Bleeding Risk in Patients with Cancer

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Abstract

The hemostatic system and cancer display a tight interconnection, and hemostatic imbalance frequently occurs in patients with cancer. While extensive knowledge about thrombotic risk has been generated, less is known about bleeding risk and associated risk factors. However, bleeding risk is of high significance as patients with cancer frequently receive therapeutic anticoagulation for various indications and/or are candidates for primary thromboprophylaxis. The risk of bleeding in patients with cancer is variable and difficult to assess in clinical practice. Certain clinical settings such as hospitalization, specific underlying risk factors (e.g., tumor type), and medications (e.g., anticoagulation) can contribute to the individual bleeding risk of a patient with cancer. In addition, some dynamic factors such as platelet count or kidney function have an impact. Particularly, data on baseline risk of bleeding are lacking to allow for risk assessment in cancer patients without anticoagulation. In contrast, risk assessment models for the prediction of bleeding events in cancer patients receiving anticoagulation have been developed; however, these have yet to be validated. The recognition of the importance of bleeding risk in cancer patients is growing, leading to an increasing number of studies investigating and reporting bleeding complications. As study designs and reporting of bleeding events vary, it is challenging to offer a clear synthesis of evidence. In this narrative review, we provide an overview of currently available data about incidence, risk factors, and clinical impact of bleeding events in patients with cancer, and critically review risk assessment models for bleeding in cancer patients during anticoagulant therapy.

Keywords
- hemorrhage
- major bleeding
- cancer
- risk

Introduction

Cancer and the hemostatic system are tightly interconnected, and a hemostatic imbalance is frequently observed in patients with cancer. Clinical manifestations of this interaction may occur as both thrombotic and bleeding complications.[1] Previous research has predominantly focused on thrombotic issues associated with cancer, such as venous thromboembolism (VTE) and arterial thromboembolic events (ATEs), yielding extensive knowledge on their incidences, risk factors, and predictive biomarkers.[2] In contrast, bleeding risk and associated risk factors have received less attention and have not been investigated in detail. However, their clinical significance is increasingly being recognized.

Various factors and challenges during the journey of cancer patients impact the hemostatic balance. Patients with cancer are often in need of long-term anticoagulation for indications such as treatment of VTE or stroke prevention in atrial fibrillation (AF) or are even candidates for primary thromboprophylaxis as recommended by clinical practice guidelines.[3–6] For initiation of anticoagulation, an accurate assessment of the bleeding risk is essential. Consequently, there is a pressing clinical need for a better understanding of

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bleeding complications and assessing their risk, both the baseline risk without anticoagulation and the risk of anticoagulation-associated bleeding.

While randomized controlled trials (RCTs) of anticoagulant therapies typically included bleeding risk as a pertinent safety measure, and reported types and incidence of bleeding events, studies investigating bleeding characteristics and risk in an uncontrolled setting (i.e., in the routine clinical practice) are scarce. Furthermore, patients at high risk of bleeding were mainly excluded from RCTs. Given its feared clinical consequences, there is a desire to have more data on and a better understanding of bleeding risk in patients with cancer with or without anticoagulation treatment. In particular, data on baseline bleeding risk (i.e., in patients with cancer not receiving anticoagulation) are urgently needed for clinical decision making to facilitate estimation of individual bleeding risk prior to initiation of anticoagulation for primary thromboprophylaxis.

This narrative review aims to summarize currently available data on bleeding risk in patients with cancer. Furthermore, we provide an overview on risk factors, biomarkers, and prediction models for the assessment of bleeding risk as well as the clinical consequences and impact of bleeding events in patients with cancer.

Baseline Risk of Bleeding in Patients with Cancer Without Anticoagulation

The baseline bleeding risk and the phenotype of bleeding in patients with cancer are currently not well characterized, as dedicated studies and data on bleeding risk in patients with cancer not receiving anticoagulation are scarce. The best available information can be deduced from the placebo groups of the RCTs investigating the efficacy of anticoagulants for primary thromboprophylaxis and studies, which have explored the effect of heparins on improving the prognosis of cancer. The incidence of major bleeding (MB) in placebo groups (i.e., without anticoagulation) of RCTs of low-molecular-weight heparins (LMWHs) for primary thromboprophylaxis was 1.1 to 3.3%, of clinically relevant non-major bleeding (CRNMB) 2.0 to 2.2% and of minor bleeding 2.7 to 7.9%.[7–10] Also the RCTs that aimed to assess direct oral anticoagulants (DOACs) for primary thromboprophylaxis in patients with a Khorana score of 2 or higher reported similar incidences of MB (1.0–1.8%) and of CRNMB (2.0–5.5%) in their placebo groups.[11,12] The trials which looked at the impact of LMWH on survival observed MB rates of about 1% and about 2.7% for minor bleeding in the placebo groups.[13–15] The differences in observed bleeding rates are partly attributable to the variance in the observation period (summarized in ►Table 1). A recent meta-analysis including all trials that assessed LMWH compared to placebo in ambulatory patients with cancer found a pooled MB rate of 1.7% and a minor bleeding rate of 12.1% in the placebo groups.[16]

However, patients included in RCTs represent a highly selected patient population, and patients with a high-risk bleeding profile might be underrepresented. Therefore, real-life data would be needed to estimate the true risk and incidence of baseline bleeding risk in patients without anticoagulation. One registry from Japan (Cancer-VTE Registry) including 9,630 patients with solid tumors reported a 1-year cumulative incidence of bleeding events (any type) of 1.4%. Important to note is, however, that 37.3% of patients received anticoagulation during the observation period and that the assessment of bleeding events in the follow-up period was not clearly described. Furthermore, the following risk factors for bleeding events were reported: the presence of VTE at baseline, lung cancer, stomach cancer, pancreatic cancer, distant metastasis, oral anticoagulant treatment, a D-dimer level of $>1.2\,\mu g/mL$, and history of intracranial hemorrhage.[17] In contrast, recent data from a prospective cohort study including patients with cancer-initiating systemic anticancer therapy showed higher incidences of bleeding events in those without anticoagulation (12-month MB cumulative incidence: 7.0%).[18] In a systematic review assessing risk in patients with cancer with thrombocytopenia, the MB bleeding rate was reported to be 2.2 per 100 patient-months in thrombocytopenic patients without anticoagulation.[19]

A further clinical setting in need of information on the baseline bleeding risk is the inpatient setting. Di Nisio et al investigated the bleeding frequency of hospitalized patients with cancer during their stay and after discharge.[20] Half of the observed patients did not receive thromboprophylaxis, of which 2 had a bleeding event during hospitalization and 11 after discharge, giving a bleeding rate of 9.4%.[20] An even more special setting is palliative care. A study of patients admitted to palliative care units, including 1,199 patients (91% with cancer), monitored them for up to 3 months for the occurrence of clinically relevant bleeding (CRB; the composite outcome of MB and CRNMB).[21] Among those not receiving thromboprophylaxis, 8.4% experienced a bleeding event and 1.8% died due to the bleeding.[21]

Studies reporting bleeding risk in patients with cancer not receiving anticoagulation and their observation time are summarized in ►Table 1.

