



Thrombosis in myeloproliferative neoplasms: A clinical and pathophysiological perspective

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ABSTRACT

Myeloproliferative neoplasms (MPNs) are clonal haematopoietic stem cell disorders characterised by myeloid progenitor proliferation in the bone marrow. Polycythaemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) are Philadelphia-chromosome negative classic MPNs defined as per the World Health Organization (WHO) 2016 classification and diagnostic criteria. Thrombosis, comprising of both arterial and venous events, is recognised as a leading cause of morbidity and mortality in ET and PV. Several patient and disease-specific characteristics have been shown to correlate with increased thrombotic risk in MPN. Clinical risk factors include age, history of previous thrombosis, cardiovascular comorbidities, and mutation status. The pathobiology of thrombosis in MPN is multifactorial and results from a complex interplay between blood cells, endothelial cells, coagulation system and inflammatory mediators. Platelets, leukocytes, and erythrocytes exist in a hyperactive and proadhesive state. Furthermore, endothelial dysfunction, haemostatic elements and cytokine dysregulation are implicated in thrombogenesis. MPN driver mutations enhance the thrombotic environment, while the chronic inflammatory state further promotes clonal expansion. Much of the current treatment paradigms for MPN focus on primary prevention of thrombosis with antiplatelet agents and cytoreduction. There is a lack of high-quality data informing the optimal approach to secondary prevention of recurrent thrombosis in MPN. Further advances in the characterisation of the cellular and molecular mechanisms underlying thrombotic tendency in MPN are necessary in order to improve personalised risk prediction/stratification and treatment strategies. This review outlines the incidence, nature, and risk factors for thrombosis in MPN, gives an overview of the mechanisms underlying hypercoagulability and discusses prevention and treatment considerations.

1. Introduction

Myeloproliferative neoplasms (MPNs) are clonal haematopoietic stem cell disorders characterised by myeloid progenitor proliferation in the bone marrow, resulting in an excess of differentiated erythrocytes, platelets and leukocytes circulating in peripheral blood [1]. Polycythaemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) are Philadelphia-chromosome negative classic MPNs defined as per the World Health Organization (WHO) 2016 classification and diagnostic criteria [2]. While distinct entities, these diseases share similar pathophysiology, bone marrow morphology and

clinical phenotype including a propensity for thrombosis formation and leukaemic transformation. While rare conditions, collectively these disorders have an estimated incidence of 6 per 100,000 per year with a prevalence of approximately 94 per 100,000, reflecting the chronicity of these diseases for many affected individuals. However, there is significant heterogeneity in reporting on the incidence of MPN, with respect to study design, geographical location, and diagnostic classification, therefore these figures likely underestimate the true disease rate in the general population [3,4].

The last 15 years yielded the discovery of unifying genetic aberrancy driving clonal haematopoietic expansion in these heterogeneous

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disorders. An acquired single point mutation at exon 14 in Janus kinase 2 gene with valine-to-phenylalanine substitution at amino acid position 617 (*JAK2* V617F), leads to constitutive tyrosine phosphorylation activity and upregulation of downstream transcription factors such as signal transducer and activator of transcription 3 (STAT3) [5]. *JAK2* V617F mutation is identified in 95% of patients with PV, 50–60% of patients with ET and 50–60% with PMF [6–9]. An alternative *JAK2* mutation, at exon 12, is present in the remainder of PV cases [10]. Somatic mutations in myeloproliferative leukaemia virus oncogene (*MPL*) and calreticulin (*CALR*) are detected in 2–3% and 20–25% of patients with ET, and 3–5% and 25–30% of patients with PMF respectively [11–13]. There remains a decreasing number of ET and PMF diagnoses for whom no driver mutation is found, commonly referred to as triple negative (TN) [14]. In addition, there is an increasing body of evidence supporting the role of co-existing, non-driver clonal mutations in MPN disease biology and clinical phenotype [15,16]. Targeted next-generation sequencing (NGS) has led to the discovery of pathological mutations in a range of genes in individuals with MPN affecting epigenetic regulation, transcription control and splicing such as *ASXL1*, *DNMT3A* and *TET2* [17]. These mutations are commonly encountered in other myeloid malignancies and are the most common gene mutations observed in individuals with clonal haematopoiesis of indeterminate potential (CHIP) [18]. Interestingly, recent studies have demonstrated that driver mutations may be acquired very early in life and may significantly pre-date the development of overt clinical malignancy [19, 20].

