Bleeding in cancer: epidemiological aspects

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ABSTRACT

Cancer is accompanied with significant changes in hemostasis caused by both the underlying malignancy and its treatment, which increases the risk of thrombotic and bleeding consequences. While cancer-related thrombosis has been extensively studied, bleeding remains relatively unexplored, despite its major contribution to morbidity and mortality in this population. The epidemiology of bleeding in cancer patients is complicated and difficult to assess. Multiple linked factors influence risk, such as tumor kind, disease stage, treatment modalities, patient clinical context, and concomitant diseases. Furthermore, bleeding risk varies over time, reflecting dynamic changes in tumor load, treatment approaches, and host variables. As a result, estimates of incidence and prevalence vary greatly depending on the population investigated, the date of cancer diagnosis, and the bleeding definitions used. The type and dosage of anticoagulant medication may also influence this risk. These problems underline the importance of a more holistic approach to bleeding in cancer care. Bleeding prevention should be prioritized in future cancer-related venous thromboembolism management regimens. To lower the clinical burden of cancer and enhance patient outcomes, we must advance our understanding of bleeding epidemiology.

Key words: cancer; hemorrhage; neoplasms; anticoagulants; epidemiology.

Introduction

Cancer is associated with alterations in normal hemostasis through a variety of diverse mechanisms, both related to the underlying disease and its treatment.[1] These alterations lead to an increased risk of both thrombotic and bleeding complications.

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While much research has been dedicated to the field of cancer-associated thrombosis, the focus on bleeding has lagged. Bleeding complications in cancer are clinically important with adverse morbidity and mortality outcomes.[1] However, the risk of bleeding in persons with cancer can be difficult to quantify, as many factors, including cancer type, treatment regimen, patient setting, and medical comorbidities contribute to the risk.[2] In addition, risk is dynamic, changing over time as changes to cancer burden, cancer therapy, and hot factors change. As such, the overall incidence and prevalence of bleeding among cancer patients varies based on the population examined, the timing of the population in relation to cancer diagnosis, and the definition of bleeding used. Furthermore, the risk may vary based on exposure to and dose of anticoagulant therapy.

Definitions of bleeding in cancer

Most evidence categorizes bleeding into major bleeding (MB), clinically relevant non-major bleeding (CRNMB), and clinically relevant bleeding (CRB) with clinically relevant bleeding being a combination of major bleeding and clinically relevant non-major bleeding. Table 1 summarizes common definitions for bleeding in cancer.

Incidence and prevalence

Absence of anticoagulant therapy

Clinical trials

Placebo-controlled primary thromboprophylaxis studies in cancer provide an opportunity to quantify the incidence of bleeding in patients exposed to anticoagulant therapy versus those unexposed. In a systematic review and meta-analysis of the AVERT and CASSINI randomized control trials (RCTs), placebo-controlled trials assessing the efficacy of apixaban and

rivaroxaban respectively, overall bleeding rates were low.[3-5] The incidence of MB in the placebo group was 1.03%, while the incidence of CRNMB was 3.24%.[5] Similar rates were noted in the placebo groups of preceding thromboprophylaxis studies in cancer patient.[6-9]

Cohort studies

The cumulative and real-world incidence of bleeding in patients with cancer not exposed to anticoagulant therapy is higher than that observed in RCTs. In a prospective observational cohort study of 791 patients with both solid and liquid malignancies treated between 2019 and 2022 at the Medical University of Vienna, they found a 12-month cumulative incidence of CRB and MB of 14.4% and 7.0% respectively in patients not exposed to anticoagulant therapy.[10]

Anticoagulant therapy

Clinical trials

Anticoagulation is a major iatrogenic driver of bleeding in cancer. In the systematic review and meta-analysis of the AVERT and CASSINI trials, the incidence of MB while on prophylactic anticoagulant therapy (absence of VTE) group was 2.02%, while the incidence of CRNMB was 4.18%.[5] This population predominately represented a new or recent diagnosis of cancer. This translated to a 2-fold increase in risk of MB (risk ratio [RR] 1.96, 95% confidence interval [CI] 0.80, 4.82) and a 1.3-fold increase in risk of CRNMB (RR 1.28, 95% CI 0.74, 2.20) when compared to patients in trial on placebo, albeit the findings were not statistically significant. Across contemporary cancer-associated VTE randomized trials evaluating full-dose anticoagulant therapy in cancer patients, major bleeding and CRNMB rates of 2-5% and 6-9%, respectively, occurred during the first 6 months of treatment.[11-15] In trials comparing direct oral anticoagulant (DOAC) therapy with low molecular weight heparin (LMWH), MB rates remain broadly similar between the two classes. In a systematic review and meta-analysis comparing treatment of cancer-associated VTE with DOAC *vs* LMWH, there was no significant difference in the 6-month cumulative index of MB (RR 1.17, 95% confidence interval [CI] 0.82, 1.67) between the DOAC *vs* LMWH.[16] However, data favors both higher CRNMB and more gastrointestinal/ genitourinary bleeding in DOAC treated patients,[17] with the same systematic review

Table 1. Definitions of bleeding commonly used in anticoagulation trials in cancer.

