Anticoagulation challenges in patients with hematological malignancy-associated thrombosis and severe thrombocytopenia

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ABSTRACT

Patients with cancer are at increased risk of venous thromboembolism (VTE), with incidence rates of 5-20% depending on tumor type, stage, and treatment. The coexistence of cancer-associated thrombosis (CAT) and thrombocytopenia is a particularly challenging therapeutic dilemma, occurring in nearly half of patients with hematologic malignancies and in about one-fifth of patients with solid tumors who require anticoagulation. This review examines the current evidence for managing anticoagulation in patients with hematological malignancy-associated thrombosis and severe thrombocytopenia (platelet count less than 50×10^9/L). Robust data are limited because pivotal trials establishing the standard of care for CAT treatment systematically excluded patients with moderate-to-severe thrombocytopenia. The existing evidence largely derives from small retrospective studies and only three prospective observational studies, which predominantly enrolled patients with hematologic cancers. These studies demonstrate variability in clinical practice encompassing full-intensity anticoagulation with platelet transfusion support, reduced-dose regimens, and treatment interruption. Major bleeding rates ranged from 3% to 13%, while VTE recurrence occurred in 0% to 6% of cases across different management approaches. Current guidelines generally agree on the need for personalized treatment decisions guided by VTE severity, bleeding risk assessment, and platelet count trajectory. However, platelet counts alone demonstrate poor predictive value for bleeding events, and maintaining platelet counts above 50×10□/L through transfusion does not consistently prevent hemorrhagic complications. Optimal management requires tailored, multidisciplinary approaches. The forthcoming START trial will compare the efficacy of dose-adjusted anticoagulation versus transfusion-supported full-dose therapy, which could establish an evidence-based standard of care for this vulnerable population.

Key words: cancer; hematological malignancy; thrombocytopenia; bleeding, venous thromboembolism; anticoagulant; platelet transfusion.

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Introduction

Patients with cancer have a 4- to 9-fold higher risk of developing venous thromboembolism (VTE) compared with the general population, with incidence rates ranging from 5% to 20% depending on malignancy type, stage, and anticancer treatment.[1] Long-term anticoagulation remains the cornerstone of cancer-associated thrombosis (CAT) management, yet it carries substantial bleeding risk with an estimated case fatality rate of 12% for major bleeding events.[2]

Thrombocytopenia also represents a frequent complication in oncology practice, particularly among patients receiving cytotoxic chemotherapy. Thrombocytopenia severity is traditionally classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (Table 1), which defines Grade 1 (75-<100×10^9/L), Grade 2 (50-<75×10^9/L), Grade 3 (25-<50×10^9/L), and Grade 4 (<25×10^9/L) thrombocytopenia. A large retrospective analysis of 15,521 patients with solid tumors and 2,537 patients with hematologic malignancies initiating chemotherapy revealed a 3-month cumulative incidence of grade 3-4 thrombocytopenia of 28% in hematologic malignancies and 6% in solid tumors.[3] While thrombocytopenia is more prevalent and severe in hematological malignancies, it also represents a clinically significant complication in patients with solid tumors receiving chemotherapy. No-

Table 1. Grades of thrombocytopenia according to the National Cancer Institute Common Terminology Criteria for Adverse Events.61

Grade	Platelet count	Severity
Grade 1	75×109/L to <100×10^9/L	Mild thrombocytopenia
Grade 2	50×109/L to <75×10^9/L	Moderate thrombocytopenia
Grade 3	25×109/L to <50×10^9/L	Severe thrombocytopenia
Grade 4	<25×10^9/L	Life-threatening thrombocytopenia

tably, specific chemotherapy regimens for solid tumors, particularly platinum-based combinations and gemcitabine-containing regimens, may induce severe thrombocytopenia in up to one-third of treated patients.[4]

The concurrent presentation of CAT and thrombocytopenia creates a precarious therapeutic dilemma. Importantly, thrombocytopenia does not protect cancer patients from thrombotic events,[5] yet anticoagulation in this setting substantially increase the risk of clinically relevant and potentially fatal, bleeding.[6] This clinical equipoise requires careful navigation between the competing risks of VTE recurrence and life-threatening bleeding.

For years, management guidance in this challenging scenario remained sparse, with recommendations largely derived from expert consensus rather than robust clinical evidence. Over the past decade, however, accumulating data from retrospective analyses and prospective cohort studies have begun to clarify the safety and efficacy of anticoagulation in patients with cancer and thrombocytopenia, gradually establishing a more evidence-based foundation for clinical practice.

Contemporary cancer care adds further complexity to this landscape. Today's patients with cancer are older, carry greater comorbidity burdens, and increasingly receive polypharmacy regimens that may include multiple antithrombotic agents. These evolving patient characteristics complicate both bleeding risk stratification and treatment decision-making, necessitating increasingly sophisticated and individualized approaches.

Methods

This narrative review synthesizes current evidence on anticoagulation management in patients with hematological malignancy-associated thrombosis and severe thrombocytopenia (platelet count <50×10^9/L). The objectives were to: i) evaluate the epidemiology and clinical characteristics of concomitant hematological malignancy-associated thrombosis and thrombocytopenia; ii) critically appraise available evidence from observational studies and clinical trials regarding anticoagulation strategies in this population; iii) compare recommendations from major international clinical practice guidelines; iv) examine factors beyond platelet count thresholds that influence bleeding risk; and v) propose a practical, evidence-informed algorithm for clinical decision-making.

