis with low-molecular-weight heparin (LMWH) as the standard of care in hospitalized internal medicine patients, including tumor patients. In cancer outpatients, thromboprophylaxis also achieved a reduction of VTEs, but the absolute number was low, and the risk of bleeding and the burden of daily injections were considered too high, so LMWH prophylaxis in outpatient tumor patients has not gained wider acceptance.[20,21] The efforts were not entirely in vain, however, since they showed there was a clinical need to better identify cancer patients with a high VTE risk. This led to the development of several risk scores, the Khorana Score being probably the best known and most widely used (►**Table 2**).[22] It indicates outpatients with a particularly high VTE risk who should be offered thromboprophylaxis. It is recommended by the German and many international guidelines. Moreover, the Khorana Score has been used in the new studies on thromboprophylaxis in tumor patients with direct-acting oral anticoagulants (DOACs). Two randomized multicenter and multinational studies evaluated the efficacy and safety of rivaroxaban and apixaban in ambulatory cancer patients with a Khorana Score $\geq$2 and found that in these high-risk ambulatory patients, treatment with DOACs leads to a substantially lower incidence of VTE (during the

Table 2 Khorana Score [VTE risk based on Mulder et al[4] and Khorana et al[22]]

Khorana Score	Points
Very high risk cancer (cancer of stomach, pancreas)	2
High-risk cancer (cancer of lung, gynecologic, genitourinary, excluding prostate)	1
Prechemotherapy platelet count $\geq 350 \times 10^9$/L	1
Hemoglobin level <10 g/dL or using RBC growth factors	1
Prechemotherapy leukocyte count >11 $\times 10^9$/L	1
Body mass index 35 kg/m^2 or higher	1
VTE risk in first 6 months	
Low risk (0 Pts.)	<5%
Intermediate (1–2 Pts.)	5–10%
High risk (3 or more Pts.)	10–15%

Abbreviation: VTE, venous thromboembolism.

intervention period), with a low incidence of major bleeding.[23,24] The Khorana Score classifies gynecologic tumors as high risk and many women undergoing chemotherapy will have one additional risk factor and then qualify for thromboprophylaxis. It is unfortunate though that neither the German AWMF (Association of the Scientific Medical Societies in Germany) S3 guideline on ovarian cancer nor the guideline on supportive care in cancer patients even mentions the Khorana Score, nor any of the other new risk scores (for review, see Gerotziafas[25]).

There is no consensus on what type of prophylaxis should be offered to cancer patients. Several studies showed equivalence between LMWH and DOACs.[23–26] Current National Comprehensive Cancer Network (NCCN) guideline recommends to consider thromboprophylaxis with LMWH, apixaban, or rivaroxaban for high-risk cancer patients (Khorana Score $\geq$ 2) undergoing chemotherapy.[14] However, in Germany thromboprophylaxis with DOACs is off label for this indication while LMWH is not. Thromboprophylaxis should be continued as long as the patient receives chemotherapy. In the AVERT and CASSINI trials, prophylaxis was intended to be given for 6 months while the current NCCN guideline recommends to consider prophylaxis even beyond 6 months if risk persists.[14,23,24]

Note that for women with pelvic cancer surgery, primary VTE prophylaxis should be continued out of hospital for up to 4 weeks after the surgery with a LMWH. There is one study that shows that DOACs are an option, but more data are needed, and not the least, DOACs for thromboprophylaxis in nonsurgical patients are off label in Germany.[26]

Diagnosis of Suspected VTE in Women

The diagnostic approach to tumor patients with symptoms suggestive of VTE is different from nontumor patients. In nontumor patients, scores such as the Wells DVT, Wells PE, or Geneva score are used, along with D-dimer testing, to assess the probability of VTE before ordering expensive diagnostic tests. In tumor patients, this is different. Simply because of the presence of cancer, there is a high pretest probability of VTE already. The D-dimer value is often elevated in tumor patients even without VTE and therefore not very sensitive. A negative D-dimer test, on the other hand, is not specific enough to safely exclude deep vein thrombosis (DVT) or PE in tumor patients and the vast majority will still require radiologic imaging.[27,28] Also, D-dimer tests have not yet been evaluated for thromboses in unusual locations (brachial, portal, mesenteric, ovarian veins), which are frequent in tumor patients. Therefore, cancer patients with suspected VTE should proceed directly to imaging to confirm or exclude a diagnosis of DVT or PE.

