International Journal of Hematology (2024) 119:516–525
https://doi.org/10.1007/s12185-023-03690-z

PROGRESS IN HEMATOLOGY

Cancer associated thrombosis and bleeding

Cancer-associated thrombosis in hematologic malignancies

Masahiko Fukatsu[1] · **Takayuki Ikezoe**[1]

Received: 1 November 2023 / Revised: 1 December 2023 / Accepted: 18 December 2023 / Published online: 25 January 2024

Abstract
Patients with hematologic malignancies are often complicated not only by severe bleeding due to thrombocytopenia and disseminated intravascular coagulation but also by thromboembolic events, just like in patients with solid cancers, and these events can negatively impact patient outcomes. Nevertheless, the prevention and treatment of cancer-associated thrombosis (CAT) in hematologic malignancies has not been adequately investigated due to the limited size, heterogeneity, and unique pathophysiology of the patient population. This article summarizes the current understanding, risk factors, prediction models, and optimal prevention and treatment strategies of CAT in hematologic malignancies on a disease-by-disease basis, including acute leukemia, lymphoma, myeloma, and myeloproliferative neoplasms. Specific considerations of novel molecular targeted therapeutics introduced in recent years, such as immunomodulatory drugs and tyrosine kinase inhibitors, are also discussed based on the latest clinical trials.

Keywords Cancer-associated thrombosis · Disseminated intravascular coagulation · Direct oral anticoagulant · Tyrosine kinase inhibitor · Immunomodulatory drug

Introduction

Since cancer patients are at high risk for both arterial and venous thrombosis compared to the general population, and appropriate prevention and treatment of cancer-associated thrombosis (CAT) is of critical prognostic impact, CAT has been the subject of intensive research, and various expert panels have published guidelines for CAT in recent years [1–4].

CAT is also a common complication among patients with hematologic malignancies. In a Danish health care registry-based population study, the adjusted standardized hazard ratios for the incidence of thrombosis by cancer type in the first six months after the cancer diagnosis were as follows: leukemia, 3.55 (95% confidence interval 2.82–4.49); non-Hodgkin lymphoma (HL) 7.44 (6.07–9.13); HL, 8.05 (5.98–10.83); and multiple myeloma (MM), 7.96 (6.30–10.04) [5].

The Khorana score is the most well-known risk assessment tool to guide the indication for anticoagulation in CAT, but the only blood cancer patients included in the original literature were those with lymphoma [6, 7]; leukemia, MM, and myeloproliferative neoplasm (MPN) patients were not enrolled in their study. The Khorana score, therefore, may not be applicable for stratifying the risk of CAT in hematologic malignancy, especially in acute leukemia, as the Khorana score is overestimated by anemia and leukocytosis [8, 9].

In recent years, a number of clinical trials have reported on the prevention [10, 11] and treatment [12–14] of CAT with direct oral anticoagulants (DOACs), and their efficacy is being established. However, most of these trials included only 10% or fewer patients with hematologic malignancies, and some studies excluded patients with acute leukemia (Table 1).

This article reviews the specific considerations of CAT in hematologic malignancies, up-to-date perspectives, and unresolved clinical questions on a disease-by-disease basis (Fig. 1).

✉ Masahiko Fukatsu
fukatsu@fmu.ac.jp

[1] Department of Hematology, Fukushima Medical University School of Medicine, 1 Hikarigaoka, Fukushima 960-1295, Japan

Table 1 Pivotal randomized-controlled trials of cancer-associated VTE prophylaxis or treatment in which hematologic malignancy patients were included

References	Design	Intervention/comparison	Patients, *N*	Patients with hematologic malignancy, *N* (%)	Primary endpoint	Key finding
Prophylaxis						
Carrier 2019 [10]	Placebo-controlled, double-blind	Apixaban vs. placebo	574	Lymphoma 145 (25.2%) Myeloma 15 (2.6%)	VTE	Favors apixaban
Khorana 2019 [11]	Placebo-controlled, double-blind	Rivaroxaban vs. placebo	841	Lymphoma 59 (7.0%)	Composite of VTE and PE	Favors rivaroxaban
Treatment						
Meyer 2002 [108]	Open-label	Enoxaparin vs. warfarin	146	Hematologic* 16 (10.9%)	Composite of recurrent VTE and major bleeding	Favors enoxaparin
Lee 2003 [109]	Open-label	Dalteparin vs. coumarin derivative	676	Hematologic* 70 (10.3%)	Symptomatic, recurrent VTE or PE	Favors dalteparin
Raskob 2018 [12]	Open-label, noninferiority	Edoxaban vs. dalteparin	1,046	Hematologic* 111 (10.6%)	Composite of recurrent VTE and major bleeding	Favors edoxaban
Young 2018 [110]	Open-label	Rivaroxaban vs. dalteparin	406	CLL 3 (0.7%) Lymphoma 23 (5.6%) Myeloma 5 (1.2%)	Recurrent VTE	Favors rivaroxaban
Agnelli 2020 [13]	Open-label, noninferiority	Apixaban vs. dalteparin	1,155	Hematologic* 85 (7.3%)	Recurrent VTE	Favors apixaban
McBane 2020 [14]	Open-label	Apixaban vs. dalteparin	300	Leukemia 4 (1.3%) Lymphoma 16 (5.3%) Myeloma 7 (2.3%) Other 1 (0.3%)	Major bleeding	Favors apixaban

CLL chronic lymphocytic leukemia, *PE* pulmonary embolism, *VTE* venous thromboembolism

*Detailed histology not available

Antithrombotic therapy in thrombocytopenic patients

The International Initiative on Thrombosis and Cancer (ITAC) clinical practice guidelines recommend low-molecular-weight heparin (LMWH) for the prevention and treatment of thrombosis associated with solid tumors [2]. However, patients with hematologic malignancies, especially those with acute leukemia, often present with severe thrombocytopenia due to underlying disease or intensive chemotherapy, which makes the bleeding risk associated with heparinoid administration a major concern.

Several clinical studies have examined the efficacy and safety of thromboprophylaxis by comparing standard versus reduced doses of LMWH in CAT patients with platelet counts below 50,000–100,000/μL [15, 16]. Reduced-dose LMWH was associated with similar or better outcomes in these large studies. In contrast, in another single-center retrospective study of 78 patients with platelet counts below 50,000/μL who needed treatment for venous thromboembolism (VTE) during chemotherapy for acute leukemia, lymphoma, and plasma cell tumors, patients who prematurely discontinued anticoagulation experienced fewer bleeding events at the cost of more recurrent VTE [17].

