LA POLICITEMIA VERA
il punto di vista dell'ematologo, del trasfusionista e dell'internista

PV: importanza dei sintomi sistemici e come quantizzarli

Dott.ssa Manuela Stulle
SC Ematologia, ASUITS

Policitemia vera

- è la più frequente NMP: prevalenza 44-57 casi/100.000/abitanti;
  MF : prevalenza 4-6 casi/100.000/abitanti

- mortalità precoce: sopravvivenza media: 14,1 aa
  rischio decesso: 1,6 volte rispetto popolazione generale

- ➢ complicanze trombotiche: microcircolo (arteriose/venose)
  macrocircolo (arteriose/venose)

- ➢ complicanze emorragiche: incidenza 6,2% per persone/aa

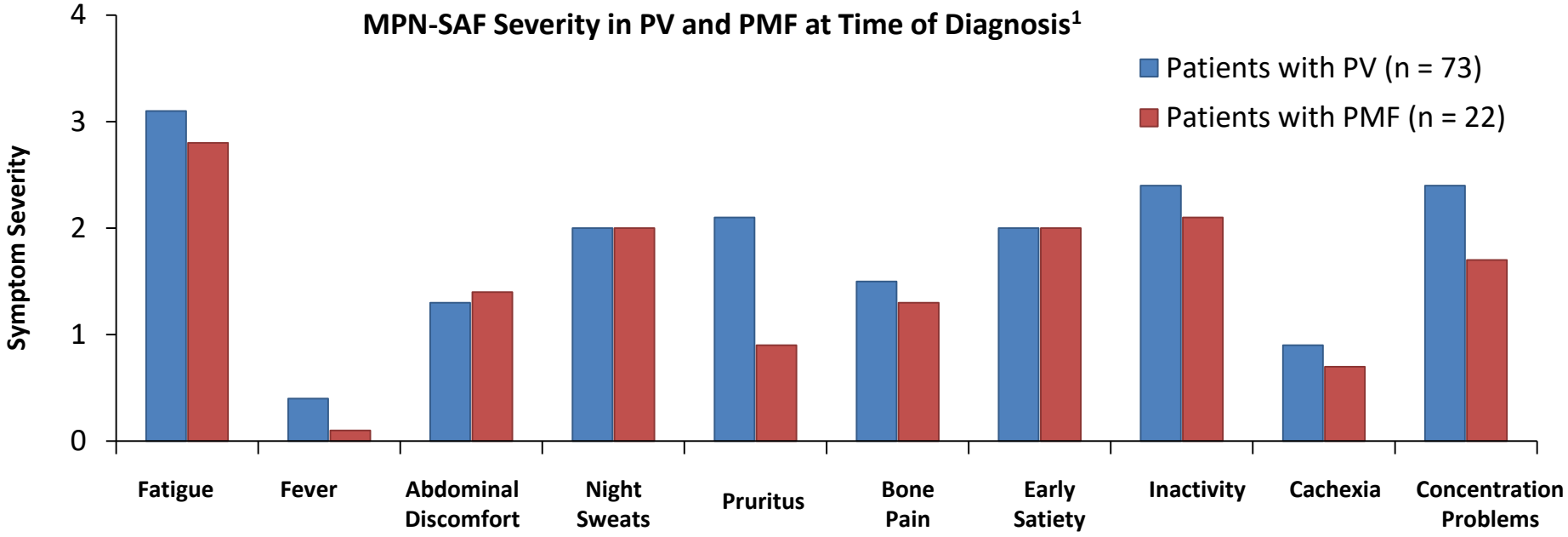
- ➢ rischio di progressione: mielofibrosi secondaria postPV (5-20% a 10 aa)
  leucemia acuta mieloide (10% a 10 aa)
- ➢ tumori

- sintomi costituzionali

Griesshammer et all, Ann Hematol (2015) 94:901-910

The Symptomatic Burden in PV

- Severity of symptoms at diagnosis in PV is as high as in PMF[1]
- PV symptoms are severe throughout course of disease[2]
- Symptoms may worsen in patients treated with conventional therapies, eg, phlebotomy or hydroxyurea[3]



1. Abelsson J et al. *Leuk Lymphoma.* 2013;54:2226-2230. 2. Scherber R et al. *Blood.* 2011;118:401-408.
3. Emanuel R et al. *Haematologica.* 2013;98:118-119

