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Anticoagulation Strategies in Patients With Cancer

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Abstract

Patients with active cancer are at an increased risk of arterial and venous thromboembolism (VTE) and bleeding events. Historically, in patients with cancer, low molecular weight heparins have been preferred for treatment of VTE, whereas warfarin has been the standard anticoagulant for stroke prevention in patients with atrial fibrillation (AF). More recently, direct oral anticoagulants (DOACs) have been demonstrated to reduce the risk of venous and arterial thromboembolism in large randomized clinical trials of patients with VTE and AF, respectively, thus providing an attractive oral dosing option that does not require routine laboratory monitoring. In this review, we summarize available clinical trial data and guideline recommendations, and outline a practical approach to anticoagulation management of VTE and AF in cancer.

Keywords

anticoagulation; atrial fibrillation; bleeding; cancer; cardiooncology; venous thromboembolism

Patients with active cancer are at increased risk of arterial and venous thromboembolism (VTE) and bleeding events. As life expectancy for many cancers increases with use of more patient- and tumor-targeted therapies, safe and effective strategies to ameliorate VTE burden and in thromboprophylaxis of atrial fibrillation (AF) are much needed. Anticoagulation strategies are a cornerstone component of management in the growing subspecialty of "cardio-oncology." The selection of patients who have an acceptable risk-benefit profile for initiation of anticoagulation is complex given individual patient goals and preferences, changing prognosis of specific cancers, common comorbidities, potential drug–drug

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interactions, malnourished/underweight states, and competing risks of morbidity and mortality. Historically, low molecular weight heparins (LMWH) have been preferred for cancer-associated VTE given prior studies demonstrating reduced risks of recurrent VTE compared with warfarin (1,2). Meanwhile, vitamin K antagonists (VKA) have been preferred for stroke prevention in AF and cancer (3). However, injectable anticoagulation therapies and oral therapies that require frequent blood testing are burdensome, costly, and may introduce excessive patient discomfort. Moreover, the landscape of oral anticoagulation is rapidly evolving with the introduction and widespread use of direct oral anticoagulants (DOACs) in VTE and AF. We summarize the epidemiology, mechanistic drivers, available clinical trial data, and guideline recommendations for treatment of VTE and AF in patients with cancer.

BURDEN OF VENOUS AND ARTERIAL THROMBOTIC COMPLICATIONS IN PATIENTS WITH CANCER

Patients with cancer face risks of a broad range of thromboembolic complications. Up to one-third of VTE is cancer-associated in contemporary community-based cohorts (4). In addition to the magnified risks of index VTE events (5), cancer patients are at a 2- to 9-fold increased risk of recurrence (6), and as many as one-half of VTE are incidentally detected (7). Cancer-associated VTE, whether symptomatic or incidental, is a marker of poor prognosis (8).

Patients with cancer are at increased risk of arterial thromboembolic events, especially in certain cancer types (e.g., lung cancer) at advanced stages (9), and after vasculotoxic cancer therapies (e.g., radiation). Indeed, arterial thromboses may be a heralding feature of occult cancer (10). Patients who experience arterial ischemic events face high risks of short- (11) and long-term mortality (12).

CANCER AND ATRIAL FIBRILLATION

AF occurs frequently (13) and is a common reason for cardiovascular consultation in the cancer population. Up to one-quarter of the overall AF population has comorbid cancer (14). New-onset AF is associated with higher rates of occult cancer diagnosis (15,16). However, a causal relationship is uncertain, as AF may be a risk marker for cancer and increased cancer diagnosis may be attributable to detection bias. AF in cancer identifies patients at heightened risk of adverse cardiovascular events, including heart failure (17).

MECHANISMS DRIVING THROMBOSIS AND BLEEDING IN CANCER

The etiology of dysregulated hemostasis in cancer is multifactorial and has been linked to extent of disease, tumor biology, local and systemic inflammation, cancer therapeutics, and patient-related factors (18,19) (Figure 1).

VENOUS AND ARTERIAL THROMBOTIC EVENT PATHOGENESIS.

Aggressive solid tumors with early metastatic potential and advanced stage are associated with higher VTE risk (19). Tumor cells elaborate procoagulants such as tissue factor–

bearing circulating microparticles (20) and inflammatory cytokines (18). Tumor vascular invasion and compression contribute to endothelial damage and stasis.

Cancer type is strongly correlated with thrombotic risk (21). Specific cancer gene mutations can also predispose to VTE (e.g., JAK2 mutations via integrin activation [22]). Solid organ malignancies (Table 1) with highest thrombotic risks include pancreatic, gastric, brain, lung, ovarian, and renal cancers. All hematological cancers appear to carry a high risk of VTE. However, most cancer-associated VTE is observed with prostate, breast, and colon cancers due to higher prevalence despite lower thrombotic risks (18).

Various cancer therapies carry important treatment-related VTE risks (23) (Table 2). Surgery is associated with a 2-fold increased risk of postoperative VTE and a 4-fold increased risk of pulmonary embolism (PE)–related death in cancer. Central venous catheters (CVCs) needed during the course of therapy are associated with thrombosis. Patient-related factors, such as functional impairment, extremes of body weight, black race, advanced age, and comorbidities, are associated with elevated VTE risks (24).

Arterial thrombosis in cancer is less well-studied compared with VTE, but both share similar risk factors. These events are likely multifactorial, with greater propensity to occur with vasculotoxic cancer therapies and greater cancer burden (25).

AF PATHOGENESIS.

Shared epidemiology and risk factors contribute to the association between cancer and AF, which both increase with age and age-related comorbidities. Pathobiologies of cancer and AF are also linked by increased sympathetic drive, anemia, pulmonary and pericardial cancer involvement, paraneoplastic processes, inflammation, and specific interventions (e.g., surgery). Certain cancer therapies may increase risk of AF (26). For instance, ibrutinib, a tyrosine kinase inhibitor, can lead to AF in 6% to 16% of treated patients (27). Broadly, proposed mechanisms driving cancer therapy–related arrhythmogenicity and AF include membrane channel–specific interactions, excess oxidative stress, and increased levels of inflammatory mediators (26).

