Prevention and Management of Thrombosis in BCR/ABL-Negative Myeloproliferative Neoplasms

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Abstract

Keywords

- management of thrombosis
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- thrombosis
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Myeloproliferative neoplasms (MPNs) are clonal disorders of the hematopoietic stem cell. Classical BCR/ABL-negative MPNs include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). Thrombotic events are a major cause of morbidity and mortality in these patients. Pathogenesis of blood clotting activation involves various abnormalities of platelets, erythrocytes, and leukocytes, as well as dysfunctions of endothelial cells. Patients with MPN can be stratified in “high risk” or “low risk” of thrombosis according to established risk factors. ET and PV clinical management is highly dependent on the patient’s thrombotic risk, and a risk-oriented management strategy to treat these diseases is strongly recommended. In this review, we give an overview of risk factors, pathogenesis, and thrombosis prevention and treatment in MPN.

Introduction

Myeloproliferative neoplasms (MPNs) are clonal disorders of the hematopoietic stem cell, characterized by an uncontrolled expansion of myeloid precursors in the bone marrow and an excess of differentiated erythrocytes, platelets, and leukocytes in the peripheral blood. According to the 2016 revised World Health Organization (WHO) Classification of myeloid neoplasm, classical BCR/ABL-negative MPNs include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), with the novel subcategory “prefibrotic/early-stage myelofibrosis” (pre-PMF).¹ Besides the transformation into secondary myelofibrosis or acute myeloid leukemia (AML), thrombotic events are a major cause of morbidity and mortality in these patients.²

We will review the risk factors, pathogenesis, and management of thrombosis in BCR/ABL-negative MPNs.

Thrombosis Incidence

The rate of arterial and venous thrombosis in MPN patients has been estimated as 3-fold and 10-fold increased, respectively,

compared with the general population.³ Arterial thromboses account for approximately two-thirds of total thrombotic events related to MPN,⁴ and include ischemic stroke, acute myocardial infarction, and peripheral arterial occlusions. The frequency of arterial events before or at initial presentation of MPN is approximately 16 to 27% in PV,^{5,6} 18% in ET,⁷ and 4% in PMF.⁸ The cumulative rate of thrombotic events in the follow-up has been estimated of 5.5, 1 to 3, and 1.75% patient-years in PV, ET, and PMF, respectively,^{6,8–10} and a cardiovascular (CV) mortality of 1.7% patient-years has been reported in PV.⁶ Venous thromboembolism (VTE) covers one-third of total thrombotic events in MPN, occurring in approximately 0.6% patient-years in ET and pre-PMF,¹¹ 0.76% in PMF,⁸ and 1% in PV.⁵ Events involving the venous system are deep vein thrombosis (DVT) of the lower extremities, pulmonary embolism (PE), splanchnic (hepatic, portal, and mesenteric), and cerebral vein thrombosis.¹² In particular, the prevalence of splanchnic and cerebral vein thrombosis is unusually high among patients with MPN,¹³ and, as such, MPN diagnosis should always be considered if thrombosis manifests at an uncommon location. Thrombotic complications considerably affect MPN patients’

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prognosis, being an independent negative prognostic factor for survival in ET and PV.^{11,14} In PMF, the other major fatal and nonfatal competing events (i.e., acute leukemia transformation, infections, etc.) may obscure the negative prognostic effect of thromboembolism, and its real incidence. Nevertheless, an accurate risk assessment for thrombosis prevention represents a cornerstone of MPN management.

Risk Factors for Thrombosis in Myeloproliferative Neoplasms

Clinical Risk Factors

Older age and a history of thrombosis are well-established independent predictors of recurrent VTE in MPN.^{6,15} In the ECLAP study, the rate of CV complications in PV was significantly higher in patients aged more than 65 years or with a history of thrombosis than in younger subjects with no history of thrombosis.⁶ In ET patients, age > 60 years and previous thrombosis were both independently associated with higher risk to develop major thrombosis in the long term.¹⁵ In MPN, the role of conventional CV risk factors for arterial thrombosis (i.e., obesity, hypertension, diabetes, dyslipidemia, and smoking) has been evaluated with conflicting results¹⁶; nevertheless, it is reasonable to assume that risk factors for atherosclerosis provide at least the same relative risk of the general population, and should be corrected in MPN patients.

JAK2, CALR, and MPL Mutations

JAK2 is a cytoplasmic tyrosine kinase protein required for signal transduction. Two types of *JAK2* mutations are associated with MPN. The gain-of-function V617F mutation in exon 14 is harbored by approximately 96, 55, and 65% of patients with PV, ET, and PMF, respectively, where mutations in exon 12 can be detected in 3% of V617F-negative PV patients.¹⁷ The second most common mutation in MPN involves the calreticulin gene (*CALR*), and occurs in 25 to 35% of patients with PMF and 15 to 24% with ET.¹⁸ Finally, mutations in the TPO receptor gene *MPL* are present in 4% of ET and 8% of PMF cases. *CALR* and *MPL* mutations are rarely reported in PV.¹⁷ Several studies have evaluated the association between *JAK2*V617F and the severity of MPN disease. In particular, two meta-analyses have evidenced a correlation between *JAK2* mutation and the risk of thrombosis in ET.^{19,20} Moreover, one study identified *JAK2* mutation as an independent risk factor for arterial thrombosis.¹⁵ A reduced thrombotic risk in *CALR*-positive as compared with *JAK2*V617F-positive patients has been reported by several studies^{21–23}; however, the inclusion of *CALR* mutational status into the international prognostic score for thrombotic risk assessment in ET (i.e., IPSET-thrombosis), which includes age more than 60 years, CV risk factors, and previous thrombosis, did not significantly modify the risk stratification of the original score.²⁴ Thus, the absence of *JAK2*V617F and not necessarily the presence of *CALR* mutation or “triple-negative” mutational status (i.e., wild-type *JAK2*, *CALR*, and *MPL*) seem to be associated with lower risk of thrombosis compared with *JAK2*-mutated cases.²⁵

Elevated Blood Cell Counts

Blood cell counts have been investigated as thrombophilic risk factors in MPN. Hyperviscosity, as a consequence of erythrocytosis, has been related to MPN prothrombotic state for a long time.²⁶ Data supporting an association between elevated hematocrit and thrombotic events, however, have not been always concordant.^{27,28} Recently, in the CYTO-PV study, patients with a hematocrit less than 45% had a significantly lower rate of CV deaths and major thrombosis than those with a hematocrit of 45 to 50%.²⁹ Moreover, a study from the Spanish Registry of Polycythemia Vera demonstrated that PV patients with higher phlebotomy requirements were at the highest risk of developing thrombotic events.³⁰

