

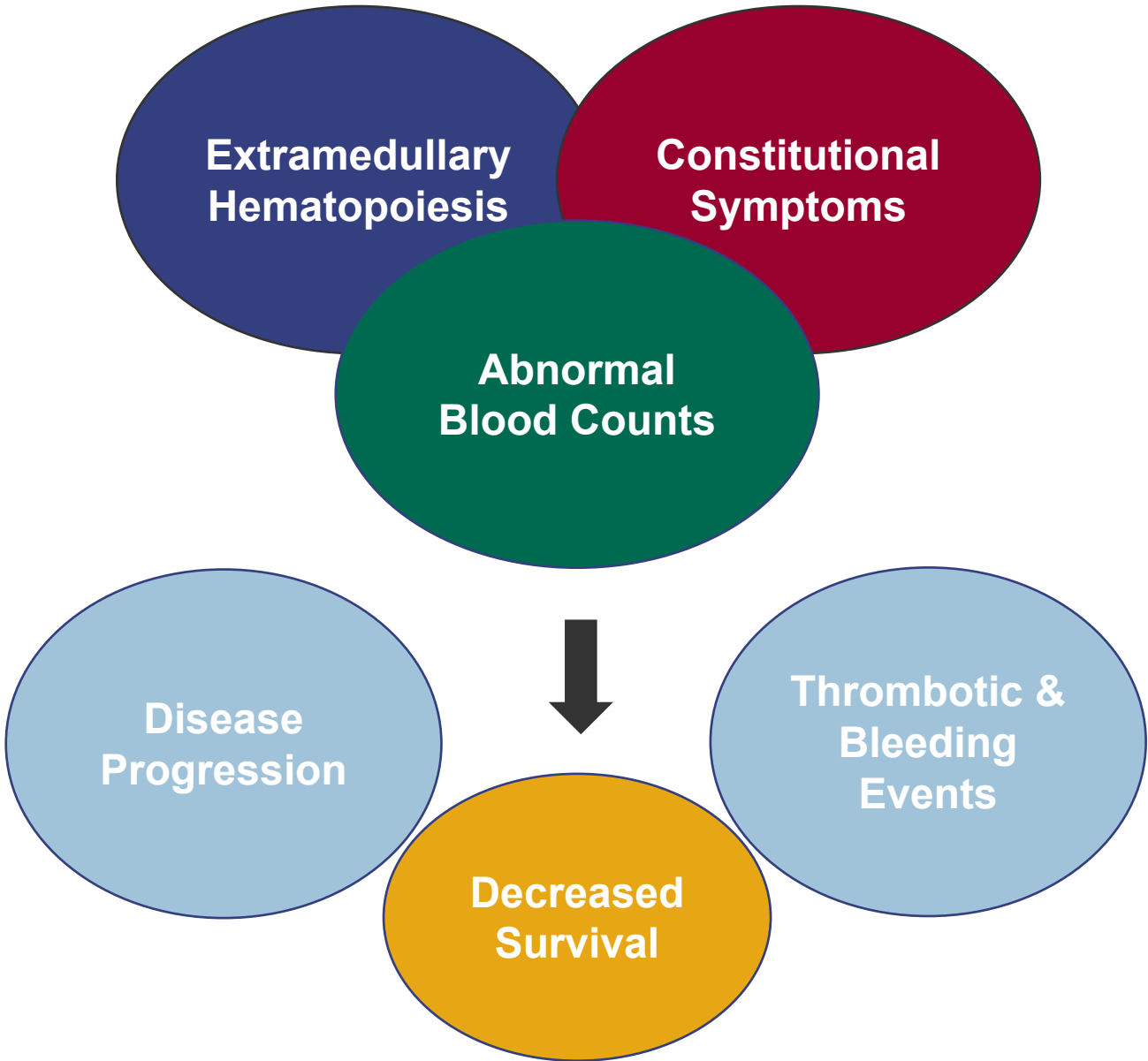
Polycythemia Vera: When is it Time to Move Beyond Phlebotomy

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Myeloproliferative Neoplasms (MPNs): Background

Table 1. Myeloproliferative neoplasms.

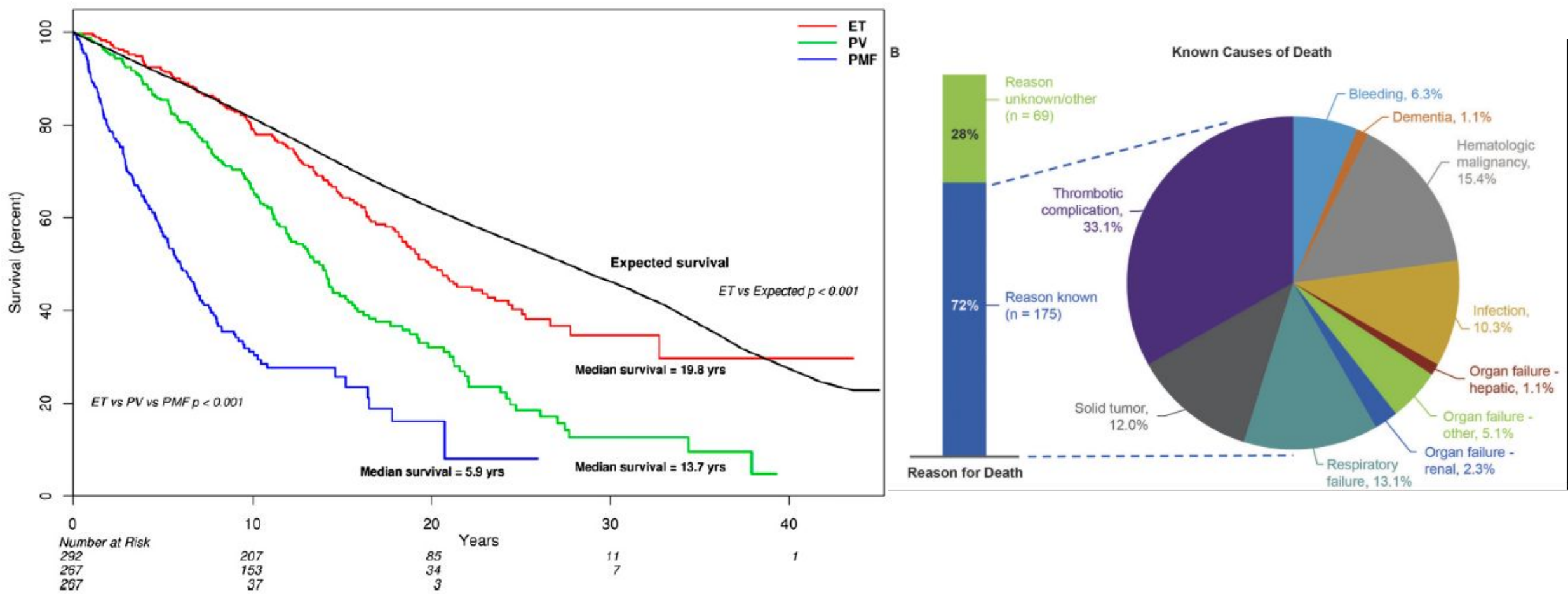
Chronic myeloid leukaemia	}	Ph Negative, Classical MPNs
Polycythaemia vera		
Essential thrombocythaemia		
Primary myelofibrosis		
Chronic neutrophilic leukaemia		
Chronic eosinophilic leukaemia		
Juvenile myelomonocytic leukaemia		
Myeloproliferative neoplasm, not otherwise specified		



