MYELOPROLIFERATIVE NEOPLASMS (B STEIN, SECTION EDITOR)

Thrombocytosis and Thrombosis: Is There Really a Correlation?

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Abstract

Purpose of Review Thrombocytosis is common to all myeloproliferative neoplasms (MPN), including essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis. Despite the traditionally held belief amongst many clinicians that thrombocytosis correlates with thrombosis risk, there is little evidence in the literature to support that claim. Herein we critically analyze the literature to better understand the relationship between thrombocytosis and risk of thrombosis in MPN.
Recent Findings Both retrospective and prospective studies argue against associations between thrombocytosis and risk of thrombosis in patients with ET and PV. Rather, most studies suggest that the presence of extreme thrombocytosis is instead associated with an increased risk of hemorrhagic events, a paradoxical phenomenon with important clinical implications.
Summary Thrombosis risk has a multifactorial set of etiologies in MPNs. While qualitative abnormalities of the platelets may contribute, associations between platelet quantity and thrombosis risk are weak in MPN patients.

Keywords Thrombocytosis · Thrombosis · Myeloproliferative neoplasms · Essential thrombocythemia · Polycythemia vera

Case Presentation and Introduction

A 59-year-old female with osteoporosis and incidentally discovered thrombocytosis is urgently referred to hematology clinic by her primary care physician due to concern that she is at imminent risk for a cerebrovascular accident. Apart from mild subjective fatigue, the patient feels well and had recently completed a triathlon. On further questioning, she denies headaches, visual changes, paresthesias, weakness, evidence of erythromelalgia, or history of thrombosis. She does note slight bruising since being started on aspirin by her PCP and is without clinical evidence of splenomegaly on exam.

Laboratory analysis is significant for WBC 6.2×10^9/L, Hgb 13.6 g/dl, and platelets 1185×10^9/L. Her iron studies and inflammatory markers are normal and *JAK2* V617F is negative. Her ristocetin activity is 105% and she is ultimately found to have a type 1 *CALR* mutation and a bone marrow suggestive of essential thrombocythemia. The central question is whether or not her thrombocytosis strongly associates with thrombosis.

The exact definition of thrombocytosis varies in the literature but is generally considered when platelet counts ≥ 400–450×10^9/L. The vast majority ($> 90\%$) of cases of thrombocytosis are reactive or secondary in nature and do not in fact reflect a primary hematologic disorder (primary thrombocytosis). Acute insults may cause transient elevation in platelet counts (i.e., trauma or infection) while more chronic conditions may present with sustained thrombocytosis (i.e., iron deficiency anemia, malignancy, chronic inflammatory conditions). Furthermore, Ruggeri et al. found that ~1% of asymptomatic patients in the general population were found to have a platelet count $> 400 \times 10^9$/L, although platelet counts normalized in $> 92\%$ on recheck within 8 months [1]. Although the data is limited, one retrospective study suggested a ~1.6% incidence of venous thromboembolic complications in patients with secondary thrombocytosis, although only when in the presence of additional risk factors such as preceding surgery, malignancy, or post-splenectomy. In the absence of additional risk factors, there was no association found between secondary thrombocytosis and thrombosis, regardless of cause [2].

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Less than 10% of cases of isolated thrombocytosis actually reflect a primary hematologic condition. The majority of these conditions fall within the spectrum of myeloproliferative neoplasms (MPN) which include essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF). These conditions are characterized by clonal proliferation of myeloid stem cells with variable morphologic maturity.

Before analyzing the association between thrombocytosis and thrombosis risk, platelet homeostasis will be briefly reviewed. Platelet production is directly regulated by thrombopoietin (TPO), a hormone predominantly synthesized in the liver. TPO regulates proliferation and differentiation of megakaryocytes in the bone marrow by binding to its receptor, c-Mpl (TPO-R), which is expressed on both the surface of megakaryocytes and circulating platelets. After TPO binds to the extracellular portion of c-Mpl, a signaling cascade is initiated via the JAK-STAT pathway leading to downstream signaling, cell growth, and megakaryopoiesis [3]. Platelet production is thus tightly regulated by the amount of TPO directly delivered to megakaryocytes in the bone marrow. As platelet mass decreases, less TPO is bound to circulating platelets and thus more able to stimulate megakaryocyte proliferation and differentiation in the bone marrow. Conversely, as platelet mass increases, more TPO is sequestered by circulating platelets and less able to stimulate megakaryopoiesis [4].