Bleeding Risk in Patients with Cancer Receiving Anticoagulation

Patients with cancer often receive anticoagulation due to various reasons, which include primary thromboprophylaxis in surgical, medically ill, and ambulatory cancer patients, and treatment of VTE, stroke prevention in AF, or mechanical heart valves.

Patients with cancer-associated VTE have a two- to three-fold increased bleeding risk during anticoagulation compared to VTE patients without cancer.[22–28] A recent study from Japan reported a cumulative MB incidence of 6.8 versus 3.6% at 90-day, 11.5 versus 5.3% at 1 year, when comparing active cancer patients (solid tumors) with no active cancer patients receiving treatment for VTE.[28] Similar numbers were also reported in the early 2000s when vitamin K antagonists (VKAs) were widely used, namely a 12-month MB cumulative incidence of 12.4% in patients with active cancer compared to 4.9% in patients without cancer.[26]

The landscape of anticoagulant treatment in patients with cancer has changed over the last two decades motivated by

Table 1 Summary of studies reporting baseline risk of bleeding in patients with cancer without anticoagulation

Study	Study design/setting	Number of patients[a]	Observation time	Frequencies
Randomized controlled trials				
Kakkar et al[13]	RCT (FAMOUS) Patients: cancer patients (stage III or IV) Dalteparin vs. placebo for improved survival Outcomes: improved survival; bleeding (ISTH definition)	184	1 y	MB: 0 in the placebo group Minor bleeding: 5 (2.7%) in the placebo group
Klerk et al[14]	RCT Patients: metastasized or locally advanced solid tumor patients Nadroparin vs. placebo for improved survival (6 wk) Outcomes: mortality, bleeding	154	Mean follow-up: 1 y	MB: 1 (1%) in the placebo group CRB: 1 (1%) in the placebo group
Agnelli et al[7]	RCT (PROTECHT) Patients: ambulatory cancer patients, anticoagulation until end of chemotherapy or for 4 mo Nadroparin vs. placebo for primary prophylaxis Outcomes: VTE, bleeding (ISTH definition), mortality	387	Median follow-up: 113 d	MB: 0 in the placebo group Minor bleeding: 38 in 30 patients in the placebo group (7.9%)
van Doormaal et al[15]	RCT Patients: prostate, NSCLC, locally advanced pancreatic cancer Nadroparin vs. placebo for survival in patients (2 wk therapeutic, 4 wk half therapeutic) Outcomes: overall survival, time to progression and bleeding (ISTH definition)	259	Median follow-up: 10.5 mo	MB: 9 (3.5%) in the placebo group CRB or MB: 21 (8.1%) in the placebo group
Agnelli et al[8]	RCT (SAVE-Onco) Patients: cancer patients starting chemotherapy Semuloparin vs. placebo for primary prophylaxis until therapy change Outcomes: VTE, bleeding (ISTH definition), mortality	1,604	Median trial time: 3.5 mo	MB + CRNMB: 32 (2%) in the placebo group MB: 18 (1.1%) in the placebo group CRNMB: 14 (0.9%) in the placebo group Fatal bleeding: 4 (0.2%) in the placebo group
Pelzer et al[10]	RCT (CONKO-004 trial) Patients: advanced pancreatic cancer patients (first line therapy) Enoxaparin vs. observation for primary thromboprophylaxis (3 mo full dose, 3 mo modified dose) Outcomes: VTE, major bleeding	152	3 mo	MB: 5 (3.3%) in the observation group Overall cumulative incidence rate of MB: 6.9% in the observation group Fatal bleedings: 2 (1.3%) in the observation group
Khorana et al[9]	RCT (PHACS) Patients: cancer patients (Khorana score $\geq$ 3) Dalteparin vs. observation for primary thromboprophylaxis Outcomes: VTE, bleeding	48	13 wk	MB: 1 (2.1%) in the observation group CRB: 1 (2.1%) in the observation group Minor bleeding: 1 (2.1%) in the observation group

(*Continued*)

Table 1 (*Continued*)

Study	Study design/setting	Number of patients[a]	Observation time	Frequencies
Randomized controlled trials				
Carrier et al[11]	RCT (AVERT trial) Patients: ambulatory cancer patients (Khorana score $\geq$ 2) starting chemotherapy Apixaban vs. placebo for primary thromboprophylaxis Outcomes: VTE, bleeding (ISTH definition), mortality	275	180 d	MB: 5 (1.8%) in the placebo group
Khorana et al[12]	RCT (CASSINI trial) Patients: cancer patients with solid tumor or lymphoma (Khorana score $\geq$ 2) Rivaroxaban vs. placebo for primary prophylaxis Outcomes: VTE, bleeding (ISTH definition), mortality	404	180 d	MB: 4 (1.0%) in the placebo group
Cohort studies				
Ohashi et al[17]	Registry (Cancer VTE registry) Patients: solid tumor Outcomes: bleeding events (ISTH definition), VTE	9,630 (37.3% received anticoagulation)	1 y	1-y cumulative incidence: 1.4% any bleeding
Studies in the inpatient setting				
Tardy et al[21]	Multicenter, prospective, observational study Patients: patients admitted to palliative care unit (91% cancer patients) Outcomes: bleeding	560	3 mo	CRB: 47 (8.4%) without thromboprophylaxis Fatal bleeding: 10 (1.8%) without thromboprophylaxis
Di Nisio et al[20]	Prospective observational cohort study, single center Patients: cancer patients admitted to ward for acute medical illness Outcomes: bleeding (ISTH definition)	139	Median hospitalization: 8 d Median follow-up: 92 d (19–110 range)	CRB: 2 (1.4%) without thromboprophylaxis during hospitalization; 11 (7.9%) without thromboprophylaxis after discharge Fatal bleeding: 1 (0.7%) patient
Meta-analyses				
Wang et al[19]	SR (19 studies) and MA (10 studies) Patients: cancer-associated thrombosis and thrombocytopenia in: - Full-dose anticoagulation - Modified dose anticoagulation - No anticoagulation Outcomes: recurrent VTE, major bleeding (ISTH definition)		100 patient-months	MB: 2.20 per 100 patient-months without anticoagulation