VTE Treatment in Women with Cancer

VTE treatment in cancer patients does not follow the standards of noncancer patients. The recurrence and bleeding risk is higher and there are many potential interactions with other medications. In the 1990s and early 2000s, there were five large, randomized trials on VTE treatment in cancer patients comparing LMWH to vitamin K antagonists.[29–33] These studies established LMWH as a standard of care in cancer patients. They did not show any different efficacy and safety for LMWH in women versus men. It might be of interest that from these five studies the CANTHANOX study did not report any gynecological bleedings[32] and the CATCH study only a small number of vaginal bleeding events.[33,34] The three other studies did not specify sites of bleeding.

Since 2009, DOACs have begun to replace LMWH as preferred treatment for VTE in noncancer patients. However, they were not endorsed in cancer patients until recently, when four studies showed equivalence between DOACs and LMWH (note: these four studies were with edoxaban, apixaban, and rivaroxaban. There is no study on the treatment of cancer-associated VTE with dabigatran). Clinically relevant nonmajor bleeding from mucosal sites seems to be more frequent with DOACs. However, these studies do not show any different efficacy and safety for DOACs in women versus men. Urogenital bleeding has been reported from few patients only and does not seem to be an issue in the treatment of cancer-associated VTE in women with DOACs.[35–39]

While DOACs have become the standard treatment in noncancer patients with VTE, one has to decide for each cancer patient individually whether a LMWH or a DOAC is more advantageous (►Fig. 2).[40] Many women with cancer-associated VTE should receive an LMWH at least at the beginning of their treatment, e.g., for the first 3 months. LMWH should be preferred, when there is a high risk of bleeding (gastrointestinal tumors, acute leukemias, thrombocytopenia, intensive chemotherapy, etc.), if the patient cannot swallow tablets (mucositis, mechanical obstructions), when intestinal absorption is impaired, with renal insufficiency (in this case consider unfractionated heparin instead of LMWH), and with relevant drug interactions (►Table 3).[41] When the clinical situation is stabilized, when the patient is not receiving intensive chemotherapy any more, then one may replace the LMWH with a DOAC.

If bleeding occurs, one will stop or reduce the anticoagulant dose. For the few patients with persistent severe gynecological bleeding, uterine or iliac artery embolization, using

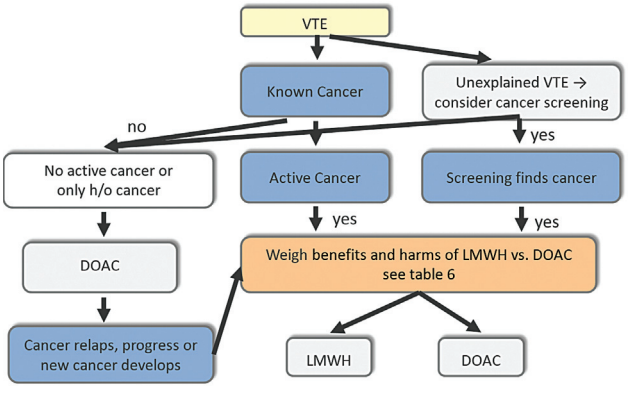

Fig. 2 Algorithm for the treatment of cancer-associated VTE[40].

Table 3 DOACs for cancer-associated VTE and potential risk factors[41]

Cancer with high bleeding risk	Acute leukemias, gastrointestinal cancer, primary brain cancer or brain metastases
Severe thrombocytopenia	Reduce dose with platelet count <50 Gpt/L[a] and stop with <25 Gpt/L.
Inability to swallow tablets	Mucositis or mechanical obstruction from cancer
Nausea, vomiting, diarrhea, other gastrointestinal problems affecting drug absorption	Nausea and vomiting, unclear absorption with intestinal fistulas, short bowel syndrome, peritoneal carcinomatosis
Reduced renal function	Do not give apixaban, edoxaban, and rivaroxaban with CrCl < 15 mL/min. Consider risk of renal function decline with platinum-containing chemotherapy, checkpoint inhibitors, and with multiple myeloma
Drug interactions	There are many potential interactions with other medications metabolized by CAP3A4 and P-GP.