Philadelphia-negative myeloproliferative neoplasms (MPN), classically including ET, PV, and PMF, are fundamentally characterized by dysregulated myeloid hematopoiesis and increased proliferation of erythroid, megakaryocytic, or granulocytic cells. The molecular pathogenesis of MPN phenotype is most commonly characterized by the presence of a driver mutation in one of the three genes, *JAK2*, *MPL*, and *CALR*. Through differing mechanisms, these mutations lead to constitutive and hyperactive JAK-STAT signaling, ultimately resulting in dysregulated cellular proliferation [5]. The first driver mutation, *JAK2-V617F*, was first discovered ~2005 and occurs in ~95% of patients with PV and 50–60% of patients with either ET or PMF [6, 7]. It is characterized by direct overactivation of JAK2 signaling, independent of growth factor, and leads to the development of an MPN phenotype. Activating mutations in *MPL* occur in 5–8% of patients with ET or PMF and cause TPO-independent activation of c-Mpl due to uninhibited dimerization, constitutive self-activation, and indirect dysregulation of JAK2 signaling [8, 9]. Finally, activating mutations in *CALR* occur in ~25–30% of patients with ET and PMF. Although still unclear, it is thought that pathologic *CALR* mutations lead to alterations in the structure and charge of calreticulin which specifically activates the TPO receptor and leads to indirect dysregulation of JAK2 signaling. As a result of these mechanisms, any of the MPNs can lead to dysregulated megakaryopoiesis and thrombocytosis.

Essential Thrombocythemia: Examining Correlations Between Thrombocytosis and Thrombosis

Amongst MPNs, essential thrombocythemia (ET) is classically characterized by thrombocytosis, thrombohemorrhagic complications (both venous and arterial), and risk for progressing to myelofibrosis or acute myeloid leukemia (AML) [10••, 11].

The literature reports an incidence rate of thrombosis of 9–22% of patients with ET at time of diagnosis [12–14]. Thrombotic manifestations may present clinically as cerebrovascular events, myocardial infarctions, or venous thromboembolic disease and are likely due to qualitative platelet dysfunction.

Despite the nearly universal presence of thrombocytosis in ET, the major risk factors that historically correlate with thrombosis risk are advanced age, history of prior thrombosis, and *JAK2* mutational status. Traditionally, the absence or presence of these risk factors helps stratify patients into very low, low, intermediate, or high risk for thrombotic complications and help guide use of cytoreductive therapy with the intent of preventing long-term thrombotic complications.

In current clinical practice, most hematologists aim to reduce platelet counts via cytoreductive therapy in high-risk ET despite multiple observational studies failing to demonstrate a relationship between elevated platelet count and thrombotic risk, either at diagnosis or during follow-up [15]. A prospective multicenter analysis of the PT-1 trial cohort which included 776 patients with essential thrombocythemia found no association between platelet count at diagnosis or follow-up and risk of future thrombotic complications ($p = 0.4$). Interestingly, the presence of thrombocytosis was instead associated with an increased immediate risk of major hemorrhage ($p = 0.001$). The authors of this study suggested that cytoreductive therapy should be used to normalize platelet counts but with the goal of minimizing immediate major hemorrhagic complications [15, 16].

Furthermore, another international collaborative study identified 891patients with ET and analyzed the incidence of major thrombotic complications. After a median follow-up of 6.2 years, ~12% of patients had experienced either a major arterial ($n = 79$) or venous ($n = 37$) thrombotic event with an overall rate of fatal and nonfatal thrombotic events of 1.9% patient-years. Based on the multivariable analysis, a platelet count of $\geq 1000 \times 10^9$/L at diagnosis was not associated with an increased risk of arterial or venous thrombotic events. Instead, the presence of "extreme thrombocytosis" (defined as plt $\geq 1000 \times 10^9$/L) was independently associated with a lower risk of arterial thrombosis (HR 0.42, $p = 0.007$) [17]. This finding may reflect the occurrence of acquired von Willebrand disease (aVWD) observed in patients with thrombocytosis and questions the utility of aggressive

antiplatelet therapy in low-risk patients with extreme thrombocytosis.

