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Review

The Approach to Thrombosis Prevention across the Spectrum of Philadelphia-Negative Classic Myeloproliferative Neoplasms

Steffen Koschmieder

Department of Medicine (Hematology, Oncology, Hemostaseology, and Stem Cell Transplantation), Faculty of Medicine, RWTH Aachen University, Pauwelsstr. 30, D-52074 Aachen, Germany; skoschmieder@ukaachen.de; Tel.: +49-241-8080981; Fax: +49-241-8082449

Abstract: Patients with myeloproliferative neoplasm (MPN) are potentially facing diminished life expectancy and decreased quality of life, due to thromboembolic and hemorrhagic complications, progression to myelofibrosis or acute leukemia with ensuing signs of hematopoietic insufficiency, and disturbing symptoms such as pruritus, night sweats, and bone pain. In patients with essential thrombocythemia (ET) or polycythemia vera (PV), current guidelines recommend both primary and secondary measures to prevent thrombosis. These include acetylsalicylic acid (ASA) for patients with intermediate- or high-risk ET and all patients with PV, unless they have contraindications for ASA use, and phlebotomy for all PV patients. A target hematocrit level below 45% is demonstrated to be associated with decreased cardiovascular events in PV. In addition, cytoreductive therapy is shown to reduce the rate of thrombotic complications in high-risk ET and high-risk PV patients. In patients with prefibrotic primary myelofibrosis (pre-PMF), similar measures are recommended as in those with ET. Patients with overt PMF may be at increased risk of bleeding and thus require a more individualized approach to thrombosis prevention. This review summarizes the thrombotic risk factors and primary and secondary preventive measures against thrombosis in MPN.

Keywords: myeloproliferative neoplasms (MPN); polycythemia vera (PV); essential thrombocythemia (ET); primary myelofibrosis (PMF); thrombosis; prevention; antiplatelet agents; anticoagulation; cytoreduction

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1. Introduction

The prevention of thrombosis is one of the main goals in the management of patients with MPN (The term "thrombosis" used in this review comprises both thrombosis and thromboembolism, including arterial and venous events, except when indicated as separate entities. In light of the broad spectrum of thrombotic events and the various MPN subtypes, as well as the multitude of data and analyses, the author apologizes if, due to space constraints, not all relevant publications may have been included in this spotlight review). This is due to the high incidence, high recurrence rate, and the high contribution to mortality of thrombosis in this patient population. The incidence of major arterial and venous thrombotic complications in the classic MPNs ranges between 1.2 and 2.2% per patient per year, accumulating to between 17% and 32% over the course of 15 years [1]. When assessed 1 year after MPN diagnosis, the incidence of thrombosis is increased in MPN patients as compared to the normal population, as evident for all types of thrombosis (2.4-fold), all arterial thrombosis (2.0-fold), including myocardial infarction (1.8-fold) and ischemic stroke (2.3-fold), and all venous thrombosis (4.7-fold), including pulmonary embolism (5.3-fold) and deep vein thrombosis (3.7-fold) [2]. Importantly, the incidence is particularly increased in young patients (18–49 years), amounting to 6.0-fold for arterial and 14.6-fold for venous events [2]. The risk of recurrent thrombosis is significantly elevated, amounting, in ET and PV, to 5.6% per patient per year and 50% at 10 years after the initial thrombosis [3]. One important

risk factor for recurrence is thrombophilia, but, again, only in younger patients [3]. Moreover, the risk of death from cardio- and cerebrovascular causes was increased in the younger MPN population vs. matched controls (over 8-fold), while older MPN patients had a similar risk of dying from these causes as their age-matched controls [4]. Among MPN subtypes, PMF patients had the highest mortality rate, while ET and PV had lower mortality rates [4,5]. Both in ET and PV, patients with vascular complications had inferior survival compared to those without such complications [6]. Given that the risk of thrombosis was particularly evident in young patients with MPN, the necessity for the prevention of thrombosis becomes more prominent in the management of these patients.

1.1. Essential Thrombocythemia (ET)

1.1.1. Risk factors for Thrombosis in ET

Patients with ET may have an elevated risk of thrombosis or of severe hemorrhage or both, depending on how the risk factors for these two complications are balanced and how they change dynamically over time. Risk factors for thrombosis in ET include advanced age above 60 years, history of thrombosis, cardiovascular risk factors, and the presence of the JAK2V617F mutation [7–10]. This has led to the establishment of the International Prognostic Score for Thrombosis in Essential Thrombocythemia (IPSET)-thrombosis score [10], which is now widely recommended and used when deciding on the use of acetylsalicylic acid (ASA) or cytoreductive therapy in patients with ET [11].