We conducted comprehensive literature searches in PubMed, Embase, and the Cochrane Library from database inception through December 2025. Search terms included combinations of: "cancer," "malignancy," "hematologic malignancy," "thrombocytopenia," "venous thromboembolism," "thrombosis," "anticoagulation," "anticoagulant," "low molecular weight heparin," "LMWH," "direct oral anticoagulants," "DOACs," "bleeding," and "platelet transfusion." We also hand-searched reference lists of key articles and recent systematic reviews to identify additional relevant studies. Clinical practice guidelines were identified through searches of guideline databases and professional society websites, including the International Society on Thrombosis and Haemostasis (ISTH), American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), European Hematology Association (EHA), European Society for Medical Oncology (ESMO), and National Comprehensive Cancer Network (NCCN).

We included observational studies (retrospective cohort studies, prospective cohort studies, case series with ≥10 patients), clinical trials, meta-analyses, systematic reviews, and clinical practice guidelines that addressed anticoagulation management in adult patients (≥18 years) with active cancer, documented venous thromboembolism, and concurrent thrombocytopenia. Studies were prioritized that specifically reported outcomes (recurrent VTE, major bleeding, clinically relevant non-major bleeding) stratified by platelet count thresholds or anticoagulation strategy. We also included studies examining bleeding risk factors and predictive scores in patients with CAT and thrombocytopenia.

We excluded case reports, studies with fewer than 10 patients, non-English language publications without available translation, and studies focusing exclusively on arterial thrombosis or thromboprophylaxis in non-thrombotic patients. Studies addressing CAR T-cell therapy were not systematically included due to the paucity of available data and lack of specific guidelines for this population.

Given the narrative nature of this review and the heterogeneity of available studies (varying definitions of thrombocytopenia severity, anticoagulation regimens, follow-up duration, and outcome reporting), we did not perform quantitative meta-analysis. Instead, findings were synthesized qualitatively, focusing on key themes including epidemiology, anticoagulation strategies, bleeding and thrombotic outcomes, guideline recommendations, and risk stratification approaches. Where available meta-analyses existed, we incorporated their quantitative findings. All authors reviewed the extracted data and contributed to the synthesis and interpretation of findings.

Concomitant thrombocytopenia is common in patients with hematological malignancy-associated thrombosis

The coexistence of CAT and thrombocytopenia is common across cancer populations. A large retrospective analysis of

3,635 patients with CAT from the Beth Israel Deaconess Medical Center revealed that, at admission, thrombocytopenia affected 22% (95% confidence interval [CI], 21-24%) of patients with solid tumors and 47% (95% CI, 43-51%) of patients with hematologic malignancies. Severe thrombocytopenia (platelet count $<50\times10^9$/L) was present in 7% (95% CI: 6-8%) and 30% (95% CI: 27-34%), respectively.[7]

The landscape of cancer treatment is rapidly evolving with the advent of novel therapies. CAR-T cell therapy, for example, is increasingly used to treat hematologic malignancies and often induces severe thrombocytopenia (15-60% grade 3-4 early-onset and 7-48% prolonged) and heightened thrombotic risk.[8] Despite low platelet counts, the incidence of VTE reaches 2.4% per person-month. Six to ten percent of patients develop VTE within the first three months post-infusion, particularly those experiencing severe cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome.[8] Thrombotic risk peaks during the first six months following treatment.[8]

Thrombocytopenia does not confer protection against thrombosis extension or VTE recurrence.[5] Data from the multinational RIETE registry demonstrate that among patients with severe thrombocytopenia, 30-day rates of fatal pulmonary embolism (PE) and fatal bleeding are similar (2.9% *vs* 2.2%, respectively).[9] Therefore, anticoagulation remains standard of care even in thrombocytopenic patients, unless absolute contraindications exist. Clinical decision-making requires meticulous individualized assessment, continuously balancing the competing risks of thrombosis and bleeding.

Despite thrombocytopenia being highly prevalent in patients with hematological malignancy-associated thrombosis, patients with moderate or severe thrombocytopenia have been systematically excluded from the pivotal randomized controlled trials (RCTs) that assessed the efficacy and safety of low molecular weight heparin (LMWH) *vs* vitamin K antagonist (VKA) for the treatment of CAT.[10,11] In the CLOT trial, dalteparin doses were reduced by about 25% for patients with platelet counts between 50×10^9/L and 100×10^9/L. Anticoagulation was withheld if platelet counts fell below 50×10^9/L.[10] Likewise, RCTs evaluating direct oral anticoagulants (DOACs) *vs* LMWH for the treatment of CAT have consistently excluded patients with moderate or severe thrombocytopenia.[12-16] Therefore, the safety and efficacy data from these pivotal trials cannot be extrapolated to patients with severe thrombocytopenia.