2. Thrombotic risk

Patients with MPN have a risk of disease progression with fibrotic or leukaemic transformation, however it is disease-related haemostatic complications that primarily negatively impact life expectancy. Thrombosis, comprising of both arterial and venous events, is recognised as the leading cause of morbidity and mortality in ET and PV [21]. Prognosis in MPN varies depending on subtype and individual risk stratification, however thrombosis has been identified to have an independent adverse effect on survival in both PV and ET [22,23]. A prospective analysis of thrombotic events in the European Collaboration on Low-dose Aspirin study (ECLAP) found that cardiovascular events accounted for 45% of all-cause mortality in PV at 2.7 years follow up [24,25]. Risk of thrombosis appears highest at the time of initial diagnosis. A meta-analysis reported a pooled prevalence of thrombosis of 20% at the time of MPN diagnosis (95% CI, 16.6–23.8%), with the pooled prevalence of arterial thrombosis and venous thromboembolism (VTE) of 16.2% (95% CI, 13.0–20.0%) and 6.2% (95% CI, 4.9–7.8%) respectively. The pooled prevalence of thrombosis was highest for PV, reported as 28.6% (95% CI, 22.0–36.3%), followed by ET at 20.7% (95% CI, 16.6–25.5%) and lowest for PMF with 9.5% (95% CI, 5.0–17.4%) events at time of initial presentation [26]. A large population-based study evaluating the risk of thrombosis in MPN compared to the general population observed a 3-fold and 10-fold elevated risk respectively for arterial and venous thrombosis. The risk is highest at or shortly after diagnosis and while it decreases thereafter, it remains significantly increased throughout a patient's lifetime. The 5-year cumulative incidence of thrombosis was overall twice as high compared to age matched population controls [27]. Furthermore, the risk of recurrent thrombosis is also high in this patient population with a recurrence rate of 5.7 per 100 patient-years (95% CI 5.1–6.4). The site of the first thrombosis (arterial or venous) predicts the site of recurrence [28].

Arterial events are twice as common as venous thrombosis and include myocardial infarction, ischaemic stroke, and peripheral arterial occlusion [29]. Pulmonary embolism (PE), deep vein thrombosis (DVT) as well as events at more unusual sites such as cerebral venous sinus thrombosis (CVST) and splanchnic venous thrombosis (SVT) contribute to the burden of VTE experienced by these patients. MPN is the commonest cause of Budd Chiari syndrome (BCS) accounting for 40% of

cases and is similarly the most prevalent non-cirrhotic, non-malignant aetiology for portal vein thrombosis, identified in 30% of cases. SVT may represent the first clinical manifestation of MPN, particularly when the *JAK2* mutation is present. MPNs presenting in this way often have unique features, including the onset at a younger age, female predominance, and thrombosis may precede abnormalities in the peripheral blood count. *JAK2* screening in patients with SVT without overt MPN features identified the diagnosis in 15.4% and 17.1% patients with PVT and BCS respectively [30,31]. In addition to macrovascular thrombosis, the symptom burden experienced by patients with PV and ET including headache, paraesthesia and erythromelalgia has been attributed to microvascular thrombi. Histopathological studies demonstrate platelet-rich arteriolar microthrombi with endothelial inflammation and symptomatic benefit is often experienced following the initiation of antiplatelet therapy [32].

