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REVIEW

Exploring thromboembolic risk factors in polycythemia vera: from current evidence to PROSPERO study design

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Abstract

Polycythemia vera (PV) is a chronic myeloproliferative neoplasm with a substantial risk of thromboembolic events (TEs), which contribute to morbidity and mortality. Traditional thrombotic risk stratification primarily considers age and thrombosis history, yet these parameters alone do not capture the complexity of thrombotic risk. Growing evidence highlights the role of additional factors influencing the risk of TEs, underscoring the need for a more comprehensive approach to patient stratification. This paper reviews the current understanding of thromboembolic risk factors in PV and provides the rationale, methodology, and expected contributions of the PROSPERO study, a prospective, multicenter study designed to improve thrombotic risk assessment in patients with high-risk PV. By examining established (advanced age, prior TEs, cardiovascular comorbidities) and emerging thromboembolic risk factors, including specific hematologic parameters, the study aims to emphasize their impact and potential synergistic interactions on thrombotic risk. This review also evaluates the efficacy and limitations of current therapies, such as hydroxyurea (HU), interferons, and ruxolitinib, in preventing TEs, and further underscores the need for comprehensive predictive models to guide individualized management strategies. The PROSPERO study focuses on high-risk PV patients who experienced at least one prior TE and receive either HU or ruxolitinib, aiming to identify predictive factors for TEs and their individual and combined contributions to thrombotic risk by collecting longitudinal data on clinical, laboratory, and treatment-related parameters. PROSPERO aims to identify and validate new variables that can inform the development of precise, integrated prediction models. The findings are expected to enable tailored treatment approaches, ultimately reducing TE recurrence in high-risk PV populations.

Keywords Polycythemia Vera · Thromboembolic risk · Risk factors · Risk stratification · Hydroxyurea · Ruxolitinib · PROSPERO study

Introduction

Polycythemia vera (PV) is a *BCR::ABL1*-negative hematologic disorder belonging to the family of myeloproliferative neoplasms (MPN). The incidence of PV is estimated at between 0.6 and 2.8 cases per 100,000 patients [1, 2]. Mutations in *Janus kinase 2* (*JAK2*) are observed in nearly all patients with PV, with *JAK2*V617F being the most frequent mutation. Upon *JAK2* mutation, the encoded JAK2 protein is constitutively active and drives the aberrant proliferation of hematopoietic cells, leading to erythrocytosis, thrombocytosis, leukocytosis, and increased cytokine production, which are all distinctive features of PV [3]. The detection of *JAK2* mutation is a major criterion for PV diagnosis, along

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with high levels of hemoglobin, hematocrit or red blood cell (RBC) mass, and panmyelosis accompanied by pleomorphic mature megakaryocytes within the bone marrow; subnormal serum erythropoietin levels are considered a minor criterion [4, 5].

Patients with PV may undergo leukemic and/or myelofibrotic transformation and are at risk of hemorrhagic episodes [6]. However, the primary concern with the disease is a significant risk of thromboembolic events (TEs), with a 2.7- to 13.1-fold higher likelihood of developing arterial and venous thrombosis, respectively, compared to age- and sex-matched controls [7]. Arterial thromboses (e.g., myocardial infarction, unstable angina, transient ischemic attack, ischemic stroke) occur more frequently than venous TEs (e.g., deep venous thrombosis of the legs, pulmonary embolism, venous thrombosis in atypical sites), with the latter accounting for approximately one-third of all TEs [8–12]. TEs frequently manifest either before or at the time of PV diagnosis, with their rate declining over time, likely due to the beneficial effect of treatment interventions [9, 11–15].

Patients with PV have a higher mortality rate than matched controls [hazard ratio (HR) (95% CI): 1.49 (1.37–1.62), $p < 0.001$] in a population-based study [16]. A history of thrombosis was the main predictor of reduced life expectancy in the European Collaboration on Low-dose Aspirin in Polycythemia Vera (ECLAP) study [17]. Accordingly, Pemmaraju et al. reported a median overall survival (OS) of just 5.1 years in patients developing a TE within 1 year of PV diagnosis, whereas the median time was not reached in patients without [18]. This observation was further supported by Barbui et al., who found that thrombosis was associated with a doubled risk of mortality and accelerated transformation to post-PV myelofibrosis or blast phase disease [19].

Risk factors for TEs in patients with PV are a major topic of extensive investigation. Among these, advanced age and a history of previous TEs are well-established and unanimously recognized predictors of future thrombosis [10, 11, 14, 16, 20]. Based on these two risk factors, patients with PV are currently classified into low-risk (absence of both risk factors) and high-risk groups (history of thrombosis and/or age ≥60 years) [21]. Reduction of thrombotic risk by giving aspirin and maintaining hematocrit values ≤45% are the cornerstones of PV treatment [21]. While periodic phlebotomies and anti-platelet therapy are required in all patients, additional cytoreductive drug therapies are recommended for patients with high-risk PV [6, 21].

A growing body of literature suggests that advanced age and prior TEs may only offer a partial view of the overall risk profile and are sometimes perceived as suboptimal for a tailored management of PV. Indeed, most patients have a high thromboembolic risk at diagnosis [22–24], but also harbor additional cardiovascular (CV) risk factors [22, 23], which further increase the risk of future TEs and death [25]. In light of this evidence, the European Leukemia Network (ELN) has recently indicated the use of cytoreductive therapy in low-risk patients who present additional criteria including, but not limited to, intolerance to phlebotomy, symptomatic progressive splenomegaly, persistent or progressive leukocytosis, extreme thrombocytosis, persistently high CV risk, high symptom burden, particularly severe itching [26]. Encouraging preliminary results have confirmed that these additional criteria identify increased thromboembolic risk across all conventionally defined risk categories [27]; however, the prognostic significance of these factors remains to be confirmed. Furthermore, it has yet to be determined which additional risk factors may predict the recurrence of TEs in high-risk populations.

