JAMA | Review

# Diagnosis and Treatment of Polycythemia Vera
## A Review

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**IMPORTANCE** Polycythemia vera (PV), a myeloproliferative neoplasm characterized by an increased red blood cell mass and increased risk of thrombosis, affects approximately 65 000 people in the US, with an annual incidence of 0.5 to 4.0 cases per 100 000 persons.

**OBSERVATIONS** Erythrocytosis (hemoglobin >16.5 mg/dL in men or >16.0 mg/dL in women) is a required diagnostic criterion, although thrombocytosis (53%) and leukocytosis (49%) are common. Patients may have pruritus (33%), erythromelalgia (5.3%), transient visual changes (14%), and splenomegaly (36%) with abdominal discomfort. More than 95% of patients have a *JAK2* gene variant, which helps distinguish PV from secondary causes of erythrocytosis, such as tobacco smoking or sleep apnea. Among 7 cohorts (1545 individuals), the median survival from diagnosis was 14.1 to 27.6 years. Prior to or at the time of PV diagnosis, arterial thrombosis occurred in 16% of patients and 7% had venous thrombotic events, which could involve unusual sites, such as splanchnic veins. PV is also associated with an increased bleeding risk, especially in patients with acquired von Willebrand disease, which can occur with extreme thrombocytosis (platelet count, $\geq 1000 \times 10^9$/L). All patients with PV should receive therapeutic phlebotomy (goal hematocrit, <45%) and low-dose aspirin (if no contraindications). Patients who are at higher risk of thrombosis include those aged 60 years or older or with a prior thrombosis. These patients and those with persistent PV symptoms may benefit from cytoreductive therapy with hydroxyurea or interferon to lower thrombosis risk and decrease symptoms. Ruxolitinib is a Janus kinase inhibitor that can alleviate pruritus and decrease splenomegaly in patients who are intolerant of or resistant to hydroxyurea. About 12.7% of patients with PV develop myelofibrosis and 6.8% develop acute myeloid leukemia.

**CONCLUSIONS AND RELEVANCE** PV is a myeloproliferative neoplasm characterized by erythrocytosis and is almost universally associated with a *JAK2* gene variant. PV is associated with an increased risk of arterial and venous thrombosis, hemorrhage, myelofibrosis, and acute myeloid leukemia. To decrease the risk of thrombosis, all patients with PV should be treated with aspirin and therapeutic phlebotomy to maintain a hematocrit of less than 45%. Cytoreductive therapies, such as hydroxyurea or interferon, are recommended for patients at high risk of thrombosis.

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Polycythemia vera (PV) is a chronic myeloproliferative neoplasm characterized by clonal proliferation of myeloid cells leading to increased red blood cell mass. An acquired activating Janus kinase 2 (*JAK2*) gene variant is present in more than 95% of patients with PV.[1] The annual incidence of PV in the US is estimated to be approximately 0.5 to 4.0 per 100 000 people, with an estimated prevalence of 65 000 people. The median age at diagnosis is 65 years, with a slightly higher incidence among men (male to female incidence ratio, 1.3-1.6).[2] Risk factors for PV include tobacco smoking, exposure to ionizing radiation, and certain environmental hazards, such as benzene, although most patients have no known toxic exposure.[3,4] Although *JAK2* gene variants are acquired, there may be inherited predispositions that promote the development of PV, as evidenced by an approximately 5-fold risk of PV among first-degree relatives.[5]

The primary complications leading to morbidity and mortality in PV are arterial and venous thrombosis, which occur in 16% and 7% of persons, respectively, before or at the time of diagnosis. After diagnosis, arterial thrombosis develops in an additional 12% and venous thrombosis in an additional 9% of patients with PV.[1,6-8] Furthermore, patients with PV are at increased risk of bleeding and bruising, especially in those with extreme thrombocytosis (platelet count, $\geq 1000 \times 10^9$/L) and acquired von Willebrand disease. Approximately 12.7% of patients with PV progress to myelofibrosis and 6.7% develop acute myeloid leukemia (AML).[9] This review summarizes current evidence regarding the diagnosis and management of PV (**Box**).

## Methods

We searched PubMed and the Cochrane databases for English-language studies published January 1, 2000, through September 1, 2024, for randomized clinical trials, meta-analyses, systematic reviews, epidemiologic studies, and observational studies (search terms

**Box. Frequently Asked Questions About Polycythemia Vera (PV)**

**How Is PV Distinguished From Secondary Erythrocytosis?**
More than 95% of patients with PV have a sequence variant in *JAK2*, which can distinguish PV from secondary erythrocytosis. In addition, patients with PV typically have low (or normal) serum erythropoietin levels, while secondary erythrocytosis is associated with an increased erythropoietin level.