Conventional Risk Stratification and Management of PV



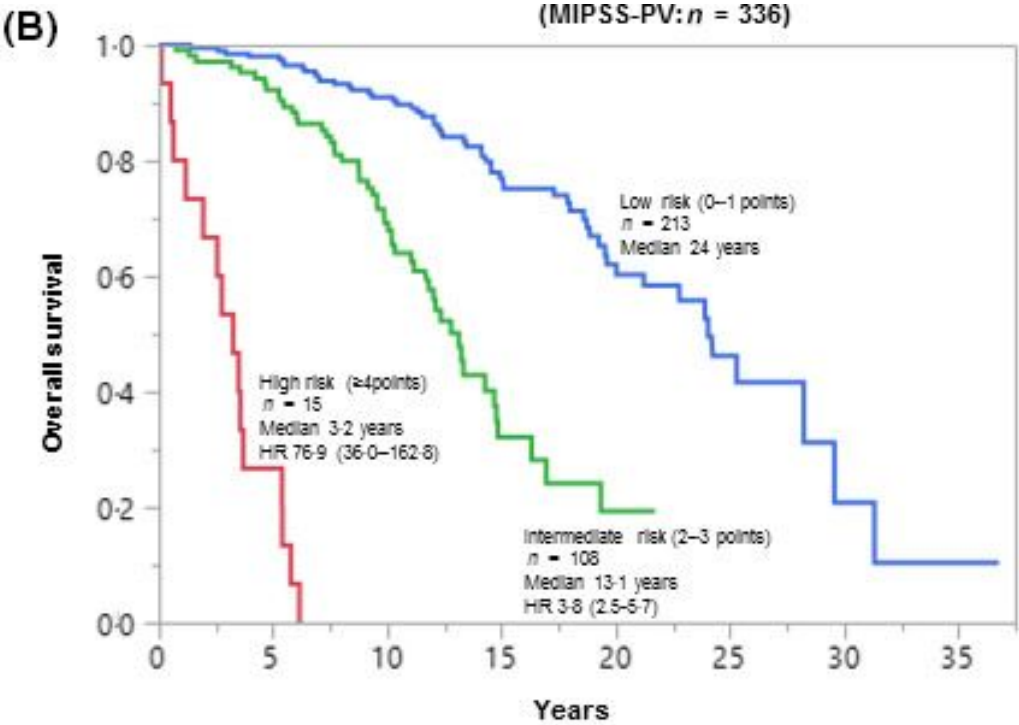
Risk of Mortality is Increased MPN Subtypes



MIPSS-PV Score Predicts OS in PV

Risk Factors:

- Adverse mutation (*SRSF2*), 3 points
- Age >67, 2 points
- Leukocyte Count ≥15, 1 point
- History of thrombosis, 1 point