Practically, the NCCN guidelines recommend the following LMWH doses for CAT with thrombocytopenia: full dose for patients with platelet counts > 50,000/μL, a dose reduction for patients with platelet counts 25,000–50,000/μL, and discontinuation for patients with platelet counts < 25,000/μL [4].

Acute promyelocytic leukemia (APL)

Sixty-to-seventy percent of newly diagnosed APL cases are complicated by disseminated intravascular coagulation (DIC). At the same time, not only DIC but also thrombosis complicates approximately 9% of cases upon diagnosis and during treatment of APL [18]. Various coagulation and platelet aggregation activators, including podoplanin, are

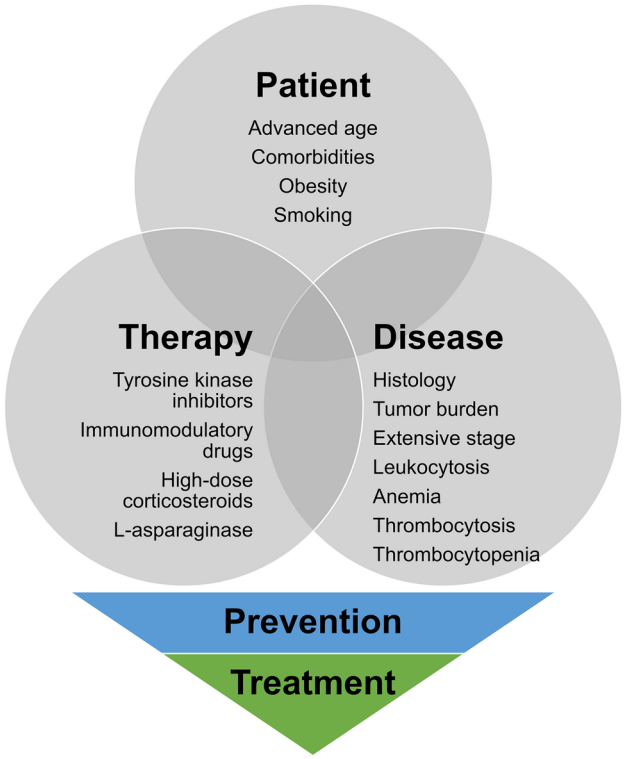

Fig. 1 Factors to consider in optimizing prevention and treatment strategies for CAT in hematologic malignancies

expressed by APL cells, which may contribute to thrombosis [19]. The binding of plasminogen and plasminogen activator to this tetramer results in efficient plasmin production and activation of the fibrinolytic system. All-*trans* retinoic acid (ATRA), a key drug in APL treatment, exerts its antifibrinolytic effect by suppressing the expression of the Annexin II/S100A10 heterotetramer, which is present on the APL cell surface [20, 21]. Several retrospective studies suggest that prompt administration of ATRA may lead to early resolution of DIC and improved survival [22, 23].

In the pre-ATRA era, antifibrinolytic therapy with the plasmin inhibitor tranexamic acid (TXA) in combination with transfusion support failed to demonstrate improvement in remission rates or early mortality due to bleeding compared to transfusion alone [24]. TXA is no longer recommended to be administered in combination with ATRA, because it can increase the risk of thrombosis [25].

Acute myeloid leukemia (AML) other than APL

DIC is also a risk factor for thrombotic events in non-APL AML, which is present in approximately 30% of AML patients at the initial presentation [26, 27]. The incidence of VTE in AML is 5–15%, most of which occurs within 3 months of AML diagnosis [9, 28–33]. In a single-center retrospective analysis of 222 AML cases, AML patients who developed thrombosis had a significantly worse prognosis than those who did not [9].

Several attempts to develop acute leukemia-specific CAT risk assessments have been reported. Previously identified risk factors for thromboembolic complications in AML include advanced age, high D-dimer, high white blood cell (WBC) count, and tobacco smoking [9, 27, 28, 33]. It is noteworthy that a preserved platelet count (> 50,000–100,000/μL) at diagnosis is also a risk factor for thromboembolic complications in AML [31] (Table 2).

Acute lymphoblastic leukemia (ALL)

The incidence of DIC in ALL is less than that in AML, approximately 10%, while thrombosis occurs at approximately the same or a slightly higher frequency in ALL than in AML [29, 34]. A retrospective analysis of 2482 ALL patients enrolled in a US cancer registry showed a 2-year cumulative incidence of thromboembolic complications of 4.5%, and the overall survival (OS) of ALL patients who developed thrombosis was inferior to that of those who did not [28].

ALL patients remain at high risk of thrombosis even after remission induction therapy, in contrast to AML patients [35, 36]. This may be partly explained by the high-dose corticosteroids and L-asparaginase (L-Asp) used to treat ALL, both of which cause an imbalance in coagulation and fibrinolysis [35]. Other known risk factors for thrombosis in ALL include advanced age, comorbidities, and high D-dimer levels, as in AML [37] (Table 2). L-Asp also inhibits the synthesis of various factors involved in blood coagulation and fibrinolysis, most notably plasma antithrombin (AT) activity and fibrinogen [38].

There have been no randomized-controlled trials (RCTs) examining the thromboprophylactic effect of AT concentrates in ALL patients receiving L-Asp, and no preventive measures with a high level of evidence have been established [39]. However, based on several retrospective analyses, the International Society on Thrombosis and Hemostasis (ISTH) recommends measuring plasma AT activity once a week and administering AT concentrates to maintain plasma AT activity above 50–60% [40, 41]. It is also weakly recommended that prophylactic fresh frozen plasma (FFP) not be administered routinely because the asparagine contained in FFP can compromise the antileukemic activity of L-Asp [41].

