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Approach to Cancer-Associated Thrombosis: Challenging Situations and Knowledge Gaps

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Abstract

Malignancy is a significant risk factor for venous thromboembolism (VTE). It is estimated that up to 20% of patients with cancer may develop VTE at some time in their cancer journey. Cancer-associated VTE can lead to hospitalizations, morbidity, delayed cancer treatment, and mortality. The optimal prevention and management of cancer-associated thrombosis (CAT) is of utmost importance. Direct oral anticoagulants have been recommended as first-line therapy for VTE treatment in the general population and their efficacy has recently been demonstrated in the cancer population, leading to increased use. However, patients with cancer have unique challenges and comorbidities that can lead to increased risks and concerns with anticoagulation. Herein we will discuss commonly encountered challenges in patients with CAT, review available literature, and provide practice suggestions. ***The Oncologist*** 2021;26:e17–e23

Implications for Practice: This article aims to specifically address cancer-associated thrombosis issues for which there is limited or absent evidence to guide best practice, for circumstances that pose unique challenges for clinicians, and for directions when the literature is conflicting. It reviews pertinent data for each selected topic and provides guidance for patient management based on the best available evidence and experiences from the panel.

Introduction

Cancer is a well-known risk factor for venous thromboembolism (VTE). Patients with cancer have a four- to seven-fold increased risk of VTE compared with patients without cancer [1]. Cancer-associated thrombosis (CAT) and its treatment can result in complications such as post-thrombotic syndrome, hemorrhage, hospitalizations, delayed cancer therapies, and mortality but also may impair cancer-directed therapy. Optimal prevention and treatment strategies for CAT are an ongoing area of research. Major recent advances include the use of direct oral anticoagulants (DOACs) in the prevention and treatment of CAT in randomized controlled trials (RCTs). However, there remains a paucity of evidence for many issues commonly encountered in patients with cancer, creating unique challenges for clinicians to best care for this high-risk population. This paper addresses 10 challenging topics (Table 1). For each topic, we summarize the challenges, review available literature, and provide suggestions for clinicians based on the best available evidence or on expert opinions when evidence is insufficient. We also identify areas for future research.

Active Gastrointestinal Luminal Lesions

Challenges

DOACs have replaced low-molecular-weight heparin (LMWH) for many patients with cancer, and four RCTs have established the role of DOACs in CAT treatment [2–5]. However, the risk of gastrointestinal (GI) bleeding is a concern with DOACs. DOACs exert anticoagulant activity within the GI tract immediately after ingestion. Therefore, DOAC use in the presence of GI

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luminal lesions could be associated with an increased risk of GI bleeding. GI luminal lesions include the tumor itself or non-neoplastic lesions, such as esophagitis, peptic/duodenal ulcers, arteriovenous vascular malformations, or foreign bodies such as nasogastric tubes. DOACs are associated with an increased risk of GI bleeding in the general population [6]. In patients with cancer, where either non-neoplastic or neoplastic lesions are common in the GI tract, it is crucial to consider the risks of GI bleeding with use of DOACs.

Literature Review

At least three meta-analyses combine the results of the four RCTs comparing DOACs with LMWH in patients with cancer with acute VTE [7–9]. They showed a trend of increased GI bleeding risk with DOACs (risk ratio [RR], 1.91; 95% confidence interval [CI], 0.96–3.82) [8, 9]. The Hokusai VTE Cancer and SELECT-D trials both showed a significantly increased risk of major GI bleeding (particularly upper GI bleeding) events with DOACs (edoxaban: 6.9%, rivaroxaban: 6%) compared with dalteparin (4% in both studies) [2, 3], predominantly in patients with GI cancers. On the contrary, the Caravaggio trial did not show an increased risk of GI bleeding events with apixaban compared with dalteparin [5]. The reasons for these discrepancies are unclear and could include differences in the DOAC agent or among the enrolled population. The Hokusai VTE Cancer and Caravaggio trials enrolled similar percentages of patients with GI cancer (∼30%) and upper GI cancer (∼5%), but the percentages of patients with intact luminal tumors were not specified. Although the results from the Caravaggio trial were promising, more details such as bleeding events by cancer types (i.e., GI cancer vs. non-GI cancer, intact luminal tumors) are essential to advance our understanding of DOAC use in this high-risk population.

