
Insights from the MPN Practice Perspectives Survey of hematologists/oncologists (N=1550)

Presented by **Raajit Rampal, MD, PhD,** MPN Expert

**POLYCYTHEMIA VERA (PV)**

# OPTIMIZING MANAGEMENT FOR THE RISK OF THROMBOSIS IN PATIENTS WITH PV

MPN
Practice Perspectives Survey

MPN=myeloproliferative neoplasm.

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# Introduction

To gain real-world practice perspectives on the management of PV, in partnership with Incyte, we recently conducted the MPN Practice Perspectives Survey over 6 months with hematologists/oncologists across the United States. We conducted this survey to better understand current patterns of monitoring Hct and WBCs to reduce risk of thrombosis and optimize management in patients with PV.

The survey uncovered some interesting trends regarding reduction in the risk of thrombosis: Many respondents do not prioritize monitoring WBC counts, allow WBC counts above 11,000, and allow a maximum Hct level above 45%.

To optimize management of PV, it is critical to address signs of uncontrolled myeloproliferation that put patients at risk for thrombosis—a leading cause of disease-related mortality. These signs require close monitoring and proactive management of blood counts that are proven risk factors for thrombosis—particularly elevated levels of Hct greater than 45% and WBC counts above $11 \times 10^9$/L.[1-6]

In this review, I will share the survey results and provide my perspectives on implementing an evidence-based strategy to lower the risk of a thrombotic event.

### Key points

- Assessing and actively managing patients with PV for the **risk of thrombosis**[1-5]
- Importance of managing WBC counts **below** $11 \times 10^9$/L[4,6]
- Importance of managing **strict** Hct control <45%[2,6]

Hct=hematocrit; WBC=white blood cell.

# Active management of Hct and WBC counts to reduce the risk of thrombosis

Preventing thrombotic events through proper management of blood counts and treatment optimization should be considered the primary goal in caring for patients with PV. Thrombotic events can be attributed independently to either RBCs or WBCs, as elevated Hct >45% and WBC counts >11 × $10^9$/L have been shown to be associated with an increase in the risk of thrombosis.[1-6]

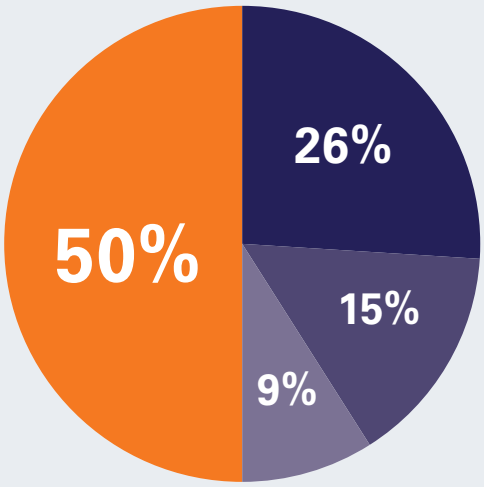
The first survey question asked hematologists/oncologists, "When it comes to managing for the risk of thrombosis, which counts are you most concerned about?" As we see below, nearly all respondents identified Hct as a concern, which is encouraging. However, results also showed that more than one-third of respondents did not select an answer that included WBC counts. This response stood out to me because clinical evidence tells us that elevated WBCs are directly correlated with an increase in thrombotic risk and should be closely monitored.[1-6] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) also recognize leukocytosis as a factor indicating whether to implement cytoreductive therapy in patients with low-risk PV or to change cytoreductive therapy in high-risk patients.[7] In my practice, I follow this evidence-based approach of managing WBC counts <11 × $10^9$/L and strict Hct control <45%, and I encourage you all to, as well, in an effort to reduce the risk of a thrombotic event.

**MPN Practice Perspectives PV Survey—Question 1**

**Managing for the risk of thrombosis is a key treatment goal for patients with PV.**

**When it comes to managing for the risk of thrombosis, which counts are you most concerned about?**

- Hct, PLT, & WBC
- Hct & PLT
- Hct & WBC
- Hct only




More than **1/3** of HCPs do not prioritize monitoring WBC counts for the risk of thrombosis

"In my practice, I follow an evidence-based approach of **managing WBC counts <11 × $10^9$/L and strict Hct control <45%,** and I encourage you all to, as well, in an effort to **reduce the risk of a thrombotic event."**

**Raajit Rampal, MD, PhD,** MPN Expert

NCCN=National Comprehensive Cancer Network; PLT=platelet; RBC=red blood cell.