Evidence from observational studies

There is limited evidence to guide anticoagulation management in patients with CAT and severe thrombocytopenia. Most data come from small retrospective studies.[17-33] Only three recent prospective studies[34-36] have assessed various anticoagulation strategies In this population (Table 2). These cohorts predominantly included patients with hematologic malignancies or undergoing hematopoietic stem cell transplantation (HSCT), most of whom received LMWH. Management approaches varied widely and encompassed full-dose anticoagulation with or without platelet transfusion support, reduced-dose regimens (for example, intermediate-dose LMWH such as enoxaparin 1 mg/kg once daily or 0.5 mg/kg twice daily, or prophylactic-dose enoxaparin 40 mg once daily), and temporary interruption of anticoagulation according to platelet-count thresholds. Across studies, these heterogeneous strategies were associated with similarly heterogeneous rates of recurrent VTE, major bleeding, and overall bleeding complications.[17-36] A recent meta-analysis reported pooled incidences of recurrent VTE of 2.65, 3.51, and 3.68 per 100 patient-months for full-dose, modified-dose, and no anticoagulation, respectively, with incidence rate ratios of 2.01 (95% CI 0.56-6.41) for modified-dose and 1.78 (95% CI 0.46-5.89) for no anticoagulation compared with full-dose.[37] The corresponding pooled incidences of major bleeding were 4.45, 4.16, and 2.20 per 100 patient-months, yielding incidence rate ratios of 0.93 (95% CI 0.39-2.15) and 0.49 (95% CI 0.11-1.47), respectively, versus full-dose therapy. Taken together, these findings suggest that dose reduction may modestly increase thrombotic risk without clearly decreasing major bleeding compared to full-dose anticoagulation.

Two recent prospective observational studies reported conflicting results. The TROVE (Thrombocytopenia Related Outcomes with Venous thromboEmbolism) study enrolled 121 patients with CAT and platelet counts below 100×10^9/L, including 85 with hematologic malignancies.[34] The anticoagulation strategy was determined by the treating physician and extracted from medical charts retrospectively. Overall, 62% of patients received full-dose anticoagulation, primarily LMWH, combined with platelet transfusion; 27% were treated with a modified-dose, defined as unfractionated heparin (UFH) with decreased activated partial thromboplastin time (aPTT) or anti–factor Xa targets; enoxaparin dose <1.5 mg/kg per 24 h; apixaban 2.5 mg twice daily; or rivaroxaban 10 mg daily; and 11% did not receive anticoagulation. Among the 27% of patients treated with a modified dose, the median platelet count was 37×10^9/L (interquartile range [IQR]: 24-48×10^9/L), compared to 65×10^9/L (IQR: 47-88×10^9/L) in patients treated with full-dose anticoagulation. Notably, 31 out of 33 patients (94%) who received a modified dose had hematological malignancies and acute deep vein thrombosis (DVT). Over a 60-day observation period, the rate of major bleeding was 12.8% in the full-dose anticoagulation group and 6.6% in the modified-dose anticoagulation group. VTE recurrence occurred in 5.6% of patients in the full-dose anticoagulation group versus none in the modified-dose anticoagulation group. These findings suggest a potentially favorable risk-benefit profile for dose reduction. The multicenter CAVEaT (Cancer Associated Venous Thrombosis and Thrombocytopenia) study prospectively included 105 patients with hematologic malignancies who developed VTE within 28 days and had platelet counts below 50×10^9/L.[35] The study primarily aimed to compare UK clinical practice with national guidance and to identify research priorities. Anticoagulation strategies again varied considerably: 53% received full-dose LMWH or unfractionated heparin, 28% received half-dose LMWH, 3% received prophylactic LMWH, 4% received direct oral anticoagulants (DOACs), and 11% received no anticoagulation. Only 43% of patients were managed in accordance with national guidelines, underscoring marked practice heterogeneity. Over 28 days, major bleeding occurred in 3% of patients on full-dose LMWH/UFH and 4% of those on modified-dose LMWH, with no major bleeding in the DOAC or no-anticoagulation groups. Recurrent VTE occurred in 4% of patients in both the full-dose and modified-dose LMWH groups, with no recurrences in the DOAC or no-anticoagulation cohorts. No clear platelet transfusion or dose-reduction threshold

emerged that reliably mitigated either thrombosis progression or bleeding, and treatment strategies were dynamic: 27% of patients changed regimen within 28 days and 51% within 90 days.

In both studies, substantial imbalances in baseline characteristics between groups and bias preclude firm conclusions about relative risk reductions in bleeding or recurrent VTE.

Data on DOACs in patients with thrombocytopenia remain extremely limited. A recent retrospective study comparing DOACs and LMWH in 42 patients with CAT and platelet counts below 100×10^9/L found that 38% received DOACs and 45% LMWH.[33] Rates of recurrent VTE were low in both groups (0% with DOACs *vs* 5.3% with LMWH), although the small sample size precludes meaningful statistical comparison. Bleeding, predominantly non-major, occurred in 19% overall, with no major hemorrhages in either group. Treatment choices were strongly influenced by patient preference and thrombocytopenia severity, and outcomes appeared broadly comparable despite differences in platelet counts and cancer types. These observations suggest that DOACs may be a feasible option in carefully selected patients, in contrast to TROVE and CAVEaT, where bleeding rates among DOAC-treated patients were notably higher. Robust prospective studies are critically needed to clarify the safety and efficacy of DOACs in the setting of CAT with thrombocytopenia.