Recent evidence has revealed that somatic mutations in blood cells, including *JAK2*V617F, present in approximately 97% of patients with PV [6], can impact CV diseases independently of elevated peripheral blood cell counts. Hematopoietic cell clones carrying the *JAK2*V617F mutation are causally linked to multiple CV diseases, including atherosclerosis and aortic thrombosis, which can lead to ischemic stroke, coronary artery disease, heart failure, pulmonary hypertension, venous thrombosis, and aortic aneurysm [28]. The presence of *JAK2*V617F mutation likely contributes to hypercoagulability and endothelial dysfunction, and has been associated with a heightened risk of thrombotic events even in the absence of myeloid disorder [29].

To address these gaps, a prospective study, the Prospective Observational Study to Identify and Describe Predictive Factors for Thromboembolic Events in Patients With High-risk Polycythemia Vera (PROSPERO) has been conceived (Trial registration number: NCT05548062, date of trial registration: September 21 st, 2022). PROSPERO aims to identify and describe specific predictive risk factors for TEs in high-risk patients with PV with a prior history of thrombosis and evaluate their contribution to the recurrence of such events. The results from this study will hopefully strengthen current evidence and highlight the most informative predictors for thromboembolic risk in high-risk patients with PV. These data could support the development of accurate algorithms for risk quantification. Here, we give an overview of the current evidence on risk factors for TEs and available treatments in patients with PV to define the context and the needs at the basis of the design and methodology of the PROSPERO study.

Literature review

Clinical risk factors

Demographic and clinical characteristics of patients with PV related to thrombosis risk have been extensively investigated. Current guidelines recommend using the cutoff age of 60 years to stratify patients into low- and high-risk PV groups [21, 30]. In several studies, age has been reported to increase the risk of TEs in PV patients [9–11, 16]. While the pivotal ECLAP study reported an increased risk of CV complications associated with age >65 years [9, 20], the International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) found this age category to be predictive only for venous thrombosis [10]. Notably, a lower age threshold (≥ 60 years) was associated with thrombotic risk in other studies [11, 16, 31, 32]. Among these, the population-based study with matched controls conducted by Enblom-Larsson confirmed that among patients with PV (n = 2604), age >60 years was associated with a greater thrombotic risk compared to younger individuals. Interestingly, the thrombotic risk further increased in patients older than 60 years (patients aged 70 years had a HR of 1.9, 95% confidence interval [CI] 1.7–2.3, $p < 0.001$) [16].

Previous TEs are highly predictive of future events, with prior arterial and venous thrombosis associated with subsequent arterial and venous events, respectively [9–11, 16, 33], as further detailed in the dedicated paragraph "*Recurrent thrombosis*".

Hypertension [10, 16, 33, 34], diabetes [35, 36], hyperlipidemia [35], and smoking habit [14] were significantly associated with major bleeding and arterial or venous TEs in multivariate analyses. Consistently, the presence of diabetes, hypertension, and hyperlipidemia increased the risk of TEs in a Japanese cohort of patients with PV [37]. Obesity is also strictly linked to CV risk factors in the context of metabolic syndrome and is associated with elevated thrombosis risk in the general population [38]. In patients with PV, evaluation of body mass index (BMI) may improve the prognostic accuracy of PV [33], and recent studies positioned this parameter among the top 10 risk factors for TEs [39, 40]. Despite this substantial evidence, there is some discrepancy in the published literature. For instance, hypertension and diabetes did not significantly increase the risk of major, arterial or venous thrombosis in the ECLAP study [14], and diabetes was not found to be a significant risk factor in the study by Enblom-Larsson et al. [16].

Splenomegaly is a common feature that can potentially influence the risk of TEs in patients with PV. Although the extent of splenomegaly was not associated with the incidence of vascular TEs [41], patients with palpable splenomegaly had a higher probability of venous thrombosis than patients without [11, 27].

Further research is warranted to determine the impact of clinical characteristics, particularly individual CV risk factors, on thrombotic risk. Given that patients with PV show an overall high risk of CV events, a comprehensive management plan, ideally discussed in a multidisciplinary team setting, should include the identification and modification of CV risk factors [25, 42].

Hematologic parameters

Maintaining hematocrit levels below 45% is recommended to reduce the risk of TEs, as elevated hematocrit is one of the major risk factors for thrombosis in patients with PV [6, 21]. In the Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) study, patients with a hematocrit below 45% had a lower incidence of deaths from CV causes or major TEs (1.1 per 100 person-years) than those with a target hematocrit of 45–50% (4.4 per 100 person-years) [8]. The Veterans' health database study confirmed the protective role of hematocrit <45% from the development of TE in patients with PV, and validated in real-world the CYTO-PV post-hoc analysis highlighting the role of white blood cell count (WBC) in thrombosis risk [43]. On the other hand, a real-world analysis in Japanese patients with PV did not find a significant association between maintaining hematocrit <45% and reduced TE. Elevated WBC and platelet counts were independent predictors of thrombosis, with WBC ≥15 × 10⁹/L and platelet ≥1000 × 10⁹/L significantly increasing TE risk (HR 2.10, 95% CI: 1.65–2.68, HR 1.98 95% CI: 1.35–2.89, respectively) [44].