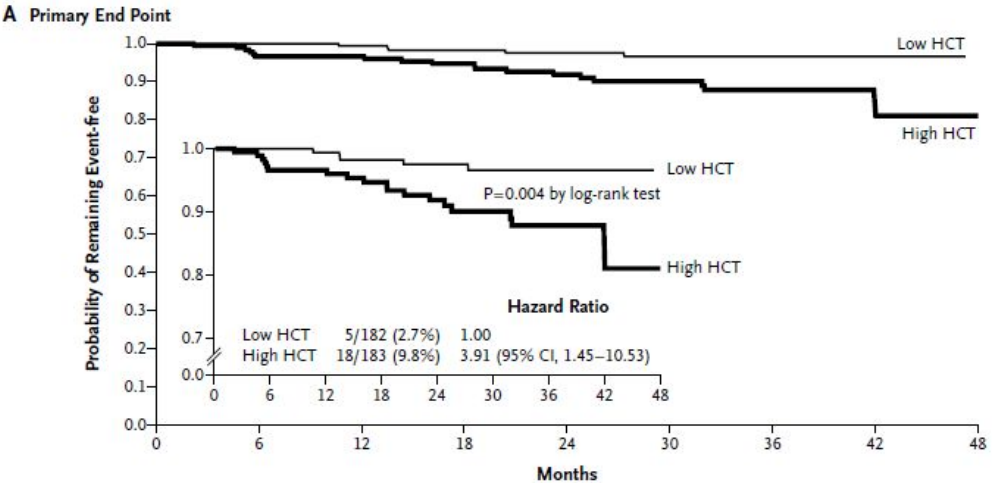


High risk	15	0	0
Intermediate risk	108	56	4
Low risk	213	149	37

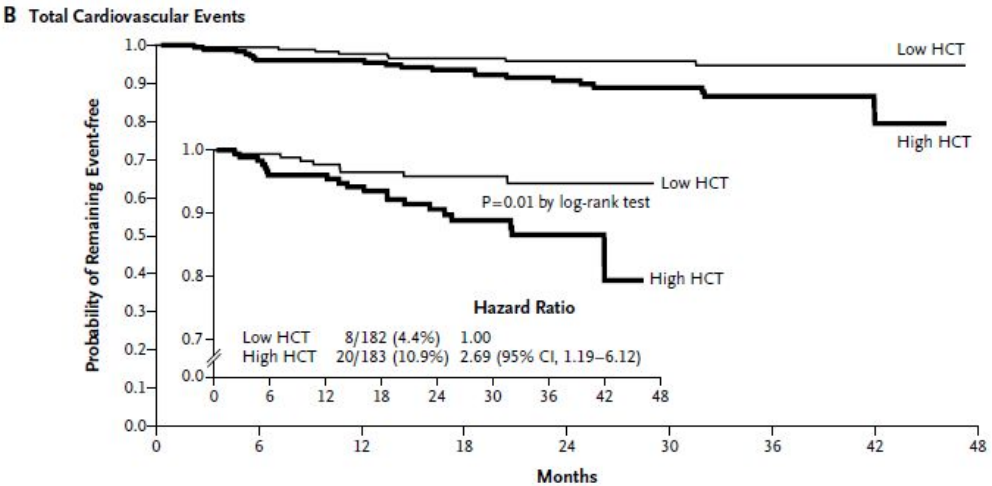
Risk Factors for Thrombosis in PV

Covariate		HR (95% CI)	P
Age, y		1.03 (1.010-1.046)	.0026
Male sex (M vs F)		0.55 (0.369-0.812)	.0028
Disease duration, y		0.98 (0.952-1.017)	.3457
History of TE (Y vs N)		2.47 (1.652-3.683)	<.0001
Treatment (HU vs none)		0.92 (0.608-1.390)	.6905
Treatment (any other vs none)		0.74 (0.370-1.485)	.3975
HCT (>45% vs ≤45%)		1.74 (1.138-2.647)	.0105

Maintenance of Hematocrit <45% is a Key Therapeutic Goal in PV



No. at Risk									
Low HCT	182 (0)	177 (1)	168 (2)	154 (1)	129 (1)	95 (0)	62 (0)	18 (0)	0
High HCT	183 (6)	168 (0)	160 (3)	143 (4)	110 (2)	92 (2)	54 (1)	12 (0)	1



No. at Risk									
Low HCT	182 (1)	176 (3)	165 (2)	151 (1)	127 (0)	94 (1)	60 (0)	18 (0)	0
High HCT	183 (7)	167 (0)	159 (4)	141 (4)	108 (2)	91 (2)	53 (1)	11 (0)	0

Real-World Studies Indicate Inadequate Hematocrit Control in Most Patients

Patients at Baseline High Risk



Patients at Baseline Low Risk



■ Always Under 45% ■ < 50%, but not always <45% ■ > 50% Sometimes ■ Always Over 50