Table 2. Recent studies in patients with cancer-associated thrombosis and thrombocytopenia.

Characteristics	TROVE[34]	CAVEaT35	TAT[36]	Abbas *et al.*[33]
Country	United States	United Kingdom	France and Switzerland	Canada
Sample size (n)	121	105	100	42
Cancer types	Hematological malignancies (70%), solid tumor (30%)	Hematological malignancies (100%)	Hematological malignancies (100%)	Hematological malignancies (52.4%), solid tumor (47.6%)
Baseline platelet threshold for enrolment	<100×10⁹/L	<50×10⁹/L	-	<100×10⁹/L
Inclusion period	January 2016-September 2019	January 2018-December 2019	January 2018-December 2021	Not reported
Anticoagulant indication	Upper limb DVT (40%), lower limb DVT (40.5%), PE (37%), other (3%)	Upper limb DVT (42%), lower limb DVT (15%), PE (33%,) other (9.5%)	VTE (79%), atrial fibrillation (15%), other (6%)	Upper limb DVT (38.1%), lower limb DVT (40.5%), PE (40.5%), other (7.1%)
VTE acuity	Within 7 days	Within 28 days	Not reported	Not reported
Initial anticoagulation	Full dose LMWH, UFH or DOAC: 75/121 (62%) Modified dose LMWH, UFH or DOAC: 33/121 (27.3%) No anticoagulation: 13/121 (10.7%)	Full dose LMWH or UFH: 56/105 (53%) Modified dose LMWH: 33/105 (31%) DOACs: 4/105 (4%) No anticoagulation: 12/105 (11%)	Full dose: 42/100 (42%) Prophylactic dose: 28/100 (28%) No anticoagulation: 30/100 (30%)	Full dose UFH: 6/42 (14.3%) Full dose LMWH: 18/42 (42.9%) Modified dose LMWH: 1/42 (4.8%) Full dose DOACs: 14/42 (33.3%) Modified dose DOACs: 2/42 (4.0%) No anticoagulation: 1/42 (2%)
Recurrent VTE at 28-30 days	-	Full dose LMWH or UFH: 4% Modified dose LMWH: 4% DOACs: 0% No anticoagulation: 0%	30-day cumulative incidence of thrombus progression/ recurrent VTE 6.2%	-
Recurrent VTE at 60 days	Full dose anticoagulation: 5.6% (95% CI 0.2-11) Modified dose anticoagulation: 0%	Not reported		-
Recurrent VTE at 90 days	-	Full dose LMWH or UFH: 6% Modified dose LMWH: 4% DOACs: 0% No anticoagulation: 0%		1 recurrent VTE (1/42; 2.4%) in a patient receiving LMWH
Major bleeding at 28-30 days	-	Full dose LMWH or UFH: 3% Modified dose LMWH: 4% DOACs: 0% No anticoagulation: 0%	WHO grade ≥2: 29.3% WHO grade 4: 7.2%	-
Major bleeding at 60 days	Full dose anticoagulation: 12.8% (95% CI 4.9-20.8) Modified dose anticoagulation: 6.6% (95% CI 2.4-15.7)			-
Major bleeding at 90 days	-	Full dose LMWH or UFH: 3% Modified dose LMWH: 4% DOACs: 1% No anticoagulation: 0%		0

CAVEaT, Cancer-associated venous thrombosis and thrombocytopenia; CI, confidence interval; DOACs, direct oral anticoagulants; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; TROVE, thrombocytopenia related outcomes with venous thromboembolism; UFH, unfractionated heparin; VTE, venous thromboembolism.

Convergence and divergence across guidelines from major International Societies

Multiple clinical practice guidelines (CPGs) addressing the treatment of CAT have been issued in recent years, including those from the American Society of Clinical Oncology (ASCO),[38] the American Society of Hematology (ASH),[39] the International Initiative on Thrombosis and Cancer (ITAC),[40] the European Society for Medical Oncology (ESMO),[41] the INNOVTE CAT Working Group,[42] and the National Comprehensive Cancer Network (NCCN).[43] In addition, guidelines specifically focused on antithrombotic treatment in patients with cancer and thrombocytopenia have been published by the International Society on Thrombosis and Haemostasis (ISTH),[6] and by the European Hematology Association (EHA) in collaboration with the European Society of Cardiology (ESC).[44]

The severity of thrombocytopenia according to the National Cancer Institute Common Terminology Criteria has largely informed the platelet count thresholds used in these CPGs. Across these CPGs, there is broad consensus that patients with platelet counts above 50×10^9/L should receive full-dose therapeutic anticoagulation, with close monitoring of platelet counts and individualized assessment of bleeding risk factors. In contrast, when platelet counts fall below 50×10^9/L, recommendations vary widely (Table 3), reflecting the lack of high-quality evidence.

For platelet counts between 25×10^9/L and 50×10^9/L, two main management strategies are generally proposed: reduced-dose anticoagulation (typically at a prophylactic dose or 50% of the therapeutic dose) without transfusion support, or full-dose anticoagulation combined with prophylactic platelet transfusions to maintain platelet counts above 50×10^9/L. The former approach may attenuate bleeding risk but could increase the risk of thrombus extension or recurrent VTE, especially in high-risk situations such as symptomatic segmental or more proximal PE, proximal DVT, or a history of recurrent VTE. The latter strategy prioritizes prevention of thrombus progression and VTE recurrence but carries a higher bleeding risk and requires considerable transfusion resources.