The revised IPSET-thrombosis study reanalyzed retrospective data from 1019 patients with WHO-defined ET initially used to establish International Prognostic Score for Thrombosis in ET (IPSET-thrombosis). This study shifted risk stratification to include age, history of thrombosis, and *JAK2* mutation status to identify four risk categories instead of the three-tiered approach in IPSET-thrombosis. These findings were subsequently validated by a retrospective study at Mayo Clinic of 585 patients with WHO-defined ET. Platelet count, yet again, was not found to be an independent risk factor for recurrent thrombosis (HR 1; $p = 0.233$) [18••, 19••].

In an attempt to limit the potential confounding effects of anti-thrombotic and/or cytoreductive during treatment of Ph-negative MPNs on future thrombotic risk, one study investigated the relationship between prior thrombosis (thrombosis that occurred prior to diagnosis and before treatment; PrTh) and characteristics at diagnosis in 977 thrombocythemic patients with MPN per WHO 2008 criteria. Both univariate and multivariate analyses demonstrated that PrTh rate was significantly related to presence of minor thrombocytosis (defined as plt $\leq 700 \times 10^9$/L), leukocytosis (WBC $> 10 \times 10^9$/L), *JAK2* V617F, older age, higher hematocrit (HCT $> 45\%$), and CV risk factors. Interestingly, the highest PrTh rate (33.9%) was associated with the coexistence of minor thrombocytosis and leukocytosis [20•]. More specifically, patients with plt $\leq 700 \times 10^9$/L at diagnosis had a prior thrombosis rate of 28% vs 15.8% in those with plt $> 700 \times 10^9$/L at diagnosis (OR 2.41; $p < 0.001$). This finding further confirms the hemostatic paradox of thrombocytosis as previously described in the literature, since there was an inverse relationship between thrombosis and thrombocytosis.

Another retrospective study performed univariate and multivariate analyses of thrombosis predictors in 416 ET patients who had been treated with hydroxyurea for at least 12 months. The authors concluded that age and previous thrombosis were independently associated with increased risk of vascular events whereas achievement of complete hematological response per European LeukemiaNet (ELN) did not. In particular, it was noted that rate of major thrombosis in three categories of response per ELN was not related to the achievement of platelet targets less than 400×10^9/L (HR 1.04; $p = 0.95$) or less than 600×10^9/L (HR 1.05; $p = 0.91$), indicating that normalization of platelet count did not reduce risk of major vascular events [21].

In accordance with the above findings, another retrospective study evaluated clinically relevant outcomes based on ELN response criteria after treatment with cytoreductive therapy, in this case anagrelide. This study evaluated 154 ET patients treated with anagrelide for a median of 2.9 years. Despite the observation that platelet count at diagnosis was higher in those with a non-complete response vs those who had a complete response (993×10^9/L vs 753×10^9/L respectively; $p < 0.001$), there was no association of any clinical benefit, including incidence of vascular complications between both groups [22].

Polycythemia Vera: Thrombocytosis and Thrombosis

As has been the case with ET, neither retrospective nor prospective studies have consistently reported a significant correlation between platelet number and thrombosis risk [23, 24]. First, the PV Study Group (PVSG) 01, the largest prospective PV cohort prior to the ECLAP cohort, demonstrated that no hematologic parameter, including platelet count, measured prior to a thrombotic event was associated with increased risk of thrombosis [25]. Similarly, the European Collaboration on Low-Dose Aspirin in PV (ECLAP) did not find an association between platelet count and thrombotic events or total mortality. This prospective study demonstrated that major thrombotic events occurred in 8.3% of patients with baseline platelet count $> 400 \times 10^9$/L vs 9.3% of those with lower platelet counts ($p = 0.8$). They similarly concluded that neither the currently proposed target of plt $< 400 \times 10^9$/L nor any other platelet count deciles were predictive of increased thrombosis risk [26].

To the contrary, a high platelet count has been instead associated with an increased risk of hemorrhagic events. Accordingly, a reduction in platelet count with cytoreductive therapy has been shown to reduce risk of bleeding [24, 25]. The association between thrombocytosis and increased risk of hemorrhagic events may once again be explained by the development of acquired von Willebrand factor deficiency [27].

