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

Federico Silvestri
Ambulatorio di Ematologia
Ospedale di Latisana

Palmanova, 21 Novembre 2019

POLICITEMIA

πolys = molto

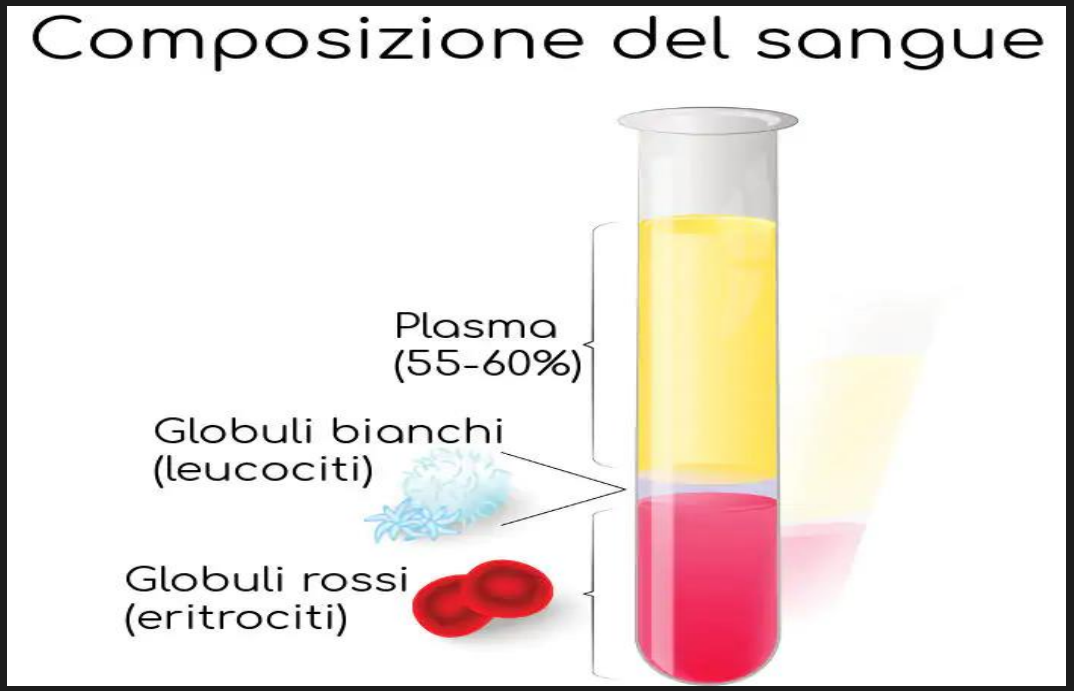
kytos = cellula

hema = sangue

HCT

Rapporto che intercorre tra gli elementi figurati del sangue ed il plasma

(rapporto % tra GR e plasma)



ERITROCITOSI

♂ Hb > 165 g/L o Ht > 49%
♀ Hb > 160 g/L o Ht > 48%

Relative

- Disidratazione
- Stress
- Terapia diuretica
- Ustioni

Assolute

Acquisite

- **Policitemia Vera (PV)**
- Altitudine
- Malattie polmonari croniche ostruttive
- Shunt cardiovascolari
- OSAS
- Tabagismo
- Malattie renali
- Tumori (HCC, polmone, ovaio)
- Androgeni
- Doping

Congenite

- PFCP (Mutazioni EPO--R)
- Mutazioni in OSP (VHL, HIF2α, PHD2)
- Metaemoglobinemia
- Hb alta affinità per O_2
- Difetti del 2,3 bifosfoglicerato

ERITROCITOSI IDIOPATICA

McMullin MF. Ther Adv Hematol. 2012;3: 391–8.