More recent analyses have included mutational data and identified the absence of ASXL1 and RUNX1 mutations, in addition to the presence of JAK2V617F, as adverse risk factors for arterial thrombosis and the absence of SRSF2 and EZH2 mutations as risk factors for venous thrombosis in ET [12].

Risk factors for major bleeding in ET patients include female sex [13], previous bleeding and ASA use [14], excessive thrombocytosis (platelet counts over 1000 G/L) and leukocytosis [15], splenomegaly [16], and acquired von Willebrand syndrome (AVWS) [17], and thus, the individual risk of bleeding has to be assessed in ET patients, using the respective diagnostic tests (e.g., complete blood counts, von Willebrand factor activity), when deciding upon antithrombotic preventive measures.

In addition to risk factors for thrombosis, multivariate risk factors for overall survival have been analyzed in ET. The IPSET score for overall survival includes age over 60 years, leukocytosis (≥11 G/L), and history of thrombosis as multivariate risk factors for survival [18], and the MIPSS-ET score includes genetic mutations (SF3B1, SRSF2, and EZH2 or U2AF1) as adverse factors for overall survival in ET [19].

1.1.2. Primary Prevention of Thrombosis in ET

Treatment of ET patients is based upon their projected clinical risk of developing major thrombosis or major bleeding events [20,21]. In a prospective case–control study of untreated low-risk ET patients and age-matched controls, the incidence of thrombosis was low (1.91 per 100 patient-years) and comparable to the general population [22].

There is no randomized controlled clinical trial of ASA monotherapy for primary prevention of thrombosis in ET. Nevertheless, there is circumstantial evidence that ET patients may benefit from primary thromboprophylaxis, particularly with ASA, if they have cardiovascular risk factors (intermediate-risk patients) or high-risk factors (age above 60 years, history of thrombosis, platelet counts above 1500 G/L). In particular, many experts have adopted the rationale from a randomized clinical trial in low-risk PV patients, demonstrating that ASA use was associated with increased event-free survival (consisting of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes +/− venous thrombosis/pulmonary embolism) vs. placebo use [23]. Since then, the use of ASA has been recommended for intermediate-risk or high-risk patients with ET, unless they have contraindications against ASA use [20,21]. In addition, ASA use is

recommended for low-risk ET patients with microvascular disturbances, such as erythromelalgia or acroparesthesias [20,21,24].

Patients with ET who lack high-risk factors and are being treated with ASA do not benefit from the addition of cytoreductive treatment with hydroxyurea (HU), as demonstrated in a randomized trial [25]. There was no significant difference in event-free survival (including arterial and venous thrombosis, serious hemorrhage, or death from vascular complications) or overall survival in patients receiving HU plus ASA vs. ASA alone [25]. Even in low-risk ET patients with excessive thrombocytosis (platelet counts above 1000 G/L), cytoreductive treatment was not associated with lower thrombosis or bleeding rates in a retrospective study [26]. Thus, cytoreductive therapy is currently not recommended in low-risk or intermediate-risk ET patients [20,21].

There are several randomized clinical trials in high-risk ET patients, showing that cytoreductive therapy (mostly in combination with ASA) is beneficial. First of all, an early randomized clinical trial demonstrated superior thrombosis-free survival in high-risk ET patients receiving hydroxyurea vs. those without cytoreductive treatment [27]. 3.6% vs. 24% of patients developed thrombotic events during the trial ($p = 0.003$), and most of these were arterial thromboses [27]. Since then, cytoreductive treatment has been recommended for high-risk ET patients [20,21]. However, although rare, long-term use of hydroxyurea has been associated with adverse events (approximately 5% of MPN patients in one series of 3411 patients [28]) such as local skin cancers (affecting 7% in a series of 172 MPN patients [29]) and, possibly, but not clearly differentiated from hydroxyurea-independent disease progression, transformation to acute leukemia [30].

Therefore, other types of cytoreductive therapy have been developed for the treatment of ET. One of such drugs is anagrelide. Two randomized clinical trials have compared anagrelide with hydroxyurea in ET.