3. Clinical risk factors

Several patient and disease-specific characteristics have been shown to correlate with increased thrombotic risk in MPN (Fig. 1). A positive correlation has been established between traditional cardiovascular risk factors and predisposition to thrombosis in MPN. Multivariable analysis of an international retrospective cohort of patients with ET identified significant predictors of arterial thrombosis including age greater than 60 years (hazard ratio (HR) = 1.7), thrombosis history (HR = 2.1), cardiovascular risk factors including tobacco use, hypertension, or diabetes mellitus (HR = 1.9). Male sex was the only significant predictor of venous thrombosis (HR = 1.9) [29]. Similarly older age and previous thrombosis independently predict cardiovascular complications in PV [25], while associations have been reported between hypertension and hyperlipidaemia and arterial events [33]. Therefore, careful consideration of co-existing co-morbidities is a crucial component of individual patient risk stratification, and minimising atherosclerotic risk represents a cornerstone of MPN management [34].

MPNs are defined by elevations in specific myeloid cell lineages and attempts have been made to delineate the independent association between blood cell counts and thrombosis. The contribution of hyper viscosity resulting from excess erythropoiesis to the hypercoagulable state is well established in PV. The CYTO-PV randomised control trial investigated thrombotic risk at different haematocrit target ranges. The rate of thrombosis was 4-fold higher in patients with a haematocrit of 45%–50% compared to those treated to a lower threshold of less than 45% [35]. Elevated platelet count can be seen in all MPN subtypes but is particularly marked in ET. Intriguingly, the degree of thrombocytosis has not been proven to significantly correlate with thrombotic complications. Paradoxically, extreme thrombocytosis is associated with a bleeding diathesis. The mechanism of bleeding is attributed to acquired von Willebrand disease resulting from increased clearance by platelets of the large von Willebrand factor (VWF) multimers [36,37]. The effect of leukocytosis on vascular events is inconsistently reported in the literature. Observational data have confirmed a significant positive relationship between elevated white cell count and thrombosis in both PV and ET [38–40]. This was supported by a meta-analysis examining over 30,000 patients with PV or ET which demonstrated a 60% excess risk of thrombosis in the presence of leukocytosis when adjusted for confounding factors. This was mainly accounted for by ET with a relative risk (RR) of 1.65 (95% CI, 1.43–1.9) and was only significant for arterial episodes (RR, 1.45; 95% CI, 1.13–1.86). Furthermore, bleeding and death, which were included as secondary outcomes, were also independently associated with leukocytosis in this study [41]. Notably, there were some criticisms of the design of this meta-analysis. Namely the inclusion of studies defining leukocytosis as a value measured at a single time point (usually at time of diagnosis), limiting the ability to confer causality [42]. Moreover, a recent publication investigating persistently elevated white cell counts over time in patients with PV failed to show a temporal relationship between leukocyte trajectory and

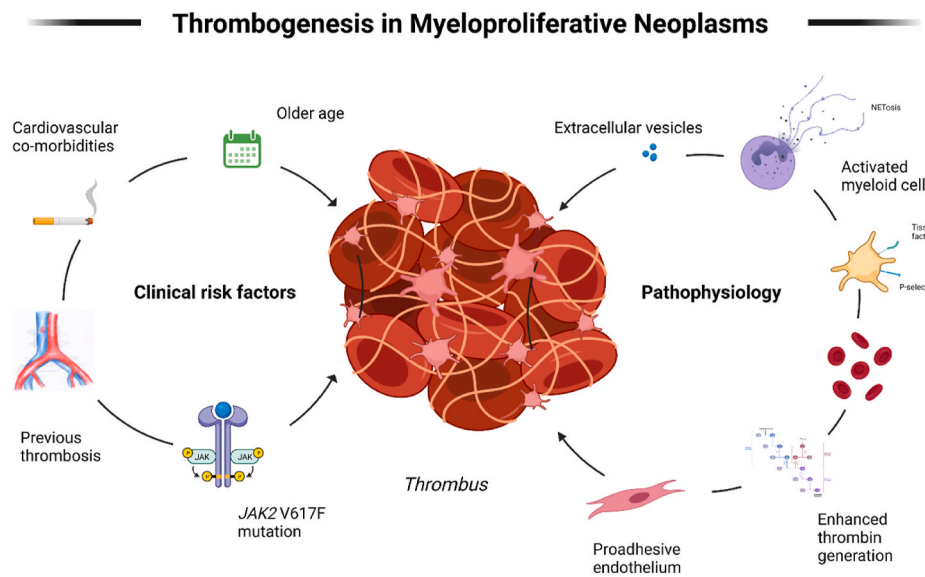


Fig. 1. Summary of clinical risk factors and pathophysiological mechanisms contributing to thrombosis in myeloproliferative neoplasms.