While no study to date has demonstrated a statistically significant correlation between platelet count and thrombosis in either PV or ET,^{6,7} extreme thrombocytosis (i.e., platelets $> 1,000 \times 10^9/L$) can favor hemorrhages in ET patients.³¹ This phenomenon has been attributed to the possible occurrence of acquired von Willebrand syndrome (AvWS), due to an increased clearance by platelets of the large von Willebrand factor multimers.³²

A growing amount of evidence has been produced regarding the role of leukocytosis as a risk factor for thrombosis in MPN patients.^{9,33–36} Although a correlation between white blood cell (WBC) count at diagnosis and/or during the follow-up and the occurrence of arterial and venous events emerges in most of the studies on this topic, results are not homogeneous and easily comparable. A recent meta-analysis showed that the relative risk of thrombosis in the presence of leukocytosis is 1.59, mainly accounting for ET and arterial thrombosis subgroups, with no significant effect on venous thrombosis alone.³⁷ As the authors underlined, the lack of a clear cut-off value for WBC counts, the design of the studies never specifically aimed at assessing the role of leukocytosis, and the differences in sample size and duration of follow-up have led to inconclusive evidence.³⁷ Thus, despite biological evidences, leukocytosis has never been formally included in risk models and prognostic scores.

Risk Classification

Based on the aforementioned studies, PV patients are classified as high risk if older than 60 years or present a history of thrombosis, and low risk in the absence of both risk factors.¹⁷ Until recently, the same risk stratification has been used in ET.³⁸ Since the role of *JAK2* mutation and CV risk factors have emerged as independent predictors of thrombosis in ET,¹⁵ these variables have been evaluated in risk stratification. First, *JAK2* mutation along with CV risk factors has been proposed as part of the score in the IPSET-thrombosis classification.³⁹ A subsequent analysis from the same group on a larger cohort of ET patients documented a weak contribution of CV risk factors in both low-risk and high-risk patients.⁴⁰ Thus, current risk stratification in ET includes four categories: very low risk (age ≤ 60 years, absence of previous thrombosis, *JAK2* wild type); low risk (age ≤ 60 years, absence of previous thrombosis, mutation of *JAK2*); intermediate risk (age > 60 years, absence of previous

thrombosis, *JAK2* wild type), and high risk (age > 60 years or previous thrombosis plus mutation of *JAK2*).¹⁷

Mechanisms of Thrombosis in Myeloproliferative Neoplasms

Even though vascular complications represent a major cause of morbidity and mortality, MPN-associated thrombophilia is poorly understood and currently believed to be multifactorial. Among the different mechanisms, the activated status of platelets, erythrocytes, and leukocytes arising from the clonal proliferation of hematopoietic progenitor cells, and the documented clotting activation, are considered major players in MPN-associated thrombosis.¹² More recently, several reports indicate that a proinflammatory MPN milieu as well as excessive interactions between qualitatively abnormal vascular cells, including red blood cells (RBC), leukocytes, platelets, and endothelial cells (EC), are implicated in the generation of thrombotic events.⁴¹ The principal prothrombotic pathogenic mechanisms involved in MPN-associated thrombosis are described in **Fig. 1**. As explained in the figure, several adhesion molecules are expressed by blood cells in MPN patients, mediating their reciprocal interaction and activation, and favoring thrombosis development. Recent studies have

evaluated blocking antibodies to some of these molecules, like crizanlizumab targeting P-selectin, for other clinical conditions,⁴² and may provide a rationale for future studies exploring the use of such drugs to reduce thrombotic complications in MPN.

Of interest, *JAK2V617F* has been detected in mature EC from splenic and liver vein of PMF and PV patients with Budd–Chiari syndrome.⁴³ Moreover, increased thrombus formation has been demonstrated in mouse models expressing *JAK2V617F* only in the endothelial compartment, overall suggesting that *JAK2*-mutant EC could contribute to the prothrombotic phenotype.⁴¹ Finally, elevated levels of circulating platelet-derived procoagulant microparticles (MPs),⁴⁴ and the occurrence of an acquired activated protein C resistance,⁴⁵ also contribute to hypercoagulability in these subjects.

Prevention of Thrombotic Complications in Myeloproliferative Neoplasms

Current treatment for PV and ET is aimed at preventing thrombotic complications, differently from PMF, where available therapies are directed to mitigate constitutional symptoms, splenomegaly, and anemia, or have curative

Fig. 1 Pathogenesis of thrombosis in MPN. In RBCs, *JAK2V617F* mutation mediates the phosphorylation of the erythroid Lutheran/basal cell adhesion molecule (Lu/BCAM) through the Rap1/Akt signaling pathway, determining an aberrant adhesion of RBCs to the endothelial cells (EC).⁹² Moreover, RBC/platelet interaction through FAS ligand (FASL)/FAS receptor (FASR) enhances the externalization of RBC phosphatidylserine, favoring thrombin generation and the formation of occlusive thrombi.⁹³ Platelets from MPN patients circulate in an activated status, as assessed by the increased expression of procoagulant proteins on their surface such as tissue factor (TF) and P-selectin.¹² P-selectin is essential for TF accumulation and fibrin formation in the developing thrombus, and also favors platelet/leukocyte interaction via counter-receptor PSGL-1 (P-selectin glycoprotein ligand-1), inducing CD11b and TF upregulation on the neutrophil surface. In turn, CD11b promotes leukocyte adherence to EC and platelets, and release of TF, proteases, and ROS.⁹⁴ MPN leukocytes show increased expression of integrins (i.e., VLA4 and LFA1) that interact with EC extracellular matrix.⁹⁵ Furthermore, neutrophils from *JAK2V617F*-positive patients are primed to form neutrophil extracellular traps (NETs),⁹⁶ structures composed of DNA, histones, and proteolytic enzymes, implicated in thrombosis as they provide suitable scaffolds for binding RBC, platelets, and von Willebrand factor (VWF). *JAK2*-mutated endothelium secretes high levels of P-selectin and vWF, and expresses adhesion molecules (i.e., ICAM-1, VCAM-1) and receptors (i.e., CD40), which favor the interaction with platelets and leukocytes, enhancing reciprocal activation. ICAM-1, intracellular adhesion molecule 1; LFA-1, lymphocyte function-associated antigen 1; STAT, signal transducer and activator of transcription; VCAM-1, vascular cell adhesion molecule 1; VLA4, very late antigen 4; FasL: Fas ligand.

intent in selected patients eligible for allogeneic stem cell transplantation.