Abbreviations: DOAC, direct-acting oral anticoagulant; VTE, venous thromboembolism.
[a]Defined in one study as rivaroxaban 10 mg twice daily during the first 3 weeks of treatment or 10 mg once daily after the first 3 weeks of treatment.[91]

mechanical devices such as coils or sclerosing agents can be tried. A more invasive treatment option is surgical ligation of vessels. Palliative radiation therapy can also be directed at the uterus and/or cervix.[42] Inferior vena cava filter placement was a common approach before. However, in recent years guidelines began to caution against the increasing and indiscriminate use of filters.[43,44] Only patients with acute VTE and absolute contraindications to anticoagulation or major complications from anticoagulation should receive an inferior vena cava filter (see ►Table 4).[43]

Breast Cancer—Low Risk, High Burden

It was mentioned before that breast cancer has per se a low VTE risk, three to four times lower than, e.g., ovarian cancer.[4,18] The large number of breast cancer patients, however, makes it to the leading women's cancer causing VTE. Overall, 10 to 15% of all cancer-associated VTEs will occur in women with breast cancer.[18,19] The VTE risk of breast cancer patients is lowest with localized disease and rises when it progresses to regional and to remote disease.[45] The risk is also high in the first months after surgery and during chemotherapy.[46] A gynecologist will therefore see many breast cancer patients with VTE and should be prepared to manage this complication.

Tamoxifen and VTE Prophylaxis

A common problem in women with breast cancer is whether they can be given tamoxifen. Many breast cancers are estrogen-receptor-positive and qualify for adjuvant or palliative treatment with tamoxifen. Tamoxifen, however, increases the VTE risk.[47] Aromatase inhibitors do not have this risk.[8] It has become common practice to avoid tamoxifen in women with a history of VTE or with known thrombophilia (note: some authors recommend thrombophilia testing before prescribing tamoxifen,[48] others do not recommend[49] while breast cancer guidelines do not mention thrombophilia testing before prescribing tamoxifen (Leitlinie der Arbeitsgemeinschaft Gynäkologische Onkologie, Leitlinie der AWMF, NCCN Leitlinie). Aromatase inhibitors are an elegant alternative to tamoxifen in postmenopausal women. Premenopausal women, however, cannot take aromatase inhibitors unless they also receive ovarian estrogen suppression with gonadotropin-releasing hormones (GnRH). This combination is associated with significant side effects, mainly hot flushes, musculoskeletal symptoms, and hypertension, and up to 20% of women stop endocrine therapy because of these symptoms.[50] Therefore, the question remains, how to proceed with antihormonal therapy in premenopausal women with a history of VTE or other relevant risk factors who do not tolerate aromatase inhibitors together with GnRH analogues? There are no guideline recommendations on this question. Thromboprophylaxis for the sole purpose to be able to give tamoxifen does not seem prudent. One would rather inform the patient about signs and symptoms of VTE, then start tamoxifen and monitor her closely.

Table 4 Management of patients with VTE who have strong contraindications to anticoagulation, e.g., life-threatening bleeding[43]

Withhold anticoagulation in patients who have a major or life-threatening bleeding episode.
Insert inferior vena cava filter in patients with deep vein thrombosis of lower extremities or inferior vena cava only if anticoagulation is strictly contraindicated.
Do not insert filter in patients with subacute or chronic vein thrombosis.
Resume anticoagulation and remove the filter (if possible) once the bleeding resolves.

Abbreviation: VTE, venous thromboembolism.

Cyclin-dependent kinase inhibitors are another new class of agents introduced into breast cancer treatment. They are combined with aromatase inhibitors. Recent studies find that they also increase VTE risk.[51] This should be handled alike. The patient does not need prophylactic LMWH but rather be informed about signs and symptoms of VTE.