Abbreviations: CRB, clinically relevant bleeding; CRNMB, clinically relevant non-major bleeding; d, day(s); ISTH, International Society of Thrombosis and Hemostasis; MA, meta-analysis; MB, major bleeding; mo, month(s); RCT, randomized controlled trial; SR, systematic review; w, week(s); y, year(s).
[a]Number of patients in the placebo arm of RCTs or cohorts without anticoagulation.

the search for improved treatment strategies for VTE while reducing bleeding risk. Recent data from a large registry gave a first hint that this quest was successful, as the authors noticed a decrease in MB over the last 20 years in patients with cancer receiving anticoagulation for the treatment of VTE.[29] It is important to note that in RCTs, always one specific LMWH was used; however, to enhance readability, the individual agents will be referred to as LMWH in this review.

In the RCTs comparing the efficacy and the safety of VKA to LMWH, a significant reduction in the risk of VTE recurrence was observed, while the rates of MB were increased, albeit nonsignificant (MB: 2.7–5.6% vs. 2.4–3.6%, respectively). The

rates of CRNMB (10.9 vs. 15.3%) and any bleeding (14 vs. 19%) were lower with LMWH versus VKA.[30,31] One could assume that minor bleeding rates might be higher in the LMWH arms due to injection-site hematoma. However, this has not been detailed in the studies. Also, a meta-analysis provided further evidence that there is a similar bleeding risk between patients receiving LMWH and VKA.[32]

After the advent of DOAC for the treatment of VTE, they have been investigated compared to LMWH for the treatment of cancer-associated VTE. To date, only the direct factor Xa inhibitors were evaluated in the cancer population for the treatment of cancer-associated VTE. There is no specific study conducted with dabigatran, an oral direct thrombin inhibitor. In this review, the term DOAC refers only to the direct oral factor Xa inhibitors apixaban, edoxaban, and rivaroxaban for better readability. Interestingly, the MB risk was comparable between these two anticoagulants, with an incidence of 3.8 to 6.9% with DOAC and 3.8 to 5.6% with LMWH. However, the incidence of CRNMB was higher with DOAC (5.8–13% vs. 2.6–6%).[33–36] In these trials, an excess in gastrointestinal (GI) or genitourinary (GU) bleeding was observed.[34,37] Furthermore, in two of the studies, GI bleeding more frequently occurred in patients with GI tumors.[34,35] When data were pooled in a meta-analysis, a comparable incidence of MB bleeding and a slight increase in CRNMB bleeding with DOACs was observed as well, but here also the risk for MB was higher in those with GI cancer.[37]

Based on the latest trials, guidelines recommend both DOAC and LMWH for the treatment of cancer-associated VTE.[3–6] However, in patients with GI and GU malignancy, caution is recommended when using a DOAC.[3–6] After 6 months of treatment, anticoagulation should be continued in patients with active cancer.[3–6] Interestingly, it seems that bleeding risk is highest in the initial phase of anticoagulation for cancer-associated VTE and declines over time. The MB risk was reported to be highest in the first month after anticoagulation starts (3.6% per patient-month). When comparing the first 6 months to the period spanning 7 to 12 months of anticoagulation therapy, the risk was notably lower (1.7 vs. 0.7% per patient-month, respectively).[38] This observation was also made in a post hoc analysis of a recent RCT with DOAC versus LMWH[39] and was also confirmed in a meta-analysis.[40]

Another indication for anticoagulation in patients with cancer is primary thromboprophylaxis, which is suggested in patients with cancer at high VTE risk.[3–6] In the initial thromboprophylaxis trials with LMWH versus placebo, the frequencies of MB ranged between 0.7 and 4.4%, of CRNMB between 1.6 and 12.0%, and of minor bleeding between 6.0 and 7.4%.[7–10] In trials investigating the effect of heparin on improving overall survival of patients with cancer, the MB frequencies with LMWH were 0.5 to 4.1%, with CRNMB 4.0 to 5.3%, and with minor bleeding 4.5%.[13–15] A recent meta-analysis including all RCTs that compared heparins with placebo or no treatment estimated a MB rate of 2.1% and a minor bleeding rate of 16.6% in ambulatory patients receiving LMWH.[16] In more recent RCTs assessing the DOAC apixaban and rivaroxaban for primary thromboprophylaxis, the MB rates (3.5 and 2%, respectively) were similar.[11,12]

Patients included in RCTs often represent a selected population. Therefore, data on bleeding risk from real-life cohort studies are more desirable, as they would better depict the true risk of bleeding in daily clinical routine. However, data from the noncontrolled setting are quite heterogeneous, with different ways of capturing and presenting the numbers, rates, and the source of data (e.g., from registries with anticoagulated cancer patients, retrospective or prospective studies including only patients with a specific type of anticoagulation).

While registry studies, including patients with different anticoagulants, reported the 1-year cumulative MB incidences to be high in patients with solid tumors from Asia (13.8%), lower incidences were reported in those of European descent (5%).[41,42] Similarly, high rates of CRB were reported in the Norwegian TROLL registry (1 year: 11.3%).[43] Population-based analyses including patients with various anticoagulants reported 1-year cumulative MB incidence of 7.5% and a rate of 4.4% per patient-year for bleeding events leading to hospitalization.[44,45] Other observational and population-based studies including patients on DOAC and LMWH observed 6-month cumulative incidences of MB between 1.9% (rivaroxaban), 3.7% (LMWH), and 6.7% (apixaban).[46–48] In contrast, lower rates were found in a retrospective analysis, using ICD codes for the identification of patients with cancer-associated VTE hospitalized for a bleeding complication (1% MB and 2.4% CRNMB requiring hospitalization).[49] Regarding different cancer types, one population-based analysis observed the highest risk in upper GI (8.6% per patient-year) and the lowest in breast cancer (2.9% per patient-year) patients,[45] while registry data suggest a lower bleeding risk in those with hematological cancer.[50] Interestingly, the bleeding risk in observational studies was highest within the first 3 months (up to 27%) and lower after the initial 3 months,[51,52] similar with data from the controlled setting.