Lymphoma

The Khorana score defines lymphoma as the highest-risk disease by cancer type [6], even though validation studies raise the question of whether it is adequate for high/

Table 2 Common and disease-specific risk factors for VTE previously reported in hematologic malignancies

Risk factor	Acute leukemia	Lymphoma	Myeloma	PV	ET
History of thrombosis	X	X	X	X	X
Advanced age	X		X	X	X
Leukocytosis	X	X		X	
Thrombocytosis	X	X			
Tumor biology		Aggressive histology	High-risk cytogenetics	*JAK2* V617F	*JAK2* V617F
CVC	X	X	X		
Corticosteroid	X		X		
Obesity		X	X		
Smoking	X				
Disease-specific	L-asparaginase DIC Elevated D-dimer	Mediastinal involvement CNS involvement B symptoms Anemia Doxorubicin	IMiDs Cafilzomib Black or non-Asian ethnicity		Male sex
References	De Stefano 2005 [35] Ku 2009 [28] Libourel 2016 [27] Al-Ani 2020 [31] Anderson 2022 [37] Martella 2022 [9] Koschade 2023 [33]	Lekovic 2010 [46] Zhou 2010 [47] Lund 2015 [48] Antic 2016 [45] Sanfilippo 2016 [49] Santi 2017 [42]	Li 2019 [55] Sanfilippo 2019 [54] Chakraborty 2022 [111] Piedra 2022 [112] Charalampous 2023 [52]	Berk 1986 [78] Landolfi 2007 [80] Vannucchi 2007 [71] De Stefano 2008 [81] Ronner 2019 [113] Carobbio 2019 [83]	Alvarez-Larrán 2010 [114] Carobbio 2011 [115] Alvarez-Larrán 2016 [105] Carobbio 2019 [83]

CNS central nervous system, *CVC* central venous catheter, *DIC* disseminated intravascular coagulation, *ET* essential thrombocythemia, *IMiDs* immunomodulatory drugs, *PV* polycythemia vera, *VTE* venous thromboembolism

intermediate risk stratification [42, 43]. A retrospective analysis of 18,018 patients with lymphoma enrolled in 29 clinical studies showed a thrombosis incidence of 6.4%, with incidences of 5.3% for deep vein thrombosis (DVT) and 1.2% for pulmonary embolism (PE) [44]. By histological type of lymphoma, the incidence of VTE was 8.3% in high-grade non-Hodgkin lymphoma (NHL), 6.3% in low-grade NHL, and 4.7% in HL.

The ITAC guidelines recommend that intermediate- and high-risk patients with a Khorana score of 2 or higher receive prophylaxis with LMWH, apixaban, or rivaroxaban [2]. However, lymphoma patients accounted for only 10% of those enrolled in the original Khorana score study. The Thrombosis Lymphoma (ThroLy) risk model was developed to specifically predict the development of VTE in patients with lymphoma [45]. The model is scored by assessing a history of thrombosis, body mass index > 30 kg/m^2, mediastinal disease, extranodal involvement, performance status, neutropenia, and hemoglobin levels. Furthermore, an increased risk of developing VTE has been reported in patients with primary central nervous system lymphoma, primary mediastinal large B-cell lymphoma, use of anthracycline or methotrexate, and B symptoms [46–49] (Table 2).

A retrospective comparison of the efficacy and safety of LMWH and warfarin in 57 patients with lymphoma showed the superiority of LMWH [50], and the ITAC guideline recommends DOAC at the same level as LMWH for this indication (Table 1) [2].

Multiple myeloma (MM)

The use of immunomodulatory drugs such as thalidomide and lenalidomide (Len) in combination with dexamethasone (Dex) in patients with MM increases the risk of developing VTE compared with their use as single agents [51]. With regard to proteasome inhibitors, a retrospective analysis of the incidence of VTE in 672 patients with newly diagnosed MM showed that carfilzomib in combination with Len/Dex increased the incidence of VTE approximately twofold (21.1% vs. 9.6%) compared with bortezomib in combination with Len/Dex [52]. The anti-CD38 monoclonal antibody daratumumab does not confer an additional risk of VTE when used in combination with other drugs [53].

The IMPEDE VTE score was developed to predict VTE risk in MM patients based on an analysis of 4,446 patients registered at the Veterans Administration Central Cancer Registry (VACCR) [54]. IMPEDE VTE was validated in a large independent cohort of the Surveillance, Epidemiology, End Results (SEER)-program database. A similar SAVED

score, conversely, was developed based on the SEER database and validated in patients registered in the VACCR [55]. Asian ethnicity is a characteristic factor associated with a reduction in the development of VTE common to IMPEDE VTE and SAVED (Table 2).

Low-dose aspirin and LMWH or DOAC are recommended for low- and high-risk MM patients, respectively, based on these risk prediction models [56, 57].

Chronic myeloid leukemia (CML)

Four meta-analyses have evaluated the impact of *BCR::ABL1* tyrosine kinase inhibitors (TKIs) on cardiovascular events in CML patients. Compared to imatinib, second- and third-generation TKIs, excluding bosutinib, were shown to increase the incidence of arterial occlusive disease but not VTE [58–61]. The adverse effects are particularly considerable with ponatinib, which may be due in part to direct cytotoxicity to the vascular endothelium [62]. Prophylactic low-dose aspirin was recommended later in clinical trials of ponatinib [63].

Common cardiovascular risk factors, such as smoking, hypertension, dyslipidemia, and diabetes, are also known to predict cardiovascular events in CML patients on TKI treatment. It is important to select an appropriate TKI based on an individual patient's risk assessment. The European Society of Cardiology has proposed Systematic Coronary Risk Evaluation (SCORE) as a comprehensive risk assessment system for coronary artery disease in general [64]. In a retrospective clinical study analyzing the incidence of cardiovascular events in 192 CML patients with hypertension, the 5-year cumulative incidence of arterial occlusive disease was 33% in patients with a SCORE of high or very high, compared to 14% in the remaining patients [65].

Asciminib, a recently approved allosteric inhibitor that targets the ABL1 myristoyl pocket, has been suggested to be potentially less toxic to the cardiovascular system than conventional TKIs in a preclinical animal study [66]. The clinical safety of asciminib remains to be verified; 8.7% of the subjects experienced arterial occlusive events in the long-term follow-up of the asciminib phase 1 trial [67].

BCR::ABL1-negative MPN: polycythemia vera (PV) and essential thrombocythemia (ET)

Both PV and ET are hematopoietic neoplasms with a high rate of arterial and venous thrombosis, which is a major prognostic factor, although the pathophysiology and treatment of these conditions differ from one another [68–70]. The common feature is that the recurrent genetic abnormality *JAK2* V617F is a significant risk factor, particularly for VTE [71–74]. In *JAK2* V617F knock-in mouse models, increased megakaryocyte migration and platelet aggregation are observed, suggesting that not only the quantity but also the quality of blood cells may contribute to the development of thrombosis [75–77].

PV

Established risk factors for thrombosis in PV are advanced age (> 60–65 years) and a history of thrombosis [78, 79]. In addition to the common cardiovascular factors, such as dyslipidemia and diabetes, leukocytosis is also a risk factor for arterial thrombosis in PV [80–83] (Table 2).

