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

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Abstract

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.

Keywords

- management of thrombosis
- prevention
- thrombosis
- myeloproliferative neoplasms

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 results[16]; 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 $>1{,}000\times10^9$/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, *JAK2*V617F 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 *JAK2*V617F 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

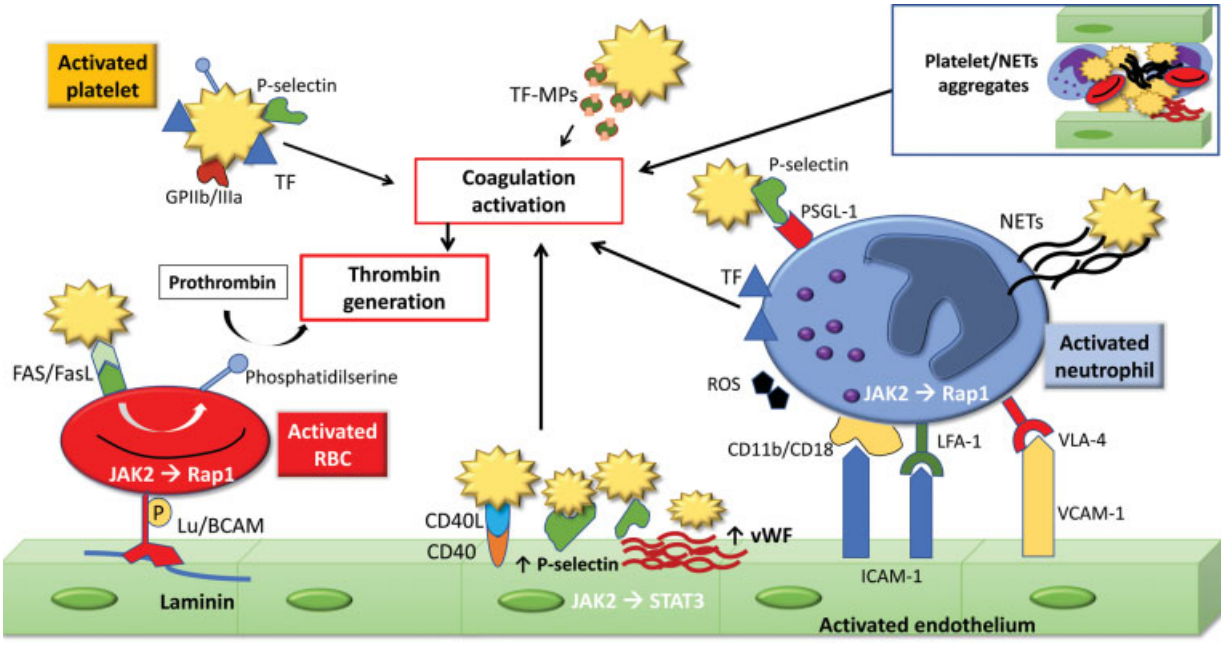

Fig. 1 Pathogenesis of thrombosis in MPN. In **RBCs**, *JAK2*V617F mutation mediates the phosphorylation of the erythroid Lutheran/basal cell-adhesion molecule (Lu/BCAM) through the Rap1/Akt signaling pathway, determining an aberrant adhesion of RBCs to the endothelial cells (EC).[92] Moreover, RBC/platelet 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 *JAK2*V617F-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)
• Phebotomy to keep HCT<45% • OD aspirin	• Consider BID aspirin if: • inadequate control of microvascular symptoms • CV risk factors • leukocytosis	• Cytoreduction 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)
• No CV risk factors: OD aspirin • CV risk factors: consider BID aspirin	• No CV risk factors: OD aspirin • CV risk factors: Cytoreduction with HU and OD aspirin	• Cytoreduction 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
• Observation	• OD aspirin	• Arterial: OD aspirin • Venous: anticoagulation • If thrombocytosis or leukocytosis: cytoreduction with HU	• Avoid aspirin • If thrombocytosis or leukocytosis: cytoreduction 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 apixaban[84] 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.

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