Several other studies have explored the association between high hematocrit and CV events in both PV and non-PV individuals. In the Copenhagen General Population Study, incidentally identified erythrocytosis (upper 5 percentiles) was linked to an increased risk of arterial thrombosis in the heart (HR 1.46; 95% CI: 1.06–2.00), corresponding to +18 events per 10,000 person-years [45]. This association was particularly stronger in young women as observed in the Framingham Study [46]. In contrast, a two-sample Mendelian randomized study using data from the MEGASTROKE consortium for stroke and the FinnGenR9 databases reported a negative correlation between high hemoglobin levels and stroke risk (OR 0.82 and 0.91 in the two databases, $p < 0.05$ in both) [47]. Elevated hematocrit has also been linked to an increased risk of major adverse cardiovascular events (MACE) in familial hypercholesterolemia [48]. In the Atherosclerosis Risk in Communities (ARIC) Study, a J-shaped relationship between hematocrit and venous thromboembolism (VTE) risk was documented, with significantly increased

risk observed only at the upper percentiles for provoked VTE (HR = 1.72; 95% CI: 1.30–2.27) [49]. Similarly, the Tromsø Study reported a 1.25-fold increase in VTE risk per 5% increment of Hct (HR 1.25; 95% CI: 1.08–1.44). Specifically, men with a hematocrit in the upper 20th percentile (≥ 46%) had a 1.5-fold increased risk of total VTE (95% CI: 1.08–2.21) and a 2.4-fold increased risk of unprovoked VTE (95% CI: 1.36–4.15) compared to men in the lower 40th percentile [50]. However, high hematocrit level was not associated with increased VTE risk in the Copenhagen General Population Study, suggesting that the relationship between hematocrit and thrombotic risk may vary depending on underlying conditions, genetic factors, and study populations [45].

Although elevated red cell distribution width (RDW) has been reported to increase the risk of thrombosis, possibly by raising blood viscosity and impairing blood flow [51], emerging data also link low RDW with higher TE risk and shorter thrombosis-free survival in high-risk patients, patients aged > 50 years, patients with previous TEs [52] and those receiving HU [40]. These contradictory findings likely reflect differences in the patient populations and clinical contexts across studies. Despite the lack of a clear explanation for the association between low RDW and higher TE risk, it has been proposed that RDW may act as a marker of erythrocyte homeostatic responses, with lower RDW suggesting preserved or even increased erythropoietic activity despite cytoreductive treatment [40], and elevated RDW reflecting dysregulated erythropoiesis [40, 52]. Thus, RDW variations, regardless of direction, may capture shifts in erythrocyte homeostasis, which in turn influence TE risk and thrombosis-free survival in PV patients.

The predictive role of leukocytosis has been widely investigated, though findings have not always been consistent. A WBC greater than 15×10^9/L correlated with a higher probability of leukemic transformation, reduced survival [53] and vascular events (HR 1.71, 95% CI: 1.10–2.65, $p = 0.017$), with the latter association being primarily driven by an elevated risk of myocardial infarction [14]. In the CYTO-PV study ($n = 365$ patients with PV), WBC levels above 11×10^9/L significantly predicted the risk of thrombosis [54]. Other studies identified leukocytosis as a risk factor for future venous TEs only [11, 53]. On the contrary, a leukocyte count > 12.4×10^9/L specifically predicted arterial TE recurrence, with the prognostic relevance of leukocytosis being age-related and significantly associated with increased thrombotic risk in patients < 60 years old only [32]. In a different study, there was no association between persistently elevated leukocyte trajectories and TEs [55]. Recently, the prospective observational study REVEAL showed that, in high-risk PV patients, WBC count > 11×10^9/L was significantly associated with increased thrombotic risk ($p < 0.0001$), being also the only significant predictor of thrombosis in low-risk PV patients ($p < 0.0120$). Moreover, WBC count > 12×10^9/L was significantly associated with thrombotic events (HR: 1.95, 95% CI: 1.066–3.554, $p < 0.0300$) independently of hematocrit levels. In this study, cytoreductive drug treatment did not mitigate thrombotic risk [56].

Beyond RBC and leukocytes, other blood cell populations may be involved in promoting thrombosis. In a recent analysis of the ECLAP study, a significant association between the risk of venous thrombosis and progressive lower counts of lymphocytes emerged, whereas an opposite relationship was observed for neutrophil absolute counts [57]. Another study revealed that high absolute neutrophil counts negatively affect venous thrombosis event-free survival [58]. Not surprisingly, the neutrophil-to-lymphocyte ratio was identified as an additional TE risk factor, with values ≥ 5 being independently associated with an increased risk of venous thrombosis [57].

The role of thrombocytosis in determining the risk of thrombosis in PV is still controversial. In several studies, thrombocytosis did not increase thrombotic risk [14, 54], whereas in others, it did [31]. Nevertheless, aspirin has been shown to reduce the rate of TEs [20]. These findings may suggest that platelet activation, rather than mere thrombocytosis, plays a crucial role in thrombosis risk [59].

JAK2V617F allele burden and additional PV genetic variants

JAK2 mutations skew bone marrow and endothelial cell metabolism to an inflammatory one, which sustains TEs especially in the venous vessels [60]. In patients with PV, an allele burden of *JAK2*V617F > 75% was associated with a higher thrombotic risk than an allele burden of < 25% (relative risk of 7.1) [59]. Recently, Guglielmelli et al. identified *JAK2*V617F allele frequency > 50% as an independent predictor of venous thrombosis after multivariate analysis [35], while in the study of Horvat et al. *JAK2*V617F allele burden (> 90.4%) was associated with an increased risk of venous thrombosis, in PV patients in univariate but not in multivariate analysis [36].