Low-dose aspirin has been shown to reduce arterial thrombosis in PV patients in double-blind RCTs and is recommended in Cochrane reviews [84, 85]. If venous thrombosis develops while on low-dose aspirin, switching aspirin to warfarin or DOACs should be considered, although high-level evidence is lacking [86].

Controlling hematocrit (Ht) with phlebotomy and/or hydroxyurea (HU) also improves OS in PV [87]. PV patients harboring *JAK2* V617F who were prospectively randomized to phlebotomy and/or HU with an intensive target Ht < 45% had fewer cardiovascular events and deaths from thrombosis than patients randomized to a control target Ht 45–50% [88]. In this trial, however, not only Ht control but also the suppressive effect of HU on leukocytes and platelets should be taken into consideration. In another study on HU-resistant PV, poor control of WBC and platelet count, not Ht, was most associated with the risk of thrombotic and bleeding events [89]. In a propensity score matching analysis of PV patients who received phlebotomy alone (342 cases) or HU alone (681 cases), OS and cumulative incidence of cardiovascular events were better in the HU group, despite the lower Ht and WBC counts in the phlebotomy group, and this association was particularly significant in high-risk PV patients [90–92].

The JAK inhibitor ruxolitinib can be chosen to alleviate splenomegaly and constitutional symptoms in PV patients resistant or intolerant to HU. JAK inhibitors have theoretically favorable pharmacological profiles to prevent thrombosis, suppressing the production of pro-thrombotic mediators such as P-selectin, von Willebrand factor, interleukin-6, and tissue factor in vitro [93]. Nevertheless, the thromboprophylactic effect of JAK inhibitors was not demonstrated until recently [94, 95]. The MAJIC-PV study showed the superiority of ruxolitinib over best available therapy in OS and event-free survival, including thrombosis as an endpoint, in HU-resistant/intolerant PV, regardless of splenomegaly [96].

ET

IPSET-thrombosis, stratified by age > 60 years, previous thrombosis, and *JAK2* V617F, is a widely accepted risk score for arterial thrombosis in ET [73, 97]. Notably, platelet count is not a significant risk factor for thrombosis [98, 99] (Table 2). ET patients with *JAK2* V617F, who are at high risk for thrombosis, tend to have paradoxically lower platelet counts than those with mutated *CALR* [72, 100].

A pivotal RCT showed improved thrombosis-free survival with HU by suppressing platelet counts to less than 600,000/μL in ET [101]. However, this study was conducted years before the detailed molecular pathogenesis and classification of ET were characterized, and the mechanisms of action of HU may not be attributable to simply the decreased platelet counts [99]. Especially in low-risk ET, defined as age younger than 60 years old, without cardiovascular risk, and with platelet counts $< 1.5 \times 10^6$/μL, cytoreduction with potentially carcinogenic HU is not recommended over aspirin alone, since the addition of HU did not improve key outcomes, such as vascular events, myelofibrosis, and leukemic transformation [102]. There is inconsistency among trials as to whether anagrelide, an alternative cytoreductive agent, is sufficient to prevent thrombosis in HU-resistant/intolerant ET [103, 104].

In contrast to PV, RCTs demonstrating the benefit of aspirin in ET are lacking, although it is empirically used in many cases [85]. In a retrospective analysis, low-dose aspirin for patients with *CALR*-mutated ET did not prevent thrombosis but rather increased bleeding [105]. Individual patient factors such as *JAK2* V617F, advanced age, and cardiovascular comorbidities should be considered to determine the indication of aspirin in ET [106, 107].

Future directions and perspectives

Many clinical questions are still unsolved in CAT, especially in hematologic malignancies, due to the limited patient population and unique pathophysiology compared to solid cancer. The safety and efficacy of DOACs, which are becoming widely used in CAT in solid cancers based on accumulating high-quality evidence, are expected to be evaluated for a range of hematologic malignancies in prospective clinical trials. Hematologists must carefully assess the patient's risk of CAT to offer appropriate prophylaxis and treatment of thromboembolic complications while minimizing the risk of bleeding and maximizing the efficacy of anticancer treatment, even in the midst of a rapidly changing landscape of clinical oncology practice.

Declarations

Conflict of interest TI received honoraria from Alexion Pharmaceuticals, Chugai Pharmaceutical, Nippon Shinyaku, Pfizer Japan, and Sanofi KK; received research funding from AbbVie, Asahi Kasei Pharma Corporation, Astellas Pharma, Janssen Japan, Nippon Shinyaku, Novartis, Otsuka Pharmaceutical, and Takeda Pharmaceutical Company.

References

1. Lyman GH, Carrier M, Ay C, Di Nisio M, Hicks LK, Khorana AA, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv. 2021;5:927–74.
2. Farge D, Frere C, Connors JM, Khorana AA, Kakkar A, Ay C, et al. 2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19. Lancet Oncol. 2022;23:e334–47.
3. Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO guideline update. J Clin Oncol. 2023;41:3063–71.
4. National Comprehensive Cancer Network. Cancer-Associated Venous Thromboembolic Disease (Version 2.2023) [Internet]. National Comprehensive Cancer Network; 2023 Jun. Report No.: Version 2.2023. Available from: https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf.
5. Mulder FI, Horváth-Puhó E, van Es N, van Laarhoven HWM, Pedersen L, Moik F, et al. Venous thromboembolism in cancer patients: a population-based cohort study. Blood. 2021;137:1959–69.
6. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008;111:4902–7.
7. Mulder FI, Candeloro M, Kamphuisen PW, Di Nisio M, Bossuyt PM, Guman N, et al. The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis. Haematologica. 2019;104:1277–87.
8. Mirza A-S, Yun S, Ali NA, Shin H, O'Neil JL, Elharake M, et al. Validation of the Khorana score in acute myeloid leukemia patients: a single-institution experience. Thromb J. 2019;17:13.
9. Martella F, Cerrano M, Di Cuonzo D, Secreto C, Olivi M, Apolito V, et al. Frequency and risk factors for thrombosis in acute myeloid leukemia and high-risk myelodysplastic syndromes treated with intensive chemotherapy: a two centers observational study. Ann Hematol. 2022;101:855–67.
10. Carrier M, Abou-Nassar K, Mallick R, Tagalakis V, Shivakumar S, Schattner A, et al. Apixaban to prevent venous thromboembolism in patients with cancer. N Engl J Med. 2019;380:711–9.
11. Khorana AA, Soff GA, Kakkar AK, Vadhan-Raj S, Riess H, Wun T, et al. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. N Engl J Med. 2019;380:720–8.
12. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med. 2018;378:615–24.
13. Agnelli G, Becattini C, Meyer G, Muñoz A, Huisman MV, Connors JM, et al. Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med. 2020;382:1599–607.