Policitemia vera - Sintomi

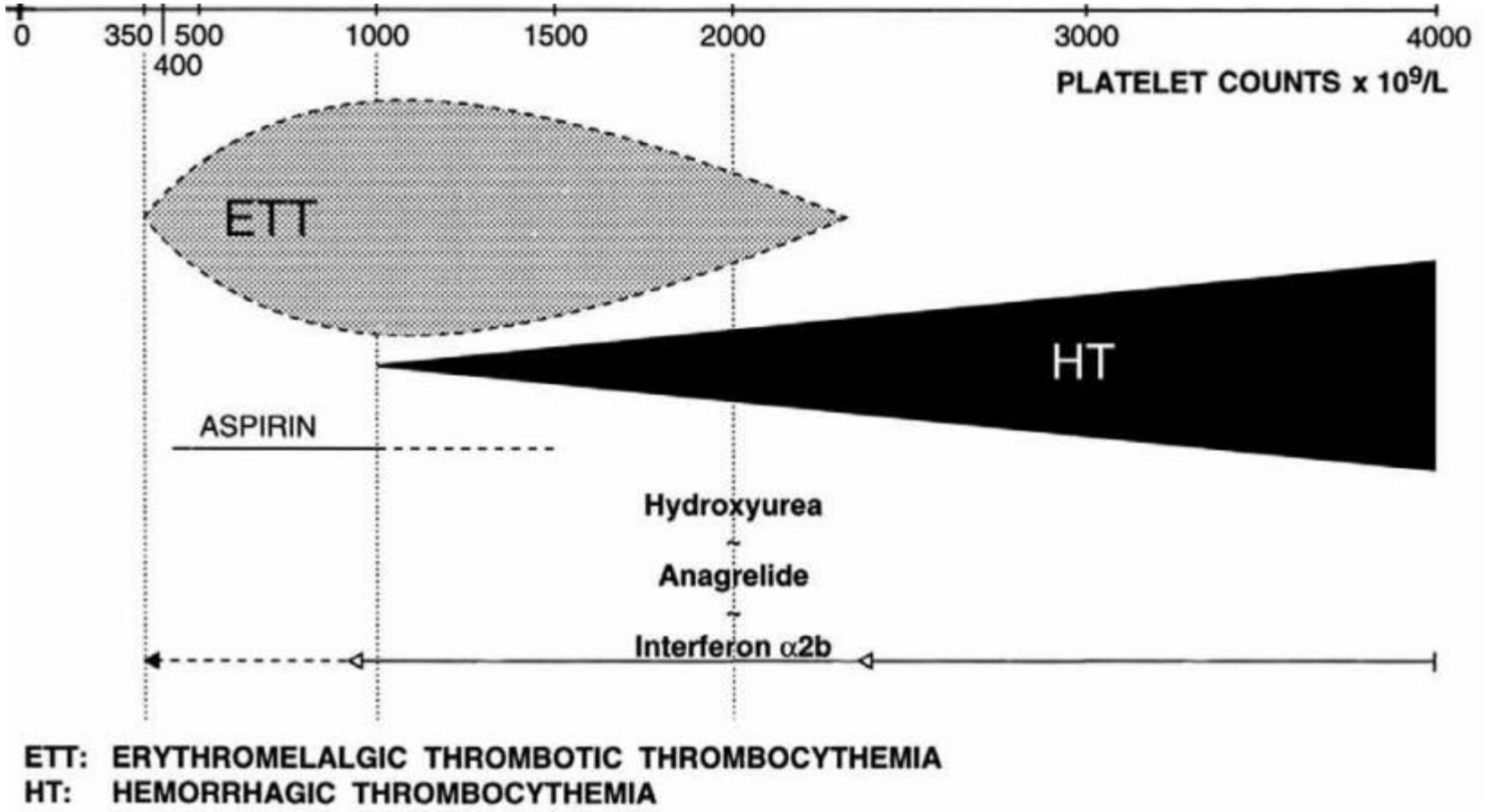
cefalea
Pain in the head

Microvascular symptoms

Vertigini soggettive
Sensation that the environment is moving

Alterazioni visive
Double vision, blurred vision, or blind spots

Microvascular circulation ischemic disturbances events in polycythemia vera including erythromelalgia, atypical and typical cerebral and ocular transient ischemic attacks and acute coronary syndromes (ETT) already occur at platelet counts between 400 and 1000x10^9 /L



Low-dose aspirin is highly effective and safe in the cure and prevention of thrombotic and ischemic events and does not elicit bleedings at platelet counts below 1000x10^9 /l. At platelet counts between 1000 and 2000 x10^9 /l, thrombosis and bleeding (ETT and HT) frequently occur in sequence or paradoxically and low-dose aspirin does prevent thrombotic complications but aggravates or may elicit bleeding symptoms.