Interestingly, Segura-Diaz et al. reported that the presence of additional, pathogenic non-driver mutations in DTA genes (*DNMT3A*, *TET2*, and *ASXL1*) was a risk factor for shorter thrombosis-free survival in both older and low-risk patients with PV, but not for patients who experienced pre-diagnostic events. DTA mutations were significantly associated with arterial TEs and only marginally with venous TEs, but no association was observed between TEs and individual DTA genes, although the

presence of a *TET2* mutation alone was associated with a nearly doubled risk [61].

Synergistic predictive factors

To date, there is limited evidence on the synergistic effects of multiple thrombosis risk factors in patients with PV. Verstovsek et al. developed a machine-learning model using a large dataset of patients with PV treated with HU to assess the key contributors to TEs and their optimal thresholds. A history of TEs was the most influential predictor of thrombotic risk, while the laboratory parameters of neutrophil percentage (NEP), WBC, lymphocyte percentage (LYP), and RDW were ranked among the overall top 10 contributors. These laboratory variables interacted synergistically in patients without any history of thrombosis. In particular, patients with RDW < 14.3% and NEP ≥ 72.05%, or RDW < 14.05% and LYP < 19.3%, had shorter thrombosis-free survival compared to patients displaying only one of these risk factors [40].

PV treatments and thromboembolic risk prevention

Periodic phlebotomy in combination with low-dose aspirin (up to 100 mg/day) is the recommended therapy for all patients with PV, irrespective of their risk category; cytoreductive therapy is recommended in all patients with high-risk PV [21, 26, 30, 62]. In the ECLAP study, aspirin reduced the risk of CV events and TEs; importantly, this double-blind, placebo-controlled randomized trial demonstrated that the treatment did not significantly increase the risk of bleeding compared to placebo [20, 63]. The use of low-dose aspirin therapy has been proposed for primary prophylaxis in low-risk patients, especially those with a higher risk for arterial thrombosis (i.e., the presence of CV risk factors and leukocytosis) in the absence of contraindications [21, 26, 30, 62].

Cytoreductive therapy is added to phlebotomy and aspirin for treating all high-risk patients with PV [21, 26, 30, 62]. Administration of cytoreductive therapy can reduce the risk of recurrent thrombosis by 47% [31]; risk reduction was greater with the addition of either antiplatelet or anticoagulant agents [31, 64]. Among available cytoreductive therapies, HU and recombinant interferon-alfa (IFN-α) are preferred in older and young patients, respectively [21, 26, 30, 62]. However, high rates of HU resistance and/or intolerance (up to 40%) have been observed in multiple real-world studies [24, 65–68].

Although HU is associated with a reduction of CV and thromboembolic risk [31, 64, 69], the TE rate is still substantial. As highlighted by Ferrari et al., patients treated with HU had a thrombosis rate approximately three times higher than the rate observed in the general population [70]. Indeed, while HU has been shown to prevent the recurrence of arterial events, it may be less effective in preventing venous thrombosis, particularly splanchnic vein thrombosis [71]. In addition, a higher risk of thrombosis was identified in the subset of HU-treated patients requiring ≥3 phlebotomies per year [72]. Collectively, these findings underscore that HU has a limited effect in reducing TEs.

The PROUD-PV study and its long-term extension CONTINUATION-PV were phase III, randomized, controlled, open-label trials that evaluated the safety and efficacy of ropeginterferon alfa-2b versus HU or best available therapy (BAT) over 6 years in patients with PV [73]. In the CONTINUATION-PV study, ropeginterferon alfa-2b significantly increased the probability of event-free survival (disease progression, TEs, and death) compared with the control group ($p = 0.04$); however, the incidence rate of major TEs was similar between the two groups (1.0%-patient-years versus 1.2%-patient-years, respectively) [74]. Notably, the median *JAK2*V617F allele burden declined continuously during ropeginterferon alfa-2b treatment, reaching a value < 1% in 19.6% of patients compared with only one patient (1.4%) in the BAT arm ($p = 0.0002$) [74]. The impact of recombinant IFN-α on the *JAK2*V617F allele burden has been confirmed in studies using peginterferon-alfa-2a [75] and in the Low-PV study, in which patients with PV at low risk were randomized to phlebotomy plus aspirin (standard treatment) with or without ropeginterferon alfa-2b [76].

Ruxolitinib, an oral JAK1/2 inhibitor, represents an alternative cytoreductive therapy for patients either intolerant to or resistant to HU. Ruxolitinib has been shown to be more effective than BAT in reducing TEs [77–80]. Overall, ruxolitinib was significantly associated with lower rates of TEs compared with standard of care or placebo, with a risk ratio of 0.45 (95% CI 0.23–0.88) [81]. A more recent meta-analysis confirmed the lower number of TEs with ruxolitinib compared with BAT, although the overall difference did not reach statistical significance [82]. In a real life study, ruxolitinib-treated patients did not experience any arterial TEs over a median follow-up of 3.7 years [83]. Compared with patients treated with BAT, patients receiving ruxolitinib had a significantly lower rate of arterial thrombosis (0.4% vs. 2.3% per year for ruxolitinib and BAT, respectively), although there were no significant differences in the rates of venous thrombosis (0.8% and 1.1% for ruxolitinib and BAT, respectively) [84].