BLEEDING PATHOGENESIS.

Increased propensity for bleeding (28) may be explained by cancer-related thrombocytopenia, disseminated intravascular coagulation, and elaboration of fibrinolytic factors by tumor cells (29). Direct invasion, especially with certain cancers (e.g., renal, gastrointestinal, melanoma), may result in increased vascular fragility. Chemotherapy-related bone marrow suppression, radiation-induced tissue damage, and post-surgical wound healing issues all increment bleeding risks.

CLINICAL DATA OF ANTICOAGULATION APPROACHES IN CANCER

LMWH have been the standard of care in treating cancer-associated VTE. Data supporting the use of LMWH over VKA are derived from 2 large randomized clinical trials (RCTs). In an initial trial of 676 cancer patients with acute VTE, 6-month treatment with dalteparin significantly reduced VTE recurrence by 52% without influencing rates of major bleeding or

mortality compared with VKA (1). More recently, in 900 cancer patients with acute VTE, 6-month treatment with tinzaparin nonsignificantly reduced the risk for VTE recurrence (7.6% vs. 10.5%; p = 0.07), did not affect major bleeding or mortality, and significantly reduced nonmajor bleeding (10.9% vs. 15.3%; p = 0.004) compared with warfarin (2). Notably, the times in therapeutic range with VKA were <50% in these trials, which may have reduced VKA efficacy.

Emerging head-to-head trials of DOACs versus LMWH have recently completed or are actively underway (Table 3). Hokusai VTE Cancer was an open-label RCT that compared 6 to 12 months of the once-daily, oral factor Xa inhibitor edoxaban versus dalteparin in symptomatic or incidental VTE in 1,050 patients with cancer. Edoxaban was noninferior to dalteparin with respect to composite recurrent VTE and major bleeding (12.8% vs. 13.5%). Recurrent VTE was reduced by edoxaban compared with dalteparin (7.9% vs. 11.3%), but major bleeding was increased (6.9% vs. 4.0%), driven by higher bleeding rates in patients with gastrointestinal cancers (13.2% vs. 2.4%) (30). The Select-D Pilot trial (31) was an open-label RCT of 406 patients with cancer and VTE treated for 6 months, and showed that rivaroxaban reduced the risk of recurrent VTE (4% vs. 11%), but increased the risk of clinically-relevant nonmajor bleeding (13% vs. 2%) compared with dalteparin (31).

Data from phase III VTE trials suggest that DOACs have similar efficacy and either comparable or superior safety (with respect to clinically relevant bleeding) compared with VKA in subgroups of cancer patients (32–37) (Table 3). However, these data should be considered hypothesis-generating given that only 2% to 5% of patients had active cancers, and few patients had metastatic cancer or were on active chemotherapy (38).

Subgroup analyses of phase III trials of AF have also demonstrated consistent safety and efficacy profiles in cancer patients. An analysis of the ENGAGE AF-TIMI 48 (Effective Anticoagulation with factor Xa next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48) trial, which included 1,153 patients who developed cancer post-randomization, demonstrated preserved efficacy and safety of edoxaban compared with warfarin, regardless of cancer status (39). Apixaban had superior safety and efficacy relative to warfarin among 157 patients with active cancer and 1,079 patients with a history of cancer enrolled in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial (40). Early observational experiences similarly have shown that rivaroxaban, when used in patients with active cancer and AF in clinical practice, was associated with low rates of ischemic stroke and clinically-relevant bleeding (41). Recent comparative effectiveness data of patients with AF and cancer consistently have shown that DOACs were associated with lower or similar risks of bleeding and stroke compared with warfarin (42).

ONGOING TRIALS TESTING NOVEL ANTICOAGULATION STRATEGIES IN CANCER

Several ongoing clinical trials (Table 4) comparing DOACs with LMWH for treatment of VTE are underway and will provide further insight into the composite efficacy and safety profile and drug-specific versus class effects of DOACs in cancer. Trials are assessing a

broader range of endpoints beyond recurrent VTE and bleeding events, including patient-reported outcomes, such as treatment satisfaction and pain. CARAVAGGIO (Apixaban for the Treatment of Venous Thromboembolism in Patients With Cancer) (NCT03045406) is the largest ongoing study (planned N = 1,168) and is an open-label, multicenter, noninferiority trial designed to assess apixaban versus dalteparin in cancer-associated VTE.

SAFETY OF DOACs: DRUG INTERACTIONS, RENAL IMPAIRMENT, AND THROMBOCYTOPENIA DRUG INTERACTIONS.

The uptake of all DOACs is influenced by the P-glycoprotein (P-gp) system (43), while DOACs are also subject to variable metabolism via the cytochrome P450 (CYP) system (dabigatran 0%, edoxaban <4%, apixaban 15%, rivaroxaban 66%) (44,45). Cotreatment of DOACs with therapies that significantly influence these systems presents a theoretical risk for drug levels outside of the therapeutic range. Coadministration of any of the DOACs is not recommended with cancer therapies that are strong P-gp inducers or inhibitors. Several cancer and adjunctive therapies (including anti-emetics, opioids, and antibiotics) can alter CYP3A4 metabolism (46). Dabigatran or edoxaban may be preferred if a DOAC is selected in patients being treated with cancer therapies that are strong CYP3A4 inducers or inhibitors. Table 5 provides a summary of anticipated drug–drug interactions between DOACs and common cancer therapies that affect CYP3A4 metabolism and/or P-gp transport (further details in Steffel et al. [3]). Clinicians should be mindful of interactions between DOACs and investigational cancer therapies and ramifications of DOAC use on patient eligibility for clinical trials. The importance of interprofessional communication when prescribing anticoagulant therapy in cancer patients cannot be overstated.

RENAL IMPAIRMENT.