14. McBane RD 2nd, Wysokinski WE, Le-Rademacher JG, Zemla T, Ashrani A, Tafur A, et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. J Thromb Haemost. 2020;18:411–21.
15. Carney BJ, Wang T-F, Ren S, George G, Al Homssi A, Gaddh M, et al. Anticoagulation in cancer-associated thromboembolism with thrombocytopenia: a prospective, multicenter cohort study. Blood Adv. 2021;5:5546–53.
16. Lecumberri R, Ruiz-Artacho P, Trujillo-Santos J, Brenner B, Barillari G, Ruiz-Ruiz J, et al. Management and outcomes of cancer patients with venous thromboembolism presenting with thrombocytopenia. Thromb Res. 2020;195:139–45.
17. Houghton DE, Key NS, Zakai NA, Laux JP, Shea TC, Moll S. Analysis of anticoagulation strategies for venous thromboembolism during severe thrombocytopenia in patients with hematologic malignancies: a retrospective cohort. Leuk Lymphoma. 2017;58:2573–81.
18. Breccia M, Avvisati G, Latagliata R, Carmosino I, Guarini A, De Propris MS, et al. Occurrence of thrombotic events in acute promyelocytic leukemia correlates with consistent immunophenotypic and molecular features. Leukemia. 2007;21:79–83.
19. Lavallée V-P, Chagraoui J, MacRae T, Marquis M, Bonnefoy A, Krosl J, et al. Transcriptomic landscape of acute promyelocytic leukemia reveals aberrant surface expression of the platelet aggregation agonist Podoplanin. Leukemia. 2018;32:1349–57.
20. Menell JS, Cesarman GM, Jacovina AT, McLaughlin MA, Lev EA, Hajjar KA. Annexin II and bleeding in acute promyelocytic leukemia. N Engl J Med. 1999;340:994–1004.
21. He K-L, Deora AB, Xiong H, Ling Q, Weksler BB, Niesvizky R, et al. Endothelial cell annexin A2 regulates polyubiquitination and degradation of its binding partner S100A10/p11. J Biol Chem. 2008;283:19192–200.
22. Di Bona E, Avvisati G, Castaman G, Luce Vegna M, De Sanctis V, Rodeghiero F, et al. Early haemorrhagic morbidity and mortality during remission induction with or without all-trans retinoic acid in acute promyelocytic leukaemia. Br J Haematol. 2000;108:689–95.
23. Altman JK, Rademaker A, Cull E, Weitner BB, Ofran Y, Rosenblat TL, et al. Administration of ATRA to newly diagnosed patients with acute promyelocytic leukemia is delayed contributing to early hemorrhagic death. Leuk Res. 2013;37:1004–9.
24. Rodeghiero F, Avvisati G, Castaman G, Barbui T, Mandelli F. Early deaths and anti-hemorrhagic treatments in acute promyelocytic leukemia. A GIMEMA retrospective study in 268 consecutive patients. Blood. 1990;75:2112–7.
25. Brown JE, Olujohungbe A, Chang J, Ryder WD, Morganstern GR, Chopra R, et al. All-trans retinoic acid (ATRA) and tranexamic acid: a potentially fatal combination in acute promyelocytic leukaemia. Br J Haematol. 2000;110:1010–2.
26. Uchiumi H, Matsushima T, Yamane A, Doki N, Irisawa H, Saitoh T, et al. Prevalence and clinical characteristics of acute myeloid leukemia associated with disseminated intravascular coagulation. Int J Hematol. 2007;86:137–42.
27. Libourel EJ, Klerk CPW, van Norden Y, de Maat MPM, Kruip MJ, Sonneveld P, et al. Disseminated intravascular coagulation at diagnosis is a strong predictor for thrombosis in acute myeloid leukemia. Blood. 2016;128:1854–61.
28. Ku GH, White RH, Chew HK, Harvey DJ, Zhou H, Wun T. Venous thromboembolism in patients with acute leukemia: incidence, risk factors, and effect on survival. Blood. 2009;113:3911–7.
29. Vu K, Luong NV, Hubbard J, Zalpour A, Faderl S, Thomas DA, et al. A retrospective study of venous thromboembolism in acute leukemia patients treated at the University of Texas MD Anderson Cancer Center. Cancer Med. 2015;4:27–35.
30. Napolitano M, Valore L, Malato A, Saccullo G, Vetro C, Mitra ME, et al. Management of venous thromboembolism in patients with acute leukemia at high bleeding risk: a multi-center study. Leuk Lymphoma. 2016;57:116–9.
31. Al-Ani F, Wang YP, Lazo-Langner A. Development of a clinical prediction rule for venous thromboembolism in patients with acute leukemia. Thromb Haemost. 2020;120:322–8.
32. Hellou T, Cohen O, Avigdor A, Amitai I, Shimoni A, Misgav M, et al. The occurrence of thrombosis during intensive chemotherapy treatment for acute myeloid leukemia patients does not impact on long-term survival. Ann Hematol. 2023;102:1037–43.
33. Koschade SE, Stratmann JA, Steffen B, Shaid S, Finkelmeier F, Serve H, et al. Early-onset venous thromboembolisms in newly diagnosed non-promyelocytic acute myeloid leukemia patients undergoing intensive induction chemotherapy. Eur J Haematol. 2023;110:426–34.
34. Mohren M, Markmann I, Jentsch-Ullrich K, Koenigsmann M, Lutze G, Franke A. Increased risk of venous thromboembolism in patients with acute leukaemia. Br J Cancer. 2006;94:200–2.
35. De Stefano V, Sorà F, Rossi E, Chiusolo P, Laurenti L, Fianchi L, et al. The risk of thrombosis in patients with acute leukemia: occurrence of thrombosis at diagnosis and during treatment. J Thromb Haemost. 2005;3:1985–92.
36. Rank CU, Toft N, Tuckuviene R, Grell K, Nielsen OJ, Frandsen TL, et al. Thromboembolism in acute lymphoblastic leukemia: results of NOPHO ALL2008 protocol treatment in patients aged 1 to 45 years. Blood. 2018;131:2475–84.
37. Anderson DR, Stock W, Karrison TG, Leader A. D-dimer and risk for thrombosis in adults with newly diagnosed acute lymphoblastic leukemia. Blood Adv. 2022;6:5146–51.
38. De Stefano V, Za T, Ciminello A, Betti S, Rossi E. Haemostatic alterations induced by treatment with asparaginases and clinical consequences. Thromb Haemost. 2015;113:247–61.
39. Rank CU, Lynggaard LS, Als-Nielsen B, Stock W, Toft N, Nielsen OJ, et al. Prophylaxis of thromboembolism during therapy with asparaginase in adults with acute lymphoblastic leukaemia. Cochrane Database Syst Rev. 2020;10:CD013399.
40. Sibai H, Chen R, Liu X, Falcone U, Schimmer A, Schuh A, et al. Anticoagulation prophylaxis reduces venous thromboembolism rate in adult acute lymphoblastic leukaemia treated with asparaginase-based therapy. Br J Haematol. 2020;191:748–54.
41. Zwicker JI, Wang T-F, DeAngelo DJ, Lauw MN, Connors JM, Falanga A, et al. The prevention and management of asparaginase-related venous thromboembolism in adults: guidance from the SSC on Hemostasis and Malignancy of the ISTH. J Thromb Haemost. 2020;18:278–84.
42. Santi RM, Ceccarelli M, Bernocco E, Monagheddu C, Evangelista A, Valeri F, et al. Khorana score and histotype predicts incidence of early venous thromboembolism in non-Hodgkin lymphomas. A pooled-data analysis of 12 clinical trials of Fondazione Italiana Linfomi (FIL). Thromb Haemost. 2017. https://doi.org/10.1160/TH16-11-0895.
43. Rupa-Matysek J, Gil L, Kaźmierczak M, Barańska M, Komarnicki M. Prediction of venous thromboembolism in newly diagnosed patients treated for lymphoid malignancies: validation of the Khorana Risk Score. Med Oncol. 2017;35:5.
44. Caruso V, Di Castelnuovo A, Meschengieser S, Lazzari MA, de Gaetano G, Storti S, et al. Thrombotic complications in adult patients with lymphoma: a meta-analysis of 29 independent cohorts including 18,018 patients and 1149 events. Blood. 2010;115:5322–8.
45. Antic D, Milic N, Nikolovski S, Todorovic M, Bila J, Djurdjevic P, et al. Development and validation of multivariable predictive model for thromboembolic events in lymphoma patients. Am J Hematol. 2016;91:1014–9.