The relationship between response to cytoreductive therapies and reduction of thrombotic risk was also investigated. The achievement of a response, as defined by ELN criteria, was not associated with a reduced thrombosis risk

in patients treated with HU [85], ropeginterferon alfa-2b [74], or ruxolitinib [86]. However, data from the MAJIC-PV study highlighted for the first time a positive association between complete response and event-free survival, including major thrombosis-free survival, with event-free survival being superior for ruxolitinib than BAT (HR, 0.58; 95% CI, 0.35 to 0.94; $p = 0.03$). Ruxolitinib was also associated with a higher rate of complete response at 1 year, and for a longer duration, than BAT [80]. In line with the latter, Guglielmelli et al. recently confirmed that the durable molecular response induced by ruxolitinib correlated with prolonged event-free and progression-free survival [87].

Beyond the recommended therapies mentioned above, patients with venous TEs may benefit from additional interventions, i.e., conventional antithrombotic agents such as vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs). While these treatments have been shown to partially reduce venous thrombosis recurrence [88–91], the effectiveness of these drugs is still suboptimal. An elevated bleeding risk may also preclude their broad use [92].

Recurrent thrombosis

The incidence rate of recurrent thrombosis has been estimated at 7.6 per 100 person-years. Sex, diagnosis (PV or essential thrombocythemia), and presence of vascular risk factors did not predict recurrence, whereas age >60 years did (HR, 1.67, 95%CI 1.19–2.32). Increased leukocyte count at the time of the first thrombosis was a risk factor for recurrence in patients <60 years old (HR 3.55, 95%CI 1.02–12.25) [31]. The risk of arterial or venous recurrence was significantly higher in patients with previous arterial thrombosis (HR 5.75, 95%CI 1.66–19.86) or venous thrombosis (HR 4.23; 95% CI 2.54–7.06), respectively [31]. Consistently, the study by Enblom-Larsson et al. highlighted a significantly higher risk of arterial events in patients with previous ischemic stroke (HR 1.72, 95% CI 1.26–2.34, $p < 0.001$) and ischemic heart disease (HR 2.09, 95% CI 1.59–2.74, $p < 0.001$).On the other hand, a history of venous thrombosis was associated with a risk of recurrent venous TEs (HR 4.43, 95% CI 3.04–6.48, $p < 0.001$) [16].

In a cohort of 206 patients with a well-characterized diagnosis of deep vein thrombosis (DVT) of the legs and/or pulmonary embolism (PE), the rates of thrombosis recurrence were 5.3 per 100 person-years for those on VKAs and 12.8 for those after discontinuing VKAs ($p = 0.008$). After stopping VKAs, the cumulative incidence of recurrence reached 42.3% at five years of follow-up [88]. In addition, patients with thrombosis in the hepatic or cerebral veins are more likely to experience recurrences [89, 93].

Despite the protective effects of VKAs in reducing the risk of recurrent thrombosis, an indirect comparison shows that patients with MPN who experienced VTE may have a higher thrombotic probability than non-MPN patients. Specifically, the cumulative incidence of recurrent thrombosis at one year and five years of VKA treatment was 7.8% and 21%, respectively [88]. Recently, the role of DOACs, such as apixaban, dabigatran, edoxaban, and rivaroxaban, has been evaluated in a large international observational study involving 442 MPN patients with nonvalvular atrial fibrillation (AF) and VTE [91]. Among 158 patients with VTE of the legs and/or PE, the incidence rate was 5.1 per 100 person-years, predominantly occurring in venous sites, with this recurrence rate being comparable to the 5.3 per 100 person-years reported in MPN patients receiving VKAs following VTE of the legs and/or PE [88]. Notably, a major concern during anticoagulation therapy is the risk of bleeding, which is particularly pronounced in MPN patients receiving both aspirin and anticoagulants, thereby precluding their broad use [92].

Cytoreduction may mitigate the risk of recurrent thrombosis. Data from retrospective cohorts and clinical trials indicated that while HU is effective in preventing recurrence of arterial thrombosis, its efficacy for prevention of recurrent venous thrombosis is questionable [69, 71]. A pooled analysis comprising 1,500 patients with MPN-related arterial ($n = 935$) or venous ($n = 565$) thromboses assessed the impact of HU combined with aspirin or oral anticoagulants [71]. Multivariate models adjusted for age and sex revealed that antiplatelet agents significantly reduced the risk of recurrent arterial thrombosis (HR: 0.49, 95% CI: 0.31–0.78, $p = 0.003$), similarly to HU (HR: 0.64, 95% CI: 0.42–0.98, $p = 0.04$), whereas VKAs only provided partial protection (HR: 0.53, 95% CI: 0.27–1.04, $p = 0.06$). Conversely, in patients with first venous thrombosis, VKAs were more effective in preventing venous recurrences (HR: 0.57, 95% CI: 0.35–0.94) than antiplatelet agents (HR: 0.71, 95% CI: 0.41–1.24, $p = 0.24$) or HU (HR: 0.75, 95% CI: 0.46–1.23, $p = 0.26$) [71]. Furthermore, HU did not demonstrate a significant effect on recurrent thrombosis rates in 218 patients with splanchnic vein thrombosis (HR: 0.81, 95% CI: 0.39–1.65, $p = 0.56$), after adjusting for age, sex, antiplatelet treatment, VKA treatment, and other cytoreductive agents [71].

Although studies have assessed the effect of ruxolitinib on thrombosis incidence, data specifically addressing recurrent thrombosis are currently lacking [82, 84]. Beyond the recommended therapies mentioned above, patients with venous TEs may benefit from additional interventions, i.e., VKAs and DOACs. While these treatments have been shown to partially reduce venous thrombosis recurrence [88–91], the effectiveness of these drugs is still suboptimal.