Choice of strategy therefore depends on multiple factors, including the acuity and severity of the index VTE event and the patient's baseline and dynamic bleeding risk. The EHA guidelines further highlight the importance of the anticipated duration of thrombocytopenia in decision-making, distinguishing short-lived nadirs after chemotherapy, where intensive platelet transfusion support to maintain therapeutic anticoagulation may be justified in high-risk acute VTE, from prolonged severe thrombocytopenia, where dose reduction or temporary interruption of anticoagulation is generally favored until platelet recovery.[44] Most guidelines recommend temporary interruption of anticoagulation when platelet counts drop below 25×10^9/L, except in highly selected circumstances. In patients with proximal DVT who are at high risk for PE and have absolute contraindications to anticoagulation, such as active major bleeding or severe, sustained thrombocytopenia, placement of an inferior vena cava (IVC) filter may be considered on an individualized, case-by-case basis, recognizing the substantial risk of complications associated with the procedure.

In cases of catheter-related thrombosis (CVC-RT) where anticoagulation is contraindicated due to severe thrombocytopenia or active bleeding, most guidelines recommend removal of the central venous catheter, particularly when it is no longer functionally required or when there are signs of catheter-related complications (infection, thrombosis extension). The decision to remove the catheter must balance the thrombotic risk of leaving it *in situ* against the bleeding risk associated with the removal procedure in thrombocytopenic patients. When catheter removal is planned, guidelines generally recommend holding anticoagulation 12 h before and after the procedure and providing platelet transfusion support immediately prior to removal to minimize procedural bleeding risk. If the catheter remains essential for ongoing cancer therapy and anticoagulation cannot be safely administered, close surveillance with serial imaging is recommended to monitor for thrombus progression.

Beyond platelet count thresholds

Despite multiple international CPGs, real-world management of anticoagulation in cancer patients with thrombocytopenia remains highly heterogeneous,[33-36] reflecting the limited evidence underpinning current recommendations.

The prospective, binational TAT study aimed to evaluated real-world strategies and outcomes in adults with hematologic malignancies who were receiving intensive chemotherapy or hematopoietic stem cell transplantation (HSCT), required anticoagulation and were expected to have platelet counts below 50×10^9/L.[36] Most patients (70%) received LMWH, and the predominant strategy was to maintain full-dose anticoagulation with platelet transfusion support to maintain platelet counts above 50×10^9/L. Nevertheless, clinically relevant bleeding occurred in approximately one third of patients; notably, about half of these events occurred at platelet counts between 20 and 50×10^9/L, and roughly one fifth occurred even above the 50×10^9/L threshold. These findings are consistent with those from previous studies and suggest that high transfusion thresholds used to support full-dose anticoagulation neither reliably prevent bleeding nor avoid substantial consumption of blood product resources.

Evidence from patients with hematologic malignancies suggests that the risk of World Health Organization (WHO) grade ≥2 bleeding increases once platelet counts fall below 80×10^9/L.[45] However, with the exception of patients undergoing autologous HSCT who had platelet counts of $1\text{-}5\times10^9$/L, no progressive increase in bleeding risk with further platelet declines below this threshold was observed.[46,47] Consistently, several studies did not identify a clear inverse relationship between platelet counts in the $10\text{-}50\times10^9$/L range and bleeding risk,[48,49] although the overall data remain conflicting. These observations underscore the urgent need to move away from rigid, numeric platelet thresholds toward a more nuanced, multifactorial risk assessment.

In addition to platelet count, several clinical variables including older age, metastatic disease, anemia, renal impairment, liver dysfunction, and concomitant anticancer therapies, also modulate bleeding risk in patients with cancer.[50] In a recent systematic review of RCTs and cohort studies assessing prognostic factors for recurrent VTE and anticoagulant-related bleeding in adults with CAT, prior major bleeding (adjusted hazard ratio [aHR] 2.41, 95% CI 1.50-3.88), Eastern Cooperative Oncology Group (ECOG) performance status ≥2 (aHR 2.10, 95% CI 1.48-2.99), and advanced-stage cancer (aHR 1.60, 95% CI 1.29–1.97) were associated with an increased risk for bleeding.[51]

Table 3. Current international guidelines on the treatment of VTE in patients with severe thrombocytopenia (platelet count <50×10⁹/L).