Thrombosis prevention will be discussed separately for PV, ET, and pre-PMF patients, respectively (→ Fig. 2).

Polycythemia Vera

In low-risk PV patients, aspirin has a confirmed antithrombotic value,⁴⁶ and current recommendations include low-dose aspirin once daily (OD) for all patients. Twice daily (BID) aspirin

Polycythemia vera			
All patients	Low risk (No thrombosis history, age ≤ 60 years)	High risk (Thrombosis history OR age > 60 years)	
<ul style="list-style-type: none">• Phebotomy to keep HCT<45%• OD aspirin	<ul style="list-style-type: none">• Consider BID aspirin if:<ul style="list-style-type: none">• inadequate control of microvascular symptoms• CV risk factors• leukocytosis	<ul style="list-style-type: none">• Cyto-reduction with HU• If HU intolerant/resistant, consider second-line drugs (ruxolitinib, INF-α in younger patients, busulfan in older patients)• If arterial thrombosis history, consider BID aspirin• If venous thrombosis history, add anticoagulation	

Essential thrombocythemia			
Low risk (No thrombosis history, age ≤ 60 years, JAK2 mutated)	Intermediate risk (No thrombosis history, age > 60 years, JAK2 WT)	High risk (Thrombosis history OR age > 60 years, JAK2 mutated)	
<ul style="list-style-type: none">• No CV risk factors: OD aspirin• CV risk factors: consider BID aspirin	<ul style="list-style-type: none">• No CV risk factors: OD aspirin• CV risk factors: Cyto-reduction with HU and OD aspirin	<ul style="list-style-type: none">• Cyto-reduction with HU• If HU intolerant/resistant, consider second-line drugs (anagrelide*, INF-α in younger patients, busulfan in older patients)• If arterial thrombosis history, consider BID aspirin• If venous thrombosis history, add anticoagulation	

Prefibrotic primary myelofibrosis			
No previous thrombosis or bleeding, no thrombotic risk factors*	No previous thrombosis or bleeding, thrombotic risk factors*	Previous thrombosis	Previous bleeding
<ul style="list-style-type: none">• Observation	<ul style="list-style-type: none">• OD aspirin	<ul style="list-style-type: none">• Arterial: OD aspirin• Venous: anticoagulation• If thrombocytosis or leukocytosis: cyto-reduction with HU	<ul style="list-style-type: none">• Avoid aspirin• If thrombocytosis or leukocytosis: cyto-reduction with HU

* Age > 60 years, or CV risk factors, or JAK2 mutation, or leukocytosis, or microvascular symptoms

Fig. 2 Risk-based approach to prophylaxis and treatment of thrombosis in patients polycythemia vera, essential thrombocythemia, and prefibrotic primary myelofibrosis. HCT, hematocrit; OD, once daily; BID, twice daily; CV, cardiovascular; HU, hydroxyurea.

should be considered in low-risk patients with inadequate control of microvascular symptoms, CV risk factors, or leukocytosis, and in high-risk patients with a history of arterial thrombosis.¹⁷ Phlebotomy is recommended in all PV patients, and controlled evidence supports the practice of maintaining the hematocrit at less than 45%.²⁹ In adjunction, high-risk patients should receive cytoreductive therapy to minimize their risk of thrombosis. Randomized studies in PV have compared hydroxyurea (HU) against pipobroman, the latter being associated with shorter survival, increased risk of leukemic transformation, and a lower risk of post-PV MF,⁴⁷ and radio phosphorus alone or with HU, reporting no difference in survival, incidence of thrombosis, or risk of transformation into post-PV PMF.⁴⁸ Nonrandomized studies have shown a lower incidence of early thrombosis in HU-treated patients compared with historical controls, and an overall low risk of leukemic transformation.^{49,50} To date, HU is the first-line drug of choice, with a starting dose of 500 mg BID. Two randomized trials (RESPONSE and RESPONSE-2) in PV patients resistant or intolerant to HU, compared the JAK1/2 inhibitor ruxolitinib to best available therapy, including acceptable doses of HU, interferon (INF) or pegylated interferon (pegINF) α , pipobroman, anagrelide, lenalidomide/thalidomide, or no medication, showing a better control in hematocrit levels and symptoms in the ruxolitinib arm.^{51,52} Moreover, a 5-year follow up analysis of the RESPONSE study showed that thrombotic complications were lower in the ruxolitinib group.⁵³ Thus, ruxolitinib is approved as second-line therapy in high-risk PV patients. Very recently, ropeginterferon alfa-2b was compared to HU in a randomized trial (PROUD-PV), and its extension (CONTINUATION-PV).⁵⁴ Although no difference in the rate of complete hematologic response with normal spleen size was observed, ropeginterferon was better in inducing complete hematological response with improved disease burden (i.e. splenomegaly, microvascular disturbances, pruritus, and headache); however, it was associated with a higher liver toxicity, and the follow-up is too short for definitive conclusions. Recent studies have demonstrated a high rate of complete hematologic response, molecular remission, and no risk of leukemic transformation in HU intolerant/resistant patients treated with busulfan,^{14,55} which is usually reserved to older patients.

Essential Thrombocythemia

According to the 2021 updated recommendations on PV and ET management, very low-risk patients with ET might not require any therapy unless in the presence of CV risk factors, where OD low-dose aspirin therapy is advised.¹⁷ A recent study compared the efficacy of OD vs BID and thrice daily (TID) aspirin in ET, based on hypothesis that increased platelet number and turnover might compromise durable inhibition of platelet COX-1; accordingly, BID/TID was more effective than OD dosing in reducing platelet activation, measured by serum thromboxane B2 level.⁵⁶ To date, it seems reasonable to use BID aspirin in patients with arterial thrombosis, or in the presence of CV risk factors associated to older age or JAK2 mutations.¹⁷ In the presence of extreme thrombocytosis (platelets $>1,000 \times 10^9/L$), the use of aspirin

