

# Polycythemia vera and management of the thrombotic risk: an update

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## ABSTRACT

Polycythemia vera (PV) is a chronic Philadelphia-negative myeloproliferative neoplasm caused by *JAK2* mutation and characterized predominantly by the overproduction of red blood cells. The current treatment strategies of PV are based on periodic phlebotomies aimed at preventing thrombotic events associated with increased hematocrit levels. Additional therapies to mitigate the thrombotic burden, which represents the most important predictor of reduced survival in PV patients, include cytoreductive therapies, low-dose aspirin, and systemic anticoagulation. This concise review summarizes the current knowledge on the management of the thrombotic risk in PV patients.

## Introduction

Polycythemia vera (PV) is a chronic Philadelphia-negative myeloproliferative neoplasm (MPN) with an incidence ranging from 2.5 to 10/100,000 inhabitants. The discovery in 2005 of the gain-of-function *JAK2V617F* mutation on the exon 14 of chromosome 9, responsible of the 98% of PV cases (the remaining cases are caused by the exon 12 *JAK2* mutation), has represented a great improvement in PV diagnosis, clearly separating it from secondary erythrocytosis (for the diagnostic criteria of

PV see the recent update by Tefferi and Barbui).<sup>1</sup> The consequent overactivation of JAK-pathway leads to an over-proliferation of hematopoietic components, with a predominance of the erythroid component in PV compared to the other MPNs (*i.e.*, essential thrombocythemia and myelofibrosis).<sup>1</sup> Beside the detection of increased hematocrit (49% in men and 48% in women) and the positivity for *JAK2* mutation, the laboratory hallmark includes leukocytosis and thrombocytosis in approximately half of the patients at diagnosis. The clinical features of PV, which is more commonly diagnosed in people over the age of 60 years (male/female ratio: 1.3), include a wide spectrum of symptoms ranging from those involving microcirculation abnormalities (headaches, dizziness, visual disturbances, distal paresthesia, acrocyanosis and erythromelalgia), aquagenic pruritus, asthenia to the more severe arterial or venous thrombosis, which are a major cause of morbidity and mortality.<sup>2</sup> On the latter issue will be dedicated this concise review.

## Pathogenesis and management of thrombotic risk in polycythemia vera

As previously mentioned, PV patients are at increased risk of thrombotic events, including venous thromboembolism (VTE), cardiovascular and cerebrovascular accidents, with an unfavorable impact on overall survival.<sup>3</sup> In the prospective REVEAL study,<sup>4</sup> nearly 20% of patients with PV experienced a thrombotic event at the time of enrolment, and in a population-based study the likelihood of thrombotic complications after a median follow-up of 20 years was estimated at 26%.<sup>5</sup> Beside the hematocrit levels, age >60 years and thrombosis history have been identified as the most important risk factors for thrombosis permitting to stratify patients in high-risk (> 60 years or thrombosis history) and low-risk (absence of both risk factors) categories.<sup>1</sup> An additional, detrimental effect on thrombotic risk is also exerted by the presence of cardiovascular risk factors (*i.e.*, hypertension, diabetes and hyperlipidemia), leukocytosis (in particular, an increased absolute neutrophil count), microvascular symptoms, *JAK2* allele burden (*i.e.*, the measurement of mutant allele versus wild type allele in hematopoietic cells), and frequent phlebotomies.<sup>6</sup>

The management of PV should take into account the thrombotic risk, which should be tailored to each patient.<sup>3</sup> Thus, while phlebotomy, aimed at reaching and maintaining hematocrit levels <45%, is considered the mainstay of PV treatment in low-