46. Lekovic D, Miljic P, Mihaljevic B. Increased risk of venous thromboembolism in patients with primary mediastinal large B cell lymphoma. Thromb Res. 2010;126:477–80.
47. Zhou X, Teegala S, Huen A, Ji Y, Fayad L, Hagemeister FB, et al. Incidence and risk factors of venous thromboembolic events in lymphoma. Am J Med. 2010;123:935–41.
48. Lund JL, Østgård LS, Prandoni P, Sørensen HT, de Nully BP. Incidence, determinants and the transient impact of cancer treatments on venous thromboembolism risk among lymphoma patients in Denmark. Thromb Res. 2015;136:917–23.
49. Sanfilippo KM, Wang TF, Gage BF, Luo S, Riedell P, Carson KR. Incidence of venous thromboembolism in patients with non-Hodgkin lymphoma. Thromb Res. 2016;143:86–90.
50. Muslimani AA, Spiro TP, Chaudhry AA, Taylor HC, Daw HA. Venous thromboembolism in lymphoma: how effectively are we treating patients? Am J Clin Oncol. 2009;32:521–3.
51. Palumbo A, Rajkumar SV, Dimopoulos MA, Richardson PG, San Miguel J, Barlogie B, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia. 2008;22:414–23.
52. Charalampous C, Goel U, Kapoor P, Binder M, Buadi FK, Dingli D, et al. Thrombosis in multiple myeloma: risk estimation by induction regimen and association with overall survival. Am J Hematol. 2023;98:413–20.
53. Sborov DW, Baljevic M, Reeves B, Laubach J, Efebera YA, Rodriguez C, et al. Daratumumab plus lenalidomide, bortezomib and dexamethasone in newly diagnosed multiple myeloma: analysis of vascular thrombotic events in the GRIFFIN study. Br J Haematol. 2022;199:355–65.
54. Sanfilippo KM, Luo S, Wang T-F, Fiala M, Schoen M, Wildes TM, et al. Predicting venous thromboembolism in multiple myeloma: development and validation of the IMPEDE VTE score. Am J Hematol. 2019;94:1176–84.
55. Li A, Wu Q, Luo S, Warnick GS, Zakai NA, Libby EN, et al. Derivation and validation of a risk assessment model for immunomodulatory drug-associated thrombosis among patients with multiple myeloma. J Natl Compr Canc Netw. 2019;17:840–7.
56. Covut F, Sanfilippo KM. Mitigating the risk of venous thromboembolism in patients with multiple myeloma receiving immunomodulatory-based therapy. Hematol Am Soc Hematol Educ Program. 2022;2022:363–7.
57. De Stefano V, Larocca A, Carpenedo M, Cavo M, Di Raimondo F, Falanga A, et al. Thrombosis in multiple myeloma: risk stratification, antithrombotic prophylaxis, and management of acute events. A consensus-based position paper from an ad hoc expert panel. Haematologica. 2022;107:2536–47.
58. Chai-Adisaksopha C, Lam W, Hillis C. Major arterial events in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors: a meta-analysis. Leuk Lymphoma. 2016;57:1300–10.
59. Douxfils J, Haguet H, Mullier F, Chatelain C, Graux C, Dogné J-M. Association between BCR-ABL tyrosine kinase inhibitors for chronic myeloid leukemia and cardiovascular events, major molecular response, and overall survival: a systematic review and meta-analysis. JAMA Oncol. 2016;2:625–32.
60. Haguet H, Douxfils J, Mullier F, Chatelain C, Graux C, Dogné J-M. Risk of arterial and venous occlusive events in chronic myeloid leukemia patients treated with new generation BCR-ABL tyrosine kinase inhibitors: a systematic review and meta-analysis. Expert Opin Drug Saf. 2017;16:5–12.
61. Haguet H, Graux C, Mullier F, Dogné J-M, Douxfils J. Long-term survival, vascular occlusive events and efficacy biomarkers of first-line treatment of CML: a meta-analysis. Cancers. 2020. https://doi.org/10.3390/cancers12051242.
62. Haguet H, Bouvy C, Delvigne A-S, Modaffari E, Wannez A, Sonveaux P, et al. The risk of arterial thrombosis in patients with chronic myeloid leukemia treated with second and third generation BCR-ABL tyrosine kinase inhibitors may be explained by their impact on endothelial cells: an in-vitro study. Front Pharmacol. 2020;11:1007.
63. Jain P, Kantarjian H, Jabbour E, Gonzalez GN, Borthakur G, Pemmaraju N, et al. Ponatinib as first-line treatment for patients with chronic myeloid leukaemia in chronic phase: a phase 2 study. Lancet Haematol. 2015;2:e376–83.
64. Graham IM, Di Angelantonio E, Visseren F, De Bacquer D, Ference BA, Timmis A, et al. Systematic coronary risk evaluation (SCORE): JACC focus seminar 4/8. J Am Coll Cardiol. 2021;77:3046–57.
65. Caocci G, Mulas O, Abruzzese E, Luciano L, Iurlo A, Attolico I, et al. Arterial occlusive events in chronic myeloid leukemia patients treated with ponatinib in the real-life practice are predicted by the Systematic Coronary Risk Evaluation (SCORE) chart. Hematol Oncol. 2019;37:296–302.
66. Singh AP, Glennon MS, Umbarkar P, Gupte M, Galindo CL, Zhang Q, et al. Ponatinib-induced cardiotoxicity: delineating the signalling mechanisms and potential rescue strategies. Cardiovasc Res. 2019;115:966–77.
67. Mauro MJ, Hughes TP, Kim D-W, Rea D, Cortes JE, Hochhaus A, et al. Asciminib monotherapy in patients with CML-CP without BCR::ABL1 T315I mutations treated with at least two prior TKIs: 4-year phase 1 safety and efficacy results. Leukemia. 2023;37:1048–59.
68. Barbui T, Tefferi A, Vannucchi AM, Passamonti F, Silver RT, Hoffman R, et al. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. Leukemia. 2018;32:1057–69.
69. Guy A, Poisson J, James C. Pathogenesis of cardiovascular events in BCR-ABL1-negative myeloproliferative neoplasms. Leukemia. 2021;35:935–55.
70. Tefferi A, Barbui T. Polycythemia vera: 2024 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023;98:1465–87.
71. Vannucchi AM, Antonioli E, Guglielmelli P, Longo G, Pancrazzi A, Ponziani V, et al. Prospective identification of high-risk polycythemia vera patients based on JAK2(V617F) allele burden. Leukemia. 2007;21:1952–9.
72. Carobbio A, Antonioli E, Guglielmelli P, Vannucchi AM, Delaini F, Guerini V, et al. Leukocytosis and risk stratification assessment in essential thrombocythemia. J Clin Oncol. 2008;26:2732–6.
73. Barbui T, Finazzi G, Carobbio A, Thiele J, Passamonti F, Rumi E, et al. Development and validation of an International Prognostic Score of thrombosis in World Health Organization-essential thrombocythemia (IPSET-thrombosis). Blood. 2012;120:5128–33 (**quiz 5252**).
74. Guglielmelli P, Loscocco GG, Mannarelli C, Rossi E, Mannelli F, Ramundo F, et al. JAK2V617F variant allele frequency >50% identifies patients with polycythemia vera at high risk for venous thrombosis. Blood Cancer J. 2021;11:199.
75. Hobbs CM, Manning H, Bennett C, Vasquez L, Severin S, Brain L, et al. JAK2V617F leads to intrinsic changes in platelet formation and reactivity in a knock-in mouse model of essential thrombocythemia. Blood. 2013;122:3787–97.
76. Edelmann B, Gupta N, Schnoeder TM, Oelschlegel AM, Shahzad K, Goldschmidt J, et al. JAK2-V617F promotes venous thrombosis through β1/β2 integrin activation. J Clin Invest. 2018;128:4359–71.
77. Matsuura S, Thompson CR, Belghasem ME, Bekendam RH, Piasecki A, Leiva O, et al. Platelet dysfunction and thrombosis in JAK2V617F-mutated primary myelofibrotic mice. Arterioscler Thromb Vasc Biol. 2020;40:e262–72.