thrombosis [43]. The independent impact of leukocytosis as an independent clinical variable contributing to MPN thrombosis remains to be determined [44].

Like all myeloid disorders the genomic landscape of MPN is complex and fascinating, and our understanding of its role in the pathophysiology of the disease continues to evolve. Mutation status pertains to diagnosis in MPN but also has an important role in clinical disease phenotype and prognostication. *JAK2* V617F has been observed to confer an approximately two-fold increased risk of thrombosis in ET, including both arterial and venous events, compared to wild type [45]. Similar outcomes have been reported in PMF [46]. *JAK2* V617F has been demonstrated to have a quantitative relationship with clinical risk of thrombosis. Recent studies have demonstrated that *JAK2* V617F variant allele frequency positively correlates with thrombosis in both PV, ET and PMF [47]. An Italian prospective cohort study found that *JAK2* allele burden greater than 50% corresponded with higher thrombotic risk for patients with ET and PMF. Thrombosis-free survival at 15 years was 35% lower in *JAK2* positive patients [48]. A prospective Spanish study quantified and followed the *JAK2*-allele burden in ET and PV over time. The incidence of thrombosis was significantly increased in those with a persistently high or unstable *JAK2* mutation load compared to those with a persistently low allele burden [49]. Meanwhile, the thrombotic risk in *CALR*-mutated ET is lower than that reported with *JAK2* V617F and comparable to triple-negative cases. Since *JAK2* V617F and *CALR* are mutually exclusive, there is the concept that the absence of *JAK2* V617F rather than the presence of *CALR* is associated with a lower risk of thrombosis. An Italian observational study of 576 patients with ET followed for a median of 6 years, reported major cardiovascular events in 30% of *JAK2* V617F positive patients versus 13.5% of individuals with a *CALR* mutation. The rate of thrombosis was relatively high in *MPL* positive patients in this study with a 10-year cumulative incidence of nearly 20% [50].

4. Mechanisms of thrombosis

4.1. Platelets

The pathogenesis of thrombosis in MPN is multifactorial and results from a complex interplay between blood cells, the coagulation cascade, endothelial cells and inflammatory mediators [51]. MPN is associated not only with a quantitative change in myeloid cell lines but qualitative differences have also been described [52]. Platelets are essential for

blood coagulation however it is also recognised that they play a crucial role in several other processes such as inflammation and pathologic sequelae [53]. Platelets are considered to circulate in a hyperactive state in MPN as evidenced by increased expression of P-selectin, CD40 ligand and tissue factor (TF) [51,54,55]. Platelet hyperactivity has been shown to correlate with *JAK2* V617F allele burden and thus abnormalities may be intrinsic to cells carrying the mutation [56]. Adenosine diphosphate (ADP)-induced platelet aggregation is significantly enhanced in ET and PV compared to controls; the highest values were observed in *JAK2* V617F positive patients [57]. In contrast, platelet activation and aggregation parameters were reduced in patients with *CALR* positive ET versus those with the *JAK2* V617F mutation which corresponds with the clinical difference observed in thrombotic phenotype [58]. Platelets contribute to the pathogenesis of various inflammatory disease states through the release of proinflammatory immune mediators from their α -granules upon activation. Chemokines such as RANTES, beta-thromboglobulin and platelet factor 4 have been demonstrated in the circulation of patients with MPN [51,59]. Moreover, platelets participate in innate immunity through the expression of toll-like receptors (TLR), which recognize inflammatory signals and trigger platelet functional responses. Enhanced response to TLR stimulation is reported in ET with increased platelet secretion and heightened platelet-leukocyte/endothelial interaction [59]. Thus, platelets play a central role in mediating and perpetuating the chronic ‘thromboinflammatory’ state in MPN.