can lead to bleeding complications because of AvWS; in this setting, screening for vWF ristocetin cofactor activity is advised, and aspirin therapy should be withheld with $<20\%$ vWF activity. Cytoreduction is recommended in patients with intermediate-risk disease and CV risk factors, and in high-risk patients.¹⁷ A controlled study showed superiority of HU in preventing thrombotic complications in high-risk patients compared to no HU.³¹ To date, HU is the first-line drug of choice, and dosing should be titrated to keep platelet count in the normal range, although suggested platelet target is not based on controlled evidence. Two randomized studies compared anagrelide to HU in ET.^{7,57} In the earlier study, HU was superior in reducing the risk of arterial thrombosis, major bleeding and fibrotic progression, while anagrelide was more protective in preventing venous thrombosis, although a significantly higher adverse drop-out.⁷ In the second study, anagrelide was not inferior to HU in the prevention of thrombotic complications; these results were restricted to patients with ET diagnosed according to the WHO system.⁵⁷ A post hoc analysis confirmed a lower rate of venous thrombotic associated to anagrelide, but also a higher rate of hemorrhagic events and arterial thrombosis.⁵⁸ Anagrelide is licensed in some countries (i.e., USA, Japan) as first-line therapy, and in Europe for patients with ET intolerant/refractory to HU, although its use could be proposed in younger patients (i.e. women with child bearing potential) for long term treatment, or as second choice (after INF) in pregnant women. Indeed, INF- α has proved effective in HU intolerant/resistant patients,⁵⁹ and is also associated with significant reduction in mutant *CALR* allele burden.⁶⁰ Finally, older patients can receive busulfan as second-line treatment.⁵⁴

Prefibrotic Primary Myelofibrosis

The clinical picture of patients with pre-PMF is heterogeneous, ranging from isolated thrombocytosis, mimicking ET,¹¹ to a more aggressive disease.⁶¹ The risk of vascular events in patients with pre-PMF is similar to that of ET.^{11,62} In studies that evaluated specifically risk factors of thrombosis in pre-PMF patients evidenced, leukocytosis at diagnosis was a significant risk factor for overall and arterial thrombosis,^{63,64} although leukocyte count during follow-up had no impact in one study.⁶⁴ Interestingly, major bleeding seems to occur more frequently in pre-PMF than in ET patients,⁶⁵ where leukocytosis, previous hemorrhage, aspirin therapy, and reticulin grade were found to be predictors of bleeding.^{65,66} In the absence of specific prognostic scores for predicting the risk of bleeding and thrombosis in pre-PMF, a proposed pragmatic approach includes no treatment or low-dose aspirin in asymptomatic patients; aspirin or oral anticoagulation if previous arterial or venous thrombosis, and hydroxyurea as first-line cytoreduction in case of thrombocytosis or leukocytosis.⁶⁷

Management of Arterial Thrombosis

MPN patients who have a vascular event despite treatment with aspirin require cytoreduction for the management of their blood cell counts. For patients with recurrence of an

arterial event, aspirin administration may be increased from OD to BID, or clopidogrel may be used instead of aspirin. Correction of CV risk factors, including blood pressure, lipid levels, smoking, and obesity, is also relevant in MPN patients. In patients at high risk of arterial events, treatment with a broad-spectrum cytoreductive agent, such as HU, rather than a narrow-spectrum strategy, such as anagrelide or phlebotomy, should be considered, to better control all the altered blood counts.⁶⁸

Treatment of Venous Thromboembolism and Secondary Prevention

Thrombosis recurrences in MPN patients preferentially involve the same arterial or venous districts affected in the first event.^{69,70} Different studies reported as risk factors for recurrence age greater than 60 years and a history of remote thrombosis,^{69,71} but not MPN subtype.^{69–71} After the first episode of VTE, the duration of secondary prophylaxis should be decided balancing the risk of hemorrhagic complications over the benefit of VTE prevention. In the general population, the cumulative rate of recurrence after discontinuation of anticoagulation at 1 and 5 years is 10 and 30% after unprovoked VTE, respectively, and 5 and 15% after VTE provoked by nonsurgical reversible factors, respectively.⁷² In MPN patients, the rate of recurrent thrombosis is 6.0, 6.5, and 7.6% patient-years according to three retrospective studies addressing this issue.^{69–71} Regarding the bleeding risk, results from two of these studies in MPN patients receiving vitamin K antagonist (VKA) treatment are conflicting.^{70,71} In particular, the cumulative probability of major bleeding at 1 year of VKA treatment is 2.8% in one study, which is higher than the counterpart value of 1.2 to 2.2% recorded in the VKA arms of trials comparing VKA versus direct oral anticoagulants (DOACs).^{73–75} Moreover, the association of antiplatelet agents plus VKA seems to further increase major bleedings compared with the use of antiplatelet agents or VKA alone.⁶⁹

Acute-Phase Venous Thromboembolism Treatment

DVT or PE in MPN patients should be approached the same as DVT/PE occurring in the general population.⁷⁶ Therefore, low-molecular-weight heparin (LMWH) or fondaparinux is suggested over intravenous or subcutaneous (SC) unfractionated heparin; early initiation of VKA aiming to target an international normalized ratio of 2.5 (range: 2.0–3.0) is recommended.⁷² Relatively frequent cases of heparin-induced thrombocytopenia (HIT) have been reported in MPN patients, so that special care is due during the heparin course in monitoring a drop of the platelet count.⁷⁷

Long-Term Prophylaxis of Venous Thromboembolism Recurrence

Vitamin K Antagonists

In the Italian cohort from the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA), VKA effectively prevented VTE recurrence in MPN patients. Excluding patients with VTE at unusual sites, long-term treatment with VKA remained effective

in preventing recurrence.⁶⁹ In the Spanish cohort from the Grupo Español de Enfermedades Mieloproliferativas Filadelfia Negativas (GEMFIN), VKA treatment was associated with a 2.8-fold reduction in the risk of thrombotic recurrence.⁷¹ In the international cohort from the European LeukemiaNet (ELN), the rate of recurrent thrombosis per 100 patient-years was 4.7 on VKA and 8.9 off VKA, and the rate of recurrent VTE was 4.2 among patients who continued VKA and 9.6 after discontinuation of VKA (relative risk: 2.2). After stopping VKA, the recurrence rate at 5 years was 42.3%.⁷⁰ Remarkably, this study evidenced that the cumulative probability of recurrent thrombosis at 1 year of VKA treatment is 7.8%,⁷⁰ particularly high compared with non-MPN population (between 1.8 and 3.5% according to the most recent studies).^{73–75} Moreover, the cumulative probability of recurrent thrombosis after discontinuation of VKA was 42% at 5 years,⁷⁰ compared with 29.1% reported in non-MPN patients.⁷⁸

Low-Molecular-Weight Heparin

Guidelines for cancer-associated VTE recommend LMWH for at least 3 to 6 months, suggesting to treat indefinitely patients with active malignancy and ongoing anticancer treatment, on the basis of the superior safety and efficacy compared with VKA.^{79,80} However, MPN is a chronic neoplastic disorder; so, continued life-long treatment with daily subcutaneous heparin can be troublesome. Moreover, given the suspected higher risk of HIT in MPN patients,⁷⁷ special caution should be adopted in prescribing long-term treatment. Finally, there is no published evidence about efficacy and safety of long-term administration of LMWH in MPN to establish recommendations for clinical practice.