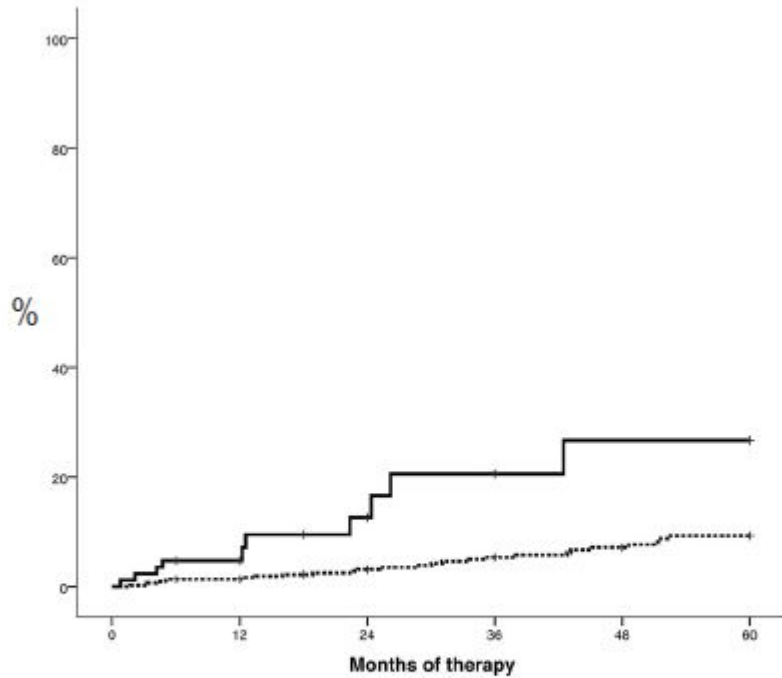
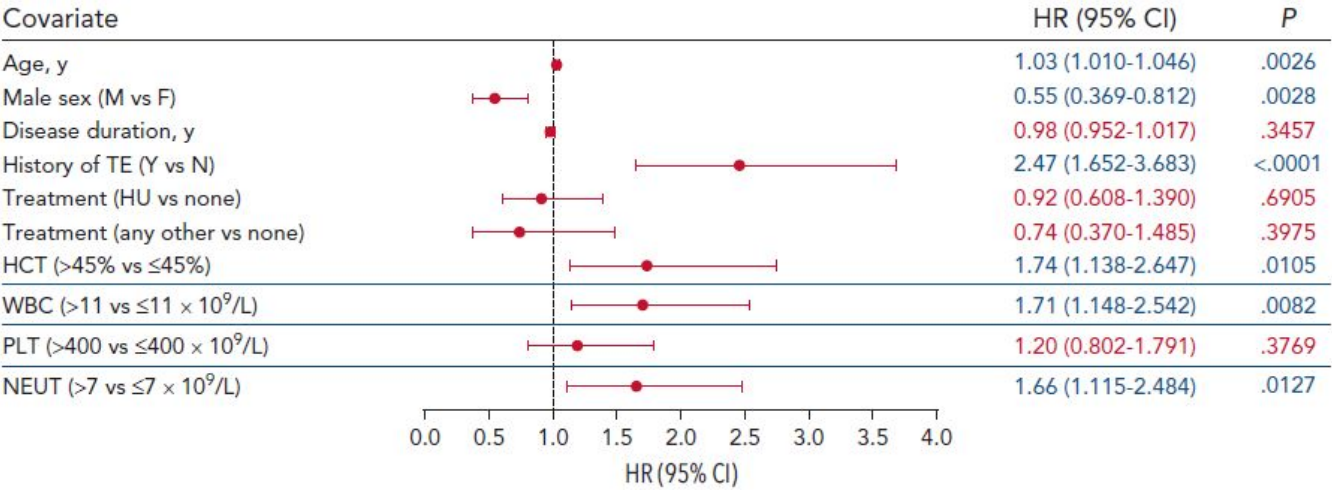
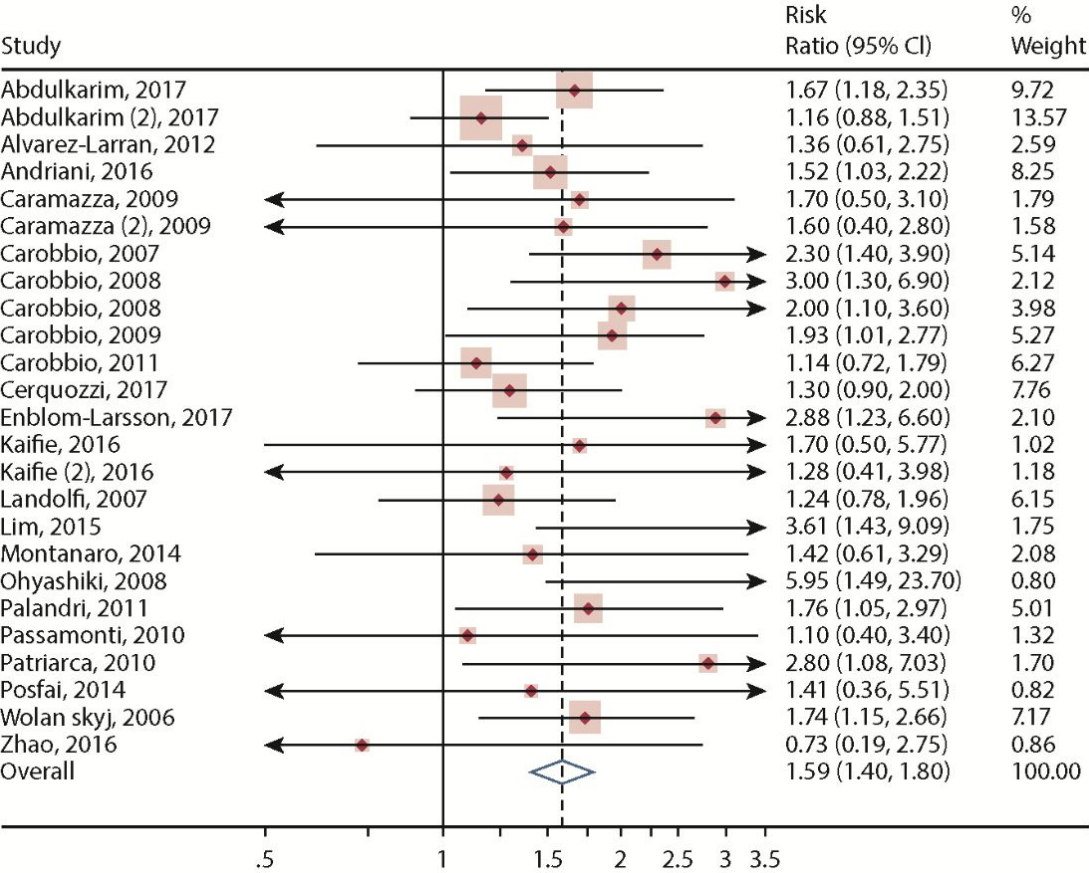


Figure 3. Time to thrombosis in patients with polycythemia vera treated with hydroxyurea (HU) and 3 or more phlebotomies per year (solid line) or with HU and 0-2 phlebotomies per year (dotted line). $P<0.0001$.

Leukocytosis is an Underappreciated Risk Factor for Thrombosis in PV

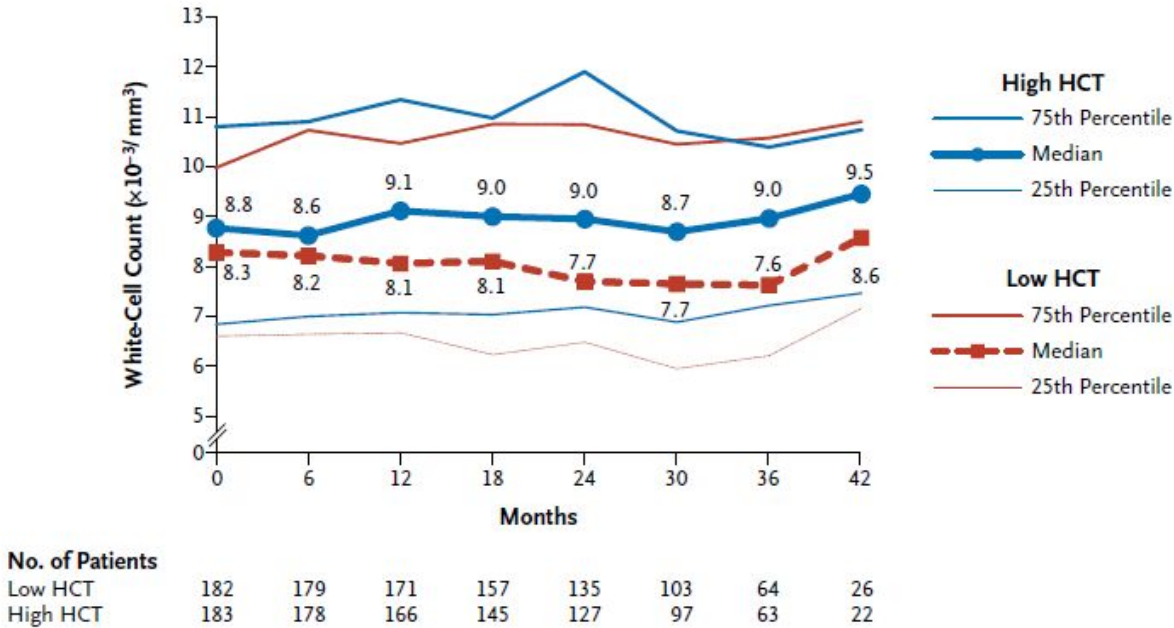


Post Hoc Analysis of CYTO-PV Study Similarly Demonstrates Impact of Leukocytosis

Table 1 Time-dependent multivariable analysis on the risk of major thrombosis in CYTO-PV study (N = 305)