4.2. Leukocytes

Leukocytes have been implicated in the mechanism of thrombus formation in patients with MPN through cross talk with other myeloid cells, endothelial cells and the haemostatic system [60]. Neutrophil activation markers including CD14, CD11b, P-selectin glycoprotein ligand 1 (PSGL-1) and leukocyte alkaline phosphatase (LAP) are highly expressed in patients with ET and PV promoting increased leukocyte aggregation with platelets and endothelial cells [54,61]. Increased plasma levels of neutrophil-granule derived proteases such as elastase and myeloperoxidase and reactive oxygen species are reported in ET and PV [62]. These intracellular enzymes in turn damage endothelium, activate platelets and the coagulation cascade promoting thrombogenesis [60]. Activated neutrophils are known to expel their nuclear content to form an intravascular, extracellular meshwork referred to as neutrophil extracellular traps (NETs). This process is a well-established

component in the pathogenesis of thrombosis through cytokine and endothelial activation. 'NETosis' induces a hypercoagulable state in MPN and interestingly, appears to be sustained by *JAK2* V617F mutated leukocytes and platelets with reduced formation in the presence of *JAK2* inhibition [56]. Enhanced monocyte activation with elevated CD25 and tissue factor expression is also seen in individuals with MPN [63]. Moreover, *JAK2* V617F mediated activation of $\beta 1$ and $\beta 2$ integrins on leukocytes has been demonstrated in mouse models, thus causing enhanced leukocyte adhesion to endothelial cells via vascular cell adhesion molecule 1 (VCAM1) and intercellular adhesion molecule 1 (ICAM1) [64].

4.3. Erythrocytes

Erythrocytes demonstrate aberrant adhesion to the endothelium and other myeloid cells in MPN. *JAK2* V617F, via the erythropoietin independent Rap1/Akt signalling pathway, promotes phosphorylation of erythroid Lutheran/basal cell adhesion molecule (Lu/BCAM) resulting in enhanced red blood cell (RBC) binding to the endothelium [65]. The laminin $\alpha 5$ chain also facilitates abnormal erythrocyte/endothelial adhesion in MPN [66]. Red cell/platelet interaction is mediated through the FAS ligand/FAS receptor which increases expression of phosphatidylserine on the surface of RBCs stimulating thrombin generation [65]. The MPN mutant clone therefore not only drives excess erythropoiesis but is also implicated in inducing conformational change to the structure and function of red cells.

4.4. Inflammation

'Thromboinflammation' is a term used to describe the functional interaction existing between inflammatory states and thrombosis, with each pathway contributing to and enhancing the other. A chronic inflammatory state exists in MPN and has an important role in promoting the hypercoagulable milieu. Proinflammatory, prothrombotic genes such as *F3* (tissue factor) and *SELP* (P-selectin) are upregulated in granulocytes of patients with MPN and thrombosis [67]. Higher levels of reactive oxygen species (ROS) have been shown in cells expressing *JAK2* V617F, which in turn increase hypoxia-inducible factors (HIF α) with downstream activation of interleukin 6 (IL6), nitric oxide (NO), integrins, plasminogen activator inhibitor-1 (PAI-1) among others [68]. Elevation of inflammatory cytokines such as tumour necrosis factor α (TNF- α) are seen in MPN which induce platelet activation and increase thrombotic risk. In addition to advancing thrombosis, chronic inflammation also plays a crucial role in selecting out MPN-driver mutated haematopoietic progenitors, thereby enhancing clonal evolution and disease progression [56,69].