In contrast to prior studies, one study evaluated 261 PV patients (median follow-up ∼ 7.2 years) who were treated with hydroxyurea (median duration of treatment ∼ 4.4 years). Unexpectedly, they found that lack of response in platelet count, defined as plt $< 400 \times 10^9$/L, was associated with both an increased risk of thrombosis ($p = 0.04$) and bleeding ($p = 0.009$). Interestingly, this study demonstrated that control of hematocrit, defined as Hct $< 45\%$, did not statistically reduce incidence of either thrombosis ($p = 0.8$) or bleeding ($p = 0.8$) [28]. This is in contradiction with the randomized CYTO-PV study published in 2013 [29].

Myelofibrosis: Thrombocytosis and Thrombosis

Similar to other Philadelphia-negative MPNs, bleeding and thrombosis are long recognized complications of myelofibrosis. Based on the available literature, the incidence of thrombotic complications in PMF ranges from 6 to 12%, an

Table 1 Studies evaluating association between thrombocytosis and thrombosis risk in MPNs

Study population/reference number	Study design/patient number	Key finding
ET [15]	Prospective, $N = 776$, ~ 22,000 f/u blood counts	Associations between thrombocytosis and hemorrhage, but not between platelet count (at diagnosis or follow-up) and thrombosis
ET [17]	Retrospective, $N = 891$	Platelet counts $> 1000 \times 10^9$//L associated with lower risk of arterial thrombosis (HR 0.42)
ET [18••, 19••]	Retrospective (IPSET-R) $N = 1019$ $N = 585$	Platelet count not associated with thrombosis risk (not included in contemporary risk classification)
Thrombocythemic patients ET, PMF, PV, U-MPN [20•]	Retrospective Total $N = 977$ • ET: $N = 496$ (50.8%) • PMF: $N = 340$ (34.8%) • PV: $N = 20$ (2.0%) • U-MPN: $N = 121$ (12.4%) Included patients with thrombosis prior to diagnosis and treatment	Rate of prior thrombosis inversely correlated with platelet count
ET [21]	Retrospective, $N = 416$	Rate of major thrombosis not associated with any of three categories of response per ELN, indicating that normalization of platelet count did not reduce risk of major vascular events
ET [22]	Retrospective, $N = 154$ Included patients treated with anagrelide for a median of 2.9y	Achievement of CR per ELN definition was not associated with measurable clinical benefit, including incidence of vascular complications
PV [25]	Prospective, $N = > 1000$	No hematologic parameter, including platelet count, associated with thrombosis risk
PV [26]	Prospective, $N = 1638$	Platelet count not association with thrombotic events or total mortality; platelet count deciles not predictive of increased thrombosis risk
"Fibrotic" PMF [31]	Retrospective, $N = 155$	Platelet count $> 450 \times 10^9$/L associated with thrombosis in univariate analysis but not multivariate
PMF [30]	Retrospective, $N = 707$ Did not differentiate between early/prefibrotic or fibrotic	Platelet count not associated with thrombotic events either on univariate or multivariate analysis
"Early/prefibrotic" PMF [33]	Retrospective, $N = 264$	Platelet count $> 870 \times 10^9$/L associated with decreased risk of thrombosis

incidence similar to that in ET but lower than PV [30–32]. Furthermore, the pathomorphologic entity of early/prefibrotic PMF may carry an even higher thrombotic risk than either ET or overt (fibrotic) PMF with frequency of thrombotic complications ranging from 15 to 30% [33, 34].

Given the associated morbidity and mortality, multiple studies have attempted to characterize risk factors of thrombosis in patients with PMF. Amongst these, age > 60, JAK2 V617F mutation status, and history of thrombosis have been the most established risk factors of thrombosis in fibrotic PMF [30, 32, 35]. More recently, Guglielmelli et al. reported age ≥ 65 years, leukocytosis, JAK2V617F mutation status, presence of CV risk factors, and high-molecular-risk mutations as independent risk factors of arterial thrombosis in early/prefibrotic PMF while only history of previous thrombosis was predictive of venous events [36]. Another large observational study which included 340 patients with either early/prefibrotic PMF or fibrotic PMF reported that when compared with major thrombocytosis (plt > 700 × 109/L), the presence of minor thrombocytosis (plt ≤ 700 × 109/L) at diagnosis was

associated with a higher risk of thrombosis and trend toward lower risk of bleeding [20•]. Despite one study reporting thrombocytosis as an independent risk factor of thrombosis in univariate analysis, other studies have found either no significant association or a paradoxical inverse relationship between thrombotic risk and platelet count [20•, 30, 31, 33].