**What Are Potential Complications of PV?**
Thrombosis, both arterial and venous, occurs in approximately 30% of patients with PV and is associated with increased morbidity and mortality. Patients with PV are also at increased risk of bleeding and developing myelofibrosis and acute myeloid leukemia. Symptoms of aquagenic pruritus, erythromelalgia, and fatigue may also occur and can negatively affect a patient's quality of life.

**How Is PV Treated?**
All patients with PV should undergo therapeutic phlebotomy to decrease hematocrit to less than 45% and receive low-dose aspirin (75-100 mg per day), unless they have a contraindication. Cytoreductive therapy with hydroxyurea or interferon-based therapy is indicated for patients at high risk of thrombosis or for those with persistent bothersome PV symptoms. The JAK1/JAK2 inhibitor ruxolitinib can be given as second-line treatment for patients intolerant of or resistant to hydroxyurea.

are reported in the eAppendix in the Supplement). Article references were also manually reviewed to identify additional sources. Systematic reviews and large observational studies were included when higher-quality evidence was lacking. Of 639 articles retrieved and reviewed, a total of 63 were included, consisting of 3 meta-analyses, 9 randomized clinical trials, 1 nonrandomized single-group interventional trial, 9 observational cohort studies, 3 case-control studies, 2 cross-sectional studies, 7 guidelines, 1 systematic review, 8 preclinical or translational studies, and 20 retrospective cohort studies.

## Pathophysiology

PV causes erythrocytosis (hemoglobin >16.5 mg/dL in men or >16.0 mg/dL in women) and is associated with a low serum erythropoietin. The underlying cause of the myeloproliferative phenotype is a *JAK2* gene variant resulting in replacement of guanine with thymine that causes a substitution of valine to phenylalanine at codon 617 within the pseudokinase domain within exon 14 (*JAK2* V617F).[10-13] This *JAK2* gene variant activates signaling cascades including JAK-STAT, and increases the sensitivity of erythroid precursor cells to erythropoietin.[11] Because the *JAK2* V617F sequence variant has been detected in pluripotent hematopoietic stem cells, it may also cause leukocytosis and thrombocytosis.[14] Other gain-of-function *JAK2* sequence variants affecting exon 12 can be detected in patients with PV who lack *JAK2* V617F, particularly in patients with prominent erythrocytosis without thrombocytosis or leukocytosis.[15]

The *JAK2* sequence variant can arise early in life, although gene lineage studies have suggested the mean time between a person acquiring the *JAK2* sequence variant and diagnosis of PV is 30 years (range, 11 to 54 years).[16,17] A *JAK2* V617F variant was detected in approximately 3.1% of the general population of Denmark without blood cell count abnormalities.[18] For these individuals, the *JAK2* sequence variant may represent clonal hematopoiesis of indeterminate potential, which was associated with an elevated risk of incident coronary heart disease compared with those without the sequence variant (hazard ratio [HR], 12.0 [95% CI, 3.8-34.4]) across 4 case-control studies (4726 cases with coronary heart disease and 3529 controls).[19]

The increased risk of developing thrombotic events in PV is multifactorial, including increased blood viscosity due to increased number of red blood cells.[20] Bleeding is often associated with the development of acquired von Willebrand disease, which can occur with extreme thrombocytosis (platelet count, $\geq 1000 \times 10^9$/L), present in 4% of patients with PV, and can be exacerbated by taking aspirin or anticoagulants.[1,21]

## Clinical Presentation

Symptoms of PV may include intense itching or a prickling sensation in response to water of any temperature (aquagenic pruritus), which occurs in approximately one-third of patients at diagnosis. Other clinical findings include erythromelalgia (5.3%), transient visual changes (14%), and splenomegaly (36%), which can cause abdominal discomfort.[1,22,23] Prior to or at the time of PV diagnosis, arterial thrombosis occurs in 16% of patients and venous thrombosis occurs in 7% of patients and can occur at unusual sites, such as splanchnic veins.[1] Arterial thrombosis includes acute coronary syndrome (8.3%) and cerebrovascular events (7.7%), while venous thrombosis includes deep vein thrombosis (4.2%) and pulmonary embolism (2.0%).[24] Venous thromboses in patients with PV can occur at atypical sites, including the splanchnic vasculature (14.5% of all thromboses), the hepatic vein (Budd-Chiari syndrome) or portal vein, as well as the cerebral venous sinus (2.7%).[25,26]