Ovarian Cancer

Ovarian cancer has a high risk of VTE[52] but it is much less common than breast cancer and the prevalence of ovarian cancer patients among all patients with CAT is low. Many VTEs are asymptomatic.[53] It has already been mentioned that women should receive extended thromboprophylaxis for 4 weeks after abdominal surgery.[8] However, extended prophylaxis is underused. It requires subcutaneous injections that must be taught to patients and might be perceived as bothersome by the patient. In addition, studies show that many physicians are not aware of the benefit of extended-duration prophylaxis.[54,55]

After surgery many women with ovarian cancer require chemotherapy and the combination of paclitaxel with carboplatin and bevacizumab is commonly used. Platin-containing combination regimens have a high risk of VTE.[56,57] Bevacizumab, an antibody directed against vascular endothelial growth factor, further increases the risk of VTE.[58] The VTE risk of women with ovarian cancer therefore persists beyond the postoperative period throughout the time of adjuvant or palliative chemotherapy. This raises the question whether thromboprophylaxis should be extended beyond the usual four postoperative weeks. There are no studies to support this notion. The author uses the Khorana Score. Ovarian cancer already gives one point and if there is an additional risk factor (anemia, high body weight, etc.), thromboprophylaxis will be offered.

Central Lines in Women with Cancer

Many women with breast or gynecologic cancer will need an implantable venous access device (portacath, chemo port) to avoid countless venipunctures and peripheral lines. This is particularly helpful for therapy with anthracyclines and other vesicant drugs that may cause necrosis when accidentally infused into subcutaneous tissue. Venous access devices, however, may cause upper extremity DVT (UEDVT).[59,60] Reported rates of symptomatic thrombi vary widely, from 0.3 to 28%.[59] The risk is highest in the first 4 to 6 weeks after implantation. There has been a long discussion, whether patients with venous access devices should be offered thromboprophylaxis. Most guidelines advise against it because studies failed to show a reduction of UEDVTs.[61,62] However, there has also been a recent meta-analysis which finds a 5.4% UEDVT reduction with prophylaxis.[63] This is a relatively small benefit and many patients, given the daily injections required, will probably forgo thromboprophylaxis. There is some hope that the new oral anticoagulants might change this but as of yet there are no studies to support giving DOACs for thromboprophylaxis with portacath systems.[64]

Other issues are regular flushings and sealing of the venous access device with heparin or saline. Heparin solution does not seem to have any influence on the incidence of catheter thrombosis.[65,66] However, some product monographs still do recommend heparin plumbing. This discrepancy between manufacturer's recommendation and the scientific evidence should be discussed with the patient in order to avoid allegations of incorrect treatment in the event of catheter thrombosis.

Most UEDVTs are asymptomatic or present with central line dysfunction. Typical symptoms are edema of the hand and arm, collateral veins, and sometimes pain on the side of the access device. A more serious complication is septic thrombophlebitis with fever and often pain at the catheter site. Diagnosis is made by Doppler or duplex ultrasound; however, more proximal VTEs cannot be visualized and then computed tomographic venography should be considered in patients with a negative ultrasound and high clinical suspicion of UEDVT. The Constans Score has been developed to support the decision on further work-up in patients suspected to have UEDVT (e.g., in a patient with a score of 1 or higher) (►Table 5). It shows that already the presence of localized pain in a patient with a central venous catheter has sufficient probability to start diagnostic work-up for UEDVT.

If thrombosis is confirmed, anticoagulation without catheter removal is the preferred option for initial treatment, provided the catheter is still functional. The duration of anticoagulation is less clear. Guidelines recommend a minimum duration of 3 months. To the knowledge of the author there is only one randomized study that assesses the efficacy and safety of one of the new DOACs in UEDVT.[67] There were few VTE recurrences but one fatal PE and 13% of patients developed bleedings. If there is no thrombosis and catheter dysfunction only, e.g., from a clot inside the catheter, recombinant tissue plasminogen activator (rtPA) is often sufficient to open it up again. rtPA (Actilyse Cathflo) is the only licensed drug for this indication in Germany.

Table 5 Probability score for UEDVT[92]

Constans Score	Points
Presence of central venous catheter or pacemaker	1
Localized pain	1
Unilateral pitting edema	1
Other diagnosis plausible	−1
Probability of UEDVT	
Score −1 and 0	12%
Score 1	20%
Score 2–3	70%

Abbreviation: UEDVT, upper extremity deep vein thrombosis.