78. Berk PD, Goldberg JD, Donovan PB, Fruchtman SM, Berlin NI, Wasserman LR. Therapeutic recommendations in polycythemia vera based on Polycythemia Vera Study Group protocols. Semin Hematol. 1986;23:132–43.
79. Marchioli R, Finazzi G, Landolfi R, Kutti J, Gisslinger H, Patrono C, et al. Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. J Clin Oncol. 2005;23:2224–32.
80. Landolfi R, Di Gennaro L, Barbui T, De Stefano V, Finazzi G, Marfisi R, et al. Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera. Blood. 2007;109:2446–52.
81. De Stefano V, Za T, Rossi E, Vannucchi AM, Ruggeri M, Elli E, et al. Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments. Haematologica. 2008;93:372–80.
82. Cerquozzi S, Barraco D, Lasho T, Finke C, Hanson CA, Ketterling RP, et al. Risk factors for arterial versus venous thrombosis in polycythemia vera: a single center experience in 587 patients. Blood Cancer J. 2017;7:662.
83. Carobbio A, Ferrari A, Masciulli A, Ghirardi A, Barosi G, Barbui T. Leukocytosis and thrombosis in essential thrombocythemia and polycythemia vera: a systematic review and meta-analysis. Blood Adv. 2019;3:1729–37.
84. Landolfi R, Marchioli R, Kutti J, Gisslinger H, Tognoni G, Patrono C, et al. Efficacy and safety of low-dose aspirin in polycythemia vera. N Engl J Med. 2004;350:114–24.
85. Squizzato A, Romualdi E, Passamonti F, Middeldorp S. Antiplatelet drugs for polycythaemia vera and essential thrombocythaemia. Cochrane Database Syst Rev. 2013;CD006503.
86. De Stefano V, Finazzi G, Barbui T. Antithrombotic therapy for venous thromboembolism in myeloproliferative neoplasms. Blood Cancer J. 2018;8:65.
87. Podoltsev NA, Zhu M, Zeidan AM, Wang R, Wang X, Davidoff AJ, et al. The impact of phlebotomy and hydroxyurea on survival and risk of thrombosis among older patients with polycythemia vera. Blood Adv. 2018;2:2681–90.
88. Marchioli R, Finazzi G, Specchia G, Cacciola R, Cavazzina R, Cilloni D, et al. Cardiovascular events and intensity of treatment in polycythemia vera. N Engl J Med. 2013;368:22–33.
89. Alvarez-Larrán A, Pereira A, Cervantes F, Arellano-Rodrigo E, Hernández-Boluda J-C, Ferrer-Marín F, et al. Assessment and prognostic value of the European LeukemiaNet criteria for clinicohematologic response, resistance, and intolerance to hydroxyurea in polycythemia vera. Blood. 2012;119:1363–9.
90. Barbui T, Vannucchi AM, Finazzi G, Finazzi MC, Masciulli A, Carobbio A, et al. A reappraisal of the benefit-risk profile of hydroxyurea in polycythemia vera: a propensity-matched study. Am J Hematol. 2017;92:1131–6.
91. Barbui T, De Stefano V, Ghirardi A, Masciulli A, Finazzi G, Vannucchi AM. Different effect of hydroxyurea and phlebotomy on prevention of arterial and venous thrombosis in Polycythemia Vera. Blood Cancer J. 2018;8:124.
92. De Stefano V, Rossi E, Carobbio A, Ghirardi A, Betti S, Finazzi G, et al. Hydroxyurea prevents arterial and late venous thrombotic recurrences in patients with myeloproliferative neoplasms but fails in the splanchnic venous district. Pooled analysis of 1500 cases. Blood Cancer J. 2018;8:112.
93. Beckman JD, DaSilva A, Aronovich E, Nguyen A, Nguyen J, Hargis G, et al. JAK-STAT inhibition reduces endothelial prothrombotic activation and leukocyte-endothelial proadhesive interactions. J Thromb Haemost. 2023;21:1366–80.
94. Vannucchi AM, Kiladjian JJ, Griesshammer M, Masszi T, Durrant S, Passamonti F, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med. 2015;372:426–35.
95. Masciulli A, Ferrari A, Carobbio A, Ghirardi A, Barbui T. Ruxolitinib for the prevention of thrombosis in polycythemia vera: a systematic review and meta-analysis. Blood Adv. 2020;4:380–6.
96. Harrison CN, Nangalia J, Boucher R, Jackson A, Yap C, O'Sullivan J, et al. Ruxolitinib versus best available therapy for polycythemia vera intolerant or resistant to hydroxycarbamide in a randomized trial. J Clin Oncol. 2023;41:3534–44.