►Table 2 provides an overview of noncontrolled studies reporting bleeding risk in patients with cancer receiving anticoagulation for the treatment of cancer-associated VTE.

Another very common indication for anticoagulation in patients with cancer is AF, as this is a highly prevalent comorbidity.[53] Patients with AF requiring anticoagulation for stroke prevention tend to be older and have more comorbidities and thus, their bleeding risk is relevant and noted to be higher than that of the noncancer population as well.[54–57] The intracranial hemorrhage risk in patients with cancer seems to be lower with DOACs given for the indication of stroke prevention.[54,58] Interestingly, the risk seems to vary depending on the tumor type in this setting as well, and again patients with breast cancer were reported to have a relatively low risk, not significantly higher than the noncancer population.[56] However, patients with hematological, lung, prostate, and colorectal cancer were observed to have an increased risk.[56]

Special Situations for Bleeding Risk in Patients with Cancer Receiving Anticoagulation

When evaluating bleeding risk in patients with cancer, another important aspect to include is special situations. First of all, inpatients and patients in the palliative care setting represent a population of special interest. A study of elderly cancer

Table 2 Summary of noncontrolled studies reporting bleeding rates in patients with cancer receiving anticoagulation

Study	Study design/setting	Number of patients	Observation time	Bleeding frequency
Registry studies				
Monreal et al[95]	RIETE registry Patients: cancer patients with VTE (acute symptomatic) receiving anticoagulation (LMWH, UFH, vitamin K antagonists) Outcome: fatal PE, fatal bleeding	2,945	3 mo	Fatal bleeding: 1% of patients
Prandoni et al[27]	RIETE registry Patients: with cancer and VTE treated with LMWH followed by VKA compared to individuals without cancer Outcomes: MB, recurrent VTE	11,365—no cancer 407—metastatic cancer 972—limited cancer disease	3 mo	MB:150 without cancer (1.3%, 19 fatal), 20 with metastasis (4.9%, 7 fatal), 16 with limited cancer disease (1.9%, 4 fatal)
Trujillo-Santos et al[92]	RIETE registry Patients: acute VTE in cancer patients treated with anticoagulation (LMWH, VKA) Outcomes: recurrent VTE, bleeding	3,806	First 90 d of anticoagulation	MB: 156 (4.1%) patients Fatal bleeding: 46 (1.2%) patients
Trujillo-Santos et al[52]	RIETE registry Patients: with cancer and VTE receiving anticoagulation (LMWH, warfarin) Outcomes: MB (ISTH definition)	4,709	Up to 1 y	MB: 200 (4.2%) patients within the first 3 mo After 3 mo: 17 (1.1%) with anticoagulation, 3 (0.1%) without anticoagulation Fatal bleeding: 16 (0.4%) patients
Mahé et al[98]	RIETE registry Patients: cancer patients with VTE LMWH or warfarin, a few edoxaban Outcomes: recurrent VTE, MB (ISTH definition), mortality	3,947	Mean duration of anticoagulation: 139 d	MB: highest in the first 6 mo Breast and colorectal: similar recurrent VTE and MB Lung: more recurrent VTE than MB Prostate: more MB than recurrent VTE
Trujillo-Santos et al[42]	RIETE registry Patients: cancer patients with acute VTE LMWH, VKA, rarely rivaroxaban Outcomes: fatal PE, fatal bleeding during and after anticoagulation	10,962	12 mo	MB: 516 (4.7%) events Fatal bleeding: 170 (80% under anticoagulation; 1.6%) patients
Lecumberri et al[50]	RIETE registry Patients: Hematological and solid tumor patients after VTE receiving anticoagulation Outcomes: recurrent VTE, bleeding (ISTH definition), mortality	15,632 with solid tumor 1,062 with hematological cancer	1 y	MB: 806 (4.8%) patients
Siguenza et al[114]	RIETE registry Patients: cancer patients with renal insufficiency after VTE receiving enoxaparin Outcomes: recurrent VTE, bleeding (ISTH definition),	2,844: 1,432 with mild, 1,168 with moderate, 244 with severe renal insufficiency	6 mo	MB: 184 (6.5%) patients Fatal bleeding: 33 (1.2%) patients Mild renal impairment: MB 5.4% and fatal bleeding 1.2%

Table 2 (*Continued*)

Study	Study design/setting	Number of patients	Observation time	Bleeding frequency
Registry studies				
	mortality in patients with mild, moderate, and severe renal insufficiency			Moderate renal impairment: MB 6.3% and fatal bleeding 1.2% Severe renal impairment: MB 13% and fatal bleeding 0.8%
McBane et al[97]	Prospective registry Patients: with cancer treated for VTE (apixaban, rivaroxaban, warfarin, LMWH) Outcomes: recurrent VTE, bleeding (ISTH definition), mortality	1,812	10 mo	MB: 98 (5.4%) patients CRNMB: 104 (5.7%) patients
Grdinic et al[43]	TROLL registry Patients: with cancer and VTE receiving anticoagulation Outcomes: bleeding (ISTH definition)	1,080	455 d	MB + CRNMB: 1-90 d: 7.7%; 1–365 d: 11.3%, 90–455 d: 4.7%
Population-based studies				
Chee et al[44]	Population-based analysis Patients: cancer patients with an acute VTE receiving anticoagulation (LMWH, warfarin) Outcomes: recurrent VTE, bleeding, mortality	4,477	1,533 person-years of follow-up	MB: 11 (73% within the first 30 d, 3 fatal), adjusted 90-d cumulative incidence: 1.9% 7-, 14-, 30-, 90-, 183-d, and 1-year cumulative incidence: 0.6, 1.1, 2.0, 2.0, 2.5, and 4.7% Minor bleeding: 15 (50% occurred within the first 7 d) 7-, 14-, 30-, 90-, 183-d, and 1-y cumulative incidence: 2.8, 3.5, 4.7, 5.4, 6.4, and 8.5%
Søgaard et al[46]	Population-based analysis Patients: cancer-associated VTE treated with rivaroxaban Outcomes: recurrent VTE, MB	476	6 mo	MB: 9 patients (absolute risk 1.9%, rate of 4.7 events per 100 person-years)
Prospective cohort studies				
Prandoni et al[26]	Prospective, observational study Patients: with first VTE (cancer and non-cancer patients) LMWH or warfarin Outcomes: recurrent VTE, bleeding	181 with cancer (842 total)	3–12 mo	MB: 17 (9.4%) patients with cancer 23 (3.5%) patients without cancer
Oyakawa et al[109]	Prospective observational study (V LEAD study) Patients: advanced metastatic cancer with DOAC for VTE treatment Outcomes: bleeding (ISTH definition), recurrent VTE	145	3 mo	MB: 8 (5.5%) patients CRNMB: 29 (20%) patients Minor bleeding: 44 (30.3%) patients
Girard et al[48]	Prospective observational study Patients: cancer patients with VTE (symptomatic and incidental)	409	6 mo	MB: 6-mo cumulative incidence of 3.7%