Cytoreductive Treatment

Cytoreductive treatment (hydroxyurea in most of the cases) reduced the risk of recurrence of arterial thrombosis in the GIMEMA cohort.⁶⁹ Conversely, in the ELN study, patients receiving VKA without cytoreduction did not show a significant rate of VTE recurrence compared with patients treated with VKA and cytoreduction.⁷⁰ Cytoreductive therapy, along with full anticoagulation, represents the standard of care for MPN patients with splanchnic vein thrombosis (SVT), although a recently proposed treatment algorithm does not recommend cytoreduction in patients with normal blood values.⁸¹

Direct Oral Anticoagulants

Dabigatran, rivaroxaban, apixaban, and edoxaban are approved for the treatment of acute VTE.⁷⁶ In the cancer population, three recent randomized clinical trials of DOACs versus LMWH demonstrated the noninferiority of edoxaban,⁸² rivaroxaban,⁸³ and apixaban⁸⁴ for VTE treatment in cancer patients. In these trials, the rate of recurrent VTE was lower in the DOACs arm, but in two of them the rate of major bleeding was higher, mainly due to upper gastrointestinal bleeding in patients with gastrointestinal cancer.^{82,83} However, a recent meta-analysis including four randomized controlled studies comparing cancer-associated thrombosis treatment with apixaban, edoxaban, or rivaroxaban with dalteparin showed that the DOACs reduced the risk of

Table 1 Studies that have evaluated DOACs in MPN patients

Study	Kaifie et al ⁸⁹	Ianotto et al ⁸⁸	Curto-Garcia et al ⁹⁰	Serrao et al ⁹¹
MPN patients	8	25	32	71
PV	3	8	12	25
ET	1	17	9	28
PMF	4	0	9	13
MPN-U	0	0	2	5
Type of DOAC				
Rivaroxaban	8	16	17	26
Apixaban	0	9	14	21
Edoxaban	0	0	1	14
Dabigatran	0	0	0	10
Thrombotic recurrence	–	1 (4)	1 (3)	0
Major bleeding	–	3 (12)	0	0
CRNMB	–	2 (8)	3 (9.3)	0
Median FU (mo)	–	25	25	15

Abbreviations: CRNMB, clinically relevant non-major bleeding; DOAC, direct oral anticoagulant; FU, follow-up; MPN-U, myeloproliferative neoplasms unclassifiable.

Source: Data are number (%).

recurrent VTE with no significant higher likelihood of major bleeding at 6 months compared with LMWH.⁸⁵

Since MPN patients are prone to either thrombotic and hemorrhagic complications, the use of DOACs might reduce the bleeding risk as compared with VKA,⁸⁶ with the capacity to protect from both arterial and venous thrombosis.⁷² However, knowledge of VTE treatment with DOACs in MPN patients is limited. Indeed, in the Hokusai trials, only 10% of recruited patients had hematological malignancies, leukemia, and lymphoma for most.^{82,87} In the ELN cohort of MPN patients with DVT and/or PE, only 3.3% of patients were treated with DOACs.⁷⁰ Studies evaluating the use of DOACs in MPN are summarized in ▶Table 1. In the OBENE registry, of 760 MPN patients, only 13 patients were receiving DOACs for atrial fibrillation (AF) and 8 for VTE.⁸⁸ In the German MPN registry of the Study Alliance Leukemia, 68 of 454 patients (14.9%) had suffered from DVT or SVT, and only 8 were treated with rivaroxaban. Although nonsignificant, patients on rivaroxaban had a lower incidence of major bleeding as compared with VKA plus double antiplatelet treatment, and to heparin.⁸⁹ Very recently, two studies were published on this issue.^{90,91} A retrospective English study evaluated 32 patients with MPN-associated VTE, including SVT and cerebral thrombosis, receiving DOACs (17 rivaroxaban, 14 apixaban, and 1 edoxaban).⁹⁰ During the follow-up, there were no VTE recurrences in 31 patients, and only one case had evidence of mesenteric ischemia. There were no episodes of major bleeding except for three patients showing clinical relevant non-major (CRNM) bleeding; notably these patients were taking aspirin in addition to a DOAC. A larger Italian study on 71 MPN patients receiving DOAC either for AF or VTE did not record thrombotic complications, nor

major or CRNM bleeding after a median follow-up of 12 months.⁹¹ Notably, 11 patients were treated with ruxolitinib, and no clinical interferences were observed.

Conclusion

Thrombosis is still a major problem in MPN patients. In the last years, new evidences concerning pathogenesis, risk factors, and treatment options have emerged. Recent reports delineate the increasingly plausible role of various cell adhesion molecules in thrombosis development, which might be explored as possible therapeutic targets. Large prospective studies are needed, especially in low-risk patients, to evaluate the possible advantage of cytoreduction for maintaining WBC within the normal range in reducing thrombotic events. Finally, the therapeutic role of DOACs should be assessed by prospective randomized trials to establish their efficacy and safety, compared with standard treatment, in this particular subset of hematological cancer patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

- Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016;127(20):2391–2405
- Barbui T, Finazzi G, Falanga A. Myeloproliferative neoplasms and thrombosis. *Blood* 2013;122(13):2176–2184
- Hultcrantz M, Björkholm M, Dickman PW, et al. Risk for arterial and venous thrombosis in patients with myeloproliferative