WBC class ($\times 10^9/L$)	Events/pts (%)	Hazard ratio (95% CI), P
<7.0	4/100 (4.0)	1.00
7.0-8.4	4/84 (4.8)	1.58 (0.39-6.43), .52
8.5-11.0	8/88 (9.1)	2.69 (0.80-9.05), .11
≥ 11.0	12/93 (12.9)	3.90 (1.24-12.3), .02

B White-Cell Count



Leukocytosis Also Correlates with Disease Progression

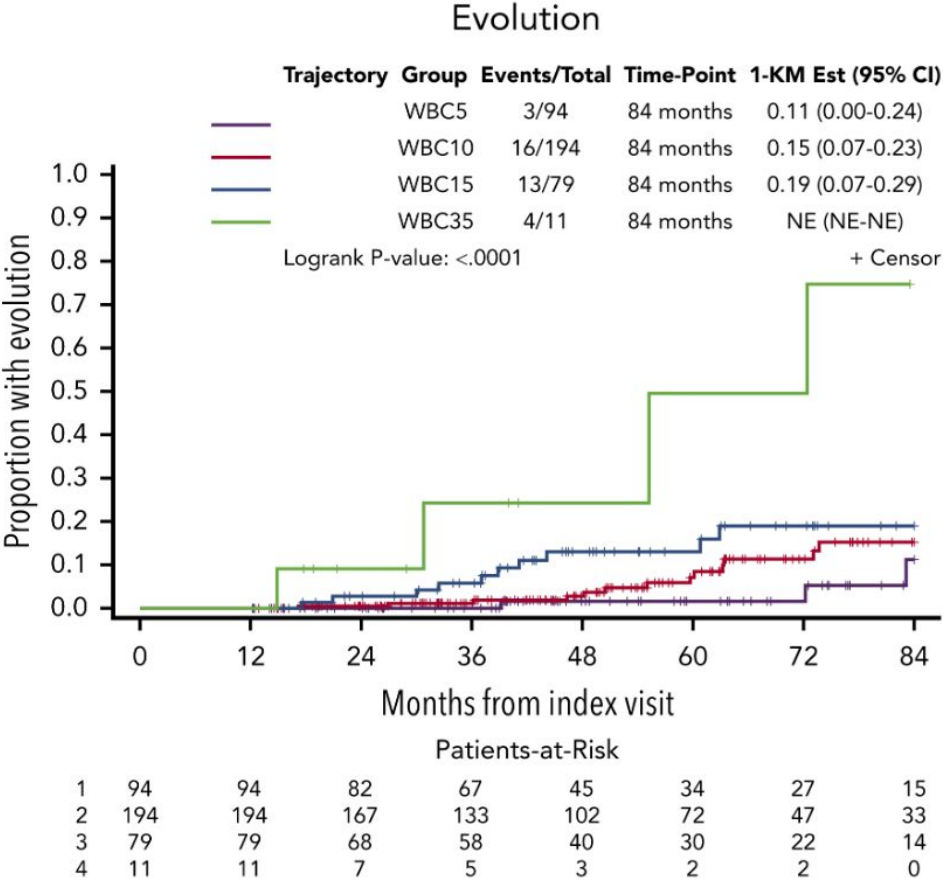
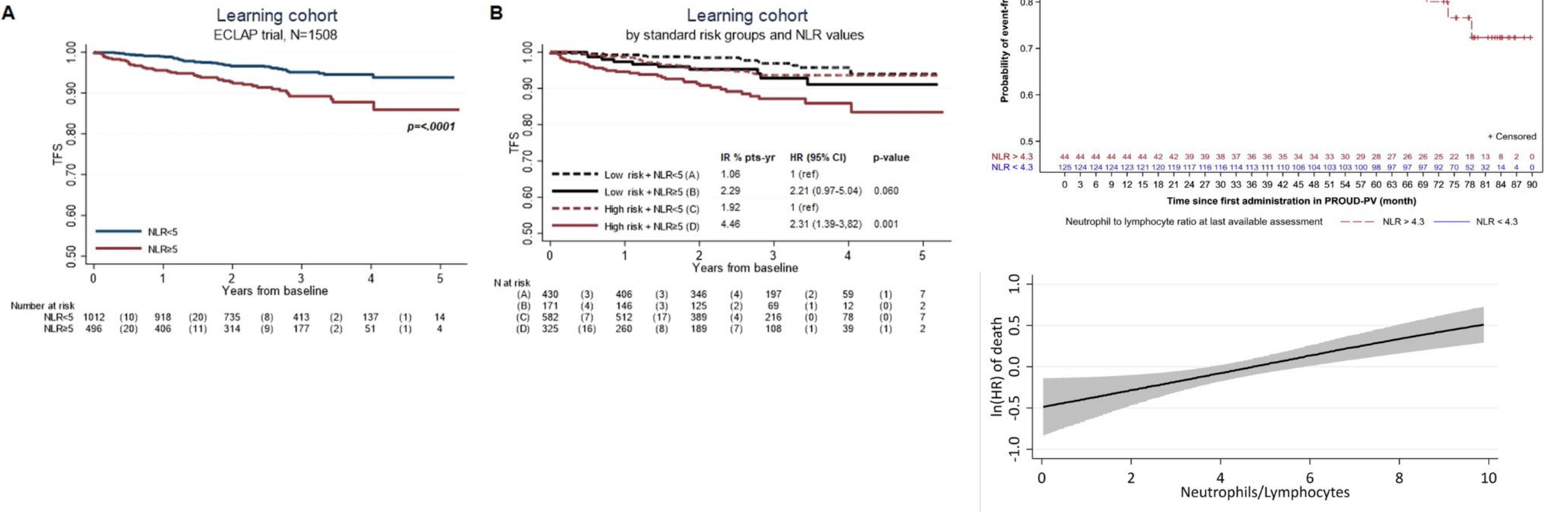