# Active management of WBC counts below 11 × $10^9$/L for the risk of thrombosis

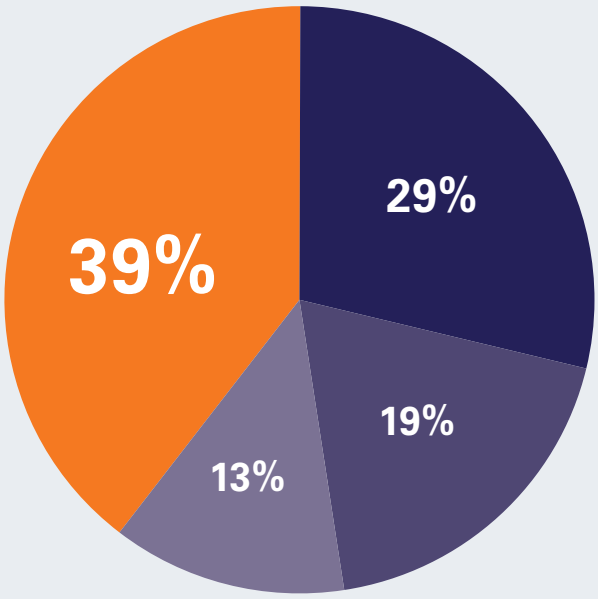
WBC counts are an independent risk factor for thrombosis and should be monitored and actively managed in patients with PV. In my practice, when a patient shows a progressive increase in WBC counts above 11 × $10^9$/L, that is an indicator that my patient needs a change in treatment.[4]

When asked about the maximum WBC counts physicians would allow when managing for the risk of thrombosis in patients with PV, the majority of respondents—approximately 60%—stated that they either do not manage WBC counts for the risk of thrombosis or are comfortable if maximum WBC counts exceed 11 × $10^9$/L.

**MPN Practice Perspectives PV Survey—Question 2**

**When it comes to managing for the risk of thrombosis, what is the maximum WBC count you would allow for your patients with PV?**

- I try to keep them ≤11 × $10^9$/L
- I do not manage WBC counts for the risk of thrombosis
- 11 to 15 × $10^9$/L
- >15 to 20 × $10^9$/L




**~60%** said they would allow WBC counts >11 × $10^9$/L when managing for the risk of thrombosis

"In my practice, when a patient shows a progressive **increase in WBC counts above 11 × $10^9$/L**, that is an indicator that my patient needs a **change in treatment.**"

**Raajit Rampal, MD, PhD,** MPN Expert

This stands out to me, because in a subanalysis of the CYTO-PV study, there was an increased risk of thrombosis when WBC counts were above 11 × $10^9$/L compared to when they were maintained below 7 × $10^9$/L **(Figure 1)**.[4,8,9]

When treating PV, I follow the evidence from studies like CYTO-PV and do everything I can to decrease the risk of thrombosis, including intervening in patients who have elevated WBC counts.