- neoplasms: a population-based cohort study. *Ann Intern Med* 2018;168(05):317–325
- 4 Rungtjirajitranon T, Owattanapanich W, Ungprasert P, Siritanaratkul N, Ruchutrakool T. A systematic review and meta-analysis of the prevalence of thrombosis and bleeding at diagnosis of Philadelphia-negative myeloproliferative neoplasms. *BMC Cancer* 2019;19(01):184
 - 5 Barbui T, Carobbio A, Rumi E, et al. In contemporary patients with polycythemia vera, rates of thrombosis and risk factors delineate a new clinical epidemiology. *Blood* 2014;124(19):3021–3023
 - 6 Marchioli R, Finazzi G, Landolfi R, et al. Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. *J Clin Oncol* 2005;23(10):2224–2232
 - 7 Harrison CN, Campbell PJ, Buck G, et al; United Kingdom Medical Research Council Primary Thrombocythemia 1 Study. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. *N Engl J Med* 2005;353(01):33–45
 - 8 Barbui T, Carobbio A, Cervantes F, et al. Thrombosis in primary myelofibrosis: incidence and risk factors. *Blood* 2010;115(04):778–782
 - 9 Carobbio A, Finazzi G, Antonioli E, et al. Thrombocytosis and leukocytosis interaction in vascular complications of essential thrombocythemia. *Blood* 2008;112(08):3135–3137
 - 10 Passamonti F, Rumi E, Arcaini L, et al. Prognostic factors for thrombosis, myelofibrosis, and leukemia in essential thrombocythemia: a study of 605 patients. *Haematologica* 2008;93(11):1645–1651
 - 11 Barbui T, Thiele J, Passamonti F, et al. Survival and disease progression in essential thrombocythemia are significantly influenced by accurate morphologic diagnosis: an international study. *J Clin Oncol* 2011;29(23):3179–3184
 - 12 Falanga A, Marchetti M. Thrombosis in myeloproliferative neoplasms. *Semin Thromb Hemost* 2014;40(03):348–358
 - 13 Sekhar M, McVinnie K, Burroughs AK. Splanchnic vein thrombosis in myeloproliferative neoplasms. *Br J Haematol* 2013;162(06):730–747
 - 14 Tefferi A, Rumi E, Finazzi G, et al. Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. *Leukemia* 2013;27(09):1874–1881
 - 15 Carobbio A, Thiele J, Passamonti F, et al. Risk factors for arterial and venous thrombosis in WHO-defined essential thrombocythemia: an international study of 891 patients. *Blood* 2011;117(22):5857–5859
 - 16 Barbui T, Barosi G, Birgegard G, et al; European LeukemiaNet. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol* 2011;29(06):761–770
 - 17 Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2021 update on diagnosis, risk-stratification and management. *Am J Hematol* 2020;95(12):1599–1613
 - 18 Tefferi A, Pardanani A. Myeloproliferative neoplasms: a contemporary review. *JAMA Oncol* 2015;1(01):97–105
 - 19 Ziakas PD. Effect of JAK2 V617F on thrombotic risk in patients with essential thrombocythemia: measuring the uncertain. *Haematologica* 2008;93(09):1412–1414
 - 20 Dahabreh IJ, Zoi K, Giannouli S, Zoi C, Loukopoulou D, Voulgarelis M. Is JAK2 V617F mutation more than a diagnostic index? A meta-analysis of clinical outcomes in essential thrombocythemia. *Leuk Res* 2009;33(01):67–73
 - 21 Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. *N Engl J Med* 2013;369(25):2379–2390
 - 22 Rotunno G, Mannarelli C, Guglielmelli P, et al; Associazione Italiana per la Ricerca sul Cancro Gruppo Italiano Malattie Mieloproliferative Investigators. Impact of calreticulin mutations on clinical and hematological phenotype and outcome in essential thrombocythemia. *Blood* 2014;123(10):1552–1555
 - 23 Rumi E, Pietra D, Ferretti V, et al; Associazione Italiana per la Ricerca sul Cancro Gruppo Italiano Malattie Mieloproliferative Investigators. JAK2 or CALR mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. *Blood* 2014;123(10):1544–1551
 - 24 Finazzi G, Carobbio A, Guglielmelli P, et al. Calreticulin mutation does not modify the IPSET score for predicting the risk of thrombosis among 1150 patients with essential thrombocythemia. *Blood* 2014;124(16):2611–2612
 - 25 Tefferi A, Barbui T. Essential thrombocythemia and polycythemia vera: focus on clinical practice. *Mayo Clin Proc* 2015;90(09):1283–1293
 - 26 Pearson TC, Wetherley-Mein G. Vascular occlusive episodes and venous haematocrit in primary proliferative polycythaemia. *Lancet* 1978;2(8102):1219–1222
 - 27 Di Nisio M, Barbui T, Di Gennaro L, et al; European Collaboration on Low-dose Aspirin in Polycythemia Vera (ECLAP) Investigators. The haematocrit and platelet target in polycythemia vera. *Br J Haematol* 2007;136(02):249–259
 - 28 Gordeuk VR, Key NS, Prchal JT. Re-evaluation of hematocrit as a determinant of thrombotic risk in erythrocytosis. *Haematologica* 2019;104(04):653–658
 - 29 Marchioli R, Finazzi G, Specchia G, et al; CYTO-PV Collaborative Group. Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med* 2013;368(01):22–33
 - 30 Alvarez-Larrán A, Pérez-Encinas M, Ferrer-Marín F, et al; Grupo Español de Neoplasias Mieloproliferativas Filadelfia Negativas. Risk of thrombosis according to need of phlebotomies in patients with polycythemia vera treated with hydroxyurea. *Haematologica* 2017;102(01):103–109
 - 31 Cortelazzo S, Finazzi G, Ruggeri M, et al. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. *N Engl J Med* 1995;332(17):1132–1136
 - 32 Landolfi R, Cipriani MC, Novarese L. Thrombosis and bleeding in polycythemia vera and essential thrombocythemia: pathogenetic mechanisms and prevention. *Best Pract Res Clin Haematol* 2006;19(03):617–633
 - 33 Landolfi R, Di Gennaro L, Barbui T, et al; European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera. *Blood* 2007;109(06):2446–2452
 - 34 Tefferi A. Leukocytosis as a risk factor for thrombosis in myeloproliferative neoplasms—biologically plausible but clinically uncertain. *Am J Hematol* 2010;85(02):93–94
 - 35 Girodon F, Dutrillaux F, Broséus J, et al. Leukocytosis is associated with poor survival but not with increased risk of thrombosis in essential thrombocythemia: a population-based study of 311 patients. *Leukemia* 2010;24(04):900–903
 - 36 Cerquozzi S, Barraco D, Lasho T, et al. Risk factors for arterial versus venous thrombosis in polycythemia vera: a single center experience in 587 patients. *Blood Cancer J* 2017;7(12):662
 - 37 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(11):1729–1737
 - 38 Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2015 update on diagnosis, risk-stratification and management. *Am J Hematol* 2015;90(02):162–173
 - 39 Barbui T, Finazzi G, Carobbio A, et al. Development and validation of an International Prognostic Score of thrombosis in World Health Organization-essential thrombocythemia (IPSET-thrombosis). *Blood* 2012;120(26):5128–5133, quiz 5252
 - 40 Barbui T, Vannucchi AM, Buxhofer-Ausch V, et al. Practice-relevant revision of IPSET-thrombosis based on 1019 patients with WHO-defined essential thrombocythemia. *Blood Cancer J* 2015;5:e369
 - 41 Guy A, Gourdou-Latyszenok V, Le Lay N, et al. Vascular endothelial cell expression of JAK2^{V617F} is sufficient to promote a pro-