Table 4. Intrinsic risk factors for disease transformation in PV and ET

Transformation	Clinical risk factors	Genetic risk factors
Post-PV MF	Age Leukocytosis Disease duration Reticulin fibrosis Splenomegaly	JAK2V617F allele burden
Post-PV Leukemia	Age Leukocytosis Reticulin fibrosis Splenomegaly	Abnormal karyotype TP53 RUNX1
Post-ET MF	Age Leukocytosis Anemia Reticulin fibrosis	Absent JAK2V617F mutation ASXL1
Post-ET leukemia	Age Leukocytosis Anemia Reticulin fibrosis Thrombosis Platelets $\geq 1000 \times 10^9/l$	TP53 RUNX1

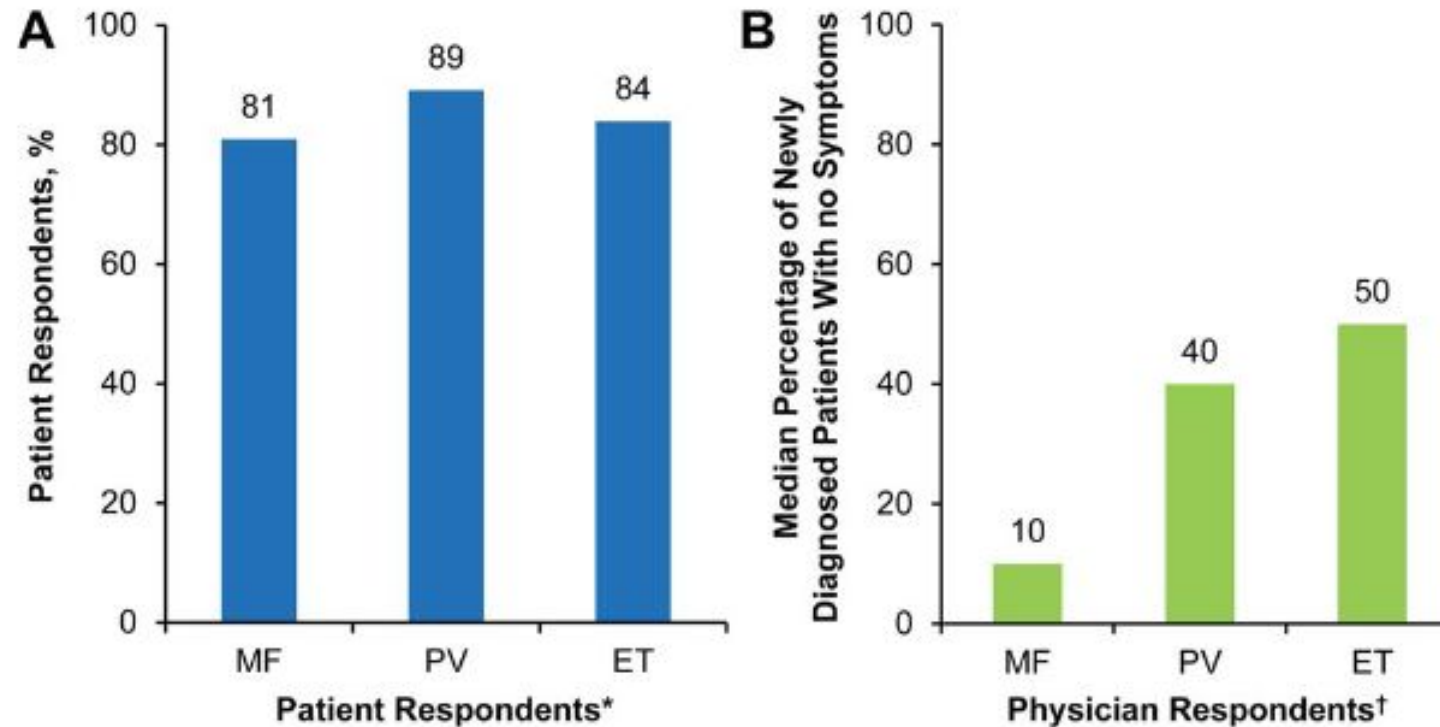
Neutrophil to Lymphocyte Ratio (NLR) as a Surrogate Disease Marker



JAK2 Allele Burden Correlates with Disease Phenotype and Outcomes

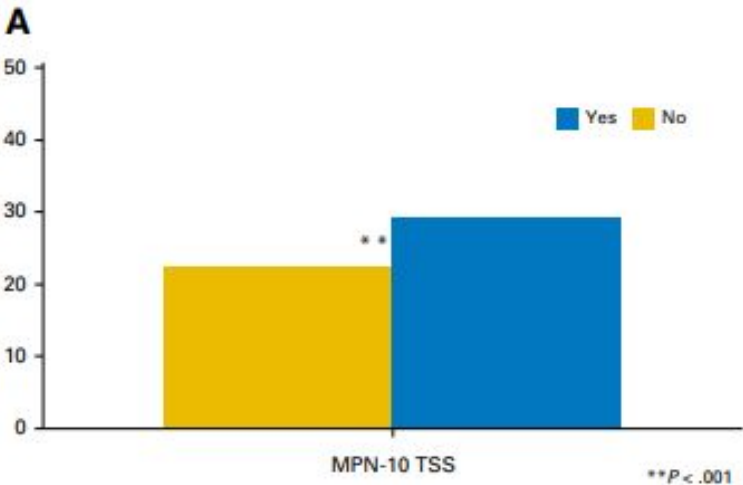
	PV JAK2 ^{V617F} VAF	
	<50%	>50%
Quantitative		
WBC, ×10 ⁹ /L	9.3 ³⁵	12.4 ³⁵
Hg, g/dL	14.6 ³⁵	15.9 ³⁵
Platelets, ×10 ⁹ /L	571 ³⁵	490 ³⁵
Qualitative		
Venous thrombosis risk ratio	1.0 ^{35,*}	2.97 ^{35,*}
CRP, mg/L	27% > 3 ³⁶	63% > 3 ³⁶
LDH, U/L	304 ¹²	480 ¹²
PRV-1 (CD177) expression, fold upregulation	20 ¹²	576 ¹²
Clonal expansion		
Splenomegaly prevalence	12% ¹²	91% ¹²
Red cell mass (% of normal)	150% ^{37‡}	180% ^{37‡}
CD34 circulation, ×10 ⁶ /L	3 ¹²	6 ¹²
15-year myelofibrosis free survival	100% ¹¹	40% ¹¹