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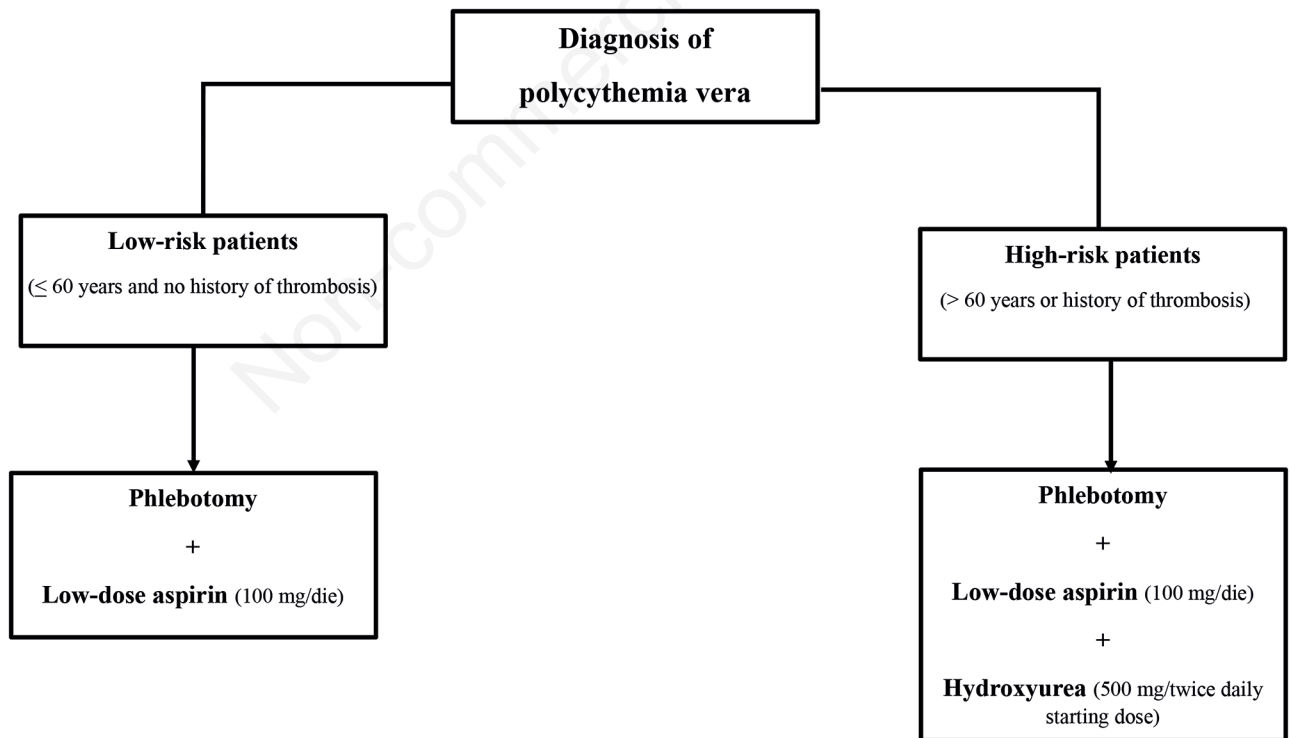
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risk patients, it could aggravate the thrombotic tendency in high-risk patients. It is well known, indeed, that repeated phlebotomies decrease body iron stores, which in turn render red blood cells (RBCs) smaller with an increased red cell mass despite a potentially normal hematocrit (RBCs occupy less of the space in the hematocrit), resulting in an enhanced thrombotic risk.<sup>1</sup> In addition, the phlebotomy-related reduction in oxygenation induces the expression of cytokines [*i.e.*, hypoxia-inducible factors 1 and 2 alpha (HIF1a and HIF2a)] that downregulate the expression of hepcidin, the main regulator of iron metabolism, leading to increased erythropoiesis.<sup>1</sup> Thus, in high-risk patients phlebotomy alone is not a sufficient therapeutic presidium but needs to be associated with cytoreductive therapy (*i.e.*, hydroxyurea which carries a low risk of leukemic transformation).<sup>1</sup> In a subset analysis of the prospective multicenter ECLAP study, hydroxyurea demonstrated an advantage over phlebotomy, nearly halving the incidence of fatal and non-fatal cardiovascular events (7.9% *versus* 13.2%).<sup>7</sup> There is also a general agreement in the fundamental therapeutic role of low-dose aspirin (100 mg/die) as antithrombotic prophylaxis in all PV patients. In a double-blind randomized controlled trial enrolling 518 PV patients, low-dose aspirin compared to placebo reduced the risk of death from cardiovascular causes without increasing the bleeding risk.<sup>8</sup> In addition, it was more effective than cytoreduction in protecting against cardiovascular events.<sup>9</sup> However, twice

daily low-dose aspirin (more effective than single dose in inhibiting platelet activation) may be necessary in low-risk patients at increased risk of arterial thrombosis, including those with cardiovascular risk factors, leukocytosis and microvascular symptoms and in high-risk patients with history of arterial thrombosis.<sup>10</sup> By contrast, adding long-term prophylactic systemic anticoagulation [*i.e.*, low-molecular weight heparin, vitamin K antagonists and direct oral anticoagulants (DOACs)] is often required in high-risk patients with previous VTE history to prevent VTE recurrence.<sup>1</sup> The association, however, between aspirin and oral anticoagulants is still under investigation due to safety concerns regarding their potential increased hemorrhagic risk. Figure 1 summarizes the current management strategies to minimize the thrombotic risk in PV patients.

## Conclusions

Since the discovery of the *JAK2* mutation causative of PV in 2005, several studies have been conducted in PV patients aimed at the identification of those risk factors influencing their outcome. Among them, thrombosis is considered, along with age, the most important determinant of worse prognosis and studies in this field have permitted to stratify patients in low- and high-risk and thus to set up adequate preventive counter-



**Figure 1.** Management strategies for patients with polycythemia vera.

Consider twice daily low-dose aspirin in low-risk patients with cardiovascular risk factors, leukocytosis, or inadequate control of microvascular symptoms and in high-risk patients with history of arterial thrombosis. Consider adding pegylated IFN- $\alpha$  in low-risk patients in the presence of frequent phlebotomies, severe and protracted pruritus, symptomatic splenomegaly, and persistent symptoms and in high-risk younger patients or in those with intolerance or resistance to hydroxyurea. Systemic anticoagulation is required in high-risk patients with venous thromboembolism history.

measures. While the management of PV patients according to their thrombotic risk profile is nowadays well consolidated, some grey areas still persist and are object of intense investigation from researchers. They include the role of DOACs and the risk-benefit ratio of prophylactic long-term systemic anticoagulation associated with aspirin in high-risk patients with previous VTE. Future clinical trials in this setting will help to optimize the anti-thrombotic management of PV patients.

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