Bleeding type	Definition	Correlating trial
International Society of Thrombosis and Haemostasis		
Major bleeding	Fatal bleeding AND/OR Symptomatic bleeding in a critical organ (*e.g.*, intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, intramuscular with compartment syndrome, etc.) AND/OR Bleeding resulting in a fall in hemoglobin ≥2.0 g/dL AND/OR Bleeding leading to transfusion of ≥2 units of packed red blood cells	ADAM VTE CARAVAGGIO* CASTA DIVA HOKUSAISELECT-D
Clinically relevant non-major bleeding	Bleeding that does not meet criteria for major bleeding but meets ≥1 of the following: Requires medical intervention by a healthcare provider AND/OR Leads to hospitalization or an increase in level of care AND/OR Prompts a face-to-face evaluation	ADAM VTE[#] CASTA DIVA[#] HOKUSAI[§] SELECT-D[#§]
National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0		
Major bleeding	CTCAE grade ≥3	CANVAS
Clinically significant bleeding	CTCAE grade 2	CANVAS
Other definitions		
Clinically relevant bleeding	Generally, a combination of major bleeding and clinically relevant non-major bleeding	
CARAVAGGIO clinically relevant non-major bleeding	Bleeding that does not meet criteria for major bleeding but meets ≥1 of the following: ISTH clinically relevant major bleeding AND/OR Bleeding compromising hemodynamics AND/OR Spontaneous hematoma >25 cm^2 or >100 cm^2 in the setting of trauma AND/OR Intramuscular hematoma documented on ultrasound AND/OR Epistaxis or gingival bleeding requiring medical intervention or tamponade AND/OR Bleeding from venipuncture lasting >5 minutes AND/OR Macroscopic hematuria that was spontaneous or lasted >24 hours after a procedure AND/OR Hemoptysis, hematemesis or spontaneous rectal bleeding requiring medical intervention or endoscopy	CARAVAGGIO[#§]

*Also included bleeding necessitating surgical intervention for major bleeding; [#]also included temporary withholding of anticoagulant therapy; [§]also included discomfort or impairment of activities of daily living.

and meta-analysis showing a higher risk of CRNMB with DOAC *vs* LMWH (RR 1.66, 95% CI 1.31, 2.09).[16]

It should be noted that the rates of MB with apixaban (3.8%) in the Caravaggio trial were lower than the rates of MB with edoxaban (6.9%) or rivaroxaban (6.0%) in the HOKUSAI and SELECT-D trials, respectively.[12,14,15] The exact reason for this difference is likely multifactorial and could be due to selection bias due to knowledge gained from proceeding trial results, a true observed effect, and/or differences in the eligible patient population. Argument for a true observed effect comes from the results of the COBRRA trial presented at the International Society of Thrombosis and Haemostasis Annual Meeting 2025.[18] This randomized trial compared anticoagulant therapy with apixaban *vs* rivaroxaban, albeit in non-cancer patients. At three months, CRB occurred in 3% of patients on apixaban *vs* 6.7% of patients on rivaroxaban (odds ratio [OR] 0.44, 95% CI 0.30, 0.63). However, exclusion criteria were more stringent for enrollment in Caravaggio compared to the preceding trials with the thrombocytopenia threshold raised from $50x10^9$/L to $<100x10^9$/L and exclusion of patients with any brain tumor. Direct comparison studies in cancer could clarify the true effect.

Cohort studies

Major bleeding rate estimates are higher in cohort studies compared to randomized control trials. In the RIETE registry, rates of MB approached that of the randomized trials within only 3 months of start of anticoagulant therapy (MB 4.2%).[19] In the Vienna prospective observational study, the 12-month cumulative incidence of CRB and MB was 16.0% and 12.8% respectively. Compared to patients not receiving anticoagulant therapy, those on therapy had a 20% higher risk of bleeding (CRB subdistribution hazard ratio [sHR] 1.16, 95% CI 0.82, 1.65; MB sHR 1.19, 95% CI 0.94, 1.50).[10]

Extended anticoagulant therapy

Because many patients with active cancer require anticoagulant therapy beyond 6 months, dose-reduction strategies have been evaluated to improve the safety margin without sacrificing efficacy.[20,21] In the API-CAT trial, extended therapy with reduced-dose apixaban (2.5 mg twice daily) for 12 months after completion of ≥6 months of anticoagulation was noninferior to full-dose apixaban (5 mg twice daily) for recurrent VTE and was associated with less CRB (12.1% *vs* 15.6%).[21] Overall, these results show that bleeding is more common in cancer patients exposed to anticoagulant therapy with high rates persisting on long term therapy.

Rate differences in randomized trials versus *cohort studies*

Importantly, rates of bleeding are consistently lower in randomized trials compared to those in cohort studies as demonstrated above (Table 2). This discrepancy provides evidence for potential risk factors for bleeding in cancer. The major differences between the populations studies are demonstrated by those excluded from participation in randomized studies (e.g., severe thrombocytopenia, active luminal lesions, brain tumors, kidney disease, liver disease, etc.).[22-24] Populations uniformly excluded from participation in the key randomized studies for cancer-associated thrombosis have demonstrated increased risk for anticoagulant-related bleeding in cancer and include the following.[25,26] Patients with thrombocytopenia defined as a platelet count of $<50x10^9$/L were excluded from all randomized

Table 2. Rates of bleeding in cancer based on antithrombotic therapy exposure.