97. Barbui T, Vannucchi AM, Buxhofer-Ausch V, De Stefano V, Betti S, Rambaldi A, et al. Practice-relevant revision of IPSET-thrombosis based on 1019 patients with WHO-defined essential thrombocythemia. Blood Cancer J. 2015;5: e369.
98. Carobbio A, Finazzi G, Antonioli E, Guglielmelli P, Vannucchi AM, Delaini F, et al. Thrombocytosis and leukocytosis interaction in vascular complications of essential thrombocythemia. Blood. 2008;112:3135–7.
99. Campbell PJ, MacLean C, Beer PA, Buck G, Wheatley K, Kiladjian J-J, et al. Correlation of blood counts with vascular complications in essential thrombocythemia: analysis of the prospective PT1 cohort. Blood. 2012;120:1409–11.
100. Rumi E, Pietra D, Ferretti V, Klampfl T, Harutyunyan AS, Milosevic JD, et al. JAK2 or CALR mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. Blood. 2014;123:1544–51.
101. Cortelazzo S, Finazzi G, Ruggeri M, Vestri O, Galli M, Rodeghiero F, et al. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. N Engl J Med. 1995;332:1132–6.
102. Godfrey AL, Campbell PJ, MacLean C, Buck G, Cook J, Temple J, et al. Hydroxycarbamide plus aspirin versus aspirin alone in patients with essential thrombocythemia age 40 to 59 years without high-risk features. J Clin Oncol. 2018;36:3361–9.
103. Harrison CN, Campbell PJ, Buck G, Wheatley K, East CL, Bareford D, et al. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. N Engl J Med. 2005;353:33–45.
104. Gisslinger H, Gotic M, Holowiecki J, Penka M, Thiele J, Kvasnicka H-M, et al. Anagrelide compared with hydroxyurea in WHO-classified essential thrombocythemia: the ANAHYDRET Study, a randomized controlled trial. Blood. 2013;121:1720–8.
105. Alvarez-Larrán A, Pereira A, Guglielmelli P, Hernández-Boluda JC, Arellano-Rodrigo E, Ferrer-Marín F, et al. Antiplatelet therapy versus observation in low-risk essential thrombocythemia with a CALR mutation. Haematologica. 2016;101:926–31.
106. Falchi L, Kantarjian HM, Verstovsek S. Assessing the thrombotic risk of patients with essential thrombocythemia in the genomic era. Leukemia. 2017;31:1845–54.
107. Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2021 update on diagnosis, risk-stratification and management. Am J Hematol. 2020;95:1599–613.
108. Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celigny P, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Arch Intern Med. 2002;162:1729–35.
109. Lee AYY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349:146–53.
110. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an oral factor xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clin Oncol. 2018;36:2017–23.
111. Chakraborty R, Rybicki L, Wei W, Valent J, Faiman BM, Samaras CJ, et al. Abnormal metaphase cytogenetics predicts venous thromboembolism in myeloma: derivation and validation of the PRISM score. Blood. 2022;140:2443–50.

112. Piedra K, Peterson T, Tan C, Orozco J, Hultcrantz M, Hassoun H, et al. Comparison of venous thromboembolism incidence in newly diagnosed multiple myeloma patients receiving bortezomib, lenalidomide, dexamethasone (RVD) or carfilzomib, lenalidomide, dexamethasone (KRD) with aspirin or rivaroxaban thromboprophylaxis. Br J Haematol. 2022;196:105–9.
113. Ronner L, Mascarenhas J, Moshier EL. Response to meta-analysis of leukocytosis and thrombosis in essential thrombocythemia and polycythemia vera. Blood Adv. 2019;3010–2.
114. Alvarez-Larrán A, Cervantes F, Pereira A, Arellano-Rodrigo E, Pérez-Andreu V, Hernández-Boluda J-C, et al. Observation versus antiplatelet therapy as primary prophylaxis for thrombosis in low-risk essential thrombocythemia. Blood. 2010;116:1205–10.
115. Carobbio A, Thiele J, Passamonti F, Rumi E, Ruggeri M, Rodeghiero F, et al. Risk factors for arterial and venous thrombosis in WHO-defined essential thrombocythemia: an international study of 891 patients. Blood. 2011;117:5857–9.