Patients with cancer have high rates of chronic kidney disease and commonly receive nephrotoxic chemotherapeutic agents (47). Renal insufficiency also affects DOAC pharmacokinetics. Individual agents have differing renal clearance (dabigatran 80%, edoxaban 50%, rivaroxaban 33%, and apixaban 27%) (48). Appropriate renal dose adjustment is critical for patients with renal dysfunction and applies to all DOACs. In patients with progressive renal impairment, switching from a DOAC to an alternative anticoagulant with less renal clearance is generally preferred over anti-Xa level monitoring (49). It is not advisable to use DOACs in patients with creatinine clearance <15 ml/min, as drug exposure increases for all DOACs in patients with stage V chronic kidney disease.

THROMBOCYTOPENIA.

Thrombocytopenia, which commonly develops from myeloablative chemotherapy, tumor invasion of the bone marrow, and secondary immune-mediated phenomena, is another safety concern. Depending on individual thrombotic risks, anticoagulation should be avoided when platelet counts fall below 50,000 to 70,000/μl (50). Below this range, platelet transfusion or use of reduced-dose anticoagulation strategies may be considered to permit uninterrupted anticoagulation (51). Regulatory approvals of targeted reversal agents (idarucizumab, humanized antidabigatran monoclonal antibody, and andexanet alfa, recombinant modified factor Xa), mitigate some of the risk associated with DOACs. Ciraparantag, a broad nonspecific small molecule that reverses the anticoagulant effects of Xa inhibitors, direct

thrombin inhibitors, unfractionated heparin, and LMWH, is currently under investigation (52).

SUMMARY OF CLINICAL PRACTICE GUIDELINES

Until recently, all guidelines recommended that cancer-associated VTE be treated with LMWH for at least 3 to 6 months (Table 6) (50,53,54). However, given encouraging interval data, the latest International Society on Thrombosis and Haemostasis guidance supports use of DOACs (with preference for edoxaban and rivaroxaban) in acute VTE and low bleeding risk if no significant drug–drug interaction is present, and LMWH in acute VTE and high bleeding risk (including intraluminal gastrointestinal and genitourinary cancers or abnormalities) (55). The National Comprehensive Cancer Network guidelines now recommend either LMWH or edoxaban (with an initial parenteral dosing with LMWH) in cancer-associated VTE (56).

The 2018 European Heart Rhythm Association practical guide notes highlights limited high-quality data on use of LMWH in thromboprophylaxis of AF. The guide endorses shared decision-making, avoidance of strong drug–drug interactions, and further study of DOACs in comorbid cancer and AF (3). Traditional risk scores (e.g., CHA_2DS_2-VASc) (57) should be applied to determine individual thrombotic risks, together with cancer- and therapy-specific factors (3). Future guidelines should consider updating recommendations in AF and cancer given recent data.

UNIQUE CLINICAL DILEMMAS IN ANTICOAGULATION MANAGEMENT IN CANCER

CENTRAL VENOUS CATHETER-ASSOCIATED VTE.

Insertion of CVCs accounts for 70% of cancer-associated upper extremity deep vein thromboses (58). Whether DOACs, which inhibit only a single clotting factor, would be as effective as less-specific anticoagulants (especially agents that inhibit the contact pathway) for CVC-related VTE is unknown. Current guidelines for CVC-associated VTE in cancer patients recommend treatment with either LMWH bridged to VKA or LMWH monotherapy ≥12 weeks without requiring removal of the catheter (unless defective, nonfunctional, or infected) (50) (Table 6). Data for the use of DOACs are limited. In a small, open-label study of CVC-associated VTE, preservation of line function was 100%, but rates of bleeding were high with 12-week treatment with rivaroxaban (59). Routine prophylactic anticoagulation is not recommended for CVCs inserted in cancer patients (60).

INTERRUPTION OF ANTICOAGULATION.

Anticoagulation frequently requires interruption for surgical or interventional procedures in cancer care. Interruption of anticoagulation is associated with heightened risks of adverse cardiovascular and cerebrovascular events (61), but limited data exist regarding strategies to limit these thrombotic risks in cancer. Given the consistent increment in bleeding risk, full-dose periprocedural bridging anticoagulation with LMWH or unfractionated heparin is not routinely recommended in patients with cancer with VTE more than 3 months prior (49).

TREATMENT FAILURE AND INFERIOR VENA CAVA FILTER PLACEMENT.

Cancer is a major risk factor for anticoagulation failure. Switching to LMWH or dose escalation (in LMWH-treated patients) are guideline-supported strategies, but have not been examined in RCTs among cancer patients. Insertion of inferior vena cava (IVC) filters may be considered in cancer patients with contraindications to anticoagulation or evidence of progression or recurrence with LMWH (Table 6). However, RCTs examining IVC filter placement in cancer are lacking. Recurrent VTE while on therapeutic LMWH identifies patients at very high short-term mortality risk (1,62). Therefore, quality of life and patient preference are important when determining treatment approach in this high-risk subset.

VENA CAVA THROMBOSIS.

Extensive vena cava thrombosis is a relatively uncommon, but morbid complication, occurring in the setting of certain cancers (e.g., renal cell carcinoma, gastrointestinal), abdominal surgery, and/or unretrieved IVC filters (63). Anticoagulation is the mainstay of therapy with limited data on use of DOACs; adjunctive interventions including surgical thrombectomy may be required in select cases (64).

DOSING IN UNDERWEIGHT CANCER PATIENTS.

Weight loss is a common feature of cancer. Dose reduction by 50% is recommended in body weight ≤60 kg for apixaban in treatment of AF in patients age ≥80 years and/or serum creatinine ≥1.5 mg/dl. Similarly, a 50% dose reduction for body weight ≤60 kg is recommended for edoxaban in patients with AF (except in the United States) and VTE (globally). Due to lack of validated dosing guidelines, monitoring anti-Xa levels in an attempt to prevent overdosing in underweight patients is not routinely recommended. However, measurement of drug concentrations and/or anti-Xa levels may be considered in emergencies (e.g., when timing of last dose is unknown or if overdosing is suspected) or in specific circumstances (e.g., coadministration with cancer therapies with uncertain pharmacokinetic interactions or in underweight patients <50 kg) under the guidance of a coagulation expert (3).

GASTROINTESTINAL MALIGNANCIES.