Antithrombotic exposure	Randomized control trial data	Reference	Cohort study data	Reference
No anticoagulant therapy	6-mo CI: MB 1.03%; CRNMB 3.24%	5	12-mo CI: MB 7.4%; CRB* 15.0%	10
Anticoagulant therapy, reduced dose, primary prophylaxis of VTE[#]	6-mo CI: MB 2.02%; CRNMB 4.18%	5		
Anticoagulant therapy, full dose, primary treatment of VTE[§]	6-mo CI: MB 4.01%; CRNMB 7.64%	16	3-mo: MB 4.2%	19
Anticoagulant therapy, full dose, secondary prophylaxis of VTE (beyond 6-mo after start of anticoagulant therapy)	12-mo: MB 4.3%; CRNMB 12.3%	21	12-mo CI: MB 12.8%; CRB* 16.0%	10
Anticoagulant therapy, reduced dose, secondary prophylaxis of VTE[^] (beyond 6-mo after start of anticoagulant therapy)	12-mo: MB 2.9%; CRNMB 10.0%	21		
Antiplatelet therapy			12-mo CI: MB 8.8%; CRB* 17.5%	10
Dual antiplatelet therapy	12-mo: MB 8.1%	33		10
Dual pathway inhibition			12-mo CI: MB 9.3%; CRB* 22.5%	

CI, confidence interval; CRB, clinically relevant bleeding; CRNMB, clinically relevant non-major bleeding; MB, major bleeding; mo, month; VTE, venous thromboembolism. *CRB, a combination of MB and CRNMB; [#]reduced dose, primary prophylaxis – refers to treatment intended to prevent VTE in cancer with anticoagulant therapy administered at doses lower than treatment intent (*e.g.*, apixaban 2.5 mg by mouth twice daily, rivaroxaban 10mg by mouth once daily, dalteparin 5000 units subcutaneously daily, etc.); [§]full dose, primary treatment of VTE; [^]reduced dose, secondary prophylaxis – refers to treatment intended to prevent recurrent VTE after completion of a primary treatment phase of therapy (*i.e.*, apixaban 2.5 mg by mouth twice daily, rivaroxaban 10mg by mouth once daily).

studies,[14,27-29] with Caravaggio and SELECT-D increasing the cutoff for exclusion to <75x10^9/L and <100x10^9/L, respectively.[12,15] Similar, these studies excluded patients with an indication to remain on antiplatelet therapy. Aside from the CANVAS trial which permitted a creatinine clearance as low as 15ml/min,[28] all other studies excluded patients with a creatinine clearance of <30ml/min.[12,14,15,27,29] All studies excluded patients with a poor performance status as defined by the Eastern Cooperative Oncology Group scale of 3-4 as well as with severe liver disease (i.e., cirrhosis),[12,14,15,27,29] aside from CANVAS which did not specify either.[28] As such, attention to the patient population of any study reporting anticoagulant-related bleeding in cancer warrants close attention and consideration.

Antiplatelet therapy

Data on antiplatelet-associated bleeding in unselected cancer populations remain limited. Available evidence suggests that aspirin monotherapy is generally well tolerated, with a modest increase in bleeding and no clear signal for increased fatal bleeding.[30] Indirect support comes from thromboprophylaxis studies in multiple myeloma patients receiving immunomodulatory agents and from small series of patients with hematologic malignancy–associated thrombocytopenia presenting with myocardial infarction, in which absolute bleeding rates on aspirin appear low.[31,32] In contrast, dual antiplatelet therapy (DAPT) in cancer, particularly after PCI, carries a clinically meaningful bleeding burden. Despite systematic undertreatment of cancer patients in routine cardiovascular practice, observational comparisons of similar DAPT regimens (e.g., aspirin plus clopidogrel) suggest that cancer is associated with a 1.5-2-fold relative increase in MB, with 1-year MB rates often ~5-10% in cancer *vs* ~3-5% in non-cancer cohorts.[33-35] Within cancer subgroups, bleeding risk appears to be further stratified by cancer activity, ongoing systemic therapy, and likely tumor site.[36,37]

Dual pathway inhibition (combination anticoagulant and antiplatelet therapy)

When antiplatelet agents are combined with therapeutic anticoagulation, bleeding risk increases substantially, although cancer-specific estimates are sparse.[38] A *post-hoc* analysis of the AVERT trial (reported as an ASH oral abstract in 2025) found that concomitant antiplatelet therapy or NSAID use among cancer patients receiving apixaban thromboprophylaxis was associated with higher CRB (HR 1.78, 95% CI 1.13, 2.78) and clinically relevant non major bleeding (CRNMB) (HR 1.98, 95% CI 1.19, 3.30), without a statistically significant reduction in VTE (HR 0.60, 95% CI 0.26, 1.39).[39] In our previously published analysis of a VA cohort of cancer-associated VTE, antiplatelet prescriptions were associated with anticoagulant-related bleeding in univariate analyses but not after multivariable adjustment.[26] In a retrospective study of patients with cancer-associated VTE, concurrent treatment with anticoagulant therapy plus low dose aspirin resulted in higher rates of MB of 12.3% *vs* 5.4% (HR 2.45, 95% CI 1.65, 3.63).[40] Taken together, these data support active reassessment of antiplatelet indications when initiating anticoagulation in patients with cancer. A description of how these factors interplay with bleeding risk is detailed below in the section *Risk Factors for Bleeding in Cancer*.