Platelets, December 2006; 17(8): 528–544

Policitemia vera - Sintomi

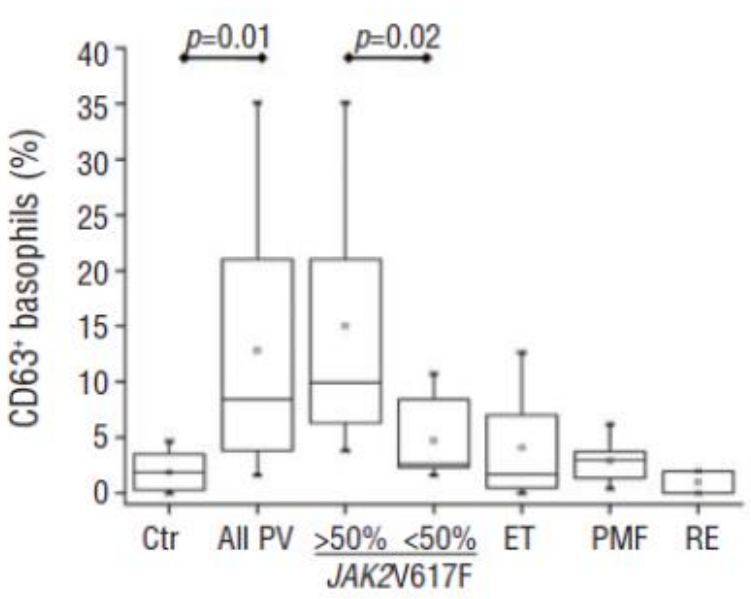
Prurito

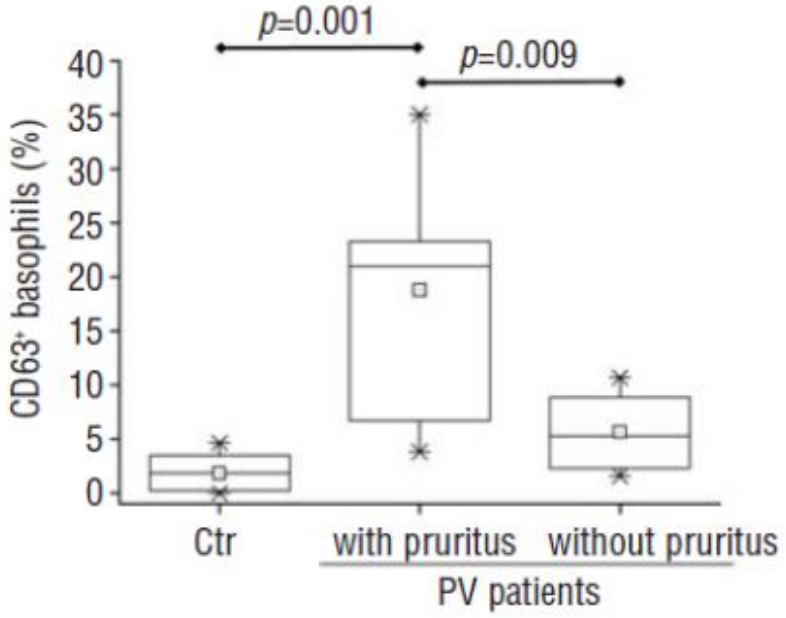
Iniezioni congiuntivali

Sintomi da
splenomegalia

Astenia marcata

JAK2V617F induces constitutive activation of basophils in PV



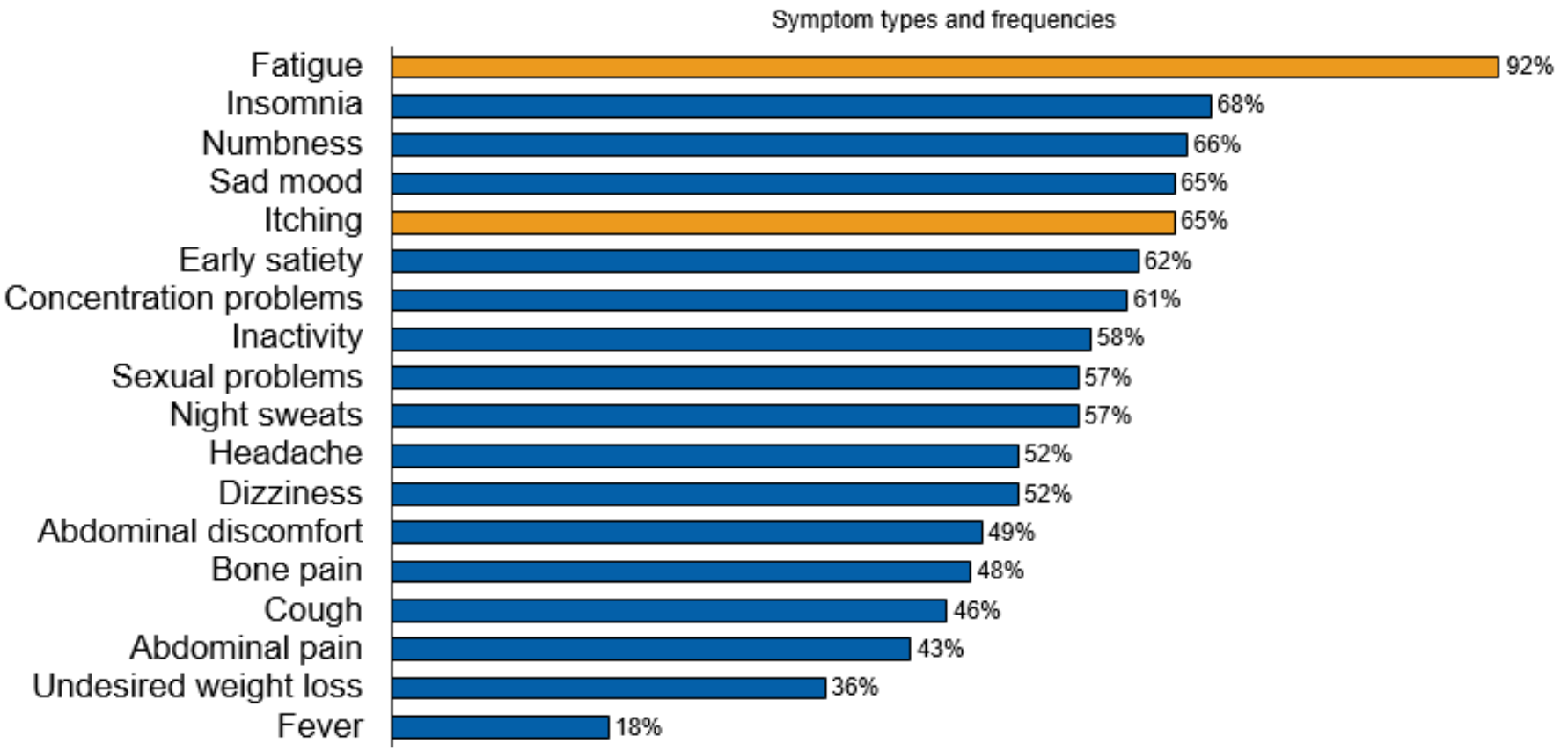


- The V617F VAF was signficantly greater in patients with pruritus (71+8%) than in those without (48+19%; p=0.002)

Pieri L et al, Haematologica 2009;94:1537

Symptoms in PV are prevalent and often severe

Symptoms are observed in a large proportion of patients

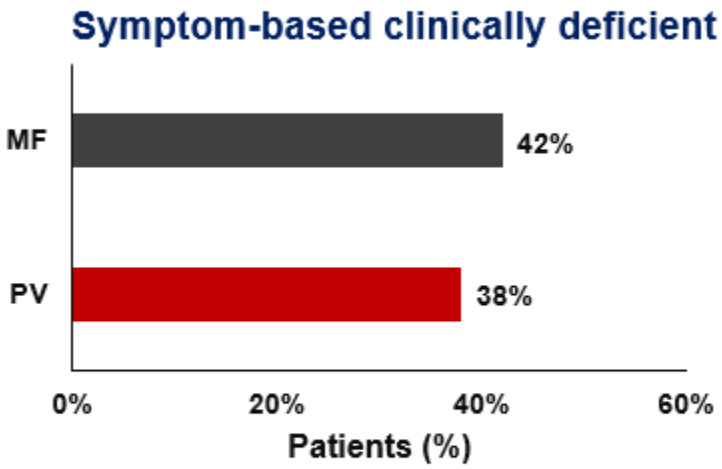


Adapted from Scherber , Blood.2011

Symptoms in PV May Be Severe

- Not only are symptoms prevalent in PV, but their severity at diagnosis is as high and as deleterious on quality of life as in primary MF[1,2]

Symptoms result in poor quality of life (QoL) in nearly as many patients with PV as in MF[1]



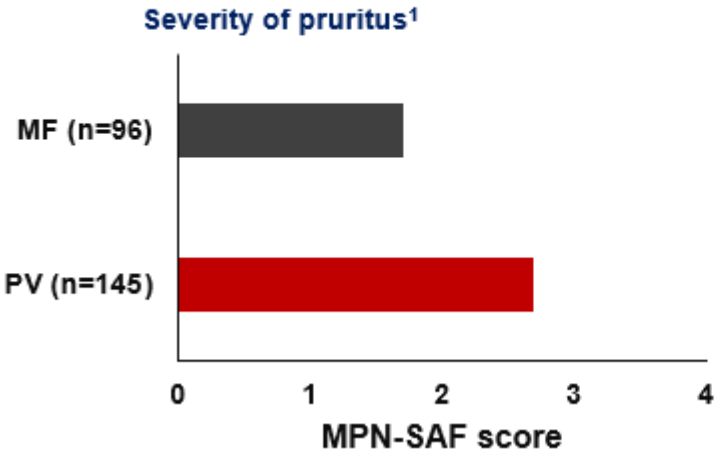
- Symptoms and complications have been associated with declines in physical, functional, and overall health status using a variety of QoL assessment tools (MPN-SAF, EORTC QLQ-C30, BFI, FACT-An, Godin LAS)[1-3]

MPN-SAF=Myeloproliferative Neoplasm Symptom Assessment Form; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; BFI=Brief Fatigue Inventory; FACT-An=Functional Assessment of Cancer Therapy-Anemia; Godin LAS=Godin Leisure Time Activity Score.