In the PT-1 trial, patients with high-risk ET received either hydroxyurea plus ASA or anagrelide plus ASA [31]. Approximately a fourth of the patients had had a prior thrombotic event. During 39 months of median follow-up, patients receiving anagrelide plus ASA were more likely to develop one of the events of the composite primary endpoint (arterial or venous thrombosis, serious hemorrhage, or death from thrombosis or hemorrhage; $p = 0.03$) than those treated with hydroxyurea plus ASA [31]. Interestingly, while patients in the anagrelide plus ASA arm showed increased rates of arterial thrombosis and serious hemorrhage, as well as transformation to myelofibrosis, the rate of venous thrombosis was lower [31]. Altogether, the rate of discontinuation was almost two-fold higher in the anagrelide plus ASA arm, and the main reasons for discontinuation were endpoint events or adverse events such as nonthrombotic cardiac and gastroenterologic events [31].

In a second trial comparing anagrelide and hydroxyurea in high-risk ET (slightly modified high-risk criteria), the ANAHYDRET trial, the use of ASA was more restricted, with only 28% of all patients receiving aspirin at baseline and 43% of these receiving a dose of less than 75 mg/d [32]. The study protocol did not mandate ASA use, but patients were allowed to remain on ASA at the discretion of the investigator. This was a non-inferiority trial assessing response and safety according to a composite endpoint of blood counts and ET-related events (major and minor thrombotic and hemorrhagic events). Non-inferiority was confirmed during the three years of observation, and while the type of adverse events differed in the anagrelide and hydroxyurea arms, the overall rate of adverse events and discontinuations was not different [32]. Importantly, the rate of thrombosis or bleeding was comparable in both treatment arms [32]. Anagrelide is currently recommended for first-line and/or second-line therapy in ET [20,21].

While no randomized trial of interferon-alpha (IFNa) has been fully published in ET patients, a variety of phase-2 trials have shown efficacy in normalizing blood counts and inducing molecular remission either in unselected ET patients (reviewed in [33]) or in selected patients with hydroxyurea-resistant or -intolerant ET (or PV) [34]. The final results of the MPD-RC 112 randomized clinical trial of pegylated IFNa-2b vs. hydroxyurea in

high-risk ET and PV were reported during the ASH 2018 meeting and showed similar rates of complete remission in the two treatment arms but a higher rate of grade 3/4 adverse events in the peg-IFNa-2b arm (no published stratification data are available for the ET arm only) [35]. PegIFNa is not approved for the treatment of ET, but due to the large amount of data demonstrating efficacy and safety of (peg) IFNa in ET, current guidelines recommend its use, particularly in younger patients [20,21]. Intriguingly, these clinical trials have reported a low rate of major thrombotic and hemorrhagic events in IFNa-treated ET and PV patients [33,34], and this was confirmed in a recent real-world analysis of IFNa-treated ET-only patients [36].

1.1.3. Secondary Prevention of Thrombosis in ET

Secondary prevention of thrombosis in ET has been studied in a variety of retrospective analyses, with most studies combining ET with PV and sometimes also PMF patients. Thus, the results may not be specific for ET.

Most guidelines recommend ASA as secondary prophylaxis after arterial events [20,37], whereas anticoagulants are recommended in MPN patients after venous events [37]. What is the evidence? Most of these data are derived from retrospective analyses of the effects of discontinuation of anticoagulation therapy in patients after a thrombotic event.

A retrospective analysis of patients with ET and PV, who had a history of thrombosis and were treated with anticoagulation and cytoreductive therapy, demonstrated a significantly higher incidence of recurrent thrombosis after cessation of vitamin K antagonist (VKA) treatment than during VKA treatment (4.5- vs. 12-fold, respectively), and multivariate analysis showed that the risk of re-thrombosis was decreased 2.8-fold with VKA treatment [38]. While the risk factors for recurrence tended to be different for arterial recurrence (cardiovascular risk) vs. venous recurrence (history of remote thrombosis), both arterial and venous rethrombosis were prevented by VKA treatment [38], as has been shown for myocardial infarction [39] and ischemic stroke [40] in the non-MPN population. These results were essentially confirmed in two additional retrospective analyses of MPN patients. One study comprising 42% ET and 46% PV patients [41] confirmed a significantly increased rate of re-thrombosis (2.2-fold) in patients off-VKA and found that, although there was a trend for an increased risk of major bleeding in patients on vs. off VKA treatment, this failed to reach statistical significance [41]. A third retrospective study of venous thrombotic events in MPN patients (35% ET, 34% PV, 27% PMF) [42] found a re-thrombosis rate of 6% per patient-year and confirmed a significantly increased thrombotic recurrence rate in patients who discontinued anticoagulation therapy vs. those who remained on anticoagulation. Major bleeding rates were not different in these two patient groups [42].