Healthcare burden and morbidity

The HOKUSAI RCT, which randomized patients with cancer-associated venous thromboembolism (VTE) to treatment with edoxaban *vs* dalteparin, quantified the morbidity of bleeding events during study participation.[41,14] Of patients with a MB event, 68.8% required admission to the hospital (most to the intensive care unit, 90.9% of admissions), 62.5% required transfusion with red blood cells (RBCs), 20.8% required a procedure related to the bleeding episode, and finally, the bleeding episode led to an interruption in cancer-directed therapy in 27.1% of patients. While lower, CRNMB episodes still carried a high rate of adverse outcomes with 26.7% required admission to the hospital, 38.4% required RBC transfusion, 40.7% requiring a procedure, and 14% having interruption in their cancer-directed therapy.

While less is reported on the morbidity of bleeding in patients with cancer not on anticoagulant therapy, the distribution of bleeding events is similar, causing speculation that morbid consequences are also similar. In the Vienna observational study, intracranial hemorrhage (ICH), gastrointestinal (GI), and genitourinary (GU) represented the most common sites of bleeding in patients exposed *vs* unexposed to anticoagulant therapy (exposed 14.8%, 70.4%, 3.7% respectively; unexposed 9.3%, 53.5%, 7.0%, respectively).[10] However, it is worthwhile to note that fatal bleeding events were higher in those not exposed to anticoagulant therapy in this study, 13.9% *vs* 3.7%. More work is required to better understand the burden of bleeding in cancer patients not on anticoagulant therapy.

Bleeding and mortality

Quantifying the causal contribution of bleeding to mortality is methodologically difficult, particularly in cohorts with thrombosis, because bleeding risk and bleeding-related death are confounded by tumor type, stage, treatment intensity, and comorbidity burden, and because death from progressive cancer and recurrent VTE represent strong competing risks. Moreover, bleeding events can trigger a clinically important downstream cascade including the interruption or discontinuation of anticoagulation and systemic anticancer therapy, each of which may increase the risks of recurrent VTE and cancer-related death. While cause cannot be determined from retrospective studies, multiple cohort studies consistently demonstrate an association between CRB and subsequent mortality in cancer after adjusting for known confounders. In a prospective cohort of patients initiating systemic therapy, the 12-month cumulative incidence of first CRB was 16.6%; seven events (5.0%) were fatal, including six in patients not receiving anticoagulation, underscoring that tumor- and host-related bleeding risk is clinically important even in the absence of antithrombotic therapy.[10] Overall CRB was associated with markedly higher all-cause mortality (HR 5.80; 95% CI 4.53, 7.43). Similar findings have been reported in specific cancer cohorts (e.g., lung cancer) using time-varying exposure models and accounting for competing mortality.[42,43] In our na-

tionwide VA analyses of patients with cancer-associated VTE, bleeding was independently associated with higher 12-month all-cause mortality in both solid and hematologic malignancies (HR 2.91, 95% CI 2.48, 3.42; and HR 3.26, 95% CI 1.96, 5.45, respectively).[44,45] The prognostic impact is heterogeneous by bleeding site and severity as we observed the strongest association with mortality after intracranial hemorrhage (~six-fold higher) and a substantial increase after gastrointestinal bleeding (~three-fold) among patients with solid tumors.[44] Case fatality after major bleeding is also higher in cancer than in non-cancer populations and appears amplified in the setting of renal impairment and advanced disease.[10,41,46] In a meta-analysis of randomized trials and prospective cohorts, the pooled case-fatality rate following MB was 8.9% (95% CI 3.5–21.1%).[47] Taken together, these data support viewing bleeding as a time-dependent, high-impact contributor to outcomes in cancer, particularly in patients with cancer-associated VTE, and not merely a tolerability endpoint.

Risk factors for bleeding in cancer

Bleeding related factors in patients with cancer are multifactorial with contribution from patient-, cancer-, comorbidity-, and treatment-related factors. We highlight some of the factors that have been consistently reported in the literature. It should be noted that many of the studied factors are dynamic and change over time. Examples of dynamic factors include cancer burden which can decrease and/or increase over time, laboratory factors such as thrombocytopenia that can wax and wane even within short periods of time, and cancer therapeutics which modify over time, especially in patients with advanced disease on long-term therapy. As such, risk of bleeding in cancer should is not static and thus should be assessed at multiple timepoints throughout the lifespan of the patient's malignancy.