4.5. Endothelium

In physiological states endothelial cells maintain normal haemostatic balance, however there is evidence of vascular dysfunction in chronic MPN, producing a prothrombotic environment through activation of the coagulation cascade and blood cells [51]. Disrupted endothelial cells in patients with MPN release procoagulant and anti-fibrinolytic proteins including VWF, PAI-1 and soluble thrombomodulin, as well as adhesion molecules such as E-selectin and P-selectin into their external milieu [61,70–72]. It has been demonstrated in murine models of MPN that the *JAK2* V617F mutation promotes a pro-adhesive, pro-inflammatory endothelial cell phenotype [73]. Furthermore, a procoagulant phenotype was seen in mice expressing *JAK2* V617F positivity in vascular endothelial cells only and the mutation has been detected in liver endothelial cells of PV patients with Budd-Chiari syndrome [74,75]. Thus, abnormal endothelial cell activity likely contributes to the development of an intravascular prothrombotic environment in MPN.

4.6. Extracellular vesicles

Extracellular vesicles (EV) are small cellular derived blood borne particles. They are important messengers containing microRNA and protein signals that regulate a diverse range of biologic and inflammatory pathologic processes such as thrombosis and vascular dysfunction. There are two main EV populations, differentiated based on size and origin, microparticles (MPs) (0.1–1 μ m), shed from the plasma membrane, and exosomes (30–100 nm), of endosomal origin [76]. MPs have been described in MPN. Compared to healthy controls, a higher number of circulating MPs expressing platelet and endothelial markers have been observed in platelet poor plasma of patients with ET [77]. MP levels are raised in MPN patients with thrombosis compared to those without ($p < 0.05$) [78]. MPs of erythrocyte origin promote arterial hyperreactivity in *JAK2* positive MPN [79]. Furthermore, MPs contribute to the hypercoagulable state in MPN demonstrated by enhanced MP-derived thrombin generation [80,81]. Microparticle mediated thrombomodulin resistance has been hypothesized as a potential underlying mechanism [82]. Exosomes have not been accurately characterised in MPN. Investigation of the genomic and proteomic contents of extracellular vesicles and how this may relate to the pathophysiology of the observed prothrombotic phenotype remains to be elucidated.

4.7. Coagulation system

Procoagulant and anticoagulant pathways are altered in MPN. It has been demonstrated that thrombin generation as measured by calibrated automated thrombography is enhanced in patients with MPN. This tool is widely used as a global measure of coagulation in vivo in the research setting. Several publications have noted increased platelet-mediated and platelet-independent thrombin generation capacity among patients with MPN [57,83–85]. Enhanced tissue factor pathway has been described as a primary mechanism promoting this phenomenon [80,84,86]. Moreover, thrombin generation parameters correlate positively with *JAK2* V617F allele burden and negatively with cytoreduction with hydroxyurea [84]. Several other plasma haemostatic proteins have been studied in the context of ET and PV. Levels of natural anticoagulants protein C, protein S (PS) and antithrombin are reduced in patients with ET and PV [87]. Lower inhibition of thrombin generation in the presence of thrombomodulin has been observed in patients with MPN compared to matched controls [82]. Acquired activated protein C resistance (APC) mediated by low free PS has been observed [86,88]. Intriguingly, proteases from platelets appear to be responsible for cleavage of PS in the circulation of ET patients and may drive the procoagulant environment by diminishing the anticoagulant activity of PS [86,89,90].

5. Treatment considerations

Much of the current treatment paradigms for MPN focus on preventing thrombotic complications. Careful risk stratification of individuals is crucial to inform appropriate management. The conventional prognostic systems in PV and ET are based upon age and history of thrombosis, which separate patients into low-risk (age <60 years and no history of thrombosis) or high-risk (age ≥ 60 years or history of prior thrombosis) categories. All patients with PV should be prescribed low dose aspirin and phlebotomy is recommended to maintain a haematocrit level <45% to minimise risk of thrombosis [91]. The International Prognostic Score for thrombosis in Essential Thrombocythaemia (IPSET-thrombosis) (Table 1) is a modern scoring system incorporated into the recently updated European Leukaemia Net (ELN) and National Comprehensive Cancer Network (NCCN) guidelines [91, 92]. The score includes *JAK2* mutation and cardiovascular risk factors in addition to standard predictors of thrombosis (age, prior thrombosis). The incidence of thrombosis is estimated at 1.03% of patients per year in the low-risk group compared to 2.35% and 3.56% in the intermediate