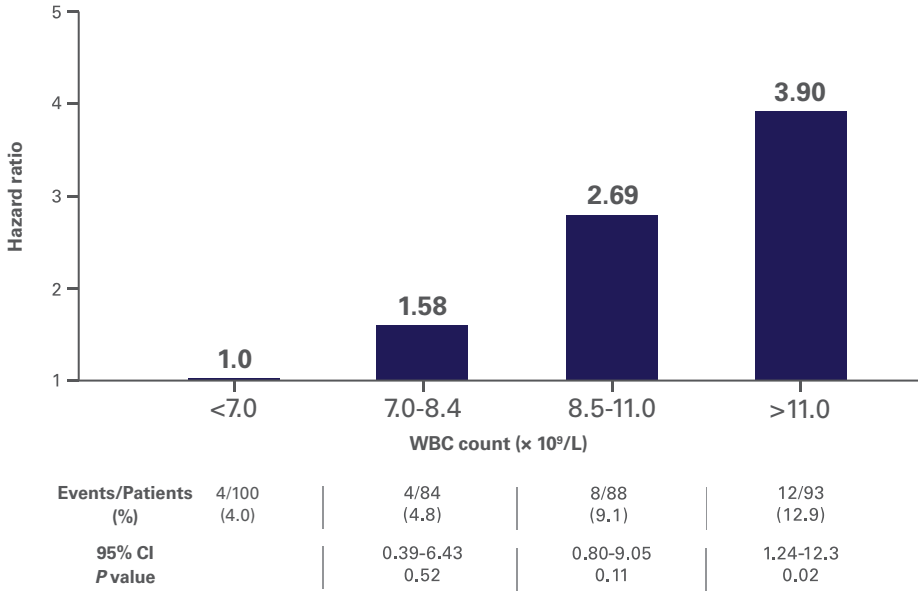
**Figure 1**

## Elevated WBC counts >11 × $10^9$/L increased the risk of thrombosis[4]

- In a multivariable time-dependent analysis, WBC counts >11 × $10^9$/L were associated with an increased risk of thrombosis (HR, 3.9; 95% CI, 1.24-12.3; *P*=0.02)[4]

### Time-Dependent Multivariable Analysis of the Risk of Major Thrombosis in the CYTO-PV Study (N=365)[4,a]

- In this analysis, there was a trend for increased risk of thrombosis with WBC count >7 × $10^9$/L (ie, HR >1) that became statistically significant in patients with WBC counts >11 × $10^9$/L[4]
- These results are consistent with other literature that suggests leukocytosis may increase the risk of thrombosis[8,9]




[a]Adjusted for age, gender, CV risk factors, previous thrombosis, and Hct levels.[4]

"**WBC counts** are an independent risk factor for thrombosis and should be **monitored and actively managed** in patients with PV."

**Raajit Rampal, MD, PhD,** MPN Expert

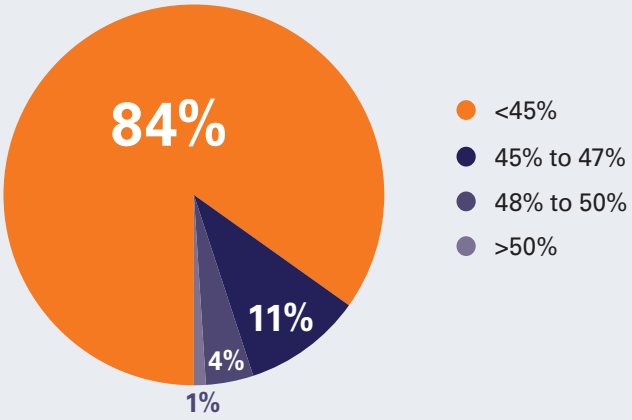
CI=confidence interval; CV=cardiovascular; CYTO-PV=Cytoreductive Therapy in Polycythemia Vera; HR=hazard ratio.

# The importance of strict Hct control <45%

When survey respondents were asked about Hct levels for managing the risk of thrombosis, the vast majority identified a target of <45%. But when we asked what maximum Hct levels healthcare professionals would allow before considering a change in treatment for patients on maximum tolerated doses of HU, 80% of my colleagues stated that they do not do anything differently if the Hct is higher than 45%. This directly conflicts with the results of the CYTO-PV study. The data showed that the rate of CV death and major thrombosis was 4 times higher among patients whose Hct was maintained between 45% and 50% compared to those whose Hct was maintained below 45%.[2]

**MPN Practice Perspectives PV Survey—Question 3**

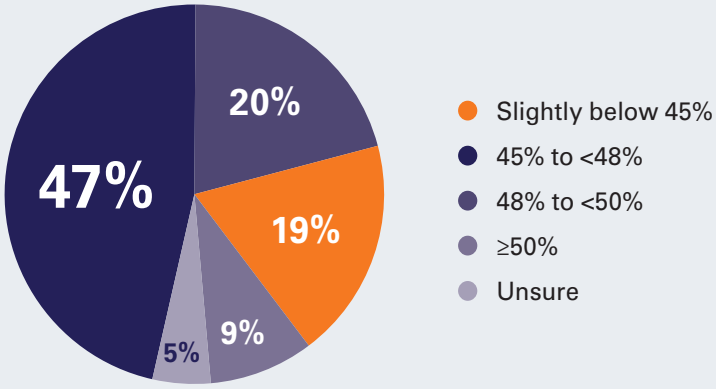
**When managing for the risk of thrombosis, what is your target Hct level for your patients with PV?**