Most of the patients in the above-mentioned analyses received VKA as their anticoagulants, and direct oral anticoagulants (DOACs) were used in only 0% [38], 3.3% [41], and 18% [42], respectively, and 3.3% in an additional retrospective cohort [43]. However, DOACs are increasingly being used in MPN patients. Therefore, a recent retrospective analysis assessed the use of DOACs in 442 MPN patients (39%, 40%, and 21% were ET, PV, and MF patients, respectively) [44]. Indication for DOAC use was atrial fibrillation (AF) and venous thromboembolism (VTE) in 46% and 54% of patients, respectively, and 90% and 27% of patients received concomitant cytoreductive therapy and/or ASA treatment, respectively [44]. During the time after DOAC initiation, the incidence of recurrent thrombosis (arterial or venous) was 2.1% and 4.5% per patient-year in the AF and VTE groups, respectively, while the incidence of bleeding was 3.0% and 2.3% in these two groups, respectively, but the overall bleeding rate was lower in ET (1.6%) than in myelofibrosis (5.6%) [44]. Among the four DOACs, dabigatran was associated with a higher rate of bleeding than rivaroxaban, apixaban, and edoxaban [44].

The duration of anticoagulation in MPN is still a matter of debate, but several "high-risk" factors favoring life-long anticoagulation have been proposed [21,45,46], including splanchnic vein thrombosis, life-threatening venous thrombosis, or unprovoked venous

thrombosis that occurred as proximal vein thrombosis, pulmonary embolism, or recurrent thrombosis.

1.2. Polycythemia Vera (PV)

1.2.1. Risk Factors for Thrombosis in PV

Risk factors for thrombosis are very similar in PV as described for ET (see above). Conventional risk factors include age above 60 years [47] or 65 years [48] and previous thrombosis [47,48]. This has led to the current classification of low-risk (age below 60 years and no prior thrombosis) vs. high-risk PV patients (either one or both of these variables) [20,21]. A more recent analysis of 587 patients with PV identified prior thrombosis and leukocytosis as multivariate risk factors for thrombosis [49].

In another retrospective analysis of 1545 PV patients [50], advanced age and venous thrombosis were multivariate risk factors for overall survival, along with leukocytosis, thrombocytosis, and abnormal karyotype. In addition, mutational analysis in PV patients has identified SRSF2 and IDH2 mutations as adverse risk factors for survival in PV [19]. Thus, genetic testing (e.g., karyotype analysis and driver oncogene mutational analysis) is included at diagnosis in patients with PV.

1.2.2. Primary Prevention of Thrombosis in PV

In PV, the use of ASA has been demonstrated to be beneficial as a primary preventive measure against thrombosis-associated events: in a randomized clinical trial of ASA vs. placebo in 518 patients with unselected PV (median age of approximately 60 years, only 10% of patients had prior thrombosis, but more than 50% of patients had phlebotomies and cytoreductive treatment), the use of ASA reduced the risk of the combined endpoint of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes, with a relative risk of 0.40 (95 percent confidence interval, 0.18 to 0.91; $p = 0.03$) [23]. In particular, the rate of major and minor thrombosis was reduced, and thrombosis-free survival was increased in patients receiving ASA vs. placebo [23]. Importantly, while the rate of bleeding (any bleeding) showed a trend towards an increase with ASA use, the rate of major bleeding was not enhanced [23]. Current guidelines recommend the use of ASA for every PV patient, except for those with contraindications against its use [20,21].

A second pivotal randomized clinical trial has provided evidence for phlebotomy +/− cytoreductive treatment as a primary preventive measure against cardiovascular events in patients with PV: the CYTO-PV trial randomly assigned 365 patients with JAK2V617F positive PV to maintain a target hematocrit of below 45% (low-hct group) vs. a target hematocrit of 45–50% through the use of phlebotomy, cytoreductive therapy, or both [51]. Mean age of the patients was 64 years, 29% of patients had had a prior thrombotic event, and 84%, 13%, 68%, and 60% of patients were receiving ASA, VKA, phlebotomies, or cytoreductive drugs, respectively, at baseline. Over the course of 42 months, median hct levels were 44–45% and 47–48% in the two groups, respectively [51]. The low-hct group demonstrated superiority concerning both the primary endpoint (death from cardiovascular causes or thrombotic events) and total cardiovascular events (primary endpoint plus superficial-vein thrombosis) as compared with the high-hct group (HR 3.91; $p = 0.004$ and HR 2.69; $p = 0.001$, respectively) [51]. Based on these data, current guidelines recommend a target hematocrit of below 45% in all PV patients [20,21].