Table 1
International Prognostic Score for Thrombosis in Essential Thrombocythaemia (IPSET-Thrombosis) [93]

Variable	Score	Risk	Annual thrombotic rate
Age >60	1	Low (0-1)	1.03%
Prior thrombosis	2	Intermediate (2)	2.35%
Cardiovascular risk factors	1	High (3-6)	3.56%
JAK2 V617F mutation	2		

and high-risk categories respectively [93]. A retrospective analysis evaluated the benefit-to-risk ratio of aspirin in low-risk ET patients who were treated with antiplatelet therapy compared to observation only. In patients carrying the *JAK2* V617F mutation, aspirin was associated with a reduced incidence of VTE with no significant impact on bleeding. By contrast, for those with *CALR* mutations antiplatelet therapy did not affect the rate of thrombosis and was associated with a higher incidence of bleeding [94]. Treatment algorithms now suggest observation alone may be adequate in a carefully selected subgroup of low-risk patients i. e., those aged less than 60, *JAK2* V617F negative, no concomitant cardiovascular co-morbidities or risk factors and no personal history of thrombosis [91,92,95]. Twice daily aspirin has been suggested for patients with PV and a history of arterial thrombosis, inadequate control of microvascular symptoms or poorly controlled cardiovascular risk factors. Similarly, it has been proposed for patients with ET and a history of arterial thrombosis or in the presence of cardiovascular comorbidities with older age or *JAK2* mutation [34]. However, this approach is not currently endorsed by guidelines and the competing risk of increased bleeding must be considered and cautiously balanced. In the presence of extreme thrombocytosis, the use of aspirin may exacerbate bleeding and screening for vWF ristocetin cofactor activity is advised [65].

Cytoreduction is recommended for patients with high-risk PV and ET [91]. A controlled study showed a lower rate of thrombotic complications in patients ET treated with hydroxycarbamide compared to observation [65]. A randomised study (PT1 trial) showed hydroxycarbamide plus aspirin was superior to anagrelide plus aspirin in reducing the risk of arterial thrombosis and major bleeding, while anagrelide was protective against VTE, although overall VTE event rates were low [96]. The ANHYDRET study found anagrelide was not inferior to hydroxycarbamide in the prevention of thrombotic complications, however post-hoc analysis reported higher arterial thrombosis and haemorrhagic events associated with anagrelide [97]. Ruxolitinib, a *JAK1/2* inhibitor, is approved for second line treatment in high-risk PV patients [91]. Five year follow up analysis of the RESPONSE trial demonstrated lower thrombotic complications in the ruxolitinib arm compared to standard treatment arm. A recent meta-analysis observed an annual incidence of thrombosis of 3.09 per year (95% CI, 1.22–4.96) with ruxolitinib and a 0.56 relative risk reduction compared to best available therapy, although this did not reach statistical significance [98]. Long-acting interferons are known to alter disease at the haematopoietic stem cell level. While the rate of vascular events in randomised trials investigating interferon therapy is low, correlation between

molecular response and modification of thrombotic risk has not been proven [44].