High-risk bleeding is a major concern when initiating anticoagulation in cancer patients. DOACs are incompletely absorbed upon ingestion (65) and may have direct topical anticoagulant effects during gastrointestinal transit (66). Indeed, early gastrointestinal or genitourinary bleeding after DOAC initiation should prompt clinicians to pursue routine interrogation of these bleeding sites for occult cancer (66). Edoxaban (60/ 30 mg) had a higher rate of gastrointestinal bleeding than warfarin in Hokusai VTE Cancer (30), a signal that was also seen with rivaroxaban, dabigatran 150 mg, and edoxaban 60/30 mg in their respective large phase III trials in patients with AF (67). However, the rates of gastrointestinal bleeding with dabigatran 110 mg and apixaban were similar to that of warfarin in RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) and ARISTOTLE (67), respectively, whereas gastrointestinal bleeding was significantly reduced with the 30/15 mg regimen of edoxaban compared with warfarin in ENGAGE AF-TIMI 48 (67). Regimens that do not increase gastrointestinal bleeding risk may be preferred in high-

risk cancer patients, although evidence is lacking in advanced gastrointestinal malignancies, and neither the lower-dose edoxaban regimen of 30/15 mg once daily (globally) nor dabigatran 110 mg twice daily (in the United States) are approved for stroke prevention in AF. PRIORITY (A Randomized Phase II Study to Compare the Safety and Efficacy of Dalteparin vs. Rivaroxaban for Cancer-associated Venous Thromboembolism) (NCT03139487) is an open-label, multicenter, phase II study comparing rivaroxaban versus dalteparin in treatment of acute VTE in patients with advanced upper gastrointestinal, hepatobiliary, and pancreatic cancers with a primary outcome of clinically-relevant bleeding. In addition, in cancer patients with gastrectomy or small bowel resections, absorption of DOACs may be affected.

INTRACRANIAL METASTASES.

Intracranial hemorrhage (ICH) is the most feared complication of anticoagulation. A retrospective study of 293 patients with brain metastases showed no increased risk of ICH in patients receiving therapeutic doses of LWMH versus no anticoagulation at 1 year (68); however, generalizability of this experience to all cancer types is uncertain. Therapeutic anticoagulation in patients with known brain metastases is not contraindicated according to several professional societies (53,54); however, it is generally avoided if attendant hemorrhage is present. Although no definitive guidance is provided for DOACs, a ~50% reduction in ICH compared with VKAs in broader populations (67) suggests that they may be a reasonable option in the setting of brain metastases. Now that reversal agents are available for DOACs, and since these drugs have rapid onset/offset, trials of DOACs in patients with brain metastases (or primary brain cancer) would be desirable.

THROMBOPROPHYLAXIS OF VTE IN CANCER PATIENTS

Because of the increased risk of VTE in cancer patients, especially during hospitalization (69) and in those undergoing oncologic surgery or receiving ambulatory chemotherapy, thromboprophylaxis for primary prevention of VTE has been an important clinical and research focus. In the ENOXACAN (Enoxaparin and Cancer) II study, extended-duration (1-month) thromboprophylaxis with enoxaparin significantly reduced VTE risk in patients undergoing laparotomy for abdominal or pelvic malignancy (70). Extended post-discharge thromboprophylaxis with LMWH or DOACs for acutely ill medical patients (including cancer) decreases recurrent VTE, but at the expense of potentially increased bleeding risks (71). Betrixaban, a once daily oral factor Xa inhibitor, was recently approved for this indication (72).

Dedicated risk scores have been developed to identify patients who are at heightened risk for cancer-related VTE (73). Two recent trials evaluated the use of DOACs as thromboprophylaxis in at-risk ambulatory patients (defined as Khorana scores ≥2) initiating systemic cancer treatment. In the CASSINI (A Study to Evaluate the Efficacy and Safety of Rivaroxaban Venous Thromboembolism [VTE] Prophylaxis in Ambulatory Cancer Participants) trial (74), 841 patients were randomized to lower-dose rivaroxaban 10 mg once daily versus placebo for 180 days. Rates of the composite VTE or VTE-related death (6.0% vs. 8.8%; p = 0.10) and of major bleeding (2.0% vs. 1.0%; p = 0.27) were similar between

rivaroxaban and placebo, respectively. In AVERT (Apixaban to Prevent Venous Thromboembolism in Patients with Cancer) (75), 574 patients randomized to lower-dose apixaban 2.5 mg twice daily or placebo were followed for 6 months. Apixaban significantly reduced composite VTE events (4.2% vs. 10.2%; $p < 0.001$), but significantly increased rates of major bleeding (3.5% vs. 1.8%; $p = 0.046$) compared with placebo. Taken together, these trials validate the use of the Khorana score, a 6-point score incorporating cancer type, blood counts, and body mass index, in identifying patients at risk for venous and arterial thrombotic events. Ambulatory patients undergoing chemotherapy with intermediate-to-high VTE risk (Khorana scores ≥2) who are at low bleeding risk should be considered for thromboprophylaxis with DOACs (Central Illustration).

HOW LONG SHOULD CANCER-ASSOCIATED VTE BE TREATED?

Data for therapeutic anticoagulation in the treatment of cancer-associated VTE beyond 6 months are limited (76,77), but suggest that LMWH therapy up to 12 months is generally safe. However, in practice, therapeutic anticoagulation is often continued in high-risk patients (e.g., widely metastatic disease and ongoing chemotherapy). In broader cohorts, “step-down” extended-duration treatment with lower-intensity DOACs after initial therapy for acute VTE has been shown to significantly decrease risk of recurrent VTE without associated increased risk of bleeding (78); this approach may be appropriate in select cancer patients.

PERSONALIZED ASSESSMENT OF THROMBOSIS RISK IN THE ERA OF PRECISION ONCOLOGY

The introduction of novel targeted cancer therapies has had diverse and unique adverse cardiovascular effects (23). In the future, a personalized approach is needed for preventative and therapeutic anticoagulation approaches in cancer patients. Recent trials have supported the use of personalized VTE risk score scores (e.g., Khorana score) and tailored anticoagulation management by cancer type (e.g., cautious DOAC use in intraluminal gastrointestinal cancers).