**16%** of respondents don't target strict Hct levels below 45%

**MPN Practice Perspectives PV Survey—Question 4**

**Your patient with PV is on their maximum tolerated dose of HU. What is the maximum Hct level you would allow before changing your management approach?**




**76%** of respondents would allow a maximum Hct level above 45%

"**Any Hct level above 45% should not be accepted** and indicates the need for a **change in treatment**. We don't want to look back on the management of any individual who may experience a thrombotic event and wish we had taken **a more active approach.**"

**Raajit Rampal, MD, PhD,** MPN Expert

HU=hydroxyurea.

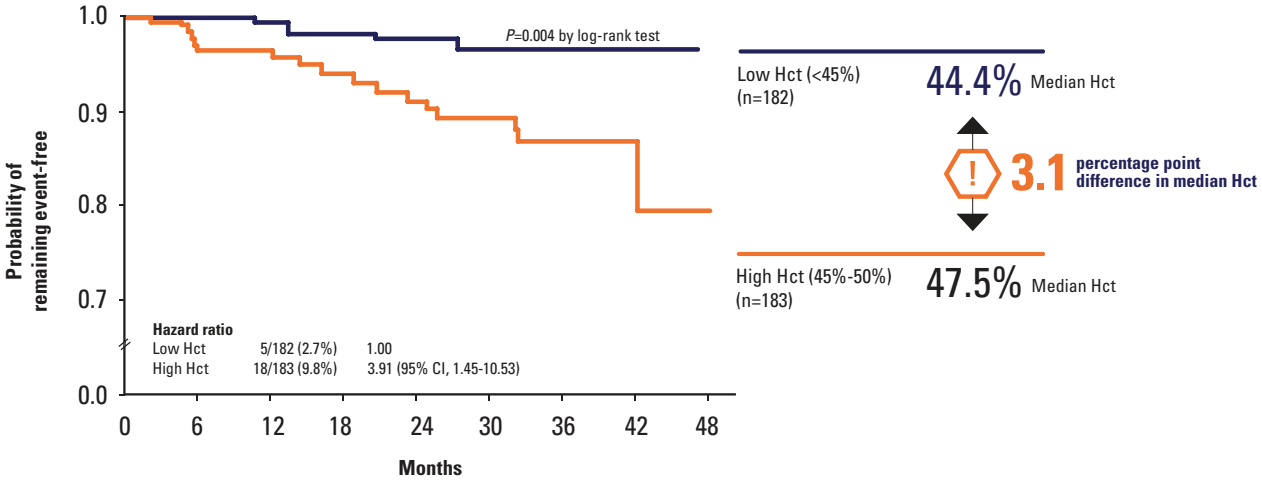
Another thing to consider is the use of phlebotomy. Overuse of phlebotomy may result in iron deficiency **(Figure 2)**. In my practice, if a patient is taking HU, receiving 4 phlebotomies a year, and is unable to maintain strict Hct levels below 45%, I believe it's time for a change in treatment. It is important that we strictly adhere to the 45% threshold, not just as a target but as the maximum we'll allow for patients with PV.[10] Any Hct level above 45% should not be accepted and indicates the need for a change in treatment.[2] We don't want to look back on the management of any individual who may experience a thrombotic event and wish we had taken a more active approach.

**Figure 2**

## Elevated Hct between 45% and 50%: 4x higher rate of CV death and major thrombosis[2]

- A significant increase in the risk of CV death and major thrombosis was demonstrated with Hct levels between 45% and 50% compared with Hct levels of <45% (HR, 3.91; 95% CI, 1.45-10.53; *P*=0.007)[2]*

### Probability of Remaining Event-free in the CYTO-PV Study (N=365)[2]




Kaplan-Meier curves for primary composite endpoint.