Furthermore, a contemporary study validated the IPSET-thrombosis score (comprised of age, history of thrombosis, JAK2 mutation, and CV risk factors), originally developed for ET, as the most accurate predictor of thrombotic risk in patients with prefibrotic PMF. It is important to note that thrombocytosis is not included amongst the risk factors for thrombosis in the IPSET-thrombosis score [36].

"Extreme" Thrombocytosis in MPN

The presence of "extreme" thrombocytosis (ExT), defined as a platelet count $> 1000–1500 \times 10^9$/L, is an important consideration when approaching treatment of patients with MPN [37].

The presence of ExT in ET and PV patients is believed to be associated with increased risk of bleeding diatheses, presumably via mechanism of a platelet count–dependent acquired von Willebrand disease. Its presence is thus an important consideration when using aspirin in patients with low-risk ET or PV due to the increased risk of bleeding complications. When present in this population, some have advised to screen for ristocetin cofactor activity with consideration to withhold aspirin therapy if results show < 30% activity. Equally important, extreme thrombocytosis neither defines high-risk disease nor independently serves as an indication for cytoreductive therapy [38].

Management of extreme thrombocytosis is heterogeneous. An international survey of Israeli, Italian, and British MPN groups, Mayo Clinic, and NCCN MPN panel regarding different clinical case scenarios for management of ExT analyzed responses from 90 physicians. Based on this survey, 74% of physicians determined a platelet count $\geq 1500 \times 10^9$/L to be an indication for cytoreduction while 11% considered a plt $\geq 2000 \times 10^9$/L and 15% would not advise treatment, regardless of platelet count, unless there was presence of an abnormal vWF:RCo. If cytoreduction deemed indicated, target platelet counts varied from normal (53%), $\leq 600 \times 10^9$/L (30%), $\leq 1000\ 10^9$/L (9%), to counts that normalized vWF:RCo [39]. In conclusion, there was no consensus on management of

extreme thrombocytosis. This was manifested by variable platelet thresholds for triggering cytoreduction in low-risk ET/PV, variable platelet count targets if cytoreduction indicated, and variable answers regarding vWF:RCo testing prior to aspirin use. Approaches to treatment also varied depending on country of response although there was less variation depending on years of practice and/or experience. The large variation in responses for management ExT under different clinical scenarios emphasizes the need for prospective, randomized trials in patients with ExT.

Conclusion

The vast majority of literature has not found an association between thrombocytosis and risk of thrombosis (Table 1). The presence of thrombocytosis has instead been associated with an increased risk of hemorrhagic events, a paradoxical phenomenon thought to be mediated in some instances but not all, via an acquired VWD. Given that the majority of data was collected from retrospective cohorts, additional prospective studies will further help validate these clinically significant findings.

Furthermore, when cytoreduction is indicated, there is a large paucity of clinical data to help guide platelet goals. As
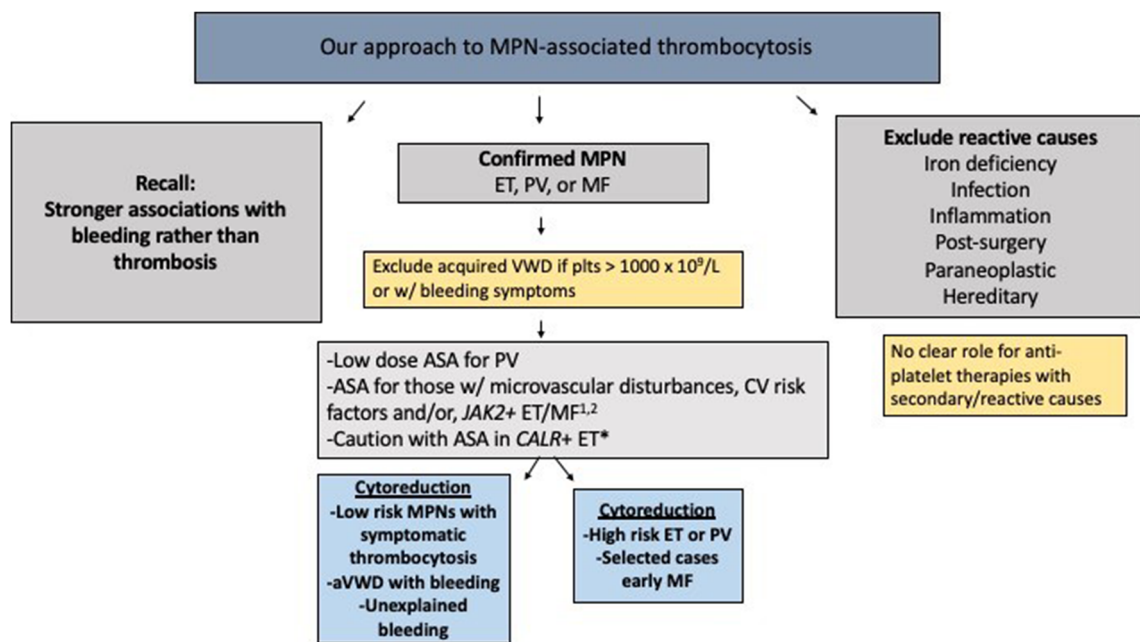