PATIENT AND PROVIDER PREFERENCES RELATED TO ANTICOAGULANT CHOICE

Ultimately, multidisciplinary care that accounts for individualized risk factors, patient preferences, and periodic clinical reassessment is warranted to identify the optimal anticoagulation regimen (Central Illustration). The acute phase of VTE (79) and major complications of AF (80) negatively affect quality of life. LMWH (in VTE) (81) and long-term oral anticoagulation (in AF) (82) are viewed as a necessary and acceptable trade-offs to prevent thrombotic complications; minimal interference with cancer treatment is a major priority among cancer patients (83). In current practice, approximately one-half of patients with cancer-associated VTE receive warfarin, 40% receive LMWH, and a minority receive DOACs (84). Similarly, 15% of patients with AF and cancer are prescribed DOACs (vs. VKA) in current practice (85); early cardiology involvement has been associated with higher

prescription fill rates (86). Given the high financial burden of global cancer care, cost-effectiveness analyses to compare anticoagulation strategies would be desirable.

SUMMARY AND FUTURE DIRECTIONS

Anticoagulation management of cancer patients should be determined with longitudinal multidisciplinary follow-up with frequent clinical reassessment. Ongoing RCTs will further our understanding of the optimal antithrombotic approach to management of VTE and AF in patients with cancer. Future studies are needed to address challenges unique to cancer patients, including use in CVC-associated thrombosis, safety and efficacy in underweight patients, protocols for thrombocytopenia, and use in malignancies with potential for high-risk bleeding (e.g., brain metastases, luminal gastrointestinal cancers). It is likely that anticoagulation decisions in cancer patients will remain highly individualized even as high-quality clinical data amount, given variation in patient preferences, thrombotic and bleeding risk factors, and disease activity. Nonetheless, DOACs represent a convenient and patient-centric anticoagulation strategy with emerging data supporting their safety and efficacy in the care of cancer patients.

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ABBREVIATIONS AND ACRONYMS

AF	atrial fibrillation
CVC	central venous catheter
DOAC	direct oral anticoagulant agent
LMWH	low-molecular weight heparins
RCT	randomized clinical trial
VTE	venous thromboembolism

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HIGHLIGHTS

- Patients with active cancer face higher risks of arterial and venous thromboembolism (VTE), atrial arrhythmias, and bleeding events.
- Historically, in patients with cancer, low-molecular weight heparins have been preferred for treatment of VTE, while warfarin has been the standard anticoagulant for stroke prevention in atrial fibrillation.
- Select direct oral anticoagulants have now been shown to safely prevent thrombotic events in recent clinical trials, and present an attractive oral dosing option for patients with cancer.
- Multidisciplinary care that accounts for individualized bleeding and thrombotic risks, drug-drug interactions, patient preferences, and periodic clinical reassessment is warranted to identify the optimal anticoagulation strategy for patients with cancer.

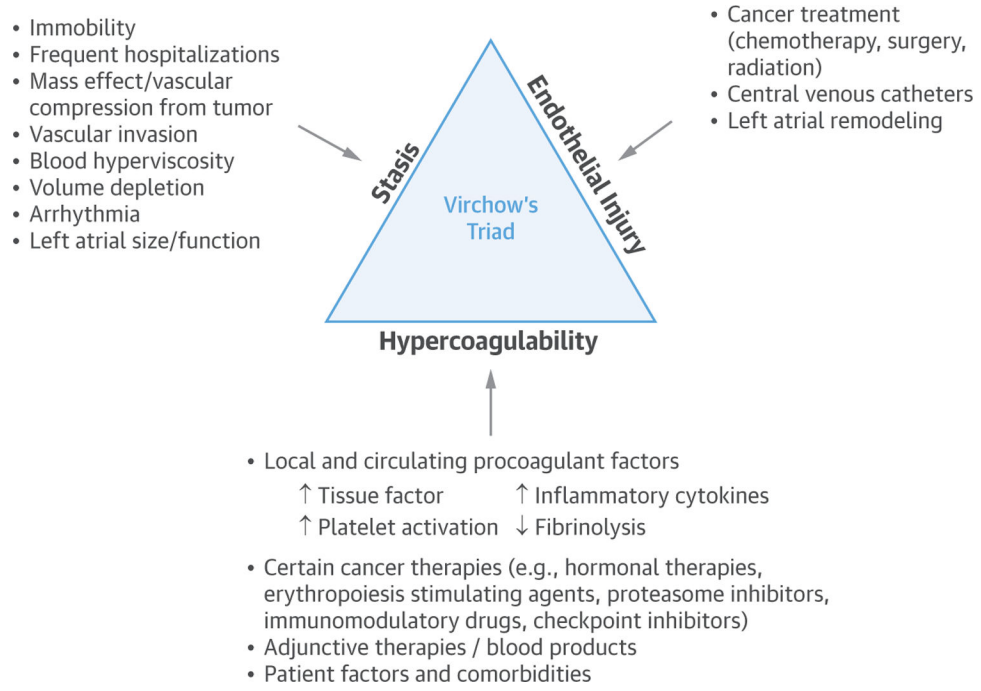
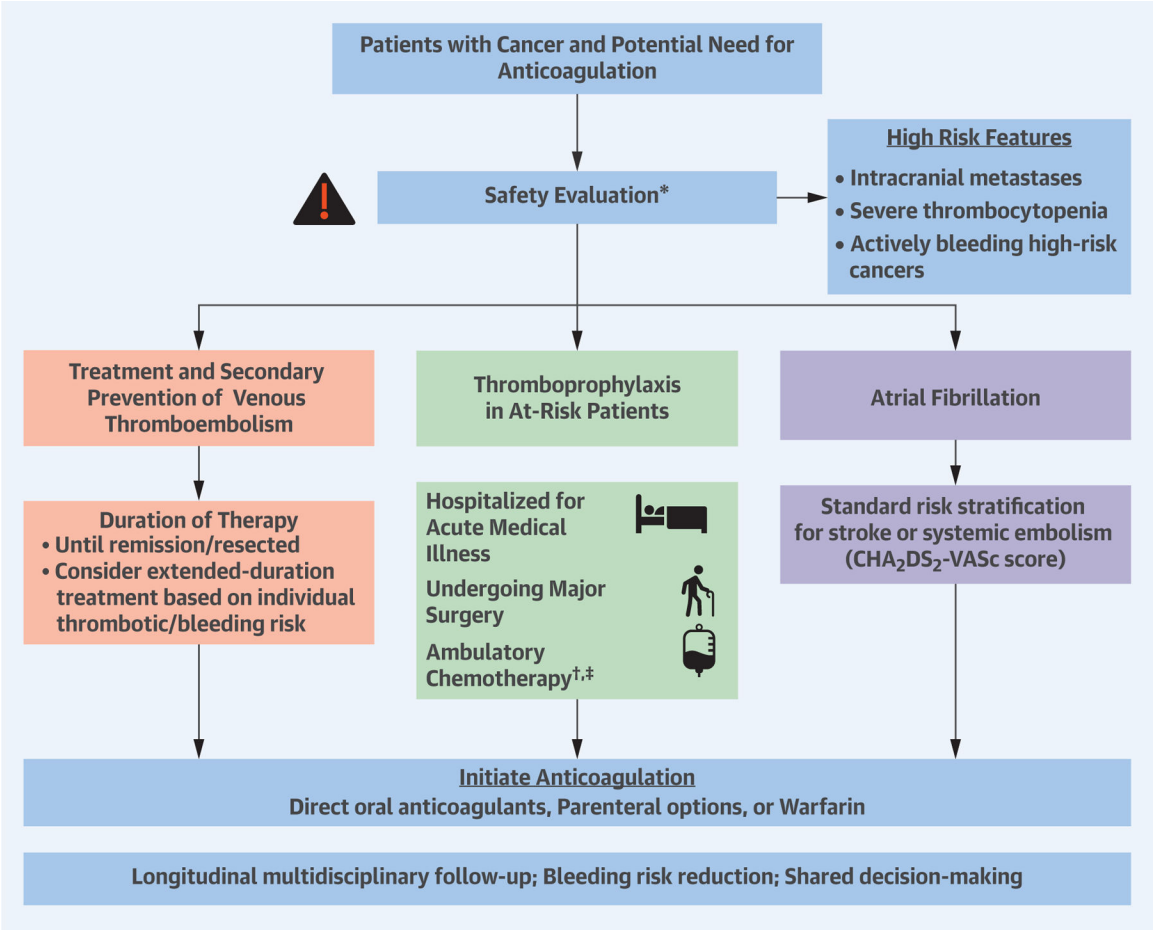