An elevated bleeding risk may also preclude their broad use [92].

In summary, antiplatelet agents and HU are the preferred treatments for MPN patients with a history of arterial thrombosis. For patients with VTE in common sites, VKAs or DOACs have been shown to halve the risk of recurrence; still, the effectiveness of these drugs remains suboptimal. The benefit of HU following VTE in addition to oral anticoagulation remains uncertain, especially in patients with splanchnic vein thrombosis [71, 88–91].

The PROSPERO study

Study design and endpoints

The Prospective Observational Study to Identify and Describe Predictive Factors for Thromboembolic Events in Patients With High-risk Polycythemia Vera study (PROSPERO) is a multicenter study designed to include 300 patients with high-risk PV from 37 Italian centers. This population includes individuals who have experienced at least one TE either post-diagnosis or within 2 years before diagnosis and who are treated with either HU (HU cohort, $n=$ 150) or ruxolitinib (ruxolitinib cohort, $n=$ 150). At enrolment, all patients are to be already receiving either HU or ruxolitinib as per clinical practice, independently of their participation in this study. Enrolment is planned to continue until 150 patients are enrolled in each cohort.

Patients will be followed for 3 years from enrolment, with scheduled visits at Months 6, 12, 18, 24, 30, and 36. A window of ±1 month is allowed for all visits. Data collection started in June 2022, with the last patient, last visit (LPLV) is planned for 2027.

Table 1 PROSPERO study: objectives and endpoints

Primary objective	Primary endpoint
Identify and describe predictive factors for TEs in high-risk patients with PV	Predictive accuracy of TE history, demographics, blood pressure, laboratory blood tests, and the use of antiplatelets or anticoagulants on the occurrence of TEs within 12 months
Secondary objectives	Secondary endpoints
• Synergy of biological predictive factors for TEs • Incidence of TEs in the hydroxyurea and ruxolitinib cohorts of patients. • Safety of ruxolitinib and HU	• Synergistic combinations of predictive factors (RDW, neutrophils, lymphocytes, neutrophil/lymphocyte ratio, and platelet counts) • Yearly incidence of TEs and its relation to predictive factors • Incidence of arterial and venous TEs in the HU and ruxolitinib cohorts • Incidence and severity of adverse events

HU Hydroxyurea; *PV* Polycythemia vera; *RDW* red cell distribution width; *TE* thromboembolic event

Patient population

Participants have to meet the following inclusion criteria to take part in the study: (1) signed informed consent; (2) age ≥18 years; (3) diagnosis of PV according to World Health Organization (WHO) 2008 or WHO 2016 criteria and high-risk stratification according to ELN classification; (4) at least one TE (either arterial or venous) occurring after diagnosis or up to 2 years before diagnosis; (5) treatment with HU at enrolment and for at least 18 months prior to enrolment, or treatment with ruxolitinib starting up to 18 months before enrolment. Switching from HU to ruxolitinib during the study is permitted. Patients will be treated and receive routine medical care (visit frequency and types of assessments) according to local prescribing information and standard clinical practice.

The planned sample size of 300 patients is primarily based on feasibility considerations. With a multivariate Cox regression model on a covariate with a standard deviation greater than or equal to 0.5, a sample of 300 patients achieves more than 80% power at a two-sided 0.05 significance level to detect a hazard ratio of at least 4, when the R-Squared of the variable of interest on the other covariates is expected to range between 0 and 0.2 and with an overall TE rate between 7% and 8% per year (nQuery version 8.5.2.0, procedure ROT6-1/Cox Regression).

Study objectives and endpoints

The primary and secondary objectives and corresponding endpoints of the study are outlined in Table 1. Briefly, the study aims to identify and describe predictive factors for TEs in high-risk patients with PV with a thrombosis history by measuring the predictive accuracy of TE history, demographics, blood pressure, laboratory blood tests, and the use of antiplatelets or anticoagulants, evaluated at 6, 12, 18, 24, 30, and 36 months, on the recurrence of TE within 12 months. Patients will be followed for 3 years from enrolment.

Secondary endpoints include evaluating predictive risk factors, identifying synergistic combinations, yearly TE recurrence and its relation to predictive factors, the incidence of arterial and venous TEs in the HU and ruxolitinib cohorts, and the incidence and severity of adverse events (Table 1). Figure 1 illustrates the PROSPERO study design, including information on patient population, analyses, and endpoints.

Measurements

Demographics and clinical characteristics will be collected at enrolment and follow-ups as detailed below:

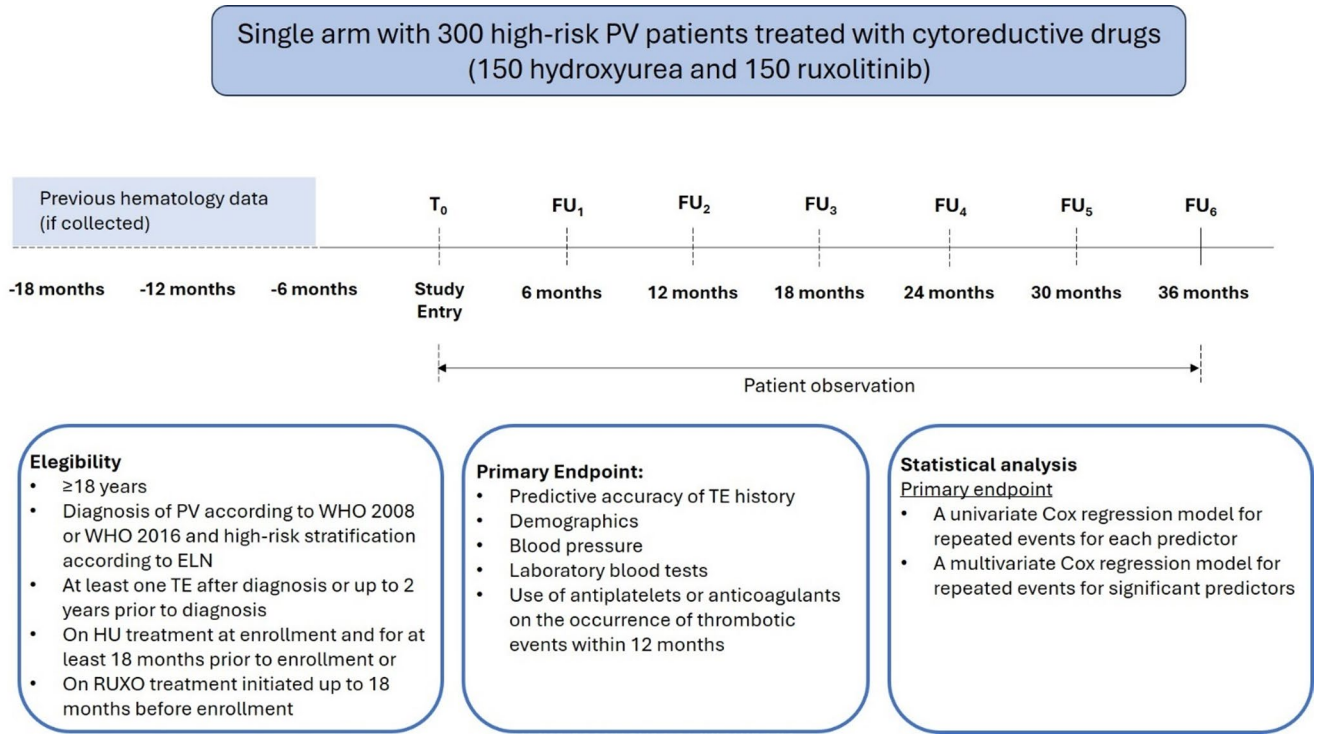

Fig. 1 Schematic illustration of the PROSPERO study design. ELN, European Leukemia Net; HU, Hydroxyurea; PV, Polycythemia vera; RUXO, Ruxolitinib; TE, thromboembolic event

- At enrolment: age, sex, ethnicity, education, medical history, vital signs, smoking and alcohol history, date of PV diagnosis, hematology and clinical biochemistry parameters, concomitant treatments, phlebotomy history, thrombosis history, therapy with either HU or ruxolitinib, spleen measurements by ultrasound, lifestyle habits (e.g., autonomy, quality of sleep, diet).
- At follow-ups (months 6, 12, 18, 24, 30, and 36): history of TEs (number, type, date and location), PV treatments (HU, ruxolitinib, phlebotomies, anticoagulants and antiplatelets), vital signs (heart rate and blood pressure), weight, hematology laboratory parameters (hematocrit, RBC, hemoglobin, platelets, RDW, WBC, neutrophil-to-lymphocyte ratio), patient-reported outcome (PRO), adverse events. Additional variables are collected according to availability as part of routine clinical practice.

Data collection

During the first visit, data will be retrieved from hospital medical records. If available, hematology data at 6, 12, and 18 months before study initiation will be collected retrospectively. Prospective data are to be collected during follow-up visits as part of routine clinical practice. Procedures are arranged according to the routine clinical practice. Treating physicians are asked to fill out the electronic case report form (eCRF) at every patient visit.

Statistical analysis

For the primary endpoint, a univariate Cox regression model for repeated events will be applied for each predictor considering all the TEs occurring within 12 months and the time from enrolment to each occurrence. A multivariate Cox regression model for repeated events will be applied for statistically significant predictors.

For the secondary endpoints, the synergy between variables will be examined through pairwise interactions in the context of time-to-event analysis. Each combination will be evaluated using Cox regression, with the most significant pairwise splits identified and reported for each variable pair. Generalized linear models will estimate annual TE incidence and 95% CIs. Adjusted estimates will also be calculated, accounting for predictive factors identified by the multivariate analysis of the primary endpoint.

Discussion

Conventional risk stratification in PV primarily relies on advanced age and previous TEs [21]. A growing body of evidence suggests that these two variables may not exhaustively predict thromboembolic risk, which seems to be influenced by a complex interplay of multiple factors. CV comorbidities, hematological parameters, and genetic

profile likely play a crucial role in the occurrence of thrombosis. A synergistic interaction between RDW and NEP, and RDW and LYP has recently been observed when predicting thrombotic risk in patients without a history of thrombosis [40]. These results highlight the need in stratifying patients for an integrated assessment of thromboembolic risk beyond traditional factors [25, 42].

Updated ELN guidelines recommend starting cytoreductive therapy to prevent TEs in low-risk patients if they present a series of clinical and laboratory criteria [26]. However, further research is needed to clarify the predictive impact of such criteria. Given that HU does not fully mitigate thromboembolic risk, as evidenced by the high rate of thrombotic recurrences in high-risk patients receiving the treatment [70], and is associated with potential toxicities, its use should be carefully considered, particularly in younger patients [94]. Furthermore, traditional antithrombotic prophylaxis treatments may not be sufficiently effective and safe, highlighting the need for more effective strategies to prevent TE risk [88–92]. Ruxolitinib may offer a viable alternative to HU, supported by promising data on its efficacy in preventing TEs [77–84]. In this context, identifying additional risk factors that reliably predict thrombosis risk and understanding their contribution to the risk in both low- and high-risk patients with PV is crucial for developing more comprehensive risk prediction models and tailoring treatment strategies to the individual risk profile.