1. Emanuel RM, et al. *J Clin Oncol.* 2012;30:4098-4103. 2. Scherber R, et al. *Blood*. 2011;118:401-408. 3. Mesa RA, et al. *Cancer*. 2007;109:68-76.

Pruritus and Fatigue are Among the Most Common and Severe Symptoms of PV

- 65% of patients with PV experience aquagenic pruritus[1,2]



15% characterize pruritus as 'unbearable' (rating of 6 on a scale of 6)[2]

94% of pruritus cases are **unresolved with traditional PV therapy**[2]

- **Pruritus** interferes with daily activities and has been associated with suicidal ideation[3]
- **Fatigue** is the most prevalent symptom associated with PV, affecting approximately 85% of patients[4]
- Fatigue was reported regardless of disease severity, occurring in patients who lacked complications of PV, such as thrombosis or splenomegaly[4]

1. Scherber R, et al. *Blood.* 2011;118:401-408. 2. Siegel FP, et al. *Am J Hematol.* 2013;88:665-669. 3. Mesa RA. *Blood.* 2009;113:5697-5698. 4. Mesa RA, et al. *Cancer*. 2007;109:68-76.

Thrombotic Risk Stratification in PV

Risk Category	Age >60 Years or Prior Thrombosis	Cardiovascular Factors*
Low	No	No
Intermediate	No	Yes
High	Yes	

*Diabetes, hypertension, dyslipidemia, tobacco use

Marchioli R et al. *J Clin Oncol*. 2005;23:2224-2232. 2. Barbui T et al. *J Clin Oncol*. 2011;29:761-770

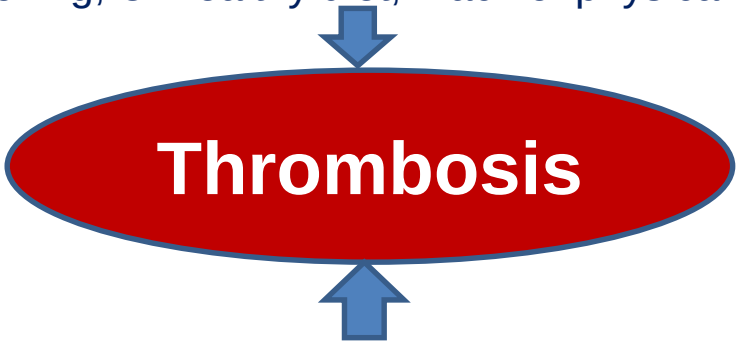
Annual rate of thrombosis in MPN and general population (% patients)

General population without risk factors*	0.6%
General population with multiple CV risk factors	0.90 %
PV patients (n=1,545) §§ (rates after 2005)	
Low-risk……	2.23 %
Highrisk……	3.14%

Potentially modifiable risk factors

Cardiovascular risk factors

Obesity Diabetes **Hypertension** Hyperlipidemia
Smoking, Unhealthy diet, Lack of physical activity



Disease related abnormalities

Hyperviscosity, Leukocyte and platelet abnormalities
Inflammation, Mutational status

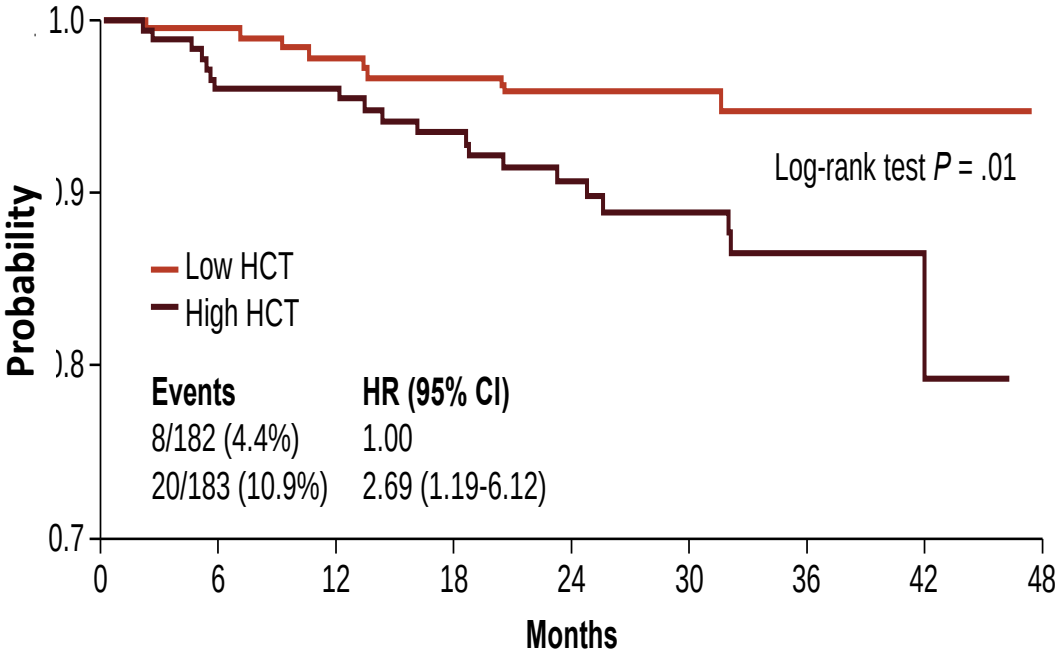
Choice of antihypertensive drugs in PV:

Clinical evidence in non clonal erythropoiesis

- Inactivation of RAS by an angiotensin-converting enzyme (ACE) inhibitor, or an angiotensin II type 1 AT1 receptor blocker represents the most effective, safe, and well-tolerated **in renal post-transplant erythrocytosis** *Kidney International, Vol. 63 (2003), pp. 1187–1194*

- A randomized clinical trial demonstrated that ACE-inhibition therapy effectively and safely **ameliorates altitude polycythaemia** *Lancet 2002: 359: 663–66*

Lower Rate of Cardiovascular Events or Major Thrombosis in Stringent Hematocrit Control Arm (Cyto-PV trial)

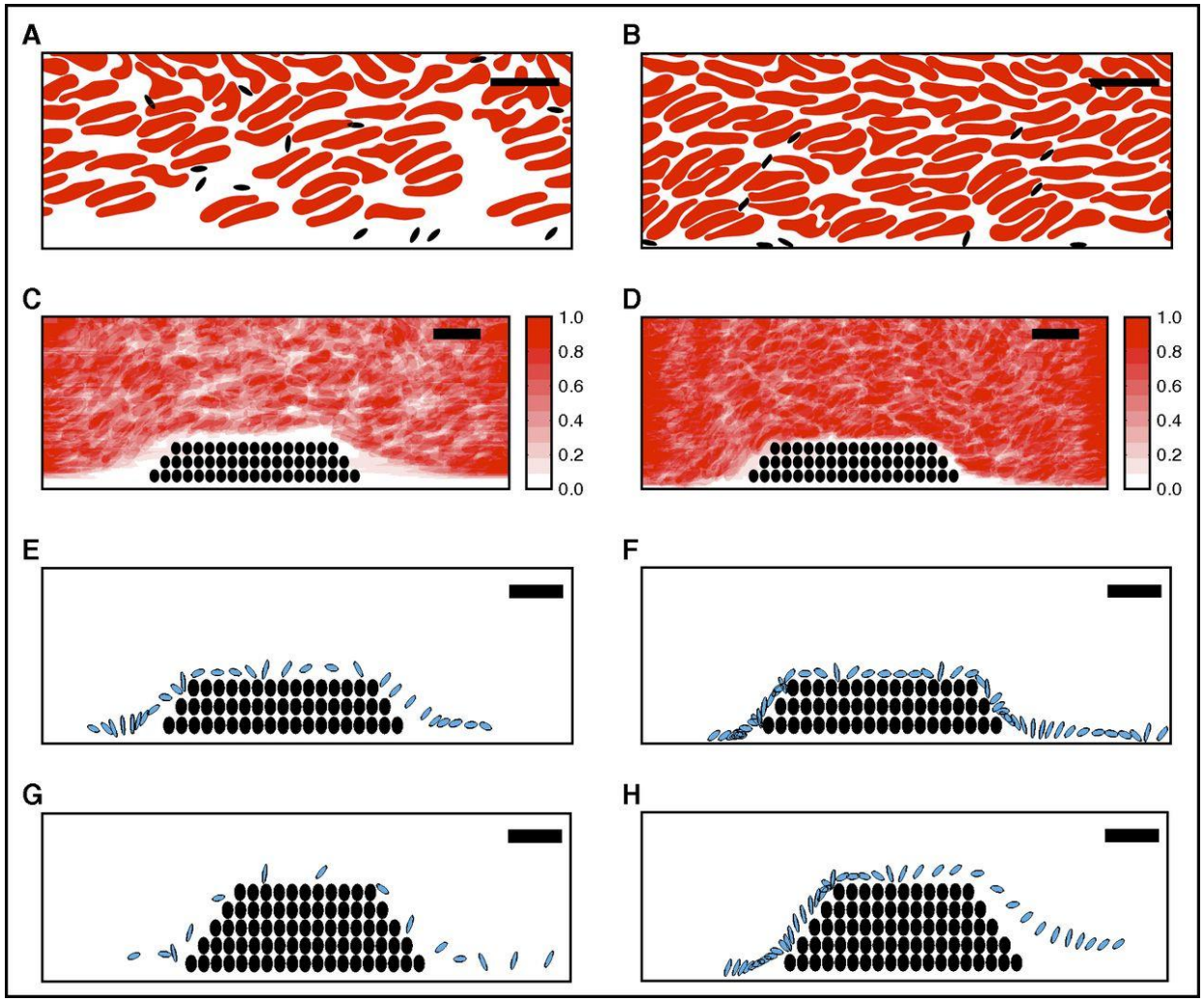


Low HCT	182	(1)	176	(3)	165	(2)	151	(1)	127	(0)	94	(1)	60	(0)	18	(0)	0
High HCT	183	(7)	167	(0)	159	(4)	141	(4)	108	(2)	91	(2)	53	(1)	11	(0)	0

In patients with **hematocrit levels ≥45%**, the risk of CV-related **death or major thrombosis** was increased approximately **4 times** (P = 0.007) versus patients with hematocrit <45%

1. Marchioli R et al. *N Engl J Med.* 2013;368:22-33.

A computational model suggests elevated hematocrit increases the time that platelets spend in proximity to a thrombus.



Bethany L. Walton et al. Blood 2017;129:2537-2546

Leukemia
https://doi.org/10.1038/s41375-018-0199-5

BRIEF COMMUNICATION

Chronic myeloproliferative neoplasms

Evidence- and consensus-based recommendations for phlebotomy in polycythemia vera

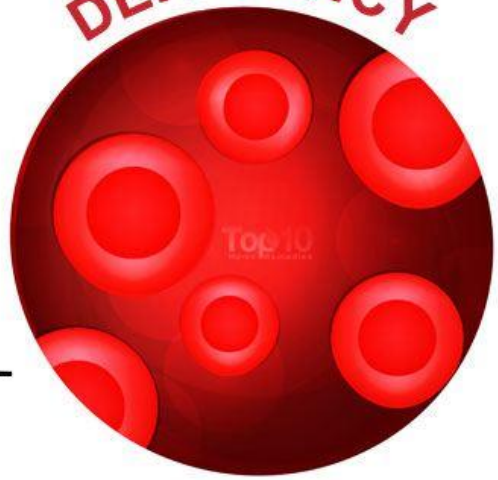
Tiziano Barbui[1] · Francesco Passamonti[2] · Patrizia Accorsi[3] · Fabrizio Pane[4] · Alessandro M. Vannucchi[5] · Claudio Velati[6] · Robert P. Gale[7] · Sante Tura[8] · Giovanni Barosi[9]