In the Hokusai VTE Cancer trial, edoxaban was associated with a significantly increased risk of major GI bleeding compared with dalteparin (hazard ratio [HR], 2.0; 95% CI, 1.09–3.66), but the increased major bleeding with edoxaban was only in patients with GI cancer (HR, 4.0; 95% CI, 1.5–10.6) and not with other cancers [10]. In patients with GI cancer, upper GI bleeding accounted for 76.2% (16/21) of major bleeding events in the edoxaban group and 0% (0/5) in the dalteparin group [10]. Out of those 16 major upper GI bleeding events in patients with GI cancer receiving edoxaban, 12 (75%) occurred in patients with unresected tumors [10]. Therefore, although data remain limited, available literature suggests that patients with intact tumors in the GI tract have higher risks of GI bleeding with DOACs.

A prospective cohort study from Memorial Sloan Kettering Cancer Center (MSKCC) of 1,072 patients with CAT treated with rivaroxaban provides support for the safety and efficacy of a DOAC [11] when its use is avoided in patients with GI and genitourinary (GU) luminal abnormalities. In this cohort, the rates of major bleeding and recurrent thrombosis were 2.2% and 4.4%, respectively.

Suggestions

Based on available evidence, the panel suggests LWMH as the anticoagulant of choice in patients with cancer with a high risk of GI bleeding, including patients with active, in situ GI luminal tumors, known non-neoplastic GI lesions, or recent (<6 months) major GI bleeding. Shared decision-making with patients is important. In patients who refuse LMWH, there is no consensus within the panel regarding the relative safety of DOACs or other anticoagulants in this population, although apixaban was suggested by some based on the Caravaggio trial.

Active Genitourinary Luminal Lesions

Challenges

Although renal clearance varies with the DOACs that have been studied for CAT (apixaban, edoxaban, rivaroxaban), biologically active DOACs are present in the urinary tract. Therefore, use of a DOAC in the presence of GU luminal lesions or instrumentation could be associated with an increased risk of urinary tract bleeding. Common non-neoplastic lesions include renal stones and strictures, whereas neoplastic lesions include cancers involving the kidney, urothelial tract, or bladder. Instrumentation within the GU tract, such as the use of nephrostomy tubes, Foley catheters, or urinary tract stents, can also increase the risk of GU bleeding. LMWHs are also cleared in the urinary tract, but in the absence of antithrombin in the urine, LMWH would not exert an anticoagulant effect and would be expected to be relatively safer [12].

Literature Review

The meta-analyses mentioned above showed a significantly increased risk of major GU bleeding events with DOACs compared with LMWH (RR, 4.99; 95% CI, 1.08–23.08) [8, 9]. Clinically relevant nonmajor bleeding (CRNMB) in the GU tract was also increased (RR, 2.2; 95% CI, 1.33–3.63) [8]. Although it might be assumed that the bleeding site correlates with the site of cancer, most studies (except for the Hokusai VTE Cancer trial) have not published subgroup analyses based on cancer types to confirm this.

In the Hokusai VTE Cancer trial, the 12-month major bleeding events in patients with GU cancer were too few for meaningful analysis (three in the edoxaban group and one in dalteparin) [10, 13]. A meta-analysis according to each cancer subtype from all DOAC studies, if possible, could be helpful.

Suggestions

Based on the currently available literature, LWMH may be preferred in patients at high risk of GU bleeding, such as those with active, unresected lesions in the GU tract, recent GU tumor surgery, or recent (<6 months) major GU bleeding. This suggestion is inferred from the current evidence that major GU bleeding is increased with DOACs.