Patient factors

Patient demographics and comorbid conditions modify bleeding risk. In patients with cancer, the impact of certain factors, such as increasing age, are complex. In broad, heterogeneous cancer cohorts, associations between older age and bleeding have been inconsistent, likely reflecting confounding by tumor type, stage, treatment intensity, and age-related comorbidity burden.[25,26,10] In contrast, age is a near universal component of bleeding risk as noted in available risk assessment models for anticoagulated patients, including cancer populations, and systematic review evidence in cancer underscores its importance.[48] In older cancer patients, prothrombotic activation coexists with fragile hemostasis, predisposing to both thrombosis and bleeding. Factors like age-related endothelial dysfunction, qualitative platelet defects, frailty (including fall risk), and polypharmacy collectively increase vulnerability to hemorrhage. Reflecting this, age ≥75 years is included in the cancer-specific CAT-BLEED bleeding risk model, while age thresholds between 65-74 years have been linked to higher bleeding risk in other cohorts of anticoagulated cancer patients.[48-50] When modeled continuously, bleeding risk has been reported to increase by approximately 4% per additional year of age and by ~10% per decade.[26,51]

Renal impairment reduces clearance of anticoagulants in those prescribe and can cause uremic platelet dysfunction in severe settings. In anticoagulated cancer populations, impaired kidney function confers a ~1.5-3-fold higher risk compared with preserved renal function across multiple studies.[23,46,49,52] In the prospective RIETE registry, severe renal dysfunction (eGFR <30 mL/min) was associated with a higher MB rate (40.8 per 100 patient-years; adjusted HR 3.5), with the signal particularly evident among patients treated with LMWH.[53,54] In carefully selected trial populations with moderate renal impairment (eGFR 30-60 mL/min), DOACs (i.e. apixaban) conferred similar bleeding risk to LMWH, but these findings may not generalize to frailer populations.[49,55,56] Evidence in severe CKD and dialysis is insufficient, and renal function clearly modulates bleeding risk, especially in real□world cohorts.[57]

Similarly, patients with cancer and severe liver disease have been systematically excluded from anticoagulant trials in cancer and robust estimates in this population are sparse.[12,14,15,27,58] Nevertheless, hepato-biliary cancer and underlying liver disease remain an important predictor of clinically significant bleeding in multiple independent cohorts, including anticoagulated cancer patients with atrial fibrillation and VTE, with a particularly strong signal for gastrointestinal bleeding.[26,59-61] Other patient-related factors, including a prior bleeding history and frailty or reduced functional capacity, have been associated with higher risk of CRB in cancer cohorts.[25,26,10,48] Several potentially modifiable predictors have also been implicated, including uncontrolled hypertension, alcohol misuse, and baseline anemia.

Cancer subtype

A variety of risk factors have been associated with bleeding in cancer, including patient-specific, cancer-specific, and therapeutic factors. More recently, genomic and proteomic risk factors have been explored.[62] The association between cancer subtype and bleeding can be related directly to tumor histology or to tumor location. Such examples include lung cancer with airway invasion or head and neck cancer with vascular invasion (tumor invasion), renal cell carcinoma as a highly vascular tumor (vascularization), involvement of mucosal surfaces of gastrointestinal or genitourinary tumors (mucosal involvement), and marrow involvement with resultant cytopenias (hematologic malignancies).[2] Studies have been published to identify and quantify these associations, especially in patients receiving anticoagulant therapy. In a secondary analysis of the CATCH trial comparing the efficacy/safety of tinzaparin versus warfarin for the treatment of acute, symptomatic VTE in cancer, intracranial malignancies were independently associated with the risk of CRB.[63] In a *post-hoc* analysis of the Caravaggio study, dalteparin *vs* apixaban in cancer -associated VTE, cancer subtypes associated with risk of MB included genitourinary and gastrointestinal primary tumors.[64] These findings are supported by those reported in cohort studies, with a recent study noting risk of anticoagulant-related bleeding highest in persons with central nervous system (CNS), unresected gastrointestinal, and genitourinary tumors.[26] A systematic review and meta-analysis of 96,753 persons with cancer-associated VTE found similar results with highest risk of anticoagulant-related bleeding amongst brain, gastrointestinal, genitourinary, and prostate cancers.[25] Overall, these studies demonstrate estimates of highest risk for

CNS/brain tumors, followed by genitourinary and then intact intraluminal gastrointestinal tumors.

When comparing the risk of MB by anticoagulant therapy, evidence from the available randomized trials suggests a higher risk of bleeding with DOAC *vs* LMWH in persons with gastrointestinal tumors. In SELECT-D, 76.5% of all MB events occurred in persons with colorectal or esophageal/gastroesophageal tumors.[15] However, of those patient populations, those treated with DOAC had double the rate of MB compared to LMWH, 11.4% *vs* 6.8% respectively. Similar, in HOKUSAI of those enrolled with colorectal, gastric, or esophageal cancer, the rate of bleeding was higher with DOAC *vs* LMWH, 12.1% *vs* 3.0%, respectively.[14] In addition, when looking at all intraluminal gastrointestinal tumors and MB, 59% of events occurred in those with unresected tumors. Finally, in Caravaggio, while there was no significant difference between MB in DOAC versus LMWH, all MB events in persons with intraluminal gastrointestinal tumors occurred in those with unresected tumors.[12]

While cohort studies demonstrate an association between intracranial tumors (primary or metastatic) and risk of bleeding, given the paucity of patients with brain tumors in randomized studies, less is known about the effect of anticoagulant therapy on this risk. In a systematic review and meta-analysis examining more than 3,000 patients with primary or metastatic brain tumors,[65] the risk of intracranial hemorrhage (ICH) increased in patients with primary brain tumors exposed to anticoagulant therapy (12.5% *vs* 4.4%, relative risk [RR] 2.63, 95% CI 1.48, 4.67) but did not in patients with metastatic brain cancer (14.7% *vs* 15.4%, RR 0.92, 95% CI 0.43, 1.93). When considering type of anticoagulant therapy, a recent meta-analysis comparing treatment with DOAC versus LMWH in 1,638 persons with brain tumors found no difference in the risk of ICH between groups for those with metastatic brain cancer (RR 1.05, 95% CI 0.71, 1.56); however, there was a significant reduction in risk of ICH for patient with primary brain tumors in favor of DOAC (RR 0.35, 95% CI 0.18, 0.69). While these data are derived completely from retrospective cohort studies, the exclusion and/or limited enrollment of persons with brain tumors in randomized studies force reliance on such data for clinical decision making.