In addition to ASA and phlebotomies, high-risk PV patients benefit from the use of cytoreductive therapy. This was demonstrated in a propensity-matching analysis of 1042 PV patients who were maintained by phlebotomy only (PHL) or hydroxyurea only (HU) in order to maintain a hematocrit level below 45% [52]. The analysis included both low-risk (35.4%) and high-risk (64.6%) patients, 33% of the patients had had a prior thrombotic episode, and 38% received ASA treatment. After a median follow-up of 30–35 months, the

rates of cardiovascular events, hematologic transformation, and overall death were significantly higher in the PHL vs. HU group [52]. Importantly, this difference was confined to high-risk patients, while low-risk patients exhibited a comparable low rate of cardiovascular events and mortality with either PHL or HU [52]. The results suggest that high-risk but not low-risk PV patients benefit from the addition of cytoreductive treatment to ASA and phlebotomies, and this is also reflected in the current recommendations for the treatment of PV patients [20,21].

Recently, a randomized clinical trial of the use of ropeg-IFNa vs. hydroxyurea/best available therapy in 257 PV patients, who were in need of cytoreductive treatment, was published [53]. After the first 12 months of ropeg-IFNa vs. hydroxyurea (HU) (PROUD-PV study), patients were eligible for continuing to the second phase (CONTINUATION-PV study), in which they either continued ropeg-IFNa or best available therapy (BAT) as selected by the investigator. Of the 127 patients in each PROUD-PV arm, 95 patients in the ropeg-IFNa and 76 patients in the BAT arm continued in the CONTINUATION-PV phase. After 12 months of PROUD-PV treatment, non-inferiority of ropeg-IFNa vs. HU concerning the composite primary endpoint of complete hematological response (CHR) with normal spleen size was not shown [53]. However, after 36 additional months of treatment within the CONTINUATION-PV part of the study, the rates of CHR with improved disease burden and CHR without the spleen criterion were significantly higher in the ropeg-IFNa vs. the HU/BAT-treated patients (p = 0.044 and p = 0.01, respectively) [53]. Importantly, the rate of molecular response was significantly higher in patients treated with ropeg-IFNa vs. HU/BAT ($p < 0.0001$). Both treatments showed acceptable toxicity, with treatment-related serious adverse events in 2% and 4% of ropeg-IFNa- and HU-treated patients, respectively, and major thromboembolic complications in 3% each [53]. Subsequently, ropeg-IFNa was approved by the EMA for the treatment of patients with PV without symptomatic splenomegaly.

Even before the results of this clinical trial were published, the use of pegylated interferon was advocated in the current treatment guidelines for PV, given the large number of phase 2 trials or amount of retrospective data on its efficacy in PV ([34,54–56], and reviewed in [33]. As stated above for ET, the final results of the MPD-RC 112 randomized clinical trial of pegylated IFNa-2b vs. hydroxyurea in high-risk ET and PV, which were reported during the ASH 2018 meeting, showed similar rates of complete remission in the two treatment arms but a higher rate of grade 3/4 adverse events in the peg-IFNa-2b arm (no published stratification data are available for the PV arm only) [35].

In patients with hydroxyurea-resistant or -intolerant PV, ruxolitinib was superior vs. best available therapy (BAT) in inducing a complete remission and reducing hematocrit, spleen volume, and PV-related symptoms [57]. Thrombotic events were also reduced by ruxolitinib in a 5-year follow-up report [58], but this was not confirmed in a larger meta-analysis of ruxolitinib trials in PV [59]. Adverse events were similar to those described in the primary analysis [57]. However, rates of nonmelanoma skin cancer were increased in the ruxolitinib arm [58], but it is currently unclear to what degree hydroxyurea pretreatment has affected this adverse event.

1.2.3. Secondary Prevention of Thrombosis in PV

Because most studies and analyses on secondary prevention have not distinguished between PV and ET, please refer to the section on secondary prevention of thrombosis in ET.