Concomitant Use of Antiplatelet Agents

Challenges

Cardiovascular disease is a common comorbidity in patients with cancer, and antiplatelet agents are frequently indicated. A large observational study showed that 15% of patients admitted with acute myocardial infarction had a history of cancer [14]. Concurrent use of antiplatelet agents beyond aspirin 100 mg once daily with anticoagulation has not been studied in the cancer population. Patients on dual

antiplatelet therapy (DAPT) were excluded from all RCTs of DOACs in cancer. Similarly, large RCTs to study combined anticoagulation and antiplatelet agents in the general population excluded patients with VTE or cancer [15, 16]. Appropriate management of patients with cancer with concomitant indications for anticoagulation and antiplatelet therapy remains a key knowledge gap.

Literature Review

There is little literature available on the effects of combined anticoagulation and antiplatelet agents in the cancer population. In general, DAPT is used for patients with coronary artery disease (CAD) and coronary stents [17]. The concomitant use of DAPT plus an anticoagulant raises concern for an unacceptably high risk of bleeding, outweighing therapeutic benefit compared with an anticoagulant and a single antiplatelet agent. The AUGUSTUS trial examined a general population of patients with recent acute coronary syndrome or percutaneous coronary intervention on a $P2Y_{12}$ inhibitor. Compared with combination therapy with a $P2Y_{12}$ inhibitor and vitamin K antagonist (with or without aspirin), the study found that apixaban plus a $P2Y_{12}$ inhibitor (without aspirin) resulted in fewer bleeding complications and hospitalizations—without an increased incidence of ischemic events [15]. It should be noted that this regimen (apixaban plus a $P2Y_{12}$ inhibitor) has not been validated in the cancer population. Given that all cancer VTE RCTs have excluded patients on concurrent DAPT and/or a $P2Y_{12}$ inhibitor, there are more clinical experiences with concurrent use of aspirin and anticoagulation.

Suggestions

We acknowledge that there are no clear cancer-specific data to guide practice and our suggestions are extrapolated from the best available evidence in the general population.

1. CAT (regardless of acute or chronic) and a new coronary stent: Based on the AUGUSTUS trial, we suggest a therapeutic dose of a DOAC (and prefer apixaban) combined with one antiplatelet agent ($P2Y_{12}$ inhibitor). This suggestion is extrapolated from data in the general population and is not specific to patients with cancer.
2. Acute CAT and stable CAD: In patients who have stable CAD—with or without a past coronary stent—and are already on DAPT and have developed a new VTE, the panel suggests starting a therapeutic dose of a DOAC and stopping at least one of the antiplatelet agents.

Concomitant Use of Strong Inhibitors or Inducers of Both Cytochrome CYP3A4 and P-glycoprotein: Drug–Drug Interactions

Challenges

Of the available anticoagulants, LWMH generally has the least likelihood of drug–drug interactions (DDIs). DOACs have fewer DDIs than warfarin; however, DDIs with DOACs should not be overlooked. Apixaban, rivaroxaban, and edoxaban are all substrates for P-glycoprotein (P-gp) cell transporter, which plays an important role in their absorption. DDIs with strong P-gp inducers or inhibitors may lead to a decrease or increase in DOAC concentrations, respectively. Apixaban and rivaroxaban, but not edoxaban, are also dependent on cytochrome CYP3A4 for hepatic metabolism. Chemotherapies or targeted cancer therapies may affect P-gp and/or CYP3A4 pathways and care is needed with concurrent use.

Studies investigating DOACs have excluded patients on concomitant use of strong inhibitors or inducers of both CYP3A4 and P-gp. There are no data on how strong an inhibitor or inducer must be to influence the efficacy or safety of DOACs. The presence of concomitant multiple inducers or inhibitors is also another knowledge gap. Although anti-Xa assays are available, there have been no data or established guidelines on the use of these assays to evaluate potential DDI or the need for dose adjustment.

Literature Review

All RCTs of DOACs for CAT treatment or prophylaxis excluded patients on concomitant use of DOACs and strong inhibitors or inducers of both CYP3A4 and P-gp. Therefore, there are few to no data available in the cancer population regarding potential DDIs.