Society	ISTH 2018[6]	ASCO 2020[38]	ASH 2021[38]	EHA 2022[44]	ITAC 2022[40]	ESMO 2023[41]	INNOVTE 2024[42]	NCCN 2025[43]
Recommendations	•High risk acute VTE (<30 days): full-dose anticoagulation (LMWH/UFH) and platelet transfusion to maintain a platelet count ≥40-50×10⁹/L. •Lower risk of recurrent VTE: dose reduction (50% of therapeutic dose).	•Relative contraindication to full-dose anticoagulation if platelet count <25×10⁹/L.	•No specific recommendations.	•Very high risk: full-dose anticoagulation and platelet transfusion to maintain a platelet count ≥40-50×10⁹/L for a maximum of 14 days. •High risk PE and in centers with appropriate expertise: systemic thrombolysis, interventional procedures of thrombus removal including catheter-based thrombolysis or pharmaco-mechanical catheter-directed reperfusion techniques •TPO-RA in patients with anticipated long duration of thrombocytopenia, but not in patients with high-thrombotic risk, acute leukemia, MDS, or extensive bone marrow infiltration. •If platelet count 25-50×10⁹/L: LMWH at prophylactic or therapeutic doses reduced by 50% in patients with acute VTE. •If platelet count <25x10⁹/L: stopping anticoagulation. •Removable inferior vena cava filter (IVCF) may be considered on an individual basis in patients with acute PE or acute lower extremity DVT up to 30 days since the diagnosis.	•Decisions on reatment and dosage should be made on a case-by-case basis with the utmost caution.	•High risk: full-dose anticoagulation and platelet transfusion to maintain platelet count ≥40-50×10⁹/L. •Low risk: intermediate to prophylactic-dose LMWH with temporary discontinuation of anticoagulation if the platelet count falls <25×10⁹/L.	•Acute VTE (first 30 days): dose-modified LMWH (25% dose reduction) in those with a platelet count between 30 and 50×10⁹/L; prophylactic dose LMWH with platelet transfusion support in those patients with a platelet count <30×10⁹/L •Considering placement of a removable IVCF on a case-by-case basis in those with persistent grade 3-4 thrombocytopenia •Acute VTE (beyond 30 days): dose-modified LMWH (50% dose reduction) in those patients with a platelet count between 30 and 50×10⁹/L.; prophylactic dose LMWH in those with a platelet count <30×10⁹/L, except in case of active bleeding; platelet transfusion support in those with persistent thrombocytopenia	•High risk of recurrent VTE: full-dose anticoagulation (LMWH/UFH) and platelet transfusion to maintain platelet count ≥50×10⁹/L, placement of a retrievable IVC filter and discontinuation of anticoagulation until platelet recovery. •Lower risk of recurrent VTE: - If platelet count 25-50×10⁹/: LMWH in prophylactic or therapeutic doses reduced by 50% in patients with acute VTE. - If platelet count <25x10⁹/: stopping anticoagulation.
Level ofevidence	Moderate consensus among the panelists	-	-	Expert opinion	Guidance	-	Expert opinion	Category 2A

DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; IVCF, inferior vena cava filter; VTE, venous thromboembolism.

Specific tumor types were also associated with higher bleeding risk, notably brain tumors (aHR 2.25, 95% CI 1.64-3.09), gastrointestinal cancers (aHR 1.74, 95% CI 1.44-2.11), and genitourinary cancers (aHR 1.90, 95% CI 1.48-2.45), In patients with hematological malignancies, additional risk factors for bleeding have been reported, including female sex,[49,52] fever,[53] allogeneic HSCT,[54,55] and a hematocrit ≤25%.[45]

Since platelet count alone is a poor predictor of bleeding, clinicians should incorporate these factors into decision-making. However, this paradigm shift is constrained by the lack of a validated bleeding risk score tailored to this complex population, reinforcing the need for individualized management and further research. Existing general VTE bleeding scores (e.g., VTE-BLEED,[56] RIETE[57]) perform poorly in CAT and are not recommended for this population. More specific scores such as CAT-BLEED[58] are not applicable in patients with CAT and significant thrombocytopenia because the score was derived in a population that largely excluded, or included very few patients with moderate or severe thrombocytopenia and has never been validated in that setting.

To refine bleeding risk assessment in patients with hematological malignancy and severe thrombocytopenia, several groups have explored global hemostasis assays. Although not conducted in patients with CAT, the prospective, observational ATHENA study offers important insights by evaluating whether rotational thromboelastometry (ROTEM) can predict bleeding in patients with hematologic malignancies and thrombocytopenia.[59] The study provided foundational evidence that viscoelastic assays may offer superior risk stratification compared with reliance on platelet count thresholds alone, supporting the concept that achieving a numerical platelet target (for example, >50×10^9/L) through transfusion does not necessarily correct the underlying hemostatic derangements. This may explain why bleeding frequently persists despite aggressive transfusion support and provides a strong rationale for developing clinico-biological bleeding scores that integrate viscoelastic or other biomarker data with clinical risk factors to guide anticoagulation and transfusion decisions.

Practical risk-adapted algorithm for bedside decision-making

We propose a practical algorithm for managing CAT in patients with hematological malignancies and severe thrombocytopenia (platelets ≤50×10^9/L), as detailed in Figure 1. This algorithm was specifically designed for patients with hematolog-