From *The New England Journal of Medicine*, Marchioli R, Finazzi G, Specchia G, et al; for the CYTO-PV Collaborative Group, Cardiovascular events and intensity of treatment in polycythemia vera, 368, Page 29. Copyright © 2013 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

*In the CYTO-PV study of 365 adult patients with PV treated with phlebotomy, HU, or both, patients were randomized to 1 of 2 groups: the low-Hct group (n=182; with more intensive therapy to maintain a target Hct level <45%) or the high-Hct group (n=183; with less intensive therapy to maintain a target Hct level of 45% to 50%). Baseline characteristics were balanced between the groups. Approximately 50% of patients had received an initial diagnosis of PV within 2 years prior to randomization. 67.1% of patients (n=245) were at high risk because they were ≥65 years of age or had experienced previous thrombosis. The composite primary endpoint was the time until CV or major thrombosis.[2]

"For patients with PV, we know that **suboptimal control of hematocrit,** which is **anything greater than 45%,** is associated with **significant risks,** even if the Hct is 47% or 48%. **So I typically intervene slightly below 45%."**

**Raajit Rampal, MD, PhD,** MPN Expert

# Conclusion

Thank you to my colleagues who took the time to participate in the MPN Practice Perspectives Survey. I thoroughly enjoyed reviewing the results and providing my perspectives on managing the risk of thrombosis and monitoring blood counts in PV.

We should continue to optimize the management of PV by actively monitoring and managing WBC counts <11 x $10^9$/L and strict Hct control <45% to reduce the risk of thrombosis for these patients.

We cannot leave any factors to chance when patients show signs of disease progression. As soon as Hct or WBC counts rise above the established thresholds we've discussed, a change in treatment strategy is necessary. By following the data and acting promptly, we can optimize our management of the risk of thrombosis in PV.[2,4,6]

## Key points

- Assessing and actively managing patients with PV for the **risk of thrombosis**[1-5]
- Importance of managing WBC counts **below** 11 × $10^9$/L[4,6]
- Importance of managing **strict** Hct control <45%[2,6]

## Find more expert perspectives

about managing for the risk of thrombosis in PV.

**References: 1.** Marchioli R, Finazzi G, Landolfi R, et al. Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. *J Clin Oncol*. 2005;23(10):2224-2232. **2.** Marchioli R, Finazzi G, Specchia G, et al; for CYTO-PV Collaborative Group. Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med*. 2013;368(1):22-33. **3.** Barbui T, Finazzi G, Falanga A. Myeloproliferative neoplasms and thrombosis. *Blood*. 2013;122(13):2176-2184. **4.** Barbui T, Masciulli A, Marfisi MR, et al. White blood cell counts and thrombosis in polycythemia vera: a subanalysis of the CYTO-PV study. *Blood*. 2015;126(4):560-561. **5.** Lu X, Chang R. Polycythemia vera. *StatPearls* [Internet]. StatPearls Publishing; 2024. Accessed August 7, 2024. https://www.ncbi.nlm.nih.gov/books/NBK557660. **6.** Verstovsek S, Passamonti F, Rambaldi A, et al. A phase 2 study of ruxolitinib, an oral JAK1 and JAK2 inhibitor, in patients with advanced polycythemia vera who are refractory or intolerant to hydroxyurea. *Cancer*. 2014;120(4):513-520. **7.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms V1.2024. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed Aug 6, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **8.** Gangat N, Strand J, Li CY, Wu W, Pardanani A, Tefferi A. Leucocytosis in polycythaemia vera predicts both inferior survival and leukaemic transformation. *Br J Haematol*. 2007;138(3):354-358. **9.** Grunwald MR, Kuter DJ, Altomare I, et al. Treatment patterns and blood counts in patients with polycythemia vera treated with hydroxyurea in the United States: an analysis from the REVEAL study. *Clin Lymphoma Myeloma Leuk*. 2020;20(4):219-225. **10.** Ginzburg YZ, Feola M, Zimran E, Varkonyi J, Ganz T, Hoffman R. Dysregulated iron metabolism in polycythemia vera: etiology and consequences. *Leukemia*. 2018;32:2105-2116.

The MPN Practice Perspectives Survey was sponsored by Incyte.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