In the general population, data addressing DDIs between DOACs and other medications are limited, but a few recent studies have provided some insights. A large database analysis showed that concomitant prescription of clarithromycin (a potent inhibitor of P-gp and CYP3A4) and DOACs caused a 1.71-fold increased risk of hospitalization for major hemorrhage within 30 days of concurrent use, compared with concomitant prescription of azithromycin (minimal effect on P-gp and CYP3A4) or without concurrent use [18]. Another single-center retrospective study showed that use of combined P-gp and moderate CYP3A4 inhibitors (such as amiodarone, diltiazem, etc.) with rivaroxaban or apixaban increased the risk of all bleeding events compared with patients without concurrent use (HR, 1.8; 95% CI, 1.19–2.73) [19].

Suggestions

Depending on the potential DDI, consider using LWMH or edoxaban (given its lack of CYP3A4 interaction) in patients where significant DDI is a concern. Dose reduction to 30 mg daily is recommended for edoxaban in patients on concurrent potent P-gp inhibitors. Apixaban has a similar dose reduction recommendation in patients receiving concurrent strong dual CYP3A4 and P-gp inhibitors, whereas avoidance is recommended for other DOACs. Measuring anti-Xa levels of DOACs when DDI is a concern has been proposed, but there are currently few data to support this practice.

Intracranial Tumors

Challenges

Intracranial tumors are associated with an increased risk of VTE. A meta-analysis showed that the risk of VTE can be as high as 20% per year in high-risk patients with brain tumors [20]. On the other hand, the risk of intracranial hemorrhage (ICH), the most severe bleeding complication, is also increased in these patients. Therefore, patients with

intracranial tumors (primary or metastatic) often face these challenging situations.

Literature Review

In the LMWH era, a matched cohort study in patients with metastatic brain tumors showed that therapeutic LMWH did not increase the risk of ICH compared with no anticoagulation [21]. A subsequent meta-analysis confirmed this result [22]. However, patients with primary brain glioma were found to have a significantly increased risk of ICH with LMWH compared with no anticoagulation (odds ratio, 3.75; 95% CI, 1.42–9.95) [22]. This was confirmed by a separate matched cohort study of 133 patients with high-grade glioma, where LMWH was associated with a 3.37-fold increased risk of major ICH compared with no anticoagulation [23]. In the same study, however, no anticoagulation was associated with an 11-fold increased risk of VTE (HR, 11.2; 95% CI, 1.5–86.3) [23].

The Hokusai VTE Cancer trial included 74 (7.1%) patients with brain tumors, and the subgroup analysis showed no significant differences in rates of the primary composite outcome between the edoxaban and dalteparin groups [2]. Other RCTs of DOACs for CAT have not contributed much more to this question. The SELECT-D trial only had three patients with intracranial tumors, the ADAM VTE trial had eight, and the Caravaggio trial excluded all patients with primary or metastatic brain tumors [3–5]. A retrospective cohort study showed that DOACs were not associated with an increased risk of ICH compared with LMWH in both patients with primary brain tumors (n = 67) and metastatic brain tumors (n = 105) [24].

Suggestions

1. Metastatic brain tumors and acute VTE: Based on available data, standard anticoagulation is recommended in these patients. A DOAC is considered at least as safe as LMWH.
2. Primary brain tumors and acute VTE: Available data indicate that there is a high risk of ICH. However, withholding anticoagulation has a high risk of recurrent CAT. Individualized risk assessment regarding the severity of thrombosis and risk of ICH is crucial. If an anticoagulant is used, literature indicates that a DOAC is at least as safe as LMWH.

Conditions Resulting in Decreased Absorption

Challenges

DAOCs are primarily absorbed in the stomach, with some additional absorption in the small intestine, especially with apixaban [25]. Patients who have previously undergone surgery leading to altered upper GI anatomy are likely to have reduced DOAC absorption, including patients who have undergone a full or partial gastrectomy for gastroesophageal cancer, as well as after bariatric surgery.