FIGURE 1. Factors Contributing to Increased Thrombotic Risks in Cancer

Three components of Virchow's Triad (stasis, endothelial injury, and hypercoagulability) intersect and contribute to excess cancer-associated thrombotic risks.



CENTRAL ILLUSTRATION. Approach to Anticoagulation in Patients With Active Cancer

*For all patients, measure safety laboratory studies, assess potential drug–drug interactions, determine individual patient bleeding risks and preferences, and use bleeding reduction strategies. †Patients with multiple myeloma receiving thalidomide or lenalidomide-based regimens with chemotherapy and/or dexamethasone should receive thromboprophylaxis with aspirin or low molecular weight heparins (LMWH) for low-risk patients and LMWH for high-risk patients. ‡The Khorana score (21) is a validated risk score to assess thrombotic risk among ambulatory patients with cancer. The score ranges from 0 to 6 and is based on site of cancer (2 points for stomach, pancreas; 1 point for lung, lymphoma, gynecological, genitourinary excluding prostate), 1 point for platelet counts ≥350,000 per mm^3, 1 point for leukocyte count ≥11,000 per mm^3, 1 point for hemoglobin <10 g/dl or use of erythropoiesis-stimulating agents, and 1 point for body mass index ≥35 kg/m^2. Khorana scores ≥2 identify patients at intermediate-to-high risk for venous thromboembolism who may benefit from thromboprophylaxis with direct oral anticoagulants.

TABLE 1

Select Cancers Associated With Thrombotic Adverse Events

	Cancers	Unique Phenotypes and Select Examples	Thrombotic Presentations
Very high risk	Pancreas thrombosis	—	Migratory thrombophlebitis; Portal vein
	Stomach	—	Migratory thrombophlebitis
	Metastatic		
High risk	Gynecological	Clear cell carcinoma	Pelvic venous obstruction
	Lung	Mucinous adenocarcinoma	
	Brain	High-grade gliomas	↑ Post-operative venous thromboses
	Hematological	Multiple myeloma; high-grade/bulky lymphomas	
	Genitourinary (excluding prostate)	Renal cell carcinoma	Renal vein and caval tumor invasion and thrombosis
Modest risk	Breast	Highly prevalent, with modest/low thrombotic risks	
	Prostate		
	Colon		

Thrombotic risk categories were adapted from the validated Khorana score (21). Deep vein thrombosis and pulmonary embolism are the most frequent thrombotic events experienced by patients with cancer, but we highlight other, unique thrombotic presentations relevant to specific cancer types.

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TABLE 2

Select Cancer Therapies Associated With Atrial Arrhythmias and Thrombotic Adverse Events