Ovarian Stimulation

Fertility preservation is an issue for younger women whose family planning is not yet complete. Ovarian stimulation and in vitro fertilization is the most commonly offered method and has an increased risk of VTE in young patients already.[68] This raises the question whether former cancer patients who are usually older and have a higher risk of VTE should undergo this procedure.[69] There is little evidence to guide recommendations, but most experts will not give routine thromboprophylaxis for ovarian stimulation (exception: ovarian hyperstimulation syndrome, prior VTE, or known high-risk thrombophilia).[70,71] It might be of interest that women with VTE during ovarian stimulation seem to have an increased risk not only for lower extremity but also for upper extremity thrombosis. This may result from drainage of increased peritoneal fluid with inflammatory properties through the thoracic duct into the subclavian vein.[72]

Uterine Bleeding

Uterine bleeding is a concern in women receiving anticoagulant therapy for VTE. A recent meta-analysis of 10 studies on the new DOACs did not report any *major bleeding*, but up to 5.9% *clinically relevant nonmajor bleedings* was reported.[73] However, rates of menorrhagia or other types of abnormal uterine bleeding not meeting criteria of clinical relevance are much higher.[73,74] These "minor" or "nuisance" bleedings are still important as patient-centric outcomes, as they influence the perception of anticoagulation, may cause anxiety, and reduce quality of life. For noncancer women with heavy menstrual bleeding under anticoagulants, tranexamic acid, hormonal therapy, and dose reduction of anticoagulants are recommended.[75] Tranexamic acid is contraindicated in cancer patients with acute VTE or a history of VTE. Hormonal therapy (gestagens or estrogens) is contraindicated in many women with hormone responsive (e.g. breast cancer). This leaves anticoagulant dose reduction as the only nonsurgical option.

Continuing Tamoxifen after VTE?

The pros and cons of thromboprophylaxis in women on tamoxifen have been discussed above (see the section Breast Cancer—Low Risk, High Burden). This is different from therapeutic anticoagulation after a patient has developed VTE while on tamoxifen. Many practitioners then ask—not least out of concern of malpractice allegations—whether they must stop tamoxifen or whether they can continue because the patient is, after all, therapeutically anticoagulated and safe. To the best knowledge of the author, there are no studies on the safety of tamoxifen in women with cancer-associated VTE under therapeutic anticoagulation (except for one expert opinion).[76] It would be helpful if professional societies or guideline authors published a formal recommendation to this clinically relevant issue.

Until then one may gather advice from hormonal therapy with estrogens in women anticoagulated for VTE. Most thrombosis experts and guidelines state that hormonal therapy with estrogens is possible and need not be stopped as long as patients are adequately anticoagulated.[77–79] The anticoagulant of choice should be LMWH or a DOAC, since vitamin K antagonists are known to interact with tamoxifen. There have been reports that tamoxifen may increase the blood levels of DOACs, which may result in a higher risk of bleeding complications.[80] Therefore, all cancer patients on tamoxifen and oral anticoagulants should be closely monitored.

Drug–Drug Interactions

Drug–drug interactions are a relevant issue in daily oncology practice. This is particularly true for anticoagulants. Vitamin K antagonists—not the first choice anticoagulant in cancer patients any more—are known for multiple drug interactions and their efficacy is also affected by changes in food habits. LMWH has relatively less interactions and the new DOACs stand in between.[81–83] Every physician who takes care of cancer patients should be familiar with his patients' medication plan and with potential drug–drug interactions of his most commonly prescribed drugs.

Besides drug interactions, cancer therapy may affect renal function and a decreasing filtration capacity will increase DOAC blood levels. This is an issue particularly with platinum-containing chemotherapies or with some of the new checkpoint inhibitors (acute kidney injury, typically caused by acute interstitial nephritis).