(*Continued*)

Table 2 (*Continued*)

Study	Study design/setting	Number of patients	Observation time	Bleeding frequency
Registry studies				
	6 months treatment with tinzaparin Outcomes: recurrent VTE, MB (ISTH definition), HIT			
Retrospective cohort studies				
Yamashita et al[22]	Retrospective cohort study (COMMAND VTE registry) Patients: with acute VTE (transient risk 28%, unprovoked 49% and cancer 23%) Outcomes: recurrent VTE, bleeding (ISTH definition), anticoagulation cessation rate	3,027 (695 with cancer)	5 y	MB: cumulative incidence of 7.9% at 90 d, 15.3% at 1 y, 21.0% at 3 y, and 26.6% at 5 y
Zakai et al[45]	Retrospective, US database Patients: patients with cancer and VTE treated with anticoagulation (warfarin, LMWH, and DOAC) Outcomes: hospital bleeding	26,894	Median follow-up: 0.6 y; 27,281 person-years	Bleeding events: 1,204 over 27,281 person-years of follow-up highest in upper GI cancers (8.6% per patient-year), lowest in breast cancer (2.9% per patient-year)
Streiff et al[25]	Retrospective, US database Patients: cancer and first VTE starting anticoagulation therapy (LMWH, warfarin, rivaroxaban) Outcomes: recurrent VTE, MB (ISTH definition)	2,428	3–6 mo	MB: higher when compared to anticoagulated without cancer (3-mo: 5.9 vs. 2.6% and 6-mo 8.7 vs. 4.2%) LMWH vs. rivaroxaban: 8.3 and 8.2% LMWH vs. warfarin: 8.5 and 8.6% Rivaroxaban vs. warfarin: 9.0 and 8.7%
Sakamoto et al[23]	Retrospective cohort study (COMMAND VTE registry) Patients: anticoagulated for VTE with active cancer, history of cancer, or no history Outcomes: recurrent VTE, MB (ISTH definition)	3,027: 695 with active cancer, 243 with a history of cancer, 2,089 with no history	Median follow-up: 1,218 d	MB: 5-y cumulative incidence of 26.6% with active cancer, 8.8% with a history of cancer, and 9.3% with no history of cancer
Nishimoto et al[41]	Retrospective cohort study (COMMAND VTE registry) Patients: cancer patients with anticoagulation for VTE Outcomes: MB (ISTH definition), risk factors for bleeding	592	Median follow-up: 199 d	MB: 72 (12.2%) patients Cumulative incidence: 5.8% at 3 mo, 13.8% at 1 y, 17.5% at 2 y, and 28.1% at 5 y Fatal bleeding: 13 (18%) patients
Cohen et al[49]	Retrospective observational cohort study Patients: with cancer and first VTE treated with anticoagulation (LMWH, vitamin K antagonists, DOACs) Outcomes: MB (ISTH definition), CRNMB requiring hospitalization (CRNMB-H), a composite of both	15,749	6 mo	MB + CRNMB-H: 537 events during 4,914 person-years (161 MB and 376 CRNMB-H) Case-fatality rate for MB: 21.1%

Table 2 (*Continued*)

Study	Study design/setting	Number of patients	Observation time	Bleeding frequency
Registry studies				
Poénou et al[51]	Retrospective observational cohort study Patients: with cancer and VTE Outcomes: MB and CRNMB (ISTH definition), assessment of risk assessment models	110	6 mo	Any bleeding: 26 patients (26.7%) with 29 bleeding events MB: 10 events CRNMB: 19 events Fatal bleeding: 4 (rate of 4.5%)
Wang et al[108]	Retrospective single-center cohort study Patients: cancer patients with VTE on anticoagulation Outcomes: influence of drug-drug interactions, recurrent VTE, CRB (ISTH definition)	267	6 mo	CRB: 18 (6.7%) patients 5 MB and 13 CRNMB (6-mo cumulative incidence: 1.9 and 4.9%) Minor bleeding: 6 (2.2%) patients
Cominacini et al[99]	Retrospective cohort Patients: patients treated for cancer-associated thrombosis LMWH vs. DOAC Outcomes: recurrent VTE, bleeding (ISTH definition)	209	6 mo	MB: 6 (5.2%) in the LMWH group 2 (2.1%) in the DOAC group CRNMB: 13 (11.4%) in the LMWH group 15 (15.8%) in the DOAC group
Chatani et al[28]	Multicenter, retrospective cohort study (COMMAND VTE registry 2) Patients: patients with VTE (with and without cancer) receiving anticoagulation Outcomes: recurrent VTE, bleeding (ISTH definition)	1,507 with cancer vs. 3,690 without cancer	5 y	MB: cumulative incidence of 6.8% at 90 d, 11.5% at 1 y, and 20.4% at 3 y CRNMB: 5-y incidence of 18.4%

Abbreviations: CRB, clinically relevant bleeding; CRNMB, clinically relevant non-major bleeding; d, day(s); DOAC, direct oral anticoagulant; GI, gastrointestinal; HIT, heparin induced thrombocytopenia; ISTH, International Society of Thrombosis and Hemostasis; LMWH, low molecular weight heparin; MB, major bleeding; mo, month(s); PE, pulmonary embolism; RCT, randomized controlled trial; UFH, unfractionated heparin; VTE, venous thromboembolism; w, week(s); y, year(s).