In summary, tumor type is strongly associated with risk of bleeding in cancer with the strongest association for unresected, intraluminal gastrointestinal tumors, genitourinary tumors, and brain tumors. Available randomized studies suggest that risk of MB in gastrointestinal and genitourinary tumors may be higher with DOAC (versus LMWH). However, retrospective data, best available data, suggests that the reverse may be true for risk of ICH in primary brain tumors with DOAC associated with lower risk (*vs* LMWH).

Cancer-directed therapy

Cancer-directed therapy is also implicated in bleeding risk for patients with cancer, notably including radiation therapy and systemic therapy.[62] Radiation therapy increases bleeding risk via mucosal erosion, ulceration, and fibrosis. Tissue damage induced by radiation can compromise vessel integrity, leading to fragile vessels that are more suspectable to hemorrhage. This can be especially pronounced in tissue beds that are adjacent to tumors or near major anatomical sites such as in head and neck cancers.[66]

Systemic therapies that increase the risk of bleeding include namely targeted therapy as well as conventional or high-dose cytotoxic chemotherapy. There is a well-established increased risk of bleeding for patients on medications that interfere with vessel integrity, including vascular epithelial growth factor receptor (VEGF) tyrosine-kinase inhibitors (TKIs) regardless of anticoagulant therapy exposure. In meta-analyses establishing this risk, sunitinib and sorafenib increased the risk of all-grade bleeding events (RR 2.0, 95% CI 1.14, 3.49) but not of high-grade events.[67] In a *post-hoc* analysis of the Caravaggio study, anticoagulant therapy combined with VEGF-TKI therapy was associated with a higher rate of major bleeding when compared to patients on active cancer therapy other than VEGF-TKI as well as when compared to patients on no systemic cancer therapy (RR 1.58 and 1.73, respectively).[68] The VEGF antagonist bevacizumab and VEGF receptor antagonist ramucirumab also have an established association with bleeding risk. In a systematic review and meta-analysis of more than 45,000 patients receiving bevacizumab or ramucirumab, both medications increased the risk of all-grade bleeding (RR 2.73 and 1.94, respectively) while only bevacizumab increased the risk of high-grade bleeding (RR 1.98) compared to control patients.[69] Finally, Bruton's tyrosine kinase (BTK) inhibitors exert platelet-specific effects promoting an increase in the risk of bleeding. This is particularly true for ibrutinib, the first human BTK inhibitor. In addition to inhibition of platelet signaling pathways, ibrutinib can also cause thrombocytopenia and increase the risk of atrial fibrillation, necessitating anticoagulant therapy. This increases the risk of bleeding.[70] In a systematic review and meta-analysis of observational and randomized trials with ibrutinib (n=2152 ibrutinib recipients), the incidence of any bleeding and major bleeding was 20.8 (19.1, 22.1) and 3.0 (2.3, 3.7) per 100 person years, respectively.[71] As such, patients receiving ibrutinib are cautioned against concurrent management with additional therapies that can promote platelet dysfunction/inhibition. Myelosuppressive therapies and conventional chemotherapy can also cause profound intermittent thrombocytopenia, a risk factor for bleeding. This will be covered in the following section focused on thrombocytopenia in cancer.

Thrombocytopenia

The rate of thrombocytopenia varies widely in cancer. Thrombocytopenia can be related to cancer-directed therapy, marrow involvement (e.g., acute leukemia), and immune mediated (e.g., secondary immune thrombocytopenia in lymphoid neoplasms). As such, the incidence varies widely with estimates ranging from <5% in patients with head and neck cancer to nearly 100% in those with acute leukemia.[72] In a large Danish cohort study of more than 52,000 patients with solid tumors between 2015 and 2018, the 1-year risk of thrombocytopenia was 23%, which increased to 30% at 4 years.[73] Receipt of cytotoxic chemotherapy was a risk factor for thrombocytopenia with nearly 50% of exposed patients developing thrombocytopenia at 4 years. Patients with thrombocytopenia had a higher hazard of bleeding requiring hospitalization (hazard ratio [HR] 1.67, 95% CI 1.36, 2.04), need for transfusions (HR 6.96, 95% CI 4.41, 10.99) and death (HR 3.54, 95% CI 3.24, 3.87) compared to those without thrombocytopenia. The risk of bleeding is enhanced by anticoagulant therapy and is dose-dependent based

on the severity of thrombocytopenia. This was demonstrated in the RIETE registry data, with the highest cumulative incidence of bleeding in patients with platelet counts below $80x10^9$/L.[74] Thus, patients with cancer who have both venous thromboembolic events and thrombocytopenia present an especially difficult scenario. A systematic review and meta-analysis examined different anticoagulation strategies among 707 patients with cancer-associated VTE and thrombocytopenia (PLT < 100K). Among patients who were not anticoagulated, the rate of major bleeding was 2.2 per 100 patient months. However, rates of bleeding were higher in those receiving anticoagulant therapy at 4.45 per 100 patient months in the full dose group and 4.16 per 100 patient months in the reduced dose group.[75] Studies are underway to evaluate optimal strategies in these patients.