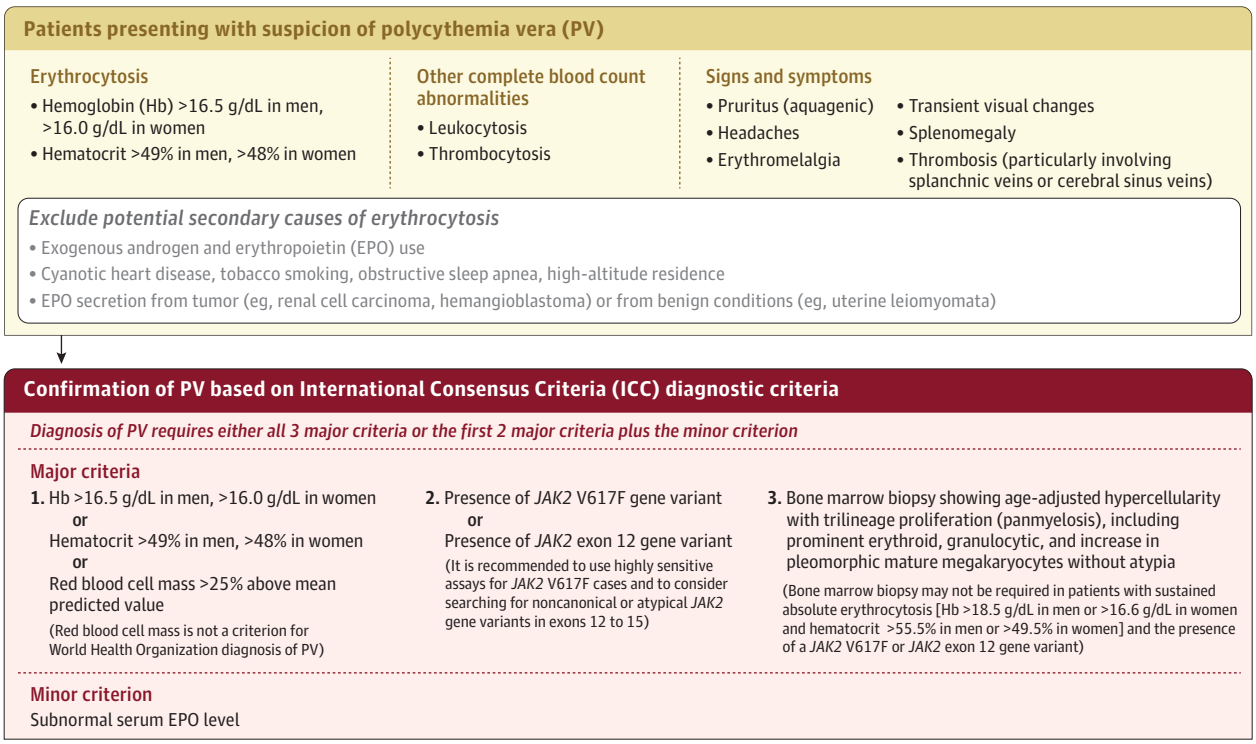
## Diagnosis and Risk Stratification for Thrombosis

The World Health Organization (WHO) and International Consensus Criteria have established diagnostic criteria for PV, last updated in 2022.[27,28] Erythrocytosis is a required diagnostic criterion (not present in other myeloproliferative disorders) with specific hemoglobin and hematocrit levels for men (>16.5 g/dL and >49%) and women (>16.0 g/dL and >48%).[27,28] Among 1545 patients with PV from 3 countries (Italy, Austria, and the US), the median hematocrit was 55%, thrombocytosis ($\geq 450 \times 10^9$/L) was noted in 53% of patients, and leukocytosis ($\geq 10.5 \times 10^9$/L) in 49% of patients.[1]

PV should be distinguished from spurious polycythemia, which is generally not persistent and is caused by a contracted plasma volume with a normal red blood cell mass (as measured by radiolabeling). PV should also be distinguished from secondary forms of erythrocytosis, which are caused by conditions that result in elevated levels of erythropoietin, such as cyanotic heart disease, tobacco smoking, obstructive sleep apnea, high-altitude residence, or secretion from certain benign conditions (eg, uterine leiomyomata) or malignant tumors (eg, renal cell carcinoma or hemangioblastoma). Exogenous androgen and erythropoietin used for athletic performance enhancement are also associated with erythrocytosis. Spurious and secondary erythrocytosis are not associated with pruritus, leukocytosis, or thrombocytosis.