1.3. Prefibrotic Primary Myelofibrosis (Pre-PMF)

1.3.1. Risk Factors for Thrombosis in pre-PMF

While overall survival was inferior in pre-PMF as compared to ET, thrombosis-free survival was found to be similar in ET and pre-PMF [60]. In one recent series of pre-PMF patients, the rates of thrombosis and major bleeding after diagnosis were 15% and 7%,

respectively, with an even distribution of arterial and venous thrombotic events [61]. Univariate risk factors in pre-PMF for arterial thrombosis included age above 65 years, leukocytosis, cardiovascular risk factors, JAKV617F positivity, and high-molecular-risk mutations, while only history of thrombosis retained significance for venous thrombosis [61]. The IPSET-thrombosis was found to be useful for risk stratification also in pre-PMF [61]. Thus, genetic analysis (e.g., karyotype and high-molecular-risk mutational analysis) is included in the basic workup of patients with MF.

1.3.2. Prevention of Thrombosis in Pre-PMF

There are no randomized trials of thrombosis prevention in pre-PMF, and most guidelines have not implemented separate recommendations for thromboprophylaxis in pre-PMF. However, it is becoming increasingly clear that patients with pre-PMF share a considerable thrombotic risk with ET or PV patients, amounting to approximately 18% after 10 years [1]. Thus, most experts manage these patients according to their clinical presentation, mostly reflecting ET [62–64].

1.4. Overt Primary Myelofibrosis (PMF), Post-PV-MF, and Post-ET-MF

Treatment guidelines for overt PMF, post-PV-MF, and post-ET-MF are not primarily based on the risk of thrombosis as in ET and PV but on the risk of dying from the disease, as patients with myelofibrosis (MF) have a decreased overall survival as compared to the normal population and to PV and ET patients, with 10-year survival rates of approximately 20%, 64%, and 68%, respectively [5]. Nevertheless, thrombotic events are an important factor for mortality and morbidity in MF patients, as demonstrated in a large population-based cohort study of 9429 MPN patients and 35,820 matched controls [2], with hazard ratios after 1 year post diagnosis of 2.7, 2.3, and 4.3 vs. matched controls for overall thrombosis, arterial thrombosis, and venous thrombosis, respectively [2]. In a different cohort of 642 MPN patients and 2568 propensity-score-matched controls, only the rate of venous thrombosis, especially at atypical sites, but not arterial thrombosis was increased in PMF patients [65]. Multivariate risk factors for arterial thrombosis in this cohort comprised advanced age, smoking, arterial hypertension, "essential" thrombocytosis, and lymphoma, while the risk factors for venous thrombosis comprised prior VTE and atrial fibrillation [65]. There was no significant correlation between the occurrence of venous or arterial thrombosis and JAK inhibitor treatment with ruxolitinib [65]. This was in contrast to a meta-analysis that found a reduction in the rate of thrombosis, but, here, both MF and PV patients were included [66].

Two further retrospective cohort analyses described a thrombosis incidence of 10.7% [67] and 31.2% [68] in patients with PMF. Multivariate risk factors for thromboembolism in these studies comprised prior thrombosis as well as post-PV-MF and splenomegaly [68].

Current guidelines of MF treatment recommend individual decisions on the use of ASA and/or anticoagulants, depending on the clinical scenario [45,63], as well as management of cardiovascular risk factors [21].

2. Conclusions

Prevention of thrombosis is one of the major goals in the treatment of MPN patients. However, the level of evidence for the current recommendations for primary and secondary prevention of thrombosis in these patients is variable. While there is evidence from a randomized clinical trial in favor of primary prevention using ASA in PV, this evidence is still lacking in ET, pre-PMF, and overt PMF. The benefits of hydroxyurea in high-risk ET are based on data from a randomized trial, but in PV, data in favor of hydroxyurea come from a nonrandomized case–control study. Meanwhile, the recommendations of phlebotomy +/− cytoreductive therapy to maintain a target hematocrit level of less than 45% in PV are also based upon a randomized trial. Moreover, the use of anagrelide in ET,

ropeginterferon in PV, and ruxolitinib in PV and MF is also backed by data from randomized trials. However, the primary endpoints of these trials did not focus on thrombosis prevention. Thus, in conclusion, while there is a large body of evidence on how to treat MPN patients, there is still a need for controlled clinical trials addressing important questions, including those about the optimal balance between prevention of thrombotic events and the avoidance of relevant bleeding complications.

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