Received: 7 March 2018 / Revised: 13 April 2018 / Accepted: 25 April 2018

Linee Guida per la Salassoterapia

- The panel recommends phlebotomy begin **as soon as possible** after the diagnosis of PV or even earlier in persons with recent, active vascular complications and a high likelihood of PV.
- The phlebotomy strategy should have an **induction phase** aimed to rapidly achieve the target hematocrit followed by a **maintenance phase**.
- In the induction phase, the phlebotomy regimen should consider a person's weight and should remove 300 to 450 mL of blood **every other day or twice a week** until the target hematocrit is achieved.
- The maintenance phase should have the same volume of blood as in the induction phase. Phlebotomy intervals should be determined by measuring hematocrit levels **monthly in the first 6 months and ≤2 months thereafter.**
- The small volume of **plasma** removed by phlebotomy **does not require replacement**.
- Oral intake of liquids of about 1 L before and after phlebotomy is recommended as is continuous blood pressure monitoring during phlebotomy.

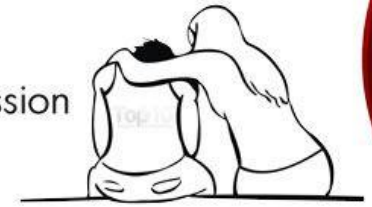
SIGNS AND SYMPTOMS OF IRON DEFICIENCY



Fatigue and Tiredness

Shortness of Breath

Depression



Hair Loss

Restless Leg Syndrome

Frequent Headaches

Increased Sensitivity to Cold

Brittle Nails

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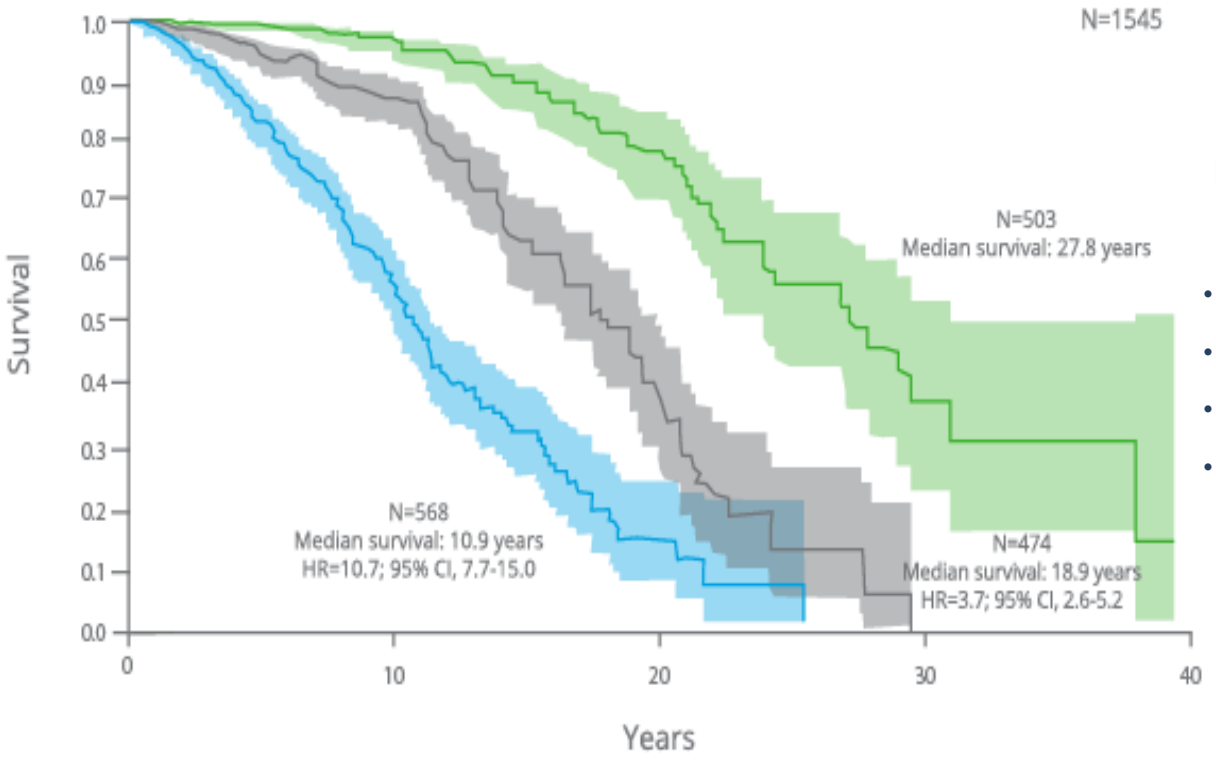
Leukocytes are recognized as key risk factor of thrombosis and reduced Overall Survival in PV