Symptoms are Prevalent in PV and Underrecognized by Physicians

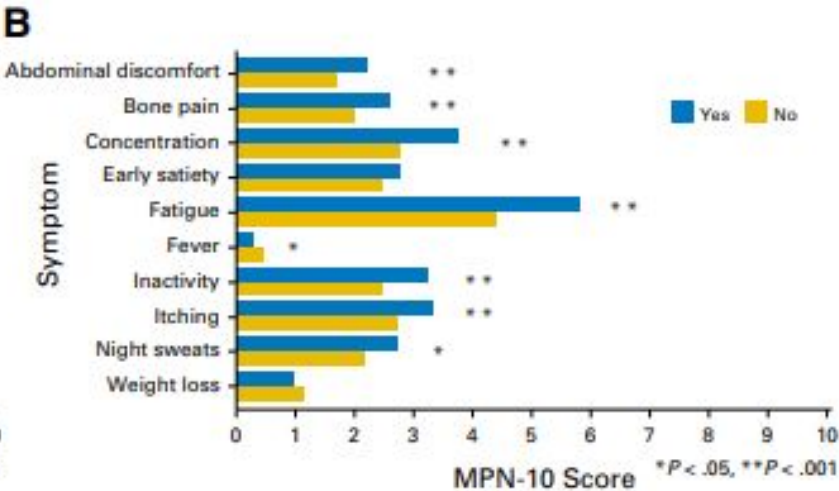
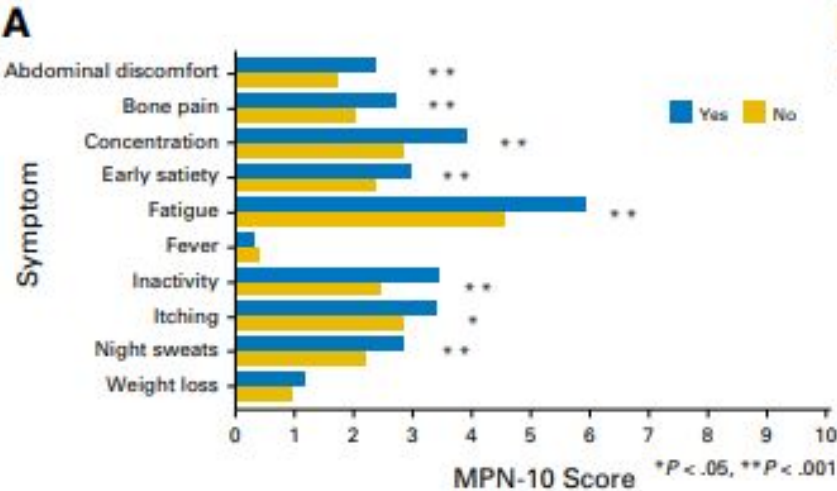
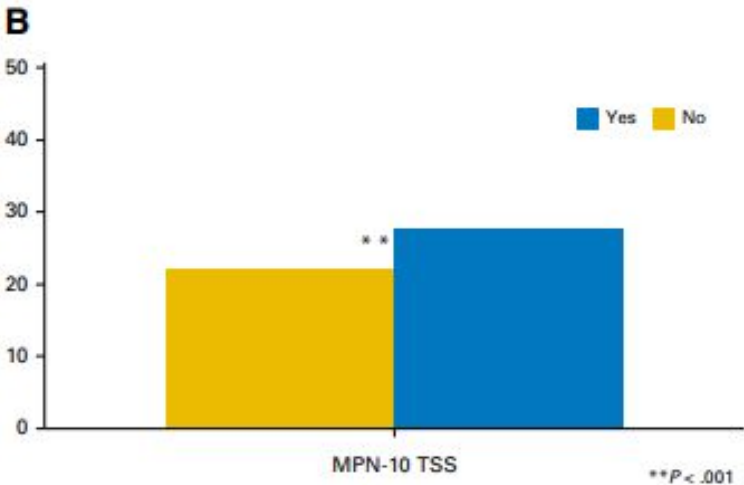


Phlebotomy and Hydroxyurea are Ineffective at Controlling Disease-related Symptoms

Hydroxyurea



Phlebotomy



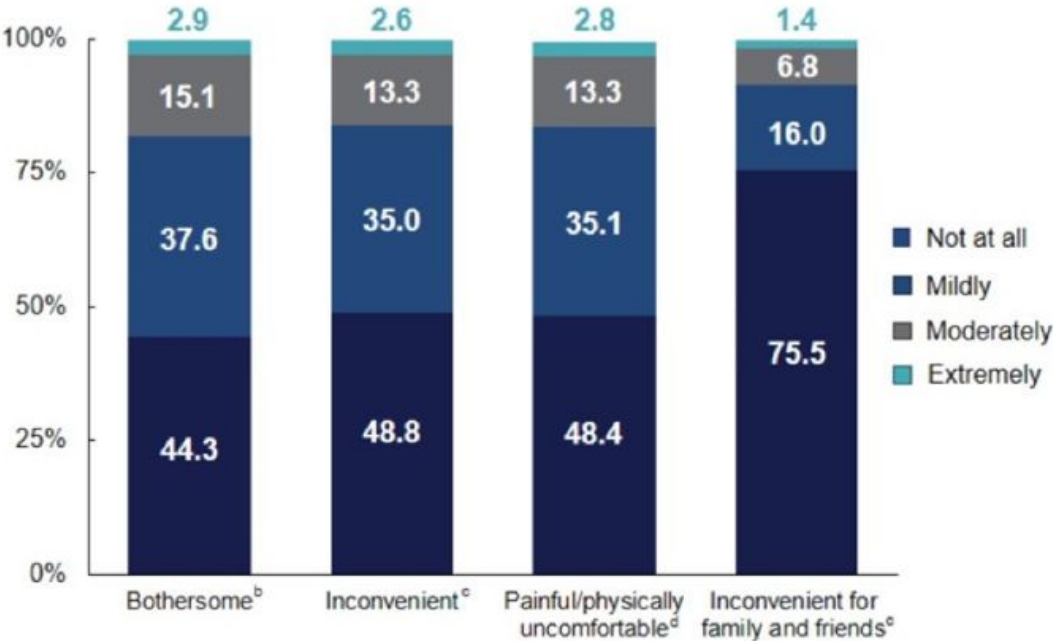
Phlebotomy May Negatively Impact Patients: Patient Perception