- thrombotic state due to increased P-selectin expression. *Haematologica* 2019;104(01):70–81
- 42 Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. *N Engl J Med* 2017;376(05):429–439
 - 43 Rosti V, Villani L, Riboni R, et al;Associazione Italiana per la Ricerca sul Cancro Gruppo Italiano Malattie Mieloproliferative (AGIMM) investigators. Spleen endothelial cells from patients with myelofibrosis harbor the JAK2V617F mutation. *Blood* 2013;121(02):360–368
 - 44 Marchetti M, Tartari CJ, Russo L, et al. Phospholipid-dependent procoagulant activity is highly expressed by circulating microparticles in patients with essential thrombocythemia. *Am J Hematol* 2014;89(01):68–73
 - 45 Marchetti M, Castoldi E, Spronk HM, et al. Thrombin generation and activated protein C resistance in patients with essential thrombocythemia and polycythemia vera. *Blood* 2008;112(10):4061–4068
 - 46 Landolfi R, Marchioli R, Kutti J, et al;European Collaboration on Low-Dose Aspirin in Polycythemia Vera Investigators. Efficacy and safety of low-dose aspirin in polycythemia vera. *N Engl J Med* 2004;350(02):114–124
 - 47 Najean Y, Rain JD. Treatment of polycythemia vera: the use of hydroxyurea and pipobroman in 292 patients under the age of 65 years. *Blood* 1997;90(09):3370–3377
 - 48 Najean Y, Rain JD;The French Polycythemia Study Group. Treatment of polycythemia vera: use of 32P alone or in combination with maintenance therapy using hydroxyurea in 461 patients greater than 65 years of age. *Blood* 1997;89(07):2319–2327
 - 49 Fruchtman SM, Mack K, Kaplan ME, Peterson P, Berk PD, Wasserman LR. From efficacy to safety: a Polycythemia Vera Study group report on hydroxyurea in patients with polycythemia vera. *Semin Hematol* 1997;34(01):17–23
 - 50 Finazzi G, Caruso V, Marchioli R, et al;ECLAP Investigators. Acute leukemia in polycythemia vera: an analysis of 1638 patients enrolled in a prospective observational study. *Blood* 2005;105(07):2664–2670
 - 51 Vannucchi AM, Kiladjan JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med* 2015;372(05):426–435
 - 52 Passamonti F, Griesshammer M, Palandri F, et al. Ruxolitinib for the treatment of inadequately controlled polycythemia vera without splenomegaly (RESPONSE-2): a randomised, open-label, phase 3b study. *Lancet Oncol* 2017;18(01):88–99
 - 53 Kiladjan J-J, Zachee P, Hino M, et al. Long-term efficacy and safety of ruxolitinib versus best available therapy in polycythemia vera (RESPONSE): 5-year follow up of a phase 3 study. *Lancet Haematol* 2020;7(03):e226–e237
 - 54 Gisslinger H, Klade C, Georgiev P, et al;PROUD-PV Study Group. Ropgeinterferon alfa-2b versus standard therapy for polycythemia vera (PROUD-PV and CONTINUATION-PV): a randomised, non-inferiority, phase 3 trial and its extension study. *Lancet Haematol* 2020;7(03):e196–e208
 - 55 Alvarez-Larrán A, Martínez-Avilés L, Hernández-Boluda JC, et al. Busulfan in patients with polycythemia vera or essential thrombocythemia refractory or intolerant to hydroxyurea. *Ann Hematol* 2014;93(12):2037–2043
 - 56 Rocca B, Tosetto A, Betti S, et al. A randomized double-blind trial of 3 aspirin regimens to optimize antiplatelet therapy in essential thrombocythemia. *Blood* 2020;136(02):171–182
 - 57 Gisslinger H, Gotic M, Holowiecki J, et al;ANAHYDRET Study Group. Anagrelide compared with hydroxyurea in WHO-classified essential thrombocythemia: the ANAHYDRET Study, a randomized controlled trial. *Blood* 2013;121(10):1720–1728
 - 58 Birgegård G, Besses C, Griesshammer M, et al. Treatment of essential thrombocythemia in Europe: a prospective long-term observational study of 3649 high-risk patients in the Evaluation of Anagrelide Efficacy and Long-term Safety study. *Haematologica* 2018;103(01):51–60
 - 59 Yacoub A, Mascarenhas J, Kosiorek H, et al. Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea. *Blood* 2019;134(18):1498–1509
 - 60 Cassinat B, Verger E, Kiladjan JJ. Interferon alfa therapy in CALR-mutated essential thrombocythemia. *N Engl J Med* 2014;371(02):188–189
 - 61 Guglielmelli P, Pacilli A, Rotunno G, et al;AGIMM Group. Presentation and outcome of patients with 2016 WHO diagnosis of prefibrotic and overt primary myelofibrosis. *Blood* 2017;129(24):3227–3236
 - 62 Rumi E, Boveri E, Bellini M, et al;Associazione Italiana per la Ricerca sul Cancro Gruppo Italiano Malattie Mieloproliferative Investigators. Clinical course and outcome of essential thrombocythemia and prefibrotic myelofibrosis according to the revised WHO 2016 diagnostic criteria. *Oncotarget* 2017;8(60):101735–101744
 - 63 Buxhofer-Ausch V, Gisslinger H, Thiele J, et al. Leukocytosis as an important risk factor for arterial thrombosis in WHO-defined early/prefibrotic myelofibrosis: an international study of 264 patients. *Am J Hematol* 2012;87(07):669–672
 - 64 Buxhofer-Ausch V, Gisslinger B, Schalling M, et al. Impact of white blood cell counts at diagnosis and during follow-up in patients with essential thrombocythemia and prefibrotic primary myelofibrosis. *Br J Haematol* 2017;179(01):166–169
 - 65 Finazzi G, Carobbio A, Thiele J, et al. Incidence and risk factors for bleeding in 1104 patients with essential thrombocythemia or prefibrotic myelofibrosis diagnosed according to the 2008 WHO criteria. *Leukemia* 2012;26(04):716–719
 - 66 Campbell PJ, Bareford D, Erber WN, et al. Reticulin accumulation in essential thrombocythemia: prognostic significance and relationship to therapy. *J Clin Oncol* 2009;27(18):2991–2999
 - 67 Finazzi G, Vannucchi AM, Barbui T. Prefibrotic myelofibrosis: treatment algorithm 2018. *Blood Cancer J* 2018;8(11):104
 - 68 Sekhar M. Prevention and management of thrombosis in myeloproliferative neoplasms. *Clin Adv Hematol Oncol* 2017;15(03):178–181
 - 69 De Stefano V, Za T, Rossi E, et al;GIMEMA CMD-Working Party. Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments. *Haematologica* 2008;93(03):372–380
 - 70 De Stefano V, Ruggeri M, Cervantes F, et al. High rate of recurrent venous thromboembolism in patients with myeloproliferative neoplasms and effect of prophylaxis with vitamin K antagonists. *Leukemia* 2016;30(10):2032–2038
 - 71 Hernández-Boluda JC, Arellano-Rodrigo E, Cervantes F, et al;Grupo Español de Enfermedades Mieloproliferativas Filadelfia Negativas (GEMFIN) Oral anticoagulation to prevent thrombosis recurrence in polycythemia vera and essential thrombocythemia. *Ann Hematol* 2015;94(06):911–918
 - 72 Barbui T, De Stefano V, Falanga A, et al. Addressing and proposing solutions for unmet clinical needs in the management of myeloproliferative neoplasm-associated thrombosis: a consensus-based position paper. *Blood Cancer J* 2019;9(08):61
 - 73 Bauersachs R, Berkowitz SD, Brenner B, et al;EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363(26):2499–2510
 - 74 Agnelli G, Buller HR, Cohen A, et al;AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;369(09):799–808
 - 75 Büller HR, Décousus H, Grosso MA, et al;Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013;369(15):1406–1415
 - 76 Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2, Suppl):e419S–e96S
 - 77 Castelli R, Gallipoli P, Schiavon R, Teatini T, Delilieri GL, Bergamaschini L. High prevalence of heparin induced thrombocytopenia with thrombosis among patients with essential