Storia della PV

- 1^ descrizione: 1892 L.H.Vaquez e 1903 W.Osler (PRV, malattia di Osler-Vaquez)
- Inclusione nei MPD: 1951 W.Dameshek
- Nascita del PVSG: 1967 (Dx*)
- Natura clonale: 1976 J.W.Anderson
- Scoperta mutazione JAK2: 2005 vari autori
- WHO classification of MPN: 2008 e 2016

CRITERI DIAGNOSTICI PVSG

- **Maggiori**: RCM ≥ 36/32 mL/Kg, Sat. O_2 ≥ 92%, Splenomegalia
- **Minori**: PLT ≥ 400.000/µL, GB ≥ 12.000/µL, ALP score > 100, Vit.B12 > 900 pg/mL
- **Dx: 3 maggiori o 2 + 2**

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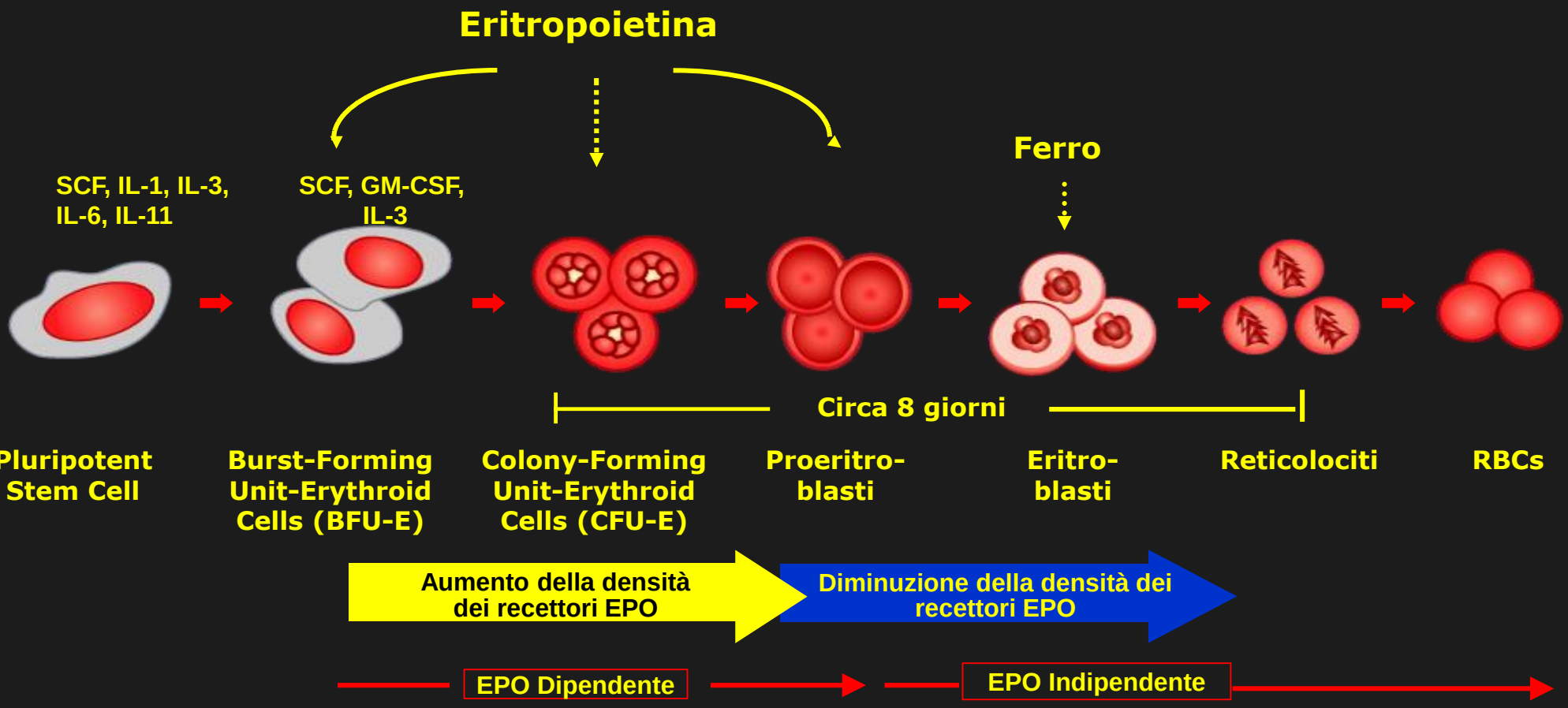
AGENDA