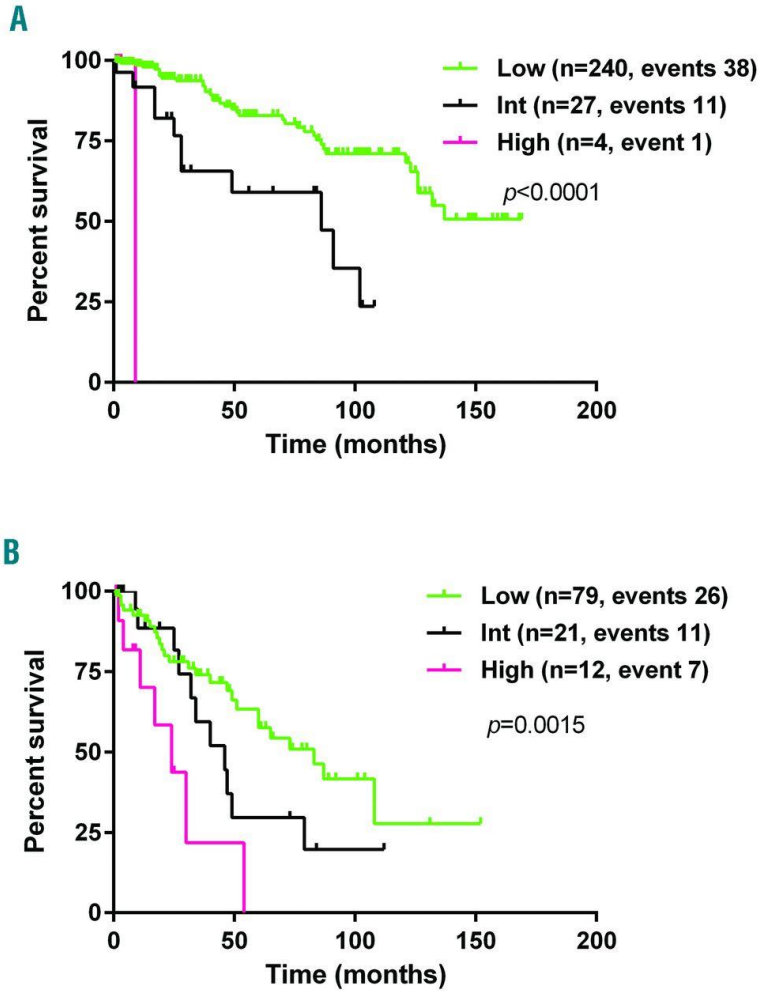


RISK VARIABLES:

- **Age ≥67 years (5 points)**
- **Age 57-66 years (2 points)**
- **Leukocytes ≥11-15 x109/L (1 point)**
- **Venous thrombosis (1 point)**

1.Landolfi et al 2007; 2. Landolfi et al 2004; 3. Tefferi A, et al. 2013

Overall survival of PV patients with different cytogenetic risk categories.



- **Low:**
  - normal karyo;
  - sole +8,+9 and other single abnormality
- **Intermediate:**
  - sole del20q, +1q,
  - other 2 abnormalities
- **High:**
  - complex karyotype

Tang G et al. Haematologica 2017;102:1511-1518

PROGNOSTIC SIGNIFICANCE OF MUTATIONS IN MPN

Mutated Gene	Polycythemia Vera (PV)
ASXL1/ SRSF2/ IDH1/2[1]	The presence of at least 1 of these 'adverse variants/mutations' is associated with inferior overall survival (compared to other sequence variants/mutations, or none) independent of age, IWG prognostic model for PV, and karyotype.[2] Adverse variants/mutations also affected myelofibrosis-free survival.
JAK2 exon 12 mutation	Patients with *JAK2* exon 12-mutated PV exhibit younger age, increased mean hemoglobin/hematocrit, and lower mean white blood cell and platelet counts at diagnosis compared to those with *JAK2 V617F*-mutated PV. However, both *JAK2* mutations are associated with similar rates of thrombosis, evolution to myelofibrosis or leukemia, and death.[3,4]

[1]Next-generation sequencing (NGS) remains a research tool in many situations. However, it may be useful to establish clonality in selected circumstances (eg, "Triple Negative" non-mutated *JAK2*, *MPL*, and *CALR*).

[2]Tefferi A, Lasho TL, Guglielmelli P, et al. Targeted deep sequencing in polycythemia vera and essential thrombocythemia. Blood Advances 2016;1(1):21-30.
[3]Passamonti F, et al. Molecular and clinical features of the myeloproliferative neoplasm associated with *JAK2* exon 12 mutations. Blood 2011;117:2813-2816.
[4]Scott L. The *JAK2* exon 12 mutations: a comprehensive review. Am J Hematol 2011;86:668–676.

Questionari

FACT Lym (versione 4)