Many patients with erythrocytosis do not have PV. In a cohort study (147 168 persons) of the general population aged 18 years or older in the Netherlands, 3.4% (7.6% of males and 0.4% of females), had erythrocytosis defined as hemoglobin greater than 16.5 g/L in males and greater than 16.0 g/L in females.[29] A subset of those with the most severe erythrocytosis (>18.5 g/L in males or >16.5 g/L in females) and either leukocytosis (white blood cell [WBC] count,

Figure 1. Evaluation of Suspected Polycythemia Vera




Possible etiologies of secondary erythrocytosis are not exhaustive. Listed diagnostic criteria are from the International Consensus Classification.[27]

≥11 × $10^9$/L) and/or thrombocytosis (platelet count, ≥450 × $10^9$/L) were matched 1:2 to those with isolated erythrocytosis (N = 133 persons). Among patients with evaluable *JAK2* variation studies, 7 of 45 persons (15.6%) who had severe erythrocytosis with leukocytosis and/or thrombocytosis had *JAK2* gene variants compared with 0 of 88 with isolated severe erythrocytosis.[29]

Patients with erythrocytosis and a low erythropoietin level, along with all patients who have thrombosis in the splanchnic vasculature[30] or cerebral sinus, should undergo genetic testing for a *JAK2* gene variant. Despite a negative *JAK2* test result, about 2% of individuals with PV are diagnosed based on erythrocytosis, a low erythropoietin level, and absence of secondary causes or hereditary causes of erythrocytosis, such as sequence variations in the erythropoietin receptor or the von Hippel–Lindau gene. Bone marrow biopsy, a major criterion for WHO diagnosis of PV, is recommended but not required in persons with sustained absolute erythrocytosis (typically 3 months or longer) at a higher threshold than diagnostic criteria (hemoglobin concentrations of >18.5 g/dL in men or >16.5 g/dL in women) and a *JAK2* gene variant. **Figure 1** outlines the diagnostic evaluation of PV.

After diagnosis of PV, patients should undergo an assessment of their risk of thrombosis, which affects prognosis and treatment decisions about cytoreductive therapy. High-risk PV is defined by the National Comprehensive Cancer Network (NCCN) and European LeukemiaNet guidelines as those patients aged 60 years or older or with prior arterial or venous thrombosis. Low-risk patients are 60 years or younger without a history of arterial or venous thrombosis.[22,31,32] Based on a multivariable model from a study of 1638 patients with PV, the relative risk (RR) for cardiovascular events progressively increases with age older than 65 years (age 66-75 years, RR, 2.08 [95% CI, 1.25-3.45]) and for those with prior thrombosis (RR, 2.09 [95% CI, 1.55-2.81]).[22]

The degree of thrombocytosis is not a risk factor for thrombosis in patients with PV.[33] However, a prospective study of 2510 patients with PV reported that thrombotic events were associated with WBC count greater than 11 × $10^9$/L (HR, 2.35 [95% CI, 1.60-3.47]; $P$ < .001) and hematocrit greater than 45% (HR, 1.84 [95% CI, 1.23-2.75]; $P$ = .01) over a median follow-up of 44.7 months.[7] In a study of 533 patients with PV treated with hydroxyurea, those who required 3 or more phlebotomies per year had a higher rate of thrombosis compared with those who required 0 to 2 phlebotomies per year (20.5% vs 5.3% at 3 years; $P$ < .001).[34]

The *JAK2* V617F allele burden has prognostic information about risk of thrombosis and myelofibrosis in patients with PV. The allele burden is obtained by extracting DNA from cells and then analyzing the *JAK2* region to quantify the percentage (0% to 100%) of *JAK2* sequencing reads that contain the *JAK2* V617F gene variant. It is typically measured from the peripheral blood, but can also be assessed from bone marrow aspirate. In an observational cohort study of 856 patients with PV, a *JAK2* V617F allele burden of 50% or higher was associated with an increased risk of venous thrombosis (14.5% vs 2.4%; HR, 3.8 [95% CI, 1.7-8.6]).[35] In a prospective study of 338 patients with PV, *JAK2* V617F allele burden of 50% or higher was also a risk factor for progression to myelofibrosis (10.5% vs 1.2%; $P$ = .03).[36]

## Treatment

### Therapeutic Phlebotomy

All patients with PV should undergo therapeutic phlebotomy to maintain hematocrit of less than 45%, as recommended by the NCCN

Table. Available Cytoreductive Therapies for the Treatment of Polycythemia Vera (PV)