- thrombocytopenia carrying V617F mutation. *J Thromb Thrombolysis* 2018;45(01):106–113
- 78 Prandoni P, Noventa F, Ghirarduzzi A, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. *Haematologica* 2007;92(02):199–205
 - 79 Lee AY, Levine MN, Baker RI, et al;Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003;349(02):146–153
 - 80 Lee AYY, Kamphuisen PW, Meyer G, et al;CATCH Investigators. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. *JAMA* 2015;314(07):677–686
 - 81 Finazzi G, De Stefano V, Barbui T. Splanchnic vein thrombosis in myeloproliferative neoplasms: treatment algorithm 2018. *Blood Cancer J* 2018;8(07):64
 - 82 Raskob GE, van Es N, Verhamme P, et al;Hokusai VTE Cancer Investigators. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med* 2018;378(07):615–624
 - 83 Young AM, Marshall A, Thirlwall J, 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(20):2017–2023
 - 84 Agnelli G, Becattini C, Meyer G, et al;Caravaggio Investigators. Apixaban for the treatment of venous thromboembolism associated with cancer. *N Engl J Med* 2020;382(17):1599–1607
 - 85 Giustozzi M, Agnelli G, Del Toro-Cervera J, et al. Direct oral anticoagulants for the treatment of acute venous thromboembolism associated with cancer: a systematic review and meta-analysis. *Thromb Haemost* 2020;120(07):1128–1136
 - 86 Gómez-Outes A, Lecumberri R, Suárez-Gea ML, Terleira-Fernández AI, Monreal M, Vargas-Castrillón E. Case fatality rates of recurrent thromboembolism and bleeding in patients receiving direct oral anticoagulants for the initial and extended treatment of venous thromboembolism: a systematic review. *J Cardiovasc Pharmacol Ther* 2015;20(05):490–500
 - 87 Raskob GE, van Es N, Segers A, et al;Hokusai-VTE Investigators. Edoxaban for venous thromboembolism in patients with cancer: results from a non-inferiority subgroup analysis of the Hokusai-VTE randomised, double-blind, double-dummy trial. *Lancet Haematol* 2016;3(08):e379–e387
 - 88 Iannotto JC, Couturier MA, Galinat H, et al. Administration of direct oral anticoagulants in patients with myeloproliferative neoplasms. *Int J Hematol* 2017;106(04):517–521
 - 89 Kaifia A, Kirschner M, Wolf D, et al;Study Alliance Leukemia (SAL) Bleeding, thrombosis, and anticoagulation in myeloproliferative neoplasms (MPN): analysis from the German SAL-MPN-registry. *J Hematol Oncol* 2016;9:18
 - 90 Curto-Garcia N, Doyle AJ, Breen KA, et al. Outcomes of patients receiving direct oral anticoagulants for myeloproliferative neoplasm-associated venous thromboembolism in a large tertiary centre in the UK. *Br J Haematol* 2020;189(03):e79–e81
 - 91 Serrao A, Breccia M, Napolitano M, et al. A multicenter real-life study on anticoagulant treatment with direct oral anticoagulants in patients with Ph-negative myeloproliferative neoplasms. *Am J Hematol* 2020;95(12):E329–E332
 - 92 De Grandis M, Cambot M, Wautier MP, et al. JAK2V617F activates Lu/BCAM-mediated red cell adhesion in polycythemia vera through an EpoR-independent Rap1/Akt pathway. *Blood* 2013;121(04):658–665
 - 93 Klatt C, Krüger I, Zey S, et al. Platelet-RBC interaction mediated by FasL/FasR induces procoagulant activity important for thrombosis. *J Clin Invest* 2018;128(09):3906–3925
 - 94 Arellano-Rodrigo E, Alvarez-Larrán A, Reverter JC, Villamor N, Colomer D, Cervantes F. Increased platelet and leukocyte activation as contributing mechanisms for thrombosis in essential thrombocythemia and correlation with the JAK2 mutational status. *Haematologica* 2006;91(02):169–175
 - 95 Edelmann B, Gupta N, Schnoeder TM, et al. JAK2-V617F promotes venous thrombosis through $\beta 1/\beta 2$ integrin activation. *J Clin Invest* 2018;128(10):4359–4371
 - 96 Wolach O, Sellar RS, Martinod K, et al. Increased neutrophil extracellular trap formation promotes thrombosis in myeloproliferative neoplasms. *Sci Transl Med* 2018;10(436):eaan8292