Disseminated intravascular coagulopathy

Certain malignancies and associated therapies confer a coagulopathic or hyperfibrinolytic state that can precipitate bleeding. For example, disseminated intravascular coagulation (DIC) is commonly seen in acute promyelocytic leukemia (APL) and advanced mucin-producing adenocarcinomas, leading to consumptive coagulopathy and hemorrhage. In a large cohort of patients with solid tumors, clinically overt DIC was diagnosed in approximately 7%, found mostly in those with advanced disease.[76] By contrast, overt DIC is reported in roughly 15-20% of patients with hematological malignancies and clinically significant coagulopathy is present in most patients with APL at diagnosis.[77,78] Liver involvement (liver metastases or hepatic cancers) can also reduce clotting factor synthesis and platelet count (hypersplenism), contributing to acquired coagulopathy.

Treatment-related coagulopathy

Beyond tumor biology, immunotherapies have introduced new, therapy-related coagulopathies. Chimeric antigen receptor (CAR) T-cell therapy, now standard for relapsed/refractory B-cell malignancies, is associated with a distinct coagulopathy tightly linked to cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS). Laboratory coagulopathy is frequent (~50%), and a smaller portion progress to DIC.[79,80] In patients who develop coagulopathy, rates of CRB of 6.2-20% have been reported and typically occur in the first 30 days post-CAR T-cell therapy.[81,82] Coexistence of DIC and severe CRS were associated with worse non-relapse mortality during the acute phase in some cohorts.[80]

Acquired hemophilia A and von Willebrand syndrome

Acquired hemophilia A (AHA) and acquired von Willebrand syndrome (aVWS) are rare but potentially life-threatening causes of severe bleeding in adults with cancer. In unselected AHA cohorts, 10-20% of cases have a concurrent or recently diagnosed underlying malignancy, most commonly of solid tumor origin.[83,84] Rare cases of AHA in association with immune checkpoint inhibitors have also been reported.[85] Patients typically present with abrupt onset of bleeding that presents in a distinct clinical pattern involving soft tissue, muscle, mucosal, and GI bleeding, often without prior bleeding history. Laboratory findings in AHA include isolated activated partial thromboplastin time (aPTT) prolongation that does not correct in mixing studies, low Factor VIII activity, and measurable inhibitors.[86] The true incidence of aVWS in cancer is uncertain and likely under-recognized. Up to 50-60% of aVWS occur in conjunction with a clonal hematopoietic proliferative disorder, with lymphoproliferative disorders being most common.[87] Mucocutaneous bleeding is the typical presentation. Proposed mechanisms in cancer include adsorption of VWF onto malignant cells, increased proteolysis, and autoantibodies.[88] Neoplastic diseases are also implicated in other rare, acquired factor deficiencies, with bleeding manifestations ranging from mild to catastrophic. Some associations are well characterized, such as acquired Factor X deficiency in systemic amyloidosis and plasma cell dyscrasias, in which adsorption to amyloid fibrils leads to accelerated Factor X clearance.[86,89]

Risk prediction models for anticoagulant-related bleeding in cancer

Anticoagulant-related bleeding risk prediction models have been developed and validated across non-cancer patient populations. These predominately center around those with atrial fibrillation,[90-93] with less focused-on persons on anticoagulant therapy for treatment of VTE.[94,95] However, these scores performed modest to poor in persons with cancer.[96,97] The reason for mediocre performance is likely multifactorial due to the prevalence of included risk factors in cancer (e.g., anemia prevalence is high which could contribute to poor discrimination) as well as absence of cancer specific bleeding risk factors (e.g., primary tumor type, cancer-specific therapy, disease stage, etc.). While two scores have been developed for cancer, they lack external validation to support implementation into clinical practice.[49,98]

Burden and future perspectives

The burden of bleeding in cancer is likely to increase over time, driven by the rising incidence of malignancy in aging populations and the parallel growth in cancer-associated thrombosis requiring anticoagulation.[99,100] Although cancer-specific data on patient-centered and economic outcomes remain limited, it is reasonable to anticipate that the downstream consequences of bleeding including impaired quality of life, treatment-related anxiety, increased healthcare utilization, and higher costs, may be magnified in oncology populations where baseline symptom burden is already substantial.