- Fundamentals
- Inquadramento nosologico
- Diagnosi e Diagnosi differenziale
- (Clinica)
- Terapia

AGENDA

- **Fundamentals**
- **Inquadramento nosologico**
- **Diagnosi e Diagnosi differenziale**
- **(Clinica)**
- **Terapia**

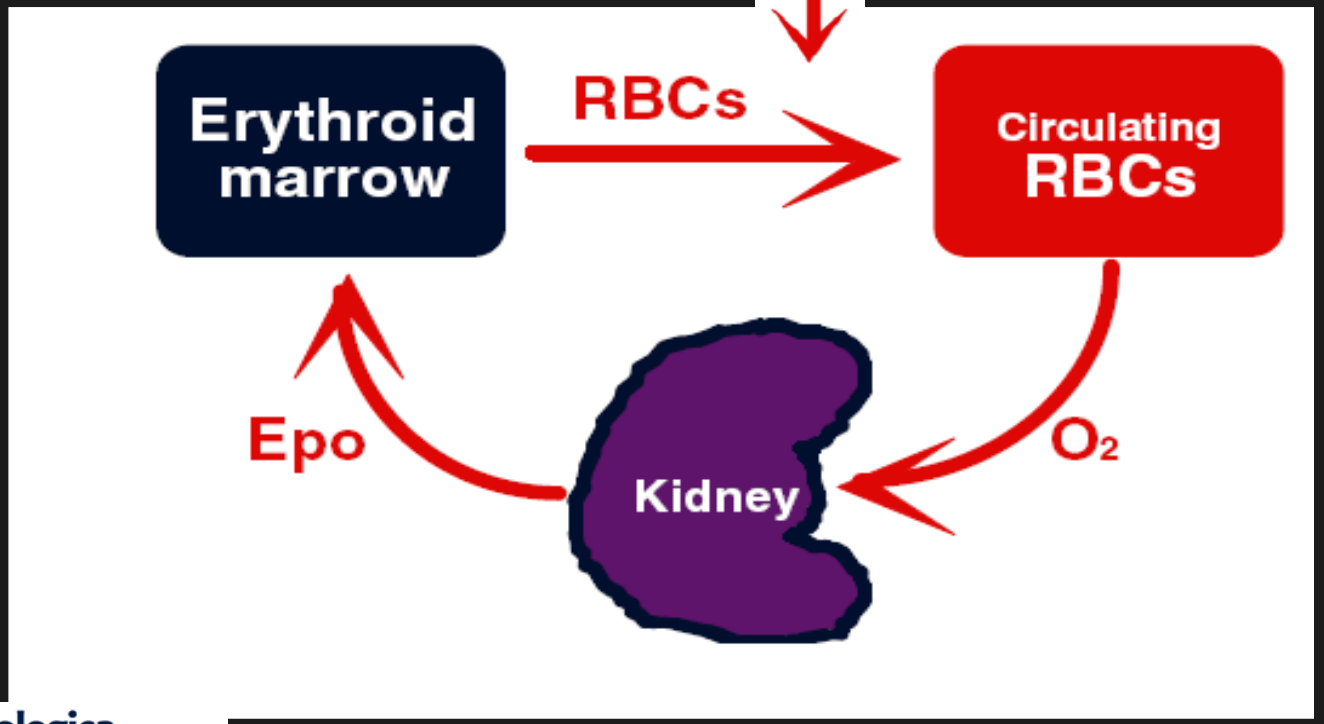
L'eritropoietina è essenziale per l'eritropoiesi



Papayannopoulou T, et al. In: Hoffman R, et al., ed. *Hematology: Basic Principles and Practice*. 4th ed. 2005;267-288.

Erythropoietin is the primary regulator of erythropoiesis