patients hospitalized for recent VTE and receiving anticoagulation observed 34 MB events in 408 patients (8.3%), during a median stay of 13 days of which 8.8% were fatal.[59] In a cohort of cancer patients hospitalized for acute medical illness receiving thromboprophylaxis, four (3.6%) CRB events in the inpatient setting and one (2.1%) CRB in a patient with ongoing prophylaxis after discharge were observed.[20] Similarly, of 3,525 hospitalized cancer patients (up to 80% received anticoagulation and 35% had hematological cancer), 2% experienced a bleeding event, with 8 events being fatal.[60] One meta-analysis evaluated the risk of bleeding with extended thromboprophylaxis and found it to be associated with approximately a twofold increase in patients with cancer compared to patients without cancer.[61] In the palliative care setting (91% of 1,199 patients with cancer included), 11% experienced bleeding with thromboprophylaxis with heparins (unfractionated, LMW, or fondaparinux).[21] Importantly, 13.7% of the patients had renal insufficiency and 9.1% had hepatic insufficiency, which can influence bleeding risk.[21] These factors and other modifying factors such as thrombocytopenia have to be considered as they are frequently present in patients in the palliative care setting.

Secondly, patients with brain tumors are difficult to manage regarding anticoagulation, especially due to the feared risk of intracranial bleeding. The evidence so far suggests that those with brain metastasis are not facing a higher intracranial bleeding risk when receiving anticoagulation (irrespective of the type of anticoagulation, i.e., DOAC or LMWH) compared to cancer patients without brain metastasis.[62] In contrast, an elevated intracranial hemorrhage risk is present in patients with primary brain cancer[62–66] which is, however, less pronounced in patients receiving DOACs compared to those receiving LMWH.[62]

Thirdly, surgical procedures in patients with cancer represent another special situation that is associated with a heightened risk of bleeding. However, surgery is also associated with a high risk of VTE and, therefore, thromboprophylaxis is given in hospitalized or immobilized patients undergoing surgical interventions. Available data on bleeding rates in patients with cancer undergoing surgery primarily emerge from studies focusing on postoperative thromboprophylaxis. Guidelines recommend extended thromboprophylaxis with LMWH for an additional 4 weeks after hospital discharge in cancer patients undergoing major

abdominal or pelvic surgery.[3–6] Data suggest that again patients with cancer face a higher bleeding risk than the noncancer population in this setting.[67–69] However, despite the elevated bleeding risk, the benefits of thromboprophylaxis in reducing VTE were reported to outweigh the increase in bleeding in patients undergoing gynecological, urinary tract, or laparoscopic abdominal cancer surgery.[70–73] In this setting, the use of a DOAC for this indication showed similar bleeding risk, indicating that it may be a safe alternative.[74–76] Except for patients undergoing major cancer surgery, patients who seem to be at high postoperative bleeding risk are the ones with head and neck cancer.[77,78]

Furthermore, the insertion and use of central venous access devices (CVADs) can be associated with bleeding complications. However, the risk of any bleeding complication is reported to be low at 0.5 to 1.6%.[79] As catheter-related thrombosis (CRT) is the most frequent complication, most data regarding bleeding complications following CVAD insertions stem from studies focused on CRT treatment. Recent studies evaluating MB and CRNMB rates in cancer patients with anticoagulation for CRT reported MB and CRNMB rates varied greatly between 0.0 and 10.3% and between 3.2 and 13.1%, respectively, as the follow-up time was very heterogeneous.[80–83]

Patients in special situations might fulfill an indication for anticoagulant dosage reduction such as renal impairment, reduced body weight, or concomitant use of a comedication which is a strong P-glycoprotein inhibitor in the case of edoxaban. For the long-term prevention of VTE recurrence in the general population, a reduced dose of apixaban or rivaroxaban is often used after an initial treatment period of 6 months. This dose reduction has been addressed in studies of patients with cancer-associated VTE.[84] The EVE study results have been recently published and demonstrated that a reduced dose of apixaban had the same efficacy; however, it was not associated with a decreased bleeding risk.[85] Further evidence regarding dose reduction is currently lacking.

Risk Factors for Bleeding in Patients with Cancer and Anticoagulation

To evaluate bleeding risk and identify high-risk patients, risk factors and predictors of bleeding risk were assessed in different studies and clinical settings. Risk factors associated with increased bleeding risk in RCTs included the following: thrombocytopenia, metastatic disease, age, kidney function, cancer type, and the presence of intracranial malignancy.[86–89] Bleeding risk increased further with a declining kidney function, especially in patients on anticoagulation with VKA.[88] Furthermore, thrombocytopenia is a risk factor for bleeding in patients with cancer. In post hoc analyses of an RCT (DOAC vs. LMWH), a higher bleeding risk in patients with thrombocytopenia was observed,[90] which was more pronounced in patients with GI malignancy receiving edoxaban and in those with hematological malignancy receiving LMWH. In a recent meta-analysis also, a higher frequency of any bleeding in patients with anticoagulation (full or modified dose) and thrombocytopenia was found.[19] Moreover, lower hemoglobin was suggested as a bleeding risk factor.[91] The risk of bleeding is further increased in patients with a poor performance status (ECOG 2 or higher), with certain cancer sites such as GU, nonresected luminal GI, and upper GI cancers.[92] Interestingly, no significant association between advanced-stage cancer and increased bleeding risk was found.[93]

In real-life cohorts or registry studies, some of these risk factors could be confirmed, such as the presence of metastatic disease, reduced kidney function, and advanced age.[23,27,41,52,94–96] Furthermore, while hemoglobin and platelet counts were confirmed as risk factors, leukocyte count was proposed as a laboratory marker of importance.[96] Additional risk factors for increased MB were a recent history of immobility, MB, and cancer diagnosis.[94,95] Reported data on the association between body weight and bleeding risk were rather controversial, as some reported an increased risk with low body weight and others with high body weight.[95,97] Regarding tumor site as a risk factor, quite heterogeneous results have been reported as well. Other cancer types with an increased bleeding risk were observed to include lung, prostate, colorectal,[98] pancreas, biliary tract, gallbladder, esophagus, and urinary tract cancer.[99]