Class	Anti-Cancer Mechanism	Select Drug Examples	Mechanism of Cardiovascular Toxicity
Cancer therapies associated with atrial arrhythmias			
Anthracyclines	Inhibition of DNA/RNA synthesis via topoisomerase inhibition	Doxorubicin	? Direct cardiotoxicity
		Daunorubicin	
		Idarubicin	
		Epirubicin	
Alkylating agents	Inhibition of DNA/RNA synthesis via formation of carbonium ions	Melphalan	Unknown
Anti-metabolites	Inhibition of DNA/RNA synthesis via acting as a pyrimidine analog	Fluorouracil	? Ischemia
Interleukins	Immunotherapy	Il-2	Inflammation
Bruton's tyrosine kinase TKIs	Inhibition of Bruton's tyrosine kinase	Ibrutinib	? Direct kinase inhibition
		Acalabrutinib	
Immune checkpoint inhibitors	Activation of immune system	Ipilimumab	Cardiac inflammation; myocarditis, pericarditis, vasculitis
		Nivolumab	
		Pembrolizumab	
Cancer therapies associated with venous/arterial thrombotic risk			
Platinum-based	Inhibition of DNA synthesis via formation of DNA cross-links	Cisplatin	Unknown
Hormonal therapy	Inhibition of estrogen signaling (activated in breast cancer)	Tamoxifen	Unknown
Anti-VEGF therapy	Inhibition of angiogenesis (may include either biologics or small molecule TKIs)	Bevacizumab	Endothelial damage; ? thrombotic microangiopathy
		Sunitinib	
		Pazopanib	
BCR-ABL TKI	Inhibition of ABL1 kinase (activated in certain leukemias)	Nilotinib	Endothelial damage
		Ponatinib	
Immunomodulators	Activation of protein degradation (specifically transcription factors activated in B-cell cancer types)	Thalidomide	Unknown
		Lenalidomide	
		Pomalidomide	
Proteasome inhibitors	Inhibition of protein degradation machinery	Carfilzomib	Unknown

DNA = deoxyribonucleic acid; IL = interleukin; RNA = ribonucleic acid; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

TABLE 3

Available Dedicated Trials or Subsets of Landmark Phase III Trials Evaluating DOACs in Cancer

Trials (Ref. #)	DOAC	Comparator	Duration	Active Cancer Patients	Efficacy Endpoint	Efficacy Endpoint: DOAC vs. VKA HR (95% CI)	
						Active Cancer at Enrollment	Cancer Diagnosed in Follow-Up
Venous thromboembolism							
Hokusai VTE Cancer (30)	Edoxaban 60 mg once daily	Dalteparin 200 IU/kg daily for 1 month, followed by 150 IU/kg daily	6–12 months	Edoxaban n = 522, Dalteparin n = 524	Recurrent VTE or major bleeding	0.97 (0.70–1.36)	N/A
Select-D™ Pilot (31)	Rivaroxaban 15 mg twice daily for 21 days, followed by 20 mg once daily	Dalteparin 200 IU/kg daily for 1 month, followed by 150 IU/kg daily	6 months	Rivaroxaban n = 203, Dalteparin n = 203	Recurrent VTE	0.43 (0.19–0.99)	N/A
RE-COVER I, II (35)	Dabigatran 150 mg twice daily	Warfarin INR 2–3	6 months	Dabigatran n = 173, Warfarin n = 162	Symptomatic recurrent VTE or VTE-related death	0.74 (0.20–2.70)	0.63 (0.20–2.0)
EINSTEIN PE/DVT (33)	Rivaroxaban 15 mg twice daily for 21 days, followed by 20 mg once daily	Warfarin or acenocoumarol INR 2–3	3, 6, or 12 months	Rivaroxaban n = 354, VKA n = 301	Symptomatic or recurrent VTE	0.62 (0.21–1.79)	0.80 (0.34–1.88)
AMPLIFY (32)	Apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily	Warfarin INR 2–3	6 months	Apixaban n = 88, Warfarin n = 81	VTE/VTE-related death	0.74 (0.20–2.70)	0.63 (0.20–2.0)
Hokusai-VTE (34)	Edoxaban 60 mg once daily	Warfarin INR 2–3	3–12 months	Edoxaban n = 109, Warfarin n = 99	Recurrent DVT, fatal or nonfatal PE	0.55 (0.16–1.51)	0.73 (0.36–1.49)
Atrial fibrillation							
ENGAGE AF-TIMI 48 (39)	Edoxaban once daily	Warfarin INR 2–3	Median follow-up 2.8 years	Edoxaban n = 758, Warfarin n = 395	Stroke or systemic embolic event	N/A	0.60 (0.31–1.15) *
ARISTOTLE (40)	Apixaban 5mg twice daily	Warfarin INR 2–3	Median follow-up 1.8 years	Apixaban n = 76, Warfarin n = 81	Stroke or systemic embolic event	0 vs. 3.3 events per 100 patient-yrs	—

* Higher-dose edoxaban regimen (60/30 mg) vs. warfarin.

AMPLIFY = Apixaban for the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis as First-Line Therapy; ARISTOTLE = Apixaban for Reduction in STroke and Other ThromboemboLic Events in atrial fibrillation; CI = confidence interval; DOAC = direct oral anticoagulants; DVT = deep vein thrombosis; EINSTEIN DVT = Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients with Acute Symptomatic Deep-Vein Thrombosis; EINSTEIN PE = Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients with Acute Symptomatic Pulmonary Embolism; Effective Anticoagulation with factor Xa next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction study 48; Hokusai-VTE = Comparative Investigation of Low Molecular Weight (LMW) Heparin/Edoxaban Versus Heparin/Warfarin in the Treatment of Symptomatic Deep-Vein Blood Clots and/or Lung Blood Clots; HR = hazard ratio; INR = international normalized ratio; PE = pulmonary embolism; RE-COVER = Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism; VKA = vitamin K antagonist.

TABLE 4

Recently Completed or Ongoing DOAC Versus LMWH in VTE Treatment Studies in Patients With Cancer

Trial	Estimated Sample Size	Planned Date of Study Completion	Phase	DOAC	Comparator	Primary Outcome
CONKO-11, NCT02583191	450	December 2018	Phase III	Rivaroxaban	LMWH	Patient-reported treatment satisfaction with rivaroxaban
CASTA-DIVA, NCT02746185	200	April 2018	Phase III	Rivaroxaban	LMWH	Symptomatic DVT, symptomatic PE, unsuspected DVT/PE, worsening pulmonary or venous obstruction within 3 months
PRIORITY, NCT03139487	176	May 2020	Phase II	Rivaroxaban	Dalteparin	Clinically relevant bleeding, interruption or discontinuation of anticoagulation, associated pain, or impairment of activities of daily living
CARAVAGGIO, NCT03045406	1,168	June 2019	Phase III	Apixaban	Dalteparin	Objectively confirmed recurrent VTE
ADAM VTE, NCT02585713	300	November 2018	Phase IV	Apixaban	LMWH	Major bleeding
COSIMO, NCT02742623	500	March 2019	Observational	Noninterventional, patients treated with standard LMWH/VKA for 4 weeks after index VTE, followed by switch to rivaroxaban		Patient-reported satisfaction with regards to use of rivaroxaban and perception of recurrent DVT/PE
CANVAS, NCT02744092	940	September 2019	Interventional; phase not specified	Dabigatran, rivaroxaban, apixaban, or edoxaban	LMWH	Cumulative VTE recurrence