Literature Review

A small study compared peak DOAC levels in 18 patients after bariatric surgery and 18 matched controls and found that 5 (27.8%) patients in the postsurgery group had a lower-than-expected peak level, compared with none (0%) in the control group. All five patients with a low level were on rivaroxaban and had sleeve gastrectomy or banding. This study raised concerns for decreased absorption of rivaroxaban in patients where a significant portion of the stomach was bypassed, although its correlation with clinical outcomes is unknown [26]. A recent single-center retrospective study showed that in 102 patients without cancer with a history of gastric bypass treated with apixaban or rivaroxaban for a VTE, there was a low rate of recurrent thrombosis (~1%), providing some reassurance [27]. There are no data on the use of DOACs in patients after gastrectomy for cancer.

Suggestions

1. After full gastrectomy: We recommend LMWH.
2. After partial gastrectomy: LMWH is preferred. However, if a DOAC is desired, one can consider initiating a DOAC and obtaining anti-Xa levels to confirm adequate absorption, although supporting literature is limited.
3. If the GI tract has not fully healed after surgery, LMWH is preferred—regardless of the amount of stomach resected.

Catheter-Associated Thrombosis

Challenges

Patients with cancer commonly require central venous catheters for frequent blood draws, transfusions, or delivery of chemotherapy. Catheter-associated thrombosis is a frequent complication, with a large prospective cohort study demonstrating an incidence of 3.6% [28]. However, there are very few studies dedicated to the management of catheter-associated thrombosis.

Literature Review

The RIETE registry reported 512 patients with acute upper-extremity deep vein thrombosis (DVT), of whom 104 had cancer and catheter-associated thrombosis [29]. The majority of patients were treated with LMWH as initial (93%) and long-term (77%) therapy. The 3-month rates of recurrent VTE and major bleeding events were 7.7% and 3.8%, respectively. The Catheter study prospectively enrolled 74 patients with cancer with catheter-associated DVT and treated with dalteparin bridged to warfarin [30]. No recurrent thrombosis was seen at 3 months, with a line preservation rate of 100% and a 4% rate of major bleeding. More recent studies have used DOACs, although data remain scarce. The Catheter 2 study, a single-arm study of 70 patients treated with rivaroxaban, showed a low rate of recurrent thrombosis (1.4%) at 12 weeks and a line preservation rate of 100% but a high rate of major bleeding (12.9%) and one fatal pulmonary embolism [31]. Another retrospective study from MSKCC identified 83 patients with catheter-associated DVT treated with rivaroxaban and showed that during the 90-day follow-up period, the line failure rate was low (3.6%), with an equally low rate of major bleeding (2.4%) and recurrent thrombosis (3.6%) [32].

The four RCTs of DOACs versus LMWH unfortunately did not provide much evidence in the management of catheter-associated thrombosis. Only the ADAM VTE trial included a

small number of patients with upper-extremity DVT (46/300, 15.3%), and it is unknown how many of these were catheter related [4].

Suggestions

DOACs are a reasonable treatment option for catheter-associated thrombosis. Supporting data are from small prospective or retrospective cohort studies.

Thrombocytopenia

Challenges

Thrombocytopenia from chemotherapy and/or malignancy itself is commonly seen in patients with cancer. Anticoagulation in the setting of thrombocytopenia would be expected to be associated with a high risk of bleeding. To further complicate the situation, the risk of CAT remains, even in the setting of thrombocytopenia. A large retrospective study of 1,514 patients undergoing stem cell transplantation showed that 4.6% developed symptomatic VTE and 15.2% had clinically significant bleeding events within 180 days of transplantation [33]. Thirty-four percent of VTE events occurred when platelet count was $<50 \times 10^9$/L. A systemic review showed that in patients with cancer with VTE and thrombocytopenia, 27% had recurrent VTE and 15% had major bleeding events, regardless of the treatment strategy [34].