While there is still uncertainty about the exact role and impact of known risk factors, multifactorial prediction models are being developed to assess thrombosis risk in patients with PV. One such model is the multiple factor-based prognostic score system for thrombosis (MFPS-PV), which classifies patients into low-, intermediate-, and high-risk groups by evaluating age ≥60 years, CV risk factors, and the presence of at least one mutation associated with a high thrombosis risk [95].

The PROSPERO study is designed to identify and describe specific predictive factors for TEs in patients with high-risk PV treated with either HU or ruxolitinib, aiming to improve current risk assessment models. This is the first prospective study on this topic conducted within the Italian clinical practice. The findings from this study will shed light on all risk factors that should be integrated into a more accurate and personalized thrombotic risk assessment model, thereby preventing thrombotic recurrence more effectively through appropriate and tailored treatment. The strengths of the PROSPERO study include its prospective design and the predictive accuracy of a comprehensive set of variables. The study investigates the combined and/or synergistic impact of various clinical, non-clinical, and laboratory factors, such as RDW, neutrophil count, and use of anti-thrombotic agents on the risk of TEs, offering new perspectives to clinicians. A large patient population will be followed up for 3 years; treatment outcomes will be reported for patients receiving HU or ruxolitinib in a real-world context. The background, rationale, and design of the PROSPERO study, as well as the expected outcomes and future implications, are summarized in Table 2.

Table 2 Summary of the background, rationale, design, expected outcomes, and future implications of the PROSPERO study

Background
Conventional thromboembolic risk stratification in PV is based on age and thrombosis history. Recent evidence suggests multiple, novel variables contribute to influence thrombotic risk in PV. However, it is still unclear which, and to what extent, additional risk factors contribute to predicting the recurrence of TEs in high-risk patients. Thromboembolic risk remains elevated even if patients receive recommended treatments.
Rationale
There is a clinical need to clarify which factors contribute to predicting the risk of TEs in patients with PV and to what extent.
Study Design
This study aims to prospectively identify and describe predictive factors and determine their individual contribution as well as combined/synergistic impact on overall thrombosis risk in patients with high-risk PV. The study also investigates the incidence of TEs and safety in cohorts of patients receiving HU and ruxolitinib.
Expected Outcomes
A more precise and personalized thrombotic risk assessment can be achieved by identifying and describing multiple risk factors and their relative impact. This will enable more effective prevention of thrombotic recurrence through the use of appropriate and tailored treatment strategies.
Future Implications
The findings are expected to inform future guidelines on risk assessment and therapeutic approaches and help advance the development of novel, integrated risk assessment models.

HU Hydroxyurea; *PV* Polycythemia vera; *TE* thromboembolic event

Although the prospective design allows for exhaustive data collection, missing data may still occur, particularly if collected retrospectively. Patients lost to follow-up are the main source of attrition bias; attrition may threaten sample representativeness if patients lost to follow-up differ from the remaining patients in characteristics at enrolment or outcomes. Furthermore, this study focuses exclusively on high-risk patients with PV; as such, it will not inform about predictive factors for patients classified as low-risk PV. The statistical analysis will be primarily descriptive, and no formal comparisons between the HU- and ruxolitinib-treated cohorts will be conducted.

Conclusions

The results from the PROSPERO study will help discriminate which clinical and hematological variables, and to which extent, should be considered in addition to age

and thrombosis history to better assess thrombosis risk in patients with high-risk PV. Furthermore, original data will be collected regarding the incidence of recurrent thrombosis during treatment with ruxolitinib, addressing a knowledge gap in the literature. The study's findings are expected to inform future clinical guidelines, advance the development of ad hoc multifactorial predictive models and improve therapeutic approaches, thus reducing the incidence of life-threatening TEs in high-risk patients with PV.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Human and animal rights This work does not contain any studies on human or animal subjects performed by any of the authors.

Ethics approval Not applicable to this work. The PROSPERO study protocol was submitted to and approved by the Ethics Committee of each participating center.

Competing interests CC and CR are Novartis employees. VDS: advisory board for AOP Health, Bristol Myers Squibb, Glaxo Smith Kline, Grifols, Novartis, SOBI, Takeda; speaker fees from Abbvie, Alexion, Amgen, Bristol Myers Squibb, Grifols, Novartis, Novo Nordisk, Sanofi, Takeda; research grant from Alexion. GB: Advisory board for Novartis, GSK; speakers bureau of Novartis, BMS, Janssen, Menarini, GSK. MB: honoraria by Novartis, Incyte, Pfizer, BMS, AOP, Abbvie, GSK. AI: speaker honoraria from AOP Health and Novartis. MM: consultant for AstraZeneca, Roche, Novartis, Gilead, MSD. E. Masselli: consultancy and honoraria from Novartis, BMS and GSK. F. Palandri: speakers bureau and advisory board of Novartis, BMS, AOP, Sierra Oncology, Incyte, Telios, Abbvie, Constellation-Morphosys, Sobi and GSK. F. Passamonti: honoraria during the last two years for lectures from Novartis, Bristol-Myers Squibb, Abbvie, GSK, AOP Orphan, Jazz and for advisory boards from Novartis, Bristol-Myers Squibb/Celgene, GSK, Abbvie, Keros, Sumitomo. NP: advisory board for Novartis, GSK; consultant for AOP. The other authors have nothing to declare. F. Palandri and M. Breccia serve as editors for the Annals of Hematology journal.

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