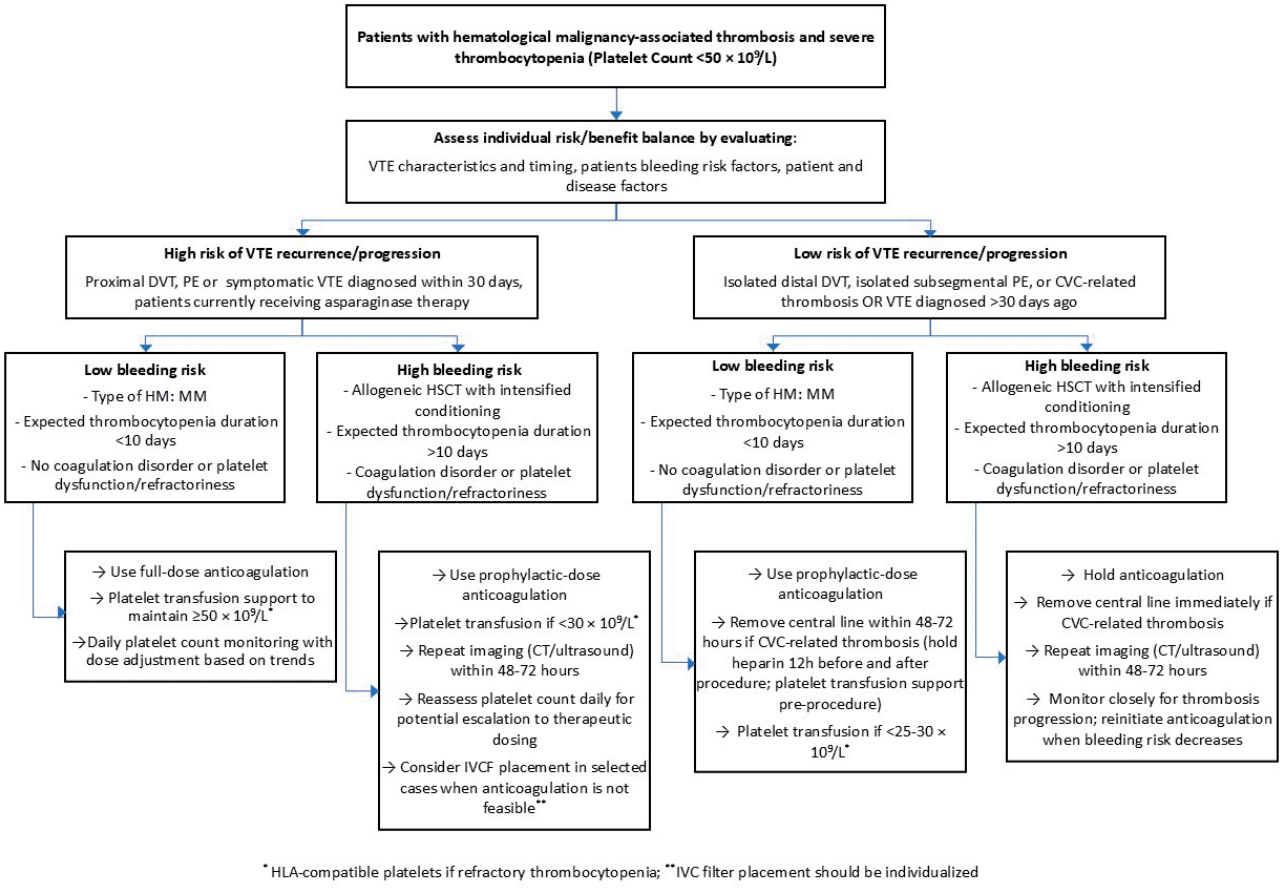

Figure 1. Management algorithm for hematological malignancy-associated thrombosis in patients with severe thrombocytopenia (platelet count <50×10^9/L). AlloHSCT, allogenic hematopoietic stem cell transplant; CVC, central venous catheter; DVT, deep vein thrombosis; IVCF, inferior vena cava filter; HM, hematological malignancy; MM, multiple myeloma; PE, pulmonary embolism; VTE, venous thromboembolism. * HLA-compatible platelets if refractory thrombocytopenia; **IVC filter placement should be individualized.

ical malignancies and severe thrombocytopenia (platelet count ≤50×10^9/L). The evidence base supporting this algorithm derives predominantly from studies in patients with hematologic cancers, who experience higher rates and longer duration of severe thrombocytopenia compared to patients with solid tumors. Additionally, patients with hematological malignancies have distinct bleeding risk profiles, including higher rates of coagulation abnormalities, platelet dysfunction, and bone marrow involvement that may not be fully applicable to solid tumor populations. While the general principles of individualized risk-benefit assessment may inform management in solid tumor patients with chemotherapy-induced thrombocytopenia, specific recommendations for this population require separate consideration and are beyond the scope of this review.

This stepwise approach begins with initial assessment to stratify VTE risk: high-risk VTE includes proximal DVT, PE or symptomatic events diagnosed within 30 days, whereas low-risk VTE encompasses isolated distal DVT, subsegmental PE, catheter-related thrombosis, or VTE diagnosed >30 days prior. Following VTE risk stratification, individualized clinical assessment of bleeding risk is performed based on factors relevant to this population, including type of hematological malignancy (e.g., post-allogeneic HSCT *vs* multiple myeloma), expected duration of thrombocytopenia (≤10 *vs* >10 days), presence of coagulation abnormalities or platelet dysfunction/refractoriness, recent or planned invasive procedures, concomitant antithrombotic therapies, and platelet transfusion feasibility. For high-risk VTE with low bleeding risk, we advise full-dose anticoagulation with platelet transfusion support to maintain platelets ≥50×10^9/L (using HLA-compatible platelets if refractory), daily platelet count monitoring, and dose adjustment based on platelet trends. For high-risk VTE with high bleeding risk, we advise modified-dose anticoagulation with platelet transfusion support to maintain platelets ≥30×10^9/L, repeat imaging (CT/ultrasound) within 48-72 h to assess for thrombus progression, and daily reassessment for potential escalation to full-dose therapy as bleeding risk improves. For low-risk VTE with low bleeding risk we advise prophylactic-dose anticoagulation with platelet transfusion support to maintain platelets ≥25-30×10^9/L, removal of central venous catheter within 48-72 h if catheter-related thrombosis (with anticoagulation held 12 h pre- and post-procedure and platelet support prior to removal), and optimization of cancer therapy. For low-risk VTE, we advise temporary hold of anticoagulation with close clinical monitoring, immediate removal of central venous catheter if catheter-related thrombosis and repeat imaging within 48-72 h to assess for thrombus progression, with plans to reinitiate anticoagulation when bleeding risk decreases.