Similarly, risk factors for bleeding have been described in hospitalized cancer patients including low hemoglobin levels or anemia, GI cancer site, thrombocytopenia, and surprisingly a BMI $\geq$40 kg/m^2.[59,60] Patients admitted to the palliative care unit receiving thromboprophylaxis were at risk for increased bleeding, if they had additional antiplatelet therapy or a recent history of bleeding.[21]

Another significant modifying factor for bleeding risk is the type of anticancer therapy. Evidence suggests that vascular epithelial growth factor inhibitor agents are associated with increased bleeding risk, especially bevacizumab, ramucirumab, sunitinib, sorafenib, and nintedanib.[100–104] This heightened risk seems to be even greater when patients receive factor Xa inhibitors (i.e., DOAC or LMWH).[105] Furthermore, ibrutinib, a Bruton-tyrosine kinase inhibitor, was shown to be associated with an increased bleeding risk, most probably by causing platelet dysfunction.[106] This even led to the recommendation of cautious use of aspirin, nonsteroidal anti-inflammatory drugs, and fish oils in patients receiving ibrutinib.[107]

Finally, the bleeding rates have been found to differ between types of anticoagulants with the highest bleeding risk in patients on VKA and DOAC as compared to LMWH.[32,37] Drug–drug interaction of anticoagulants may also add to an increased bleeding risk. However, in a recent study, no significant association of concurrent anticoagulation and anticancer or supportive care therapies with bleeding risk was found,[108] whereas an increased risk was reported in patients taking both nonsteroidal anti-inflammatory drugs and DOACs.[109] Lastly, platelet inhibiting agents (such as aspirin or ADP receptor blockers) can modify the bleeding risk in patients with cancer.[110]

►Fig. 1 provides an overview of factors associated with an increased bleeding risk in patients with cancer receiving anticoagulation.

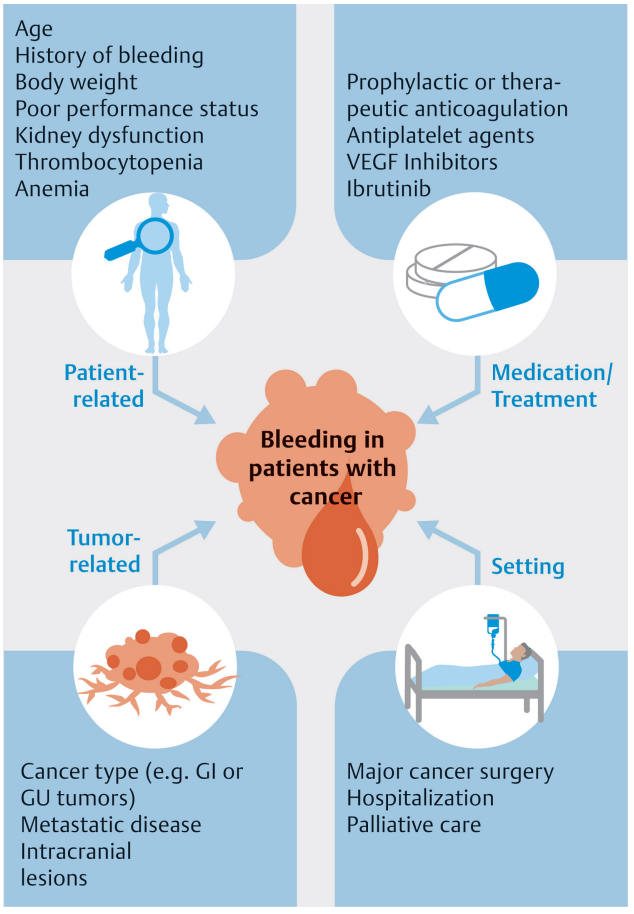

Fig. 1 Risk factors for bleeding in patients with cancer receiving anticoagulation. GI, gastrointestinal; GU, genitourinary.

Risk Assessment Models for Bleeding Events

Bleeding risk assessment tools and models that were developed for the general population often include the presence of cancer as an independent predictor for bleeding events, assigning patients with cancer predominantly to the high-risk groups of the models and not allowing to further stratify the bleeding risk. Not surprisingly, nearly all scores have been shown to perform poorly when restricted to cohorts of patients with cancer.[51,111]

Recently, two risk assessment models were developed in cohorts of patients with cancer receiving anticoagulation. The CAT-BLEED score was derived from the Hokusai VTE cancer study, a RCT comparing edoxaban versus dalteparin for the treatment of cancer-associated VTE (►**Table 3**). The discriminatory ability in the derivation cohort for the outcome of interest, which was defined as CRB within 6 months of the start of anticoagulation therapy, was moderate (c-statistics of 0.63).[111] So far, only one study tried to externally validate this score and showed a poor discriminatory ability (c-statistics: 0.47–0.48).[43]

A second risk assessment model, the B-CAT score, was developed in a retrospective observational cohort study of patients with cancer-associated VTE on anticoagulation therapy. This score includes 17 predictors that were all assigned with 1 score point (►**Table 3**). Important to note is that here the outcome of interest was either MB or MB plus CRNMB which led to hospitalization. The discriminatory ability of the B-CAT score in the derivation cohort (c-statistics for significant bleeds: 0.70 [0.65–0.75], c-statistics for MB: 0.76 [0.68–0.84]) was good.[49] This score has not been externally validated yet.

New approaches such as machine-learning models have been applied to identify and develop risk assessment tools in patients with cancer-associated VTE receiving anticoagulation, and in the TROLL registry, the machine-learning model performed better than existing risk models such as the CAT-BLEED score in predicting the risk of bleeding.[43] However, such models need further validation until they can be applied in routine clinical practice.