Patients undergoing cancer therapy should therefore not only have their blood counts regularly checked, but also liver and kidney functions (for details on liver and kidney function impairment and dose adjustments or contraindications of DOACs, see the prescribing information). On each visit, their medication plans should be reviewed for potential drug interactions (►**Tables 3** and **6**).[84]

Anticoagulation during Palliative Care

Many cancer patients unfortunately cannot be cured, cancer progresses, and the patient will eventually need palliative and hospice care. Studies show that many patients still receive prophylactic or therapeutic anticoagulation when transferred to hospice.[85,86] In this last phase of life, when treatment should primarily focus on optimizing patients' quality of life, the use of antithrombotics needs to be reconsidered since the risk–benefit ratio may have changed. It is true that symptomatic VTE may still occur during this terminal phase, but at the same time up to 10% of patients experience a clinically relevant bleeding, with about one-fifth of these bleedings contributing to death.[87] The current AWMF guideline for palliative care recommends reviewing the indication for anticoagulant drugs and discontinue them if possible.[88] However, if patients are symptomatic with pain or swelling from venous thrombosis, then therapeutic anticoagulation should be given to reduce symptom burden.[89]

Table 6 Practical approach for assessing and managing risk of bleeding during[84]

Step 1	At diagnosis of VTE, before starting anticoagulation • Rule out absolute contraindications for anticoagulation, e.g., active bleeding, recent life-threatening bleeding
Step 2	At discharge from hospital • Chose optimal anticoagulant (LMWH or DOAC) and dose • Provide information to patient and subsequent caregivers • Identify risk factors[a]
Step 3	Next ambulatory control • Re-assess optimal anticoagulant and dose • Assess for side effects and risk factors[a]
Step 4	Regular ambulatory control during long-term treatment: • Re-assess optimal anticoagulant and dose • Re-assess need for continued anticoagulation • Check for side effects[a]

Abbreviations: DOAC, direct-acting oral anticoagulant; LMWH, low-molecular-weight heparin.
[a]Risk factor assessment includes hemoglobin, platelet count, liver and renal function, blood pressure, co-medications, and drug adherence.

Clinical Case (Cont.)

This woman with portacath-related UEDVT received initial therapeutic dose anticoagulation with LMWH. The catheter was functional and left in place. Symptoms of pain and swelling resolved within 2 days and a repeat ultrasound showed patency of axillary and subclavian vein. During her chemotherapy (additional 4 months) with potential decreases in platelet counts, she was left on daily subcutaneous LMWH. Then she underwent breast conserving surgery. Before starting antihormonal therapy, her hormone levels were measured, and she was found to be still premenopausal. She was referred to this institution with the question of long-term anticoagulation and whether she could be given tamoxifen.

The recommendation was to start tamoxifen and continue therapeutic dose anticoagulation as long as the portacath was in place and as long as she would take tamoxifen (a switch to aromatase inhibitor planned after 5 years). Considering long-term anticoagulant treatment and since there was no obvious contraindication, we switched her from LMWH to a DOAC. Initially she was seen monthly, then three-monthly and eventually in longer intervals to assess anticoagulant efficacy and side effects. She was educated what symptoms of VTE or bleeding to look for and whom to contact if this happens.

Conclusion (Who Should Be in Charge?)

The GARFIELD study shows that cancer-associated VTE is often managed by general internists or family physicians.[18] In parallel, the patient sees a gynecologist or oncologist who directs cancer treatment. Many cancer therapies interfere with anticoagulants and vice versa. Does the general internist always know which anticancer regimen the patient is currently on and how this affects the anticoagulation's efficacy and safety? Does the cancer specialist know which anticoagulants his patient is currently taking and how they affect cancer treatment safety and efficacy? A written medication plan, such as the national medication plan (sog. Bundeseinheitlicher Medikationsplan) is a step toward the right direction. However, with tumor patients it needs frequent updates and adaptations, and practical experience has unfortunately shown that many patients do not have up-to-date medication plans "on hand." Patient empowerment, a process through which patients gain more competence and understanding for decisions and actions affecting their health, is one important step to improve medical care, particularly in cancer patients. At the same time, all specialists caring for cancer patients should have basic knowledge of the most common cancer treatment complications even if the complications are not central to their field of practice. The management of cancer-associated VTEs is definitively on the top of this list.

Conflict of Interest

The authors declare that they have no conflict of interest.

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