| Agent name | Mechanism of action | Typical starting dose | Route of administration | Efficacy from clinical trials | Notable adverse effects (%) |
|---|---|---|---|---|---|
| **Treatment naive** | | | | | |
| Hydroxyurea[a] | Ribonucleotide reductase inhibitor | 500 mg daily | Oral | Complete hematologic response of 30% at 12 mo[40,b] | Mucositis (16), headache (15), dizziness (11), rash (10), anorexia (10), edema (10) |
| Pegylated interferon alfa-2a[a] | Immunomodulator | 45 µg once weekly | Subcutaneous | Complete hematologic response of 28% at 12 mo[40,b] | Headache (26), injection site reaction (22), flu-like symptoms (24), peripheral neuropathy (20), pruritus (19), depression (15), ALT increase (14) |
| Ropeginterferon alfa-2b[c] | Immunomodulator | 100 µg every 2 wk | Subcutaneous | Complete hematologic response of 43% at 12 mo[b]<br>Complete hematologic response of 51% at 36 mo[41,b] | GGT elevation (24), ALT increase (17), arthralgia (13), AST increase (12) |
| **Hydroxyurea resistant/intolerant** | | | | | |
| Pegylated interferon alfa-2a[a] | Immunomodulator | 45 µg once weekly | Subcutaneous | Complete hematologic response of 22%[42,b] | Diarrhea (40), injection site reaction (34), headache (26), nausea (24), pruritus (22), edema (18), flu-like symptoms (18), arthralgia (14), dizziness (14), constipation (14), ALT increase (10) |
| Ruxolitinib[c] | JAK1/JAK2 inhibitor | 10 mg twice daily | Oral | Hematocrit control in 60%<br>Spleen volume reduction by ≥35% in 38%[43] | Headache (16), diarrhea (15), pruritus (14), dizziness (12), muscle spasms (12), dyspnea (10) |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase.

[a] Off-label use for PV.

[b] Complete hematologic response is hematocrit <45%; platelet count <400 × $10^9$/L; and white blood cell count <10 × $10^9$/L.

[c] US Food and Drug Administration approved for PV.

based on the Cytoreductive therapy in PV (CYTO-PV) study.[37] This trial randomized 365 patients with PV to a hematocrit goal of less than 45% or 45% to 50% achieved by therapeutic phlebotomy (68% of patients; initiated at 250-500 mL of blood every other day or twice per week until the hematocrit goal was reached) and/or cytoreductive therapy (52.6% of patients; typically hydroxyurea at an initial dose of 500-1000 mg daily). The primary end point of cardiovascular death or major thrombosis was 2.7% in the hematocrit less than 45% group vs 9.8% in the hematocrit 45% to 50% group ($P$ = .007).[31,37] Although females typically have lower baseline hematocrit levels than males, lower hematocrit targets for females with PV have not been rigorously evaluated. In addition, although thrombosis may be more common in patients residing at high altitude (>5000 ft, 1524 m)[38] because chronic hypoxia causes higher hematocrit levels, adjustments in treatment targets for those with PV living at high altitude have not been prospectively studied.

### Antiplatelet Agents

Low-dose aspirin (75-100 mg per day) is recommended for all patients with PV without contraindications for use of antiplatelet medications. In a trial of 518 patients with PV without another indication for antiplatelet therapy (such as stroke prevention or coronary artery disease), patients randomized to aspirin, 100 mg, daily had a reduced risk of the combined primary end point of nonfatal myocardial infarction, nonfatal stroke, venous thromboembolism, or death from cardiovascular causes compared with placebo (3.2% vs 7.9%; $P$ = .03).[39] However, this study did not report a significant difference in overall or cardiovascular-specific mortality and there was a nonsignificant increase in major bleeding (1.2% vs 0.8%) in the aspirin group.[39]

There are currently no published studies about use of clopidogrel or other P2Y12 inhibitors for primary thromboprophylaxis in patients with PV. For patients with a thrombotic event, there are currently no data to guide the selection or appropriate duration of anticoagulation. Concurrent aspirin and anticoagulation therapy in patients with PV was associated with an increased risk of bleeding (HR, 5.83 [95% CI, 3.36-10.11]; $P$ < .001).[21] Therefore, clinicians often stop aspirin therapy when prescribing anticoagulation, although this strategy has not been prospectively analyzed.

## Cytoreductive Therapies

Cytoreductive therapies, which reduce blood cell counts and decrease thrombosis risk, include hydroxyurea, interferon formulations (ropeginterferon alfa-2b and pegylated interferon alfa-2a), and ruxolitinib (**Table**). Cytoreductive therapy can be used in addition to aspirin and therapeutic phlebotomy and is indicated for patients at high thrombotic risk (eg, those aged 60 years or older or those with prior arterial or venous thrombosis) and can be considered for low-risk patients with PV who have persistent headaches, dizziness, difficulty concentrating, uncontrolled pruritus, or splenomegaly despite use of antiplatelet therapy and therapeutic phlebotomy. In a randomized trial of 127 low-risk patients with PV, the frequency of moderate to severe symptoms in the phlebotomy and aspirin group increased from 43% to 67% after 24 months, while those randomized to ropeginterferon alfa-2b, phlebotomy, and aspirin had a reduction in moderate to severe symptoms from 39% to 33% ($P$ value not reported).[44]

The NCCN and European LeukemiaNet guidelines also recommend cytoreductive therapy for low-risk patients with PV who have persistent leukocytosis and/or thrombocytosis[31,45]; however, the white blood cell and platelet threshold to initiate therapy and the efficacy of cytoreductive therapy for thrombosis prevention in those with leukocytosis or thrombocytosis has not been fully established. Patients undergoing cytoreductive therapy should continue to receive aspirin and therapeutic phlebotomy with a goal hematocrit of less than 45%.