Literature Review

Multiple retrospective, single-center cohort studies reported results on the management of CAT and thrombocytopenia, all with LMWH [34]. In general, regimens incorporated dose reduction or temporary holding of LMWH, depending on platelet count. The current National Comprehensive Cancer Network guideline recommends half-dose enoxaparin for platelet count of $25–50 \times 10^9$/L and temporarily holding enoxaparin for platelet count $<25 \times 10^9$/L [35]. For patients at high risk of recurrent thrombosis and severe thrombocytopenia ($<25 \times 10^9$/L), platelet transfusions to maintain platelet count above $25–50 \times 10^9$/L may be used to allow for anticoagulation. For platelet count $>50 \times 10^9$/L, full-dose anticoagulation is recommended.

The four RCTs comparing DOACs versus LMWH excluded patients with severe thrombocytopenia (Hokusai VTE Cancer and ADAM VTE trials: platelet count $<50 \times 10^9$/L; SELECT-D trial: $<100 \times 10^9$/L; Caravaggio trial: $<75 \times 10^9$/L) [2–5]. Results from these trials could not apply to patients with platelet count $<50 \times 10^9$/L, so there are no current data on the use of DOACs in this population.

Suggestions

1. For patients with platelet count >50 x10^9/L, full-dose anticoagulation is recommended.
2. For patients with platelet count <25 x10^9/L, we recommend holding anticoagulation.
3. For patients with platelet count of 25-50 x10^9/L, we suggest half-dose anticoagulation. The data are most robust with LMWH, but a half-dose DOAC may be an acceptable alternative.

Severe Renal Insufficiency

Challenges

Acute and chronic renal insufficiency may develop in cancer patients due to malignancy, treatment, or associated complications. Patients with severe renal insufficiency are at higher risk of arterial and venous thrombosis, as well as bleeding [36]. In addition, most DOACs are at least partially renally cleared. However, patients with severe renal insufficiency—creatinine clearance (CrCl) <30 mL/min—were excluded in pivotal RCTs both in the general and cancer populations.

Literature Review

Patients with CrCl <30 mL/min were excluded from RCTs of CAT. While there is accumulating evidence from retrospective studies and database analysis (not cancer-specific) on the use of apixaban in patients on dialysis, most data focused on patients with atrial fibrillation (AF) and not VTE. For example, a large retrospective claims database analysis matched 25,523 patients with end-stage renal disease and AF starting apixaban with those starting warfarin [37]. No difference was noted in the risk of ischemic stroke, but apixaban was associated with a lower risk of bleeding (HR, 0.72, 95% CI, 0.59-0.87). Full-dose apixaban (5 mg twice daily) had more favorable outcomes than reduced-dose apixaban (2.5 mg twice daily) or warfarin in terms of stroke and mortality. Data from well-designed prospective studies or RCTs are lacking, so one should be cautious in the routine use of apixaban in these patients.

Suggestions

1. In patients with CrCl <30 mL/minute, apixaban is preferred (given approval by the U.S. Food and Drug Administration) if a DOAC is used, although this is based on limited data. Dose-adjusted LMWH (with anti-Xa level monitoring) is an appropriate alternative.
2. In patients with CrCl ≥30 mL/minute, the panel has no preference for the type of DOAC used.

Hematological Malignancy

Challenges

Patients with hematological malignancy have unique challenges, including more prolonged and severe thrombocytopenia, due to frequent bone marrow involvement and myeloablative chemotherapy regimens. However, hematological malignancies are underrepresented (approximately 10% or less) in major RCTs. Many patients with hematological malignancy were excluded from these RCTs because of thrombocytopenia, as all trials excluded patients with platelet count $<50 \times 10^9$/L. The SELECT-D trial also excluded patients with a white blood cell count $<2 \times 10^9$/L and the Caravaggio trial excluded patients with acute leukemia and history of stem cell transplantation [3, 5].

Literature Review

The subgroup analysis from the Hokusai VTE Cancer trial showed that in patients with hematological malignancy, there were comparable thrombotic and bleeding outcomes with edoxaban versus dalteparin, although the number of patients

was small (n = 111) [13]. More data on the use of DOACs in patients with various hematological malignancies are needed.