Table 1. Patient-Reported Effects of Phlebotomy

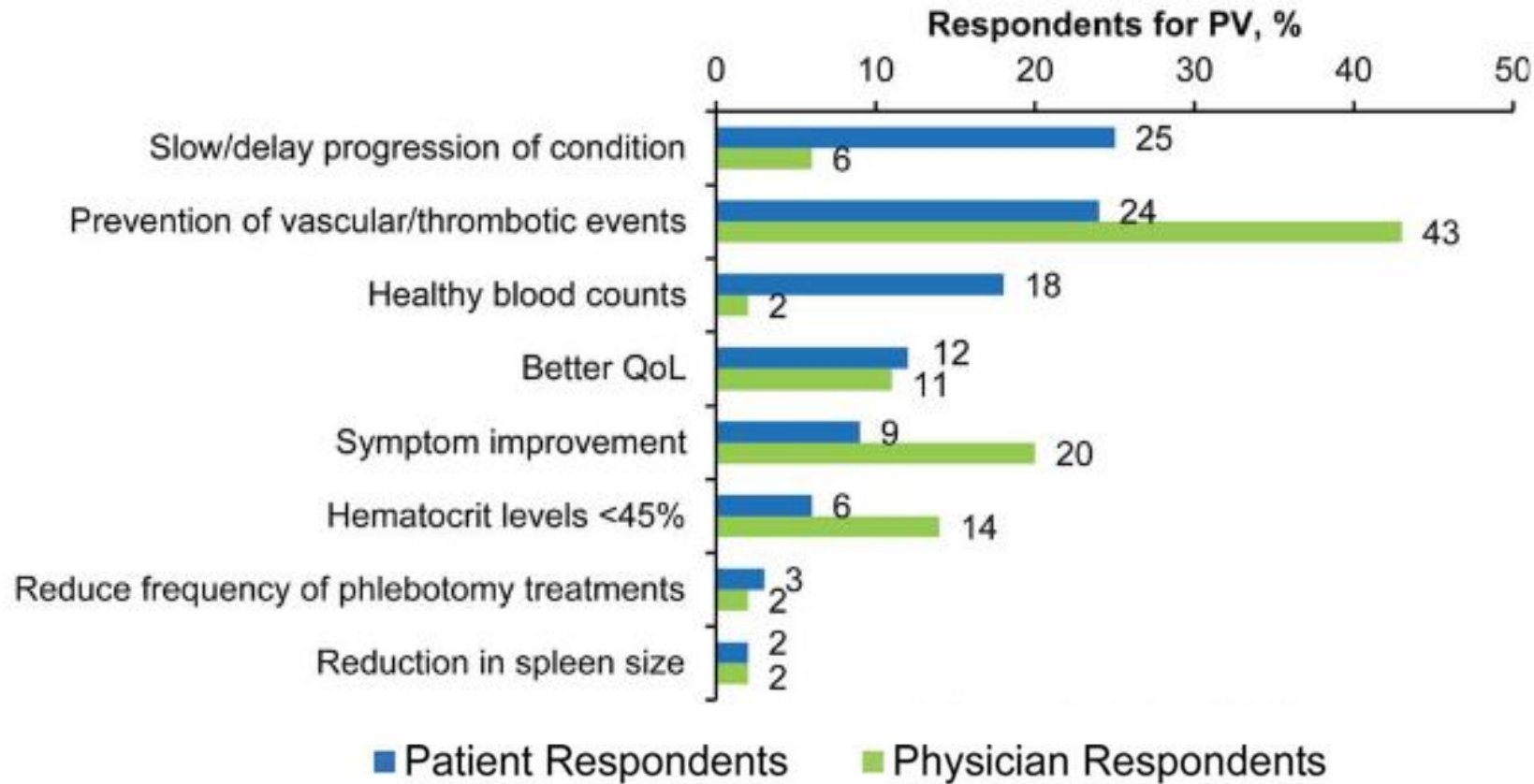
Effect, n (%)	Patients Who Received a Phlebotomy (n=400*)				
	Not Applicable†	Not at All	Mildly	Moderately	Extremely
Fatigue	16 (4.0)	178 (44.5)	104 (26.0)	78 (19.5)	24 (6.0)
Bruising	5 (1.3)	215 (53.8)	116 (29.0)	43 (10.8)	21 (5.3)
Dehydration	10 (2.5)	282 (70.5)	73 (18.3)	25 (6.3)	10 (2.5)
Dizziness	9 (2.3)	253 (63.3)	83 (20.8)	45 (11.3)	10 (2.5)
Fainting	12 (3.0)	359 (89.8)	17 (4.3)	10 (2.5)	2 (0.5)
Loss of appetite	9 (2.3)	326 (81.5)	39 (9.8)	21 (5.3)	5 (1.3)

*Patients who received a phlebotomy procedure in the past 3 months.
†Patient did not experience the symptom within 24 hours after phlebotomy.

Phlebotomy-Related Bother and Inconvenience^a



Treatment Goals: Patient vs. Physician Perspective



Key Points

- Polycythemia vera can substantially impact patients' quality and quantity of life
 - Thrombosis and disease progression are leading causes of mortality
- Conventional risk stratification may be suboptimal and additional factors such as leukocytosis (or NLR) and *JAK2* allele burden should be considered
- Despite being a key therapeutic goal, hematocrit control is suboptimal in most patients in the real-world setting
 - Phlebotomy may be ineffective and contribute to poor symptom control, as well as iron deficiency
- Treatment goals should be individualized to the patient