NCCN guidelines recommend either hydroxyurea or interferon formulations for high-risk patients with PV.[31] The choice of agents should be individualized based on patient preference,

personal goals of therapy (eg, reduction in symptom burden), and potential adverse events associated with these medications.

### Hydroxyurea

Hydroxyurea is a daily oral medication that is typically started at a dose of 500 mg twice daily and may be titrated up to 1000 mg twice daily. Hydroxyurea is generally well-tolerated but is contraindicated in patients who are pregnant or attempting to conceive because of its teratogenic effects in animal studies. Adverse effects of hydroxyurea may include mucositis, skin ulcers, and hair thinning.[40] In addition, there is an increased risk of nonmelanoma skin cancer associated with hydroxyurea (odds ratio, 2.28 [95% CI, 1.15-4.51]), based on a nested case-control study of 127 cases and 244 controls.[46]

A propensity score–matched retrospective analysis of 681 patients with PV treated with hydroxyurea matched to 342 patients with PV treated with phlebotomy alone reported a significantly lower number of fatal and nonfatal cardiovascular events in patients treated with hydroxyurea vs phlebotomy (3.0 vs 5.8 per 100 person-years; $P = .002$). However, this benefit was seen only in patients with PV at high risk of thrombosis.[47]

Approximately 15% of patients with PV treated with hydroxyurea have intolerance of or resistance to hydroxyurea, defined as the need for therapeutic phlebotomy; platelet count of greater than $400 \times 10^9$/L; WBC count of greater than $10 \times 10^9$/L; failure to alleviate symptoms related to splenomegaly after at least 3 months of hydroxyurea at a dose of a minimum of 2000 mg per day; or development of neutropenia, anemia, or thrombocytopenia at the lowest dose required to achieve a complete hematologic response (hematocrit <45%; platelet count $<400 \times 10^9$/L; and WBC count $<10 \times 10^9$/L).[48] Patients who develop resistance to or are intolerant of hydroxyurea should be treated with second-line therapy, such as interferons or ruxolitinib.[49]

### Interferons

Two interferon formulations are currently available for patients with PV: ropeginterferon alfa-2b (US Food and Drug Administration approved) and pegylated interferon alfa-2a (off-label). Ropeginterferon alfa-2b is administered subcutaneously every 2 weeks and pegylated interferon alfa-2a is administered subcutaneously weekly. Interferon dosing is uptitrated over months to achieve complete hematological response. For patients with PV who are pregnant or attempting to conceive, pegylated interferon alfa-2a has demonstrated safety.[50]

Use of interferons is associated with increased risk of depression and anxiety, so should be avoided in patients with these mental health conditions. Interferons should also not be prescribed to patients with severe or untreated autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, due to the risk of exacerbating these conditions. Adverse effects of interferons may include headache, injection site reactions, elevated serum alanine aminotransferase, peripheral neuropathy, and flu-like symptoms (Table).[40]

In an open-label trial of 127 low-risk patients with PV, the primary end point of hematocrit control less than 45% without disease progression was more common among those randomized to receive ropeginterferon alfa-2b with phlebotomy (81.3%) compared with phlebotomy alone (59.7%; $P < .001$).[44] Ropeginterferon alfa-2b was also associated with decreased disease progression over 12 months compared with phlebotomy and aspirin alone (0% vs 12.7%; $P < .001$), although disease progression events in the comparator group were primarily thrombocytosis (9.5%) and no patients progressed to myelofibrosis in either group. Adverse events were more common in the ropeginterferon alfa-2b group, including grade 3 or 4 neutropenia in 9% of patients.[44] Pegylated interferon alfa-2a was evaluated in a single-group interventional trial of 50 patients with PV who were resistant to or intolerant of hydroxyurea and 60% had a complete hematologic response at 12 months.[42]

#### Studies Comparing Hydroxyurea With Interferon-Based Therapies

Two randomized trials have compared hydroxyurea with interferon-based therapies specifically in patients with PV. The Myeloproliferative Neoplasm Research Consortium (MPN-RC) 112 study randomized 87 patients with PV to pegylated interferon alfa-2a or hydroxyurea.[40] Complete response at 12 months (defined as complete hematologic response and resolution of both splenomegaly and disease-related symptoms, such as microvascular symptoms, headaches, and pruritus) did not differ significantly between the groups (28% with pegylated interferon alfa-2a vs 30% with hydroxyurea [$P = .86$]). Mild to moderate depression was more common among patients treated with pegylated interferon alfa-2a (15%) compared with hydroxyurea (3%).