As in cancer-associated VTE, novel biomarkers may be promising to identify cancer patients at risk of bleeding and refine risk prediction. So far, in one study, growth differentiation factor-15 (GDF-15), a stress-response protein of the transforming growth factor-β superfamily, was investigated for the prediction of bleeding risk in patients with cancer, as it was previously shown to be predictive of bleeding in patients with AF and incorporated in a bleeding risk score.[112] Higher levels of GDF-15 were associated with increased bleeding risk. The discriminatory ability (together with the ABC score that includes GDF-15) in patients with cancer receiving apixaban as primary thromboprophylaxis was good to moderate (c-statistics GDF-15: 0.73; c-statistics ABC score: 0.65).[91]

Impact of Bleeding Events on Prognosis of Cancer

Bleeding events in patients with cancer are associated with increased morbidity and mortality. One of the most dreaded events is bleeding into critical sites or organs of the body with a fatal consequence. Fatal bleeding incidents can occur in both patients with cancer with or without anticoagulation. The latest RCTs comparing LMWH versus DOAC reported low numbers of fatal bleeding events, such as 0.0 to 0.5% for both LMWH and DOAC.[33–36] However, the case-fatality rate of MB events among cancer patients with VTE receiving anticoagulation was 8.9% according to a meta-analysis.[113] A recent retrospective study found a higher case-fatality rate of 21.1% after MB.[49] A more alarming case-fatality rate of bleeding was observed among patients admitted to palliative care units. In total, 34 MB events occurred in 32 palliative care patients and of those, 23 were fatal, resulting in a case-fatality rate of MB of 71.9% and all bleeding events of 19.8%.[21]

Interestingly, the timing of fatal bleeding events was suggested to be linked to the duration of anticoagulation. In a registry-based analysis, most MB occurred after 10 days of initiation of anticoagulation, while fatal PE was more common in the first 5 days.[42,114] In another study, approximately half of patients with a bleeding event died within 1 week.[95]

Bleeding events could also impact long-term mortality risk in patients with cancer. Similar to VTE, bleeding events were reported to be associated with poor overall survival.[44] Importantly, already CRNMB was shown to impact the prognosis of cancer patients.[97]

Table 3 Summary of risk assessment models for bleeding risk prediction in patients with cancer receiving anticoagulation

Score	Derivation cohort	Validation cohort	Predictors included	Calculation
CAT-BLEED[108]	Hokusai VTE Cancer study (RCT comparing edoxaban vs. dalteparin for treatment of cancer-associated VTE)	TROLL registry (registry of patients with cancer-associatedVTE)	◦ Regionally advanced or metastatic cancer ◦ Genitourinary cancer ◦ Creatinine clearance ◦ Recent use of anticancer therapies associated with gastrointestinal toxicity ◦ Age $\geq$ 75 y ◦ Interaction term between the type of anticoagulant (i.e., edoxaban vs. dalteparin) ◦ Gastrointestinal cancer	Formula for 6-mo survival free of clinically relevant bleeding
B-CAT[49]	Retrospective database of patients with cancer-associated VTE treated with anticoagulation	None	◦ Bladder, central nervous system, cervix, kidney, malignant melanoma, prostate, or upper gastrointestinal tract cancer ◦ Metastatic cancer ◦ Minor surgery and trauma ◦ History of MB (any time) and of CRNMB (last 2 y) ◦ CRNMB not leading to hospitalization after the initial cancer-associated VTE ◦ Anemia ◦ Known coagulation disorders ◦ Gastroduodenal disease ◦ Stroke	1 point per item Low-risk: 0–1 points Medium-risk: 2–3 points High-risk: 4+ points

Abbreviations: CRNMB, clinically relevant non-major bleeding; d, day(s); m, month(s); RCT, randomized controlled trial; VTE, venous thromboembolism.

Discussion

In summary, patients with cancer face a substantial risk of bleeding. According to some publications, bleeding events may have a significant impact on the prognosis of patients, which exceeds the case-fatality of VTE.[44,97] Due to differences in the study designs, observation times, definitions, analyses, and reporting of bleeding events, a comparison between studies is challenging. There is an increasing awareness of the heightened bleeding risk in patients with cancer and its clinical relevance is gaining more attention. The ISTH definition for nonsurgical bleeding[115] is the most widely used one to assess and report MB events in interventional trials and other studies. However, some challenges and limitations might occur when it is applied to studies of patients with cancer. For instance, some items of the ISTH definitions such as hemoglobin drop of at least 2 g/dL and transfusion of two erythrocyte concentrates as two of the defining criteria of an MB event might occur in a patient with cancer even in the absence of bleeding due to cancer itself, anticancer treatment leading to anemia, or both.

At present, data from RCTs, general observational cohorts, or cohorts including patients with specific anticoagulants (mainly DOACs) are available, although it is hard to pool and interpret their findings. This heterogeneity could contribute to the observed differences regarding bleeding risk/rates or risk factors for bleeding events. At present, the most robust conclusions can only be made for patients with cancer receiving anticoagulation. They face an increased bleeding risk when receiving anticoagulation for the treatment of VTE or other indications (e.g., AF).[22–28,54–57] The bleeding risk depends on the class of anticoagulants, with the highest risk seen with VKA and lower risk with LMWH. Other anticoagulants such as DOACs seem to have specific risk profiles that might lead to different bleeding patterns and necessitate a careful selection of the right agent in the right dose for the individual patient. It is worth noting that the number of patients with hematologic cancer included in RCTs was small and often patients with acute leukemia were excluded. However, clinical decision-making based on individual risk assessment is difficult, as findings regarding risk factors have been sometimes controversial and not confirmed in published studies. One relevant risk factor is the site of cancer, with higher bleeding risk (especially from the GI tract) in patients with GI tumors in the majority of studies.[34,35,60,90,92] Also an impaired kidney function has been associated with an increased bleeding risk in most of the studies.[41,86–88,94–96] Bleeding risk is also higher in patients with metastatic disease.[17,52,87,92–96] Among laboratory parameters, low platelet counts and hemoglobin levels are commonly reported as risk factors.[19,59,60,90,91,96] A history of bleeding, especially when it occurred recently, is associated with future bleeding events.[21,94,98] Finally, special situations such as hospitalization, palliative care, or surgery can modify the bleeding risk in patients with cancer.[20,21,68]

Bleeding risk assessment models have been developed for cancer patients undergoing anticoagulation, which require further validation in independent cohorts.[49,111] However,

estimating and predicting the bleeding risk in patients with cancer in various clinical settings is still imperfect, and there is an urgent need for the development of more precise and validated bleeding risk assessment tools.

For cancer patients without anticoagulation, more research is needed to investigate their baseline bleeding risk and identify bleeding risk factors. Most of the currently available data derive from placebo groups of RCTs evaluating primary thromboprophylaxis, which represent selected populations and do not accurately reflect the bleeding risk in daily clinical practice. A better understanding of bleeding risk would facilitate an individual risk–benefit evaluation (bleeding vs. VTE risk) of primary thromboprophylaxis.

Conflicts of Interest

C.E. reports no conflicts of interest.

N.V. reports no conflicts of interest.

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