In exceptional circumstances where anticoagulation is contraindicated due to prohibitive bleeding risk (e.g., active bleeding, severe refractory thrombocytopenia) but the risk of fatal pulmonary embolism from proximal deep vein thrombosis remains high, placement of a retrievable inferior vena cava filter may be considered on an individual basis following multidisciplinary discussion. The decision should weigh procedural risks in thrombocytopenic patients, device-related complications, and feasibility of timely removal once bleeding risk improves.

Frequent platelet count reassessment is essential. Daily platelets count monitoring is recommended for patients receiving full-dose anticoagulation with platelet transfusion support, particularly during active chemotherapy or early post-transplant periods. For patients on modified-dose anticoagulation with stable thrombocytopenia, monitoring every 2-3 days is generally advised, with more frequent assessment if platelet counts are declining. Monitoring frequency may be reduced to twice weekly once platelet counts stabilize and begin to recover.

This risk-adapted approach standardizes clinical decision-making while maintaining the flexibility necessary to balance the competing risks of VTE recurrence and major bleeding in this challenging patient population

The START trial: defining the standard of care

The ongoing START (STrategies for Anticoagulation in patients with thRombocytopenia and cancer-associated Thrombosis, NCT05255003) trial is an important step forward to define the optimal management strategy for patients with CAT and severe thrombocytopenia.[60] This prospective, multicenter, open-label randomized controlled trial will enroll adults with active cancer and acute CAT who have platelet counts below 50×10^9/L due to malignancy or its treatment. Participants will be randomly assigned to receive either modified-dose anticoagulation (50% LMWH for platelet counts between 25 and 50×10^9/L, with treatment withheld below 25×10^9/L) or platelet transfusions to support higher-dose anticoagulation (100% LMWH for platelet counts between 25 and 50×10^9/L, and 50% LMWH for platelet counts below 25×10^9/L).[60]

The feasibility phase aims to recruit 50 patients, identify barriers to enrollment, and validate key study parameters to inform the design of a subsequent large-scale trial. Although this pilot study is not statistically powered to compare clinical outcomes directly between the two strategies, all bleeding and thrombotic events will be prospectively captured and reported. The START trial is therefore poised to provide critical evidence to address the longstanding clinical dilemma of whether to prioritize effective CAT treatment with transfusion support or to minimize bleeding risk through anticoagulant dose modification. Until its results become available, clinicians must continue to rely on existing guidance and clinical judgment to navigate this complex therapeutic balance.

Conclusions

In patients with CAT and severe thrombocytopenia requiring anticoagulation, the risk of anticoagulant-related bleeding must be carefully weighed against the risk of thrombus extension or recurrent VTE. Thrombocytopenia does not protect against VTE; even at low platelet counts, fatal PE remains a persistent threat. Current management strategies include full-dose anticoagulation with platelet transfusion support, dose adjustments, or temporary interruption of anticoagulation. Acute VTE diagnosed within the previous 30 days generally requires more aggressive management because of the higher risk of fatal PE and thrombus progression. Complete cessation of anticoagulation should be reserved for situations of profound thrombocytopenia.

Optimal management in this population necessarily follows an individualized approach that integrates platelet trends, competing risks of bleeding and thrombosis, cancer status and prog-

nosis, and patient preferences. However, critical knowledge gaps persist, and prospective randomized trials are urgently needed to develop evidence-based management strategies. Specifically, studies comparing reduced-dose heparin with full-dose anticoagulation supported by platelet transfusions would clarify optimal dosing protocols and transfusion thresholds. Given heparin's potential advantages (reversibility, shorter half-life, and ease of monitoring) in patients with dynamic platelet counts, such trials are particularly relevant. Furthermore, randomized, head-to-head trials comparing reduced-dose heparin versus low-dose DOACs in patients with platelet counts between 30 and 50×10^9/L are essential to determine the safest and most effective anticoagulant class in this specific range of moderate thrombocytopenia, where both approaches are commonly used but lack comparative evidence. While the forthcoming START trial is expected to clarify the most effective therapeutic strategy, these additional trials are essential to move beyond expert opinion and observational data. Current practice demands a pragmatic, dynamic framework - one that emphasizes frequent reassessment, tailored anticoagulant adjustments, and judicious use of platelet transfusion support. Shared decision-making within a multidisciplinary team remains essential to navigating this complex clinical landscape.

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