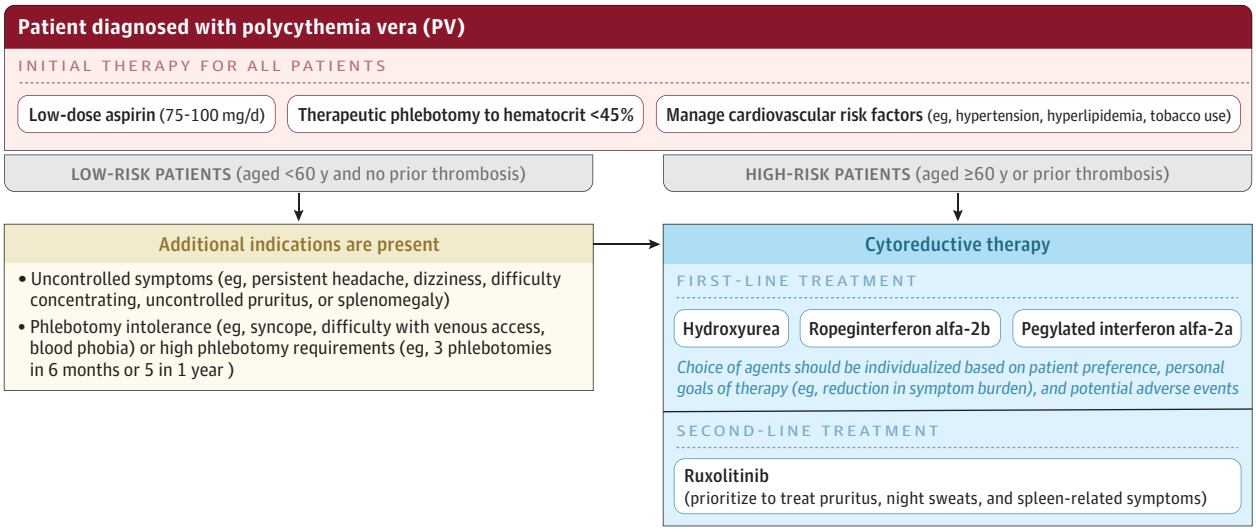
A phase 3 randomized study of 254 patients with early-stage PV (defined as no prior use of cytoreductive treatment or less than 3 years of hydroxyurea treatment) reported no difference in complete hematologic response rates at 12 months with ropeginterferon alfa-2b vs hydroxyurea (43% vs 46%; $P = .63$).[41] However, there was an improved hematologic response at 36 months with ropeginterferon alfa-2b vs hydroxyurea (67/95 [71%] vs 38/74 [51%]; $P = .01$) in 171 patients who participated in the extension phase of the trial.[41] At the conclusion of the trial, 169 patients were followed up as they continued their treatment for 5 additional years; patients treated with ropeginterferon alfa-2b had a 94% event-free survival rate (thrombosis, disease transformation, or death) compared with the control group, which had an 82% event-free survival rate ($P = .04$).[51]

### Ruxolitinib

The JAK1/JAK2 inhibitor ruxolitinib is an oral medication, typically started at 10 mg twice a day, and can be titrated up to 25 mg twice a day. Ruxolitinib is generally well-tolerated, but is associated with weight gain and an increased risk of herpes zoster infection (approximately 4% of treated patients) likely due to the immunosuppressive effects of ruxolitinib.[52] Therefore, administration of a recombinant vaccine against herpes zoster is recommended prior to initiation of ruxolitinib.[31] Ruxolitinib use has also been associated with an increased risk of nonmelanoma skin cancers (5.1 per 100 patient-years in patients treated with ruxolitinib compared with 2.7 in those treated with other therapy [$P$ value not reported]).[53]

Several randomized clinical trials have demonstrated benefits of ruxolitinib in patients previously treated with hydroxyurea. A trial of 222 patients with PV and splenomegaly who were intolerant of or resistant to hydroxyurea were randomized to either ruxolitinib or investigator-selected best-available cytoreductive therapy at a dose tolerated by the patient. The primary composite end point of hematocrit control (<45%) and spleen size reduction (at least 35% by imaging at 32 weeks) was attained in 20.9% of patients treated with

Figure 2. Treatment of Polycythemia Vera




Of note, hydroxyurea and ruxolitinib are teratogenic in animal models, while interferons have demonstrated safety in pregnant patients with PV. This algorithm has not been validated in clinical trials.