ADAM VTE = Apixaban or Dalteparin in Reducing Blood Clots in Patients with Cancer Related Venous Thromboembolism; CANVAS = Direct Oral Anticoagulants versus LMWH Warfarin for VTE in Cancer; CARRAVAGIO = Apixaban for the Treatment of Venous Thromboembolism in Patients with Cancer; CASTA-DIVA = Cancer Associated Thrombosis, a Pilot Treatment Study using Rivaroxaban; CONKO-11 = Rivaroxaban in the Treatment of Venous Thromboembolism in Cancer Patients; COSIMO = Cancer-associated ThrOmboSIs - Patient-reported OutcoMes with RivarOxaban; DOAC = direct oral anticoagulants; DVT = deep vein thrombosis; LMWH = low-molecular weight heparins; PE = pulmonary embolism; VTE = venous thromboembolism.

TABLE 5

Anticipated Drug–Drug Interactions Between Common Anticancer Drug Classes and DOACs

	P-Glycoprotein Interaction (All DOACs Affected)	CYP3A4 Interaction (Strongly Affects Rivaroxaban and Apixaban)
Inhibition	• Immune-modulating agents (e.g., tacrolimus; strong to moderate to competition to none) • Tyrosine kinase inhibitors (e.g., imatinib; strong to moderate to competition to none) • Hormonal agents (e.g., abiraterone; strong to competition to none)	• Immune modulating agents (e.g., cyclosporine; moderate to mild to competition) • Tyrosine kinase inhibitors (e.g., nilotinib; moderate to mild to competition) • Hormonal agents (e.g., bicalutamide; moderate to mild to competition to none) • Topoisomerase inhibitors (e.g., etoposide; mild to competition to none) • Anthracyclines (e.g., idarubicin; mild to competition to none) • Alkylating agents (e.g., cyclophosphamide; mild to competition to none)
Induction	• Anthracyclines (e.g., doxorubicin; strong to competition to none) • Antimitotic agents (e.g., vinblastine; strong to competition) • Immune-modulating agents (e.g., dexamethasone; strong to competition to none)	• Immune-modulating agents (e.g., dexamethasone; strong to moderate to competition) • Antimitotic agents (e.g., paclitaxel; moderate to mild to competition) • Tyrosine kinase inhibitors (e.g., vemurafenib; moderate to competition) • Hormonal agents (e.g., enzalutamide; strong to competition to none)
Minimal to no Interaction	• Alkylating agents (e.g., bendamustine; competition to none) • Antimetabolites (e.g., methotrexate; competition to none) • Monoclonal antibodies (e.g., rituximab; none) • Platinum based agents (e.g., cisplatin; none) • Intercalating agents (e.g., bleomycin; none)	• Monoclonal antibodies (e.g., brentuximab; competition to none) • Antimetabolites (e.g., pemetrexed; none) • Platinum based agents (e.g., oxaliplatin; none) • Intercalating agents (e.g., mitomycin C; none)

Anticipated interactions are offered within anticancer drug classes as no interaction, competition, or potential interaction (mild, moderate, or strong). Intraclass differences exist in inhibition/induction and presence and strength of interaction. Table 4 of the 2018 European Heart Rhythm Association practical guide (3) offers more detailed drug–drug interactions and anticipated effects on DOAC drug levels.

CYP3A4 = Cytochrome P450 3A4; DOAC = direct oral anticoagulants.

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TABLE 6

Summary of Guidelines for Anticoagulation in Cancer

	EHRA 2018	ITAC-CME 2016	ASCO 2015	ACCP 2016	ISTH 2018	NCCN 2018
VTE prophylaxis						
Acute VTE treatment		LMWH, UFH or fondaparinux for initial treatment; LMWH for at least 3 months	LMWH preferred over VKA for at least 6 months	LMWH preferred over VKA and DOACs, treat >3 months in active cancer	If low bleeding risk and no DDIs, DOACs preferred. If high bleeding risk (especially GI/ GU), LMWH preferred.	LMWH for first 6 months in proximal DVT or PE Edoxaban with initial parenteral dosing with LMWH
DOACs			Not recommended	LMWH preferred	Select DOACs (edoxaban and rivaroxaban are the only ones directly compared with LMWH thus far) preferred in low-bleeding risk, acute VTE	Edoxaban with initial parenteral dosing with LMWH or UFH Apixaban and rivaroxaban are considered other alternatives in patients who have reasons to avoid LMWH
IVC filters		Contraindication to anticoagulation or recurrence on treatment	Contraindication to anticoagulation or progression on LMWH			Contraindication to anticoagulation in proximal DVT or PE, or poor cardiopulmonary reserve
Catheter-associated thrombosis		Anticoagulation for 3 months using LMWH				Anticoagulation for >3 months or as long as catheter is in place
Brain metastases		Not a contraindication for anticoagulation	Anticoagulation recommended for VTE in primary CNS malignancies as in other cancers			
Atrial fibrillation	No demonstrated efficacy of LMWH in thromboprophylaxis; further data required for DOACs; close examination of DDIs					

ACCP = American College of Chest Physicians; ASCO = American Society of Clinical Oncology; CNS = central nervous system; DDI = drug-drug interactions; DOACs = direct oral anticoagulants; DVT = deep vein thrombosis; EHRA = European Heart Rhythm Association; GI = gastrointestinal; GU = genitourinary; ISTH = International Society on Thrombosis and Haemostasis; ITAC-CME = International Initiative on Thrombosis and Cancer; LMWH = low-molecular weight heparins; NCCN = National Comprehensive Cancer Network; PE = pulmonary embolism; UFH = unfractionated heparin; VKA = vitamin K antagonist.