EORTC QLQ C 30 Version 3

MPN SAF

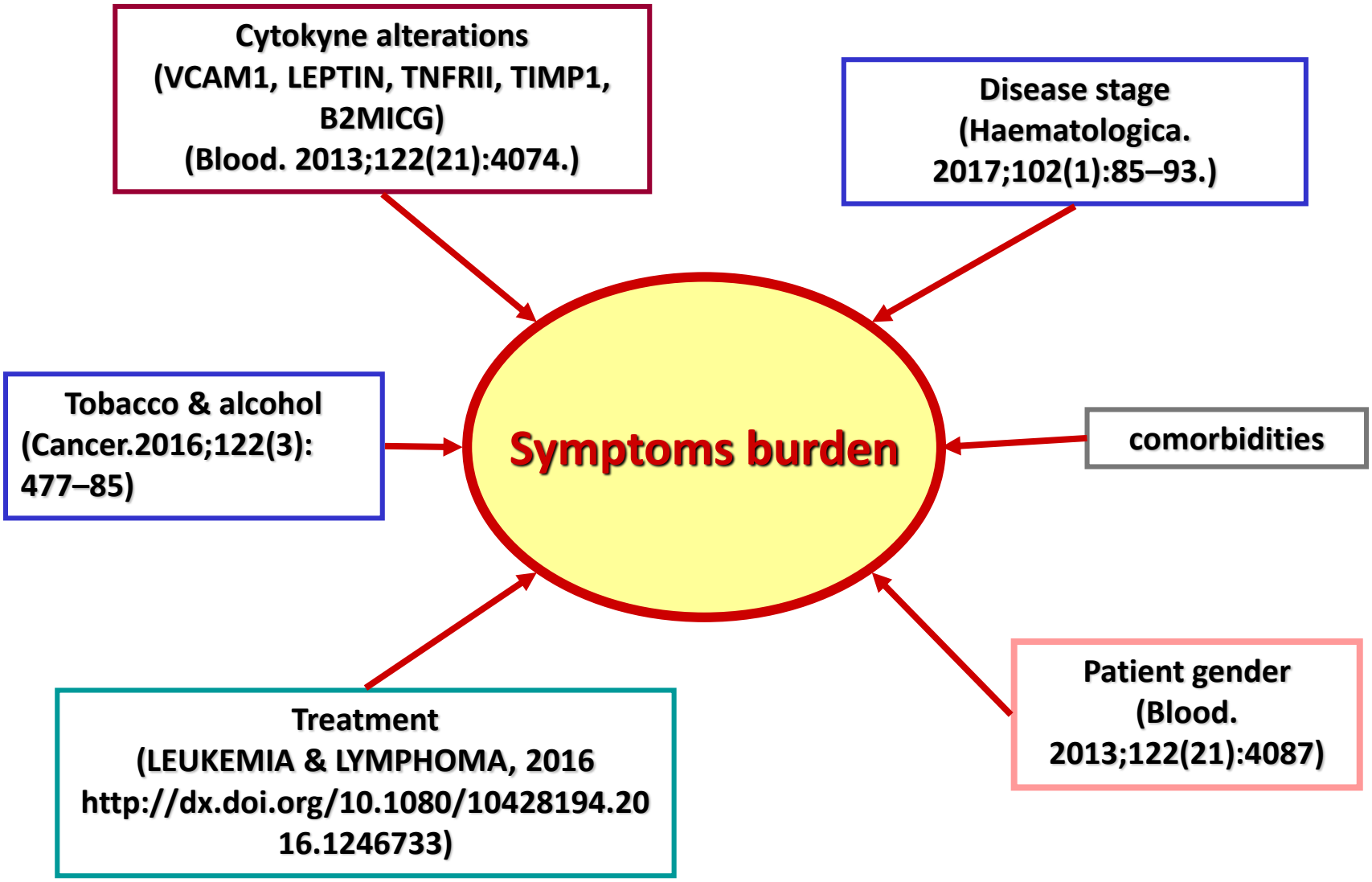
PSIS

PGIC

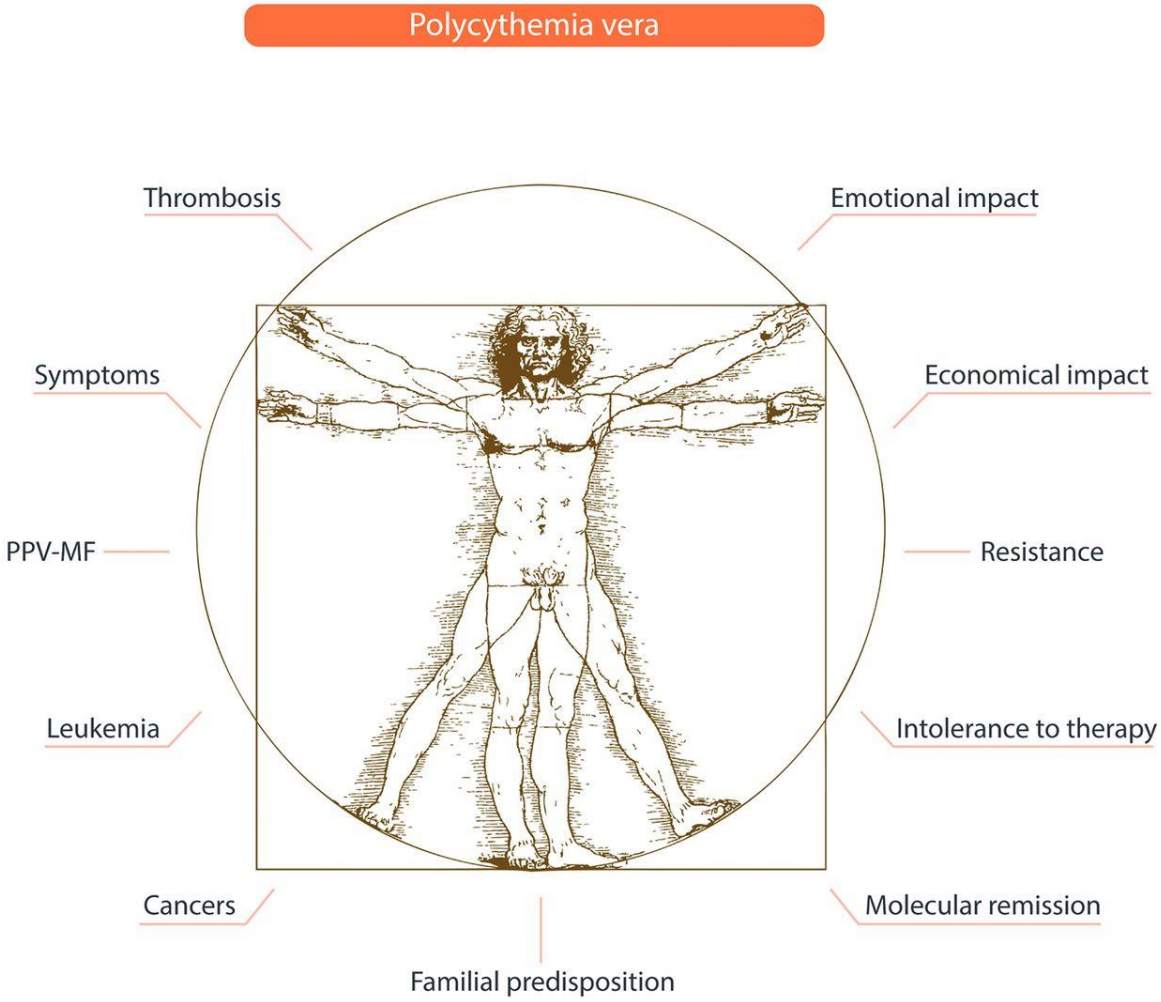
Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)

Symptom	1 to 10 (0 if absent) ranking 1 is most favorable and 10 least favorable
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours*	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Circle the one number that describes how, during the past week how much difficulty you have had with each of the following symptoms	
Filling up quickly when you eat (Early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration - Compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Numbness/ Tingling (in my hands and feet)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

* Question used with permission from the MD Anderson Cancer Center Brief Fatigue Inventory ©


Cytokyne alterations
(VCAM1, LEPTIN, TNFRII, TIMP1, B2MICG)
(Blood. 2013;122(21):4074.)
Disease stage
(Haematologica. 2017;102(1):85–93.)
Tobacco & alcohol
(Cancer.2016;122(3): 477–85)
Symptoms burden
comorbidities
Treatment
(LEUKEMIA & LYMPHOMA, 2016 http://dx.doi.org/10.1080/10428194.2016.1246733)
Patient gender
(Blood. 2013;122(21):4087)

The burden of disease in a patient with polycythemia vera



Vannucchi AM Haematologica 2017;102:18

Goals of Therapy in Patients with PV

Barbui T, et al. *J Clin Oncol.* 2011;29:761-770.