ruxolitinib vs 0.9% in the standard therapy group (hydroxyurea, interferon, lenalidomide, thalidomide, pipobroman, or no therapy). A greater than 50% reduction in the 14-item Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score occurred in 49% of patients treated with ruxolitinib vs 5% in the standard therapy group (*P* value not reported), with improvements mostly in pruritus, night sweats, and early satiety.[43] In addition, an open-label study of 173 patients with PV without splenomegaly reported a significant improvement in hematocrit control with ruxolitinib vs standard therapy at week 28 (62% vs 19%; *P* < .001).[54]

A 2023 study that randomized 180 patients who were resistant to or intolerant of hydroxyurea for PV to ruxolitinib vs best-available therapy reported a complete hematologic response and normalization of spleen size at 1 year (43% vs 26%, respectively; *P* = .02) and symptom improvement (61% vs 30%, respectively; *P* = .001).[55] This study also demonstrated superiority in event-free survival (major thrombosis, hemorrhage, transformation, and death) with ruxolitinib compared with best-available therapy (HR, 0.58; *P* = .03; absolute rates not given), largely due to a reduction in the number of thrombotic events (HR, 0.56; *P* = .05; absolute rates not given). In addition, mutational response (≥50% reduction in *JAK2* V617F allele burden) was higher with ruxolitinib (56% vs 25%; *P* < .001), which was associated with a reduced rate of progression (39% vs 11%; *P* = .001) and improved event-free (54% vs 25%; *P* = .001) and overall (24% vs 8%; *P* = .01) survival during follow-up.[55]

However, a phase 3b double-blind study of 110 patients with PV taking hydroxyurea who had PV-related symptoms reported no significant difference with ruxolitinib vs placebo at 16 weeks for the primary end point of a 50% reduction in patient symptom scores for tiredness, itching, muscle aches, night sweats, and sweats while awake (43.3% with ruxolitinib vs 29.6% with placebo [*P* = .14]).[56]

The Table summarizes the typical dosing, efficacy, and adverse events associated with the above cytoreductive therapies; **Figure 2** details the current treatment paradigm for PV.

## Prognosis

In an international multicenter study (7 centers, 1545 patients), the median age at diagnosis was 61 years, with a median survival after PV diagnosis of 14.1 to 27.6 years in the 5 centers that reached median survival.[1] When including all 7 centers in a survival analysis, the median survival was 18.9 years, which did not differ (*P* = .14) compared with individuals of the same age and sex from a US total population. Factors associated with reduced survival included age 67 years or older (HR, 8.5 [95% CI, 5.7-12.6]), WBC count of 15 × $10^9$/L or greater (HR, 2.2 [95% CI, 1.6-3.0]), and prior venous thrombosis (HR, 1.8 [95% CI, 1.1-2.8]).[1] In a US cohort study evaluating patients from 1967 to 2017, those younger than 40 years at diagnosis (361 patients) had a median overall survival of 37 years.[57] Additionally, in a study of 404 patients with PV, gene variants in serine/arginine-rich splicing factor 2 (*SRSF2*), which control splicing of pre-mRNAs, have been associated with reduced survival compared with patients without these sequence variants (HR, 13.3 [95% CI, 4.3-35.3]).[58]

PV may evolve to myelofibrosis and acute myeloid leukemia. In a cohort of 267 patients with PV with a follow-up time of 11.8 years, 12.7% of patients developed myelofibrosis and 6.7% developed AML.[9] Survival after transformation to myelofibrosis was approximately 8.1 years.[59] Factors associated with an increased risk of myelofibrosis or AML included persistent leukocytosis,[60] *JAK2* V617F allele burden of 50% or higher (10.5% vs 1% risk of transformation to myelofibrosis or AML),[36] sequence variants in *SRSF2* or *IDH2*,[61] and gain of chromosome 1q.[62] A bone marrow biopsy, while not required for diagnosis of PV, may identify baseline bone marrow fibrosis, which is associated with an increased risk of progression to myelofibrosis.[63]

## Limitations

This review has limitations. First, the quality of included articles was not formally evaluated. Second, there are no randomized clinical trials involving large numbers of patients with sufficient follow-up times to assess the effect of any particular therapeutic approach on

overall survival to a high degree of certainty. Third, some articles may have been missed.

## Conclusions

PV is a clonal myeloproliferative neoplasm that causes erythrocytosis and is typically associated with a *JAK2* gene variant. Patients with PV have increased risk of arterial and venous thrombosis, hemorrhage, stroke, myocardial infarction, myelofibrosis, and acute myeloid leukemia. All patients with PV should be treated with aspirin (if no contraindications) and therapeutic phlebotomy to maintain a hematocrit below 45% to decrease the risk of thrombosis. Cytoreductive therapies, such as hydroxyurea or interferon, are recommended for patients with PV at high risk of thrombosis.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