Primary thromboprophylaxis in selected high-risk ambulatory cancer patients is increasingly used and appears cost-effective, despite a modest increase in on-treatment bleeding. However, longer-term data are lacking on the trade-offs between preventing acute VTE and minimizing cumulative bleeding exposure, particularly strategies that avoid sustained full-intensity anticoagulation (e.g., dose reduction after acute phase treatment).[101] Progress in this area requires more accurate identification of patients at high bleeding risk and a better understanding of the baseline bleeding risk in cancer. Current

bleeding risk assessment models have limited discrimination in cancer and should evolve toward dynamic prediction that incorporates time-varying clinical trajectories rather than relying on static baseline variable.[102] Therapeutic trials exploring anticoagulant therapy with lower bleeding profiles (e.g., Factor XI inhibitors) remain warranted, especially for patients with high bleeding risk. In parallel, aggressive management of modifiable bleeding risk factors remains a practical and immediately actionable approach. Using population-attributable fraction methods in our prior work, we estimated that eliminating modifiable predictors (alcohol misuse, anemia, concomitant antiplatelet therapy, and uncontrolled hypertension) could reduce the 1-year probability of anticoagulant-related bleeding by approximately 23%.[103]

Collectively, these considerations argue for future guidance that treats bleeding prevention as a core objective of cancer-associated VTE management and for additional high-quality studies to inform dynamic risk stratification, de-escalation strategies, and safer anticoagulant options. While the intent of this review is not to generate guidance, taking into consideration the data presented, Figure 1 implements some of these strategies which could decrease the burden of bleeding in cancer. Future studies are needed to better understand evidence-based strategies to eliminate or mitigate risk.

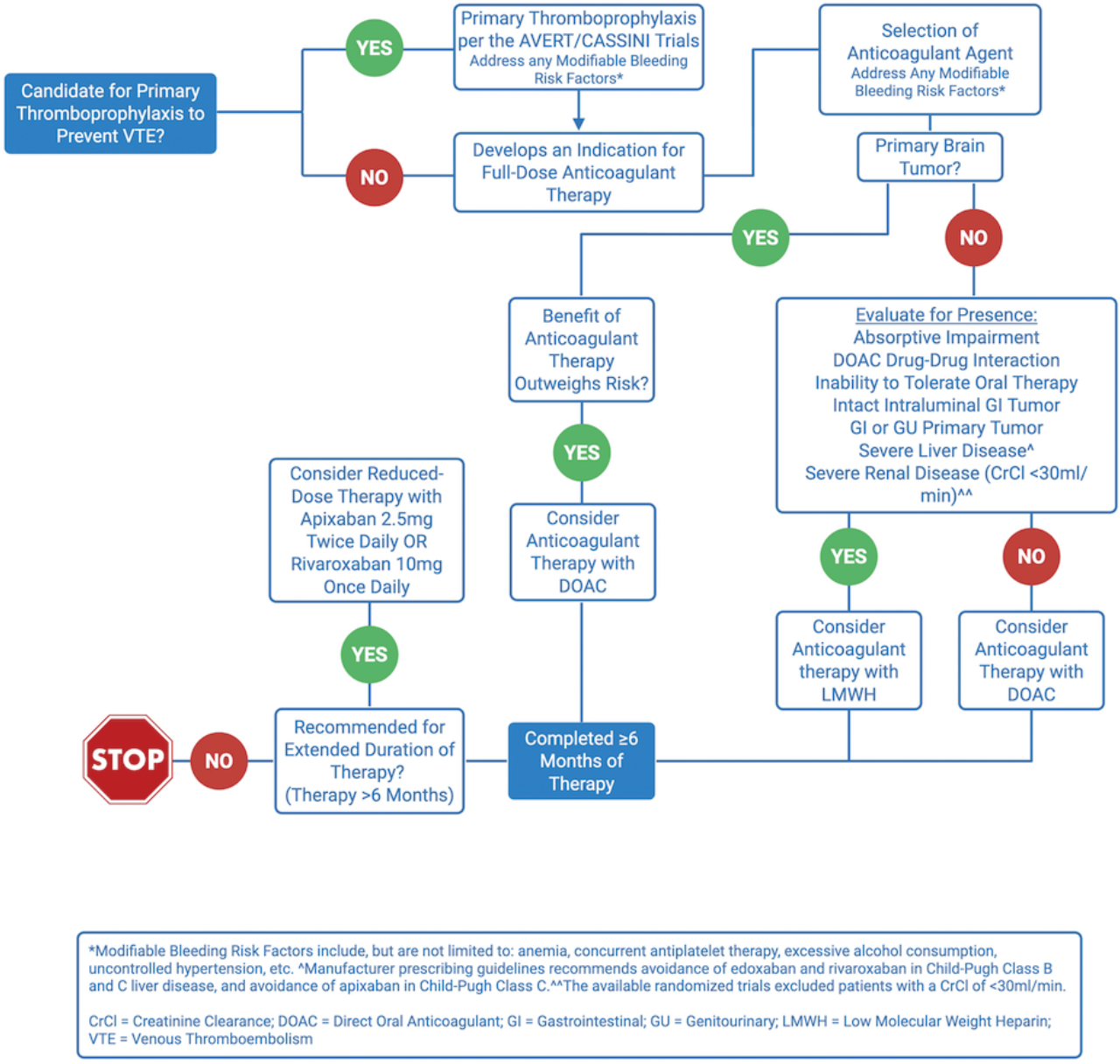

Figure 1. Selection of anticoagulant therapy, attention to bleeding risk factors. Created with BioRender. Sanfilippo, K. (2026) https://BioRender.com/cl06ipe

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