Within hematological malignancies, myeloproliferative neoplasm (MPN) and multiple myeloma are known to have increased risks of VTE, related to either disease characteristics (JAK2 mutation) or cancer therapy (immunomodulatory drugs). Although LMWH had been the anticoagulant of choice, DOACs are increasingly used. In the OBENE registry, 25 (3.3%) patients were treated with a DOAC, with a modest rate of thrombosis (4%) and major bleeding (12%) [38]. A recent retrospective study in the U.K. reported that in 102 patients with MPN and VTE, 32 (31.4%) received DOACs. There was no VTE recurrence or major bleeding, with 3 (9.3%) CRNMB events after a median follow-up of 2.6 years [39]. In several small studies, apixaban has been used as primary prophylaxis in myeloma patients with good efficacy and safety signals [40, 41].

VTE treatment in patients with acute leukemia or stem cell transplantation and prolonged and severe thrombocytopenia has not been adequately studied (see Thrombocytopenia section). VTE prophylaxis with DOACs in patients with MPN or myeloma is being investigated in clinical trials. More definitive studies are needed.

Suggestions

We suggest that patients with hematological malignancies be treated in a similar fashion as those with solid tumors, although data are scarce. For patients with prolonged and severe thrombocytopenia (such as acute leukemia), please refer to the Thrombocytopenia section.

Conclusion

Patients with cancer commonly face unique challenges and complications when they develop VTE. Here we hope to have provided a concise review of the available literature and practical suggestions for clinicians in the management of these high-risk situations, and a concise summary of our suggestions is shown in Table 1.

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Table 1. Summary of suggestions in challenging situations

Clinical scenarios in patients with cancer	Suggestions
1. Active GI luminal lesions	LWMH is preferred for patients with a high risk of GI bleeding. There is no consensus in patients who refuse LMWH, but apixaban is suggested.
2. Active GU luminal lesions	LWMH is preferred in patients with high risk of GU bleeding.
3. Concomitant use of antiplatelet agents	1. CAT (regardless of acute or chronic) and a new coronary stent: Initiate therapeutic dose of DOAC (apixaban preferred) combined with one antiplatelet agent ($P2Y_{12}$ inhibitor). 2. Acute VTE and stable CAD: Initiate therapeutic dose of DOAC and stop at least one antiplatelet agent.
4. Concomitant use of strong inhibitors or inducers of both cytochrome CYP3A4 and P-gp (DDI)	Consider LWMH or edoxaban in patients with concern of significant DDI. Monitoring anti-Xa levels is suggested if a DOAC is desired.
5. Intracranial tumors	Use standard anticoagulation (either DOAC or LMWH), but be cognizant of increased risk of ICH in patients with primary brain tumors.
6. Conditions resulting in decreased absorption	1. Use LMWH after full gastrectomy. 2. LMWH is suggested after partial gastrectomy, but if a DOAC is desired, monitoring anti-Xa levels is suggested. 3. LMWH is preferred if the GI tract has not fully healed after surgery, regardless of the amount of stomach resected.
7. Catheter-associated thrombosis	DOACs are commonly used and reasonable.
8. Thrombocytopenia	1. Platelet count >50 $\times$ 10^9/L: Use full-dose anticoagulation. 2. Platelet count <25 $\times$ 10^9/L: Hold anticoagulation. 3. Platelet count of 25-50 $\times$ 10^9/L: Use half-dose anticoagulation. The data are most robust with LMWH, but a half-dose DOAC may be an acceptable alternative.
9. Severe renal insufficiency	1. CrCl ≥30 mL/minute: No preference for the type of DOAC used. 2. CrCl <30 mL/minute: Use dose-adjusted LMWH (with anti-Xa level monitoring) or consider apixaban.
10. Hematological malignancy	Treat in a similar pattern as those with solid tumors.

Abbreviations: CAD, coronary artery disease; CAT, cancer-associated thrombosis; CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; DDI, drug–drug interaction; DOAC, direct oral anticoagulant; GI, gastrointestinal; GU, genitourinary; ICH, intracranial hemorrhage; LMWH, low-molecular-weight heparin; P-gp, P-glycoprotein; VTE, venous thromboembolism.

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