The prevention of recurrent thrombosis in MPN is a significant knowledge gap relying on expert opinion and extrapolated data to support clinical decision making. The optimal duration of anticoagulant therapy for prophylaxis of recurrent VTE in this patient cohort is not supported by randomised data [99]. In the general population VTE recurrence risk is driven by factors that were present at the time of the index event, with duration of anticoagulation directed according to ongoing risk. VTE recurrence rates at 24 months were suggested to be 3.3% (95% CI, 2.8–3.9), 0.7% (95% CI, 0–1.5), 4.2% (95% CI, 2.8–5.6), and 7.4% (95% CI, 6.5–8.2) per patient year in patients with a transient risk factor, a surgical risk factor, a nonsurgical risk factor, and unprovoked VTE, respectively [100]. Retrospective studies estimate the overall rate of recurrent thrombosis in MPN at 7.6% per patient year, with an incidence of 5.3 per 100 patient-years (95% CI, 3.2–8.4) among patients on vitamin K antagonists (VKA) and 12.8 (95% CI, 7.3–20.7) after discontinuation of anticoagulation. The cumulative probability of major bleeding was 2.8% at 1 year of VKA therapy in this study, with higher bleeding rates among those on antiplatelet agents plus VKA [101, 102]. A recent systematic review evaluating 10 observational studies of 1295 patients with MPN and a history of VTE reported an overall recurrence rate of 22.6% for subsequent arterial or venous thrombosis. Treatment regimens involving the combination of oral anticoagulation and cytoreduction report the lowest risk of recurrent VTE [103]. This is reflected in the ELN and NCCN guidelines which recommend the initiation of cytoreduction in patients with previous thrombosis [91,92]. Guidelines for cancer-associated thrombosis advise treatment with anticoagulation for 3–6 months, suggesting continuation of treatment beyond that timeframe in patients with ongoing active malignancy or anti-cancer therapy [104]. As MPN is a chronic neoplastic disorder, life-long treatment is likely appropriate for secondary prevention of venous thrombosis in the absence of major competing bleeding risks [65]. Consensus statements suggest prolonged anticoagulation after unprovoked proximal DVT or PE, a life-threatening VTE or a VTE recurrence in MPN, but there are no controlled studies addressing this issue [99].

There is a paucity of evidence on the safety and efficacy of direct oral anticoagulants (DOACs) in MPN [99]. Based on international registry data it is known that VTE treatment with VKA provides protection against recurrence in patients with MPN following a thrombotic event. However, as previously discussed rates of both recurrent thrombosis and

major bleeding remain higher compared to individuals without MPN [101]. In the general population DOACs have largely replaced warfarin as the anticoagulant of choice [105]. Similarly in cancer associated thrombosis prospective trials have demonstrated that DOACs are non-inferior to low molecular weight heparin (LMWH) [106]. Knowledge of VTE treatment with DOACs in patients with MPN is limited and informed by poor quality data, predominantly retrospective and observational in nature. In the Hokusai and SELECT D CAT trials, only 10% of recruited patients had haematological malignancies, predominantly leukaemia, multiple myeloma, or lymphoma [107,108]. Several MPN registries exist, however data is sparse as only 1.7%–3.3% of all patients received anticoagulation with a DOAC [101]. Two small retrospective series of patients with MPN treated with a DOAC reported no recurrent thrombotic events and no episodes of major bleeding with minimal clinically relevant non-major bleeding (which was associated with use of antiplatelet in combination with oral anticoagulant), however no controlled studies exist [109,110]. A recent systematic review noted recurrent VTE in 3.2% (95% CI, 0.4–11.0) of patients treated with DOAC plus cytoreduction versus 13.1% (95% CI 9.3–17.7) of patients on VKA plus cytoreduction. In the 77 DOAC-treated patients, 3 major bleeding episodes (all related to interventions), 3 clinically relevant non major episodes, and 2 minor bleeding episodes were observed. The authors conclude that DOACs may represent a reasonable alternative to VKA with a low risk of recurrent thrombosis and bleeding complications, although the uncertainty of the evidence and the urgent need for more data is highlighted [103,111].

6. Conclusion

Individuals with MPN are at higher risk of arterial and venous thrombosis compared to the general population. Furthermore, microvascular thrombosis has been implicated in the debilitating symptoms that impact the quality of life of some patients. Despite recent advances in our understanding of the clinical and pathophysiological factors contributing to thrombogenesis in MPN, thrombosis remains a leading cause of morbidity and mortality for these patients. Further advances in the characterisation of the cellular and molecular mechanisms underlying thrombotic tendency in MPN are necessary in order to improve personalised risk prediction/stratification and treatment strategies.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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