Fig. 1 Our approach to MPN-associated thrombocytosis. Our approach when evaluating suspected MPN-associated thrombocytosis. Once thrombocytosis confirmed to be MPN-associated, indications for antiplatelet and/or cytoreductive therapy are dependent on disease risk classification and presence of acquired VWD or unexplained bleeding. *Retrospective study reported that low-dose ASA did not reduce risk of thrombosis but did increase risk of bleeding in low-risk *CALR*+ ET [41]. [1]Compared with daily dosing of low-dose ASA in patients with ET,

twice-daily (BID) dosing associated with improved parameters of platelet inhibition including more consistent inhibition of platelet aggregation and lower and more consistent levels of serum thromboxane B_2, a validated biomarker of platelet COX-1 activity; no assessment of true thrombosis risk reduction [42, 43•]. [2] Metanalysis of twenty-four observational studies evaluating aspirin use in adults with ET reported overall inconsistency and imprecision amongst studies and thus high uncertainty regarding net effect of ASA in this patient population [40•]

previously discussed, it is even unclear whether complete normalization of platelet count by cytoreduction reduces thrombosis-free survival. In accordance with the aforementioned relationship between thrombocytosis and bleeding, some studies have suggested that normalizing platelet counts may instead reduce the risk of hemorrhagic events.

Finally, even the management of ExT is heterogenous and varies widely depending on geographic location. Interestingly, this variability is less so when clinicians are instead stratified by years of clinical practice and/or experience. This overall large variability in clinical practice emphasizes the need for prospective, randomized trials that would help optimize outcomes for this patient population.

Given the morbidity and mortality associated with both thrombosis and bleeding in MPNs, careful consideration must be made when recommending aspirin therapy for primary and secondary prevention of vascular events. Despite a clear benefit in patients with PV, a meta-analysis of twenty-four observational studies revealed imprecise and inconsistent findings regarding the net benefit of antiplatelet therapy in patients with ET [40•]. Furthermore, another study reported that primary prevention with antiplatelet therapy did not reduce thrombotic risk but significantly increased risk of bleeding in patients with low-risk *CALR*-mutated ET [41]. Even when aspirin therapy deemed indicated, the ideal dosing is also in question. Recent studies suggest that when compared with daily dosing of low-dose ASA in patients with ET, twice-daily (BID) dosing was associated with improved parameters of platelet inhibition including more consistent inhibition of platelet aggregation and more profound and consistent inhibition of serum thromboxane B2, a validated biomarker of platelet COX-1 activity [42, 43•]. Although these findings suggest that a BID dosing regimen may optimally reduce thrombotic risk in patients with ET, further validation is needed by additional studies assessing for a true reduction in thrombotic risk.

In keeping with the literature reviewed here, the patient in the above vignette was counseled about signs and symptoms of thrombosis, but was not started on cytoreduction, noting distribution in very low-risk thrombosis classification by IPSET-R (younger age, lack of thrombosis history, JAK2 negative). As demonstrated in Fig. 1, our management approach to MPN-associated thrombocytosis is multifaceted and individualized based on disease, risk classification, mutation status, and presence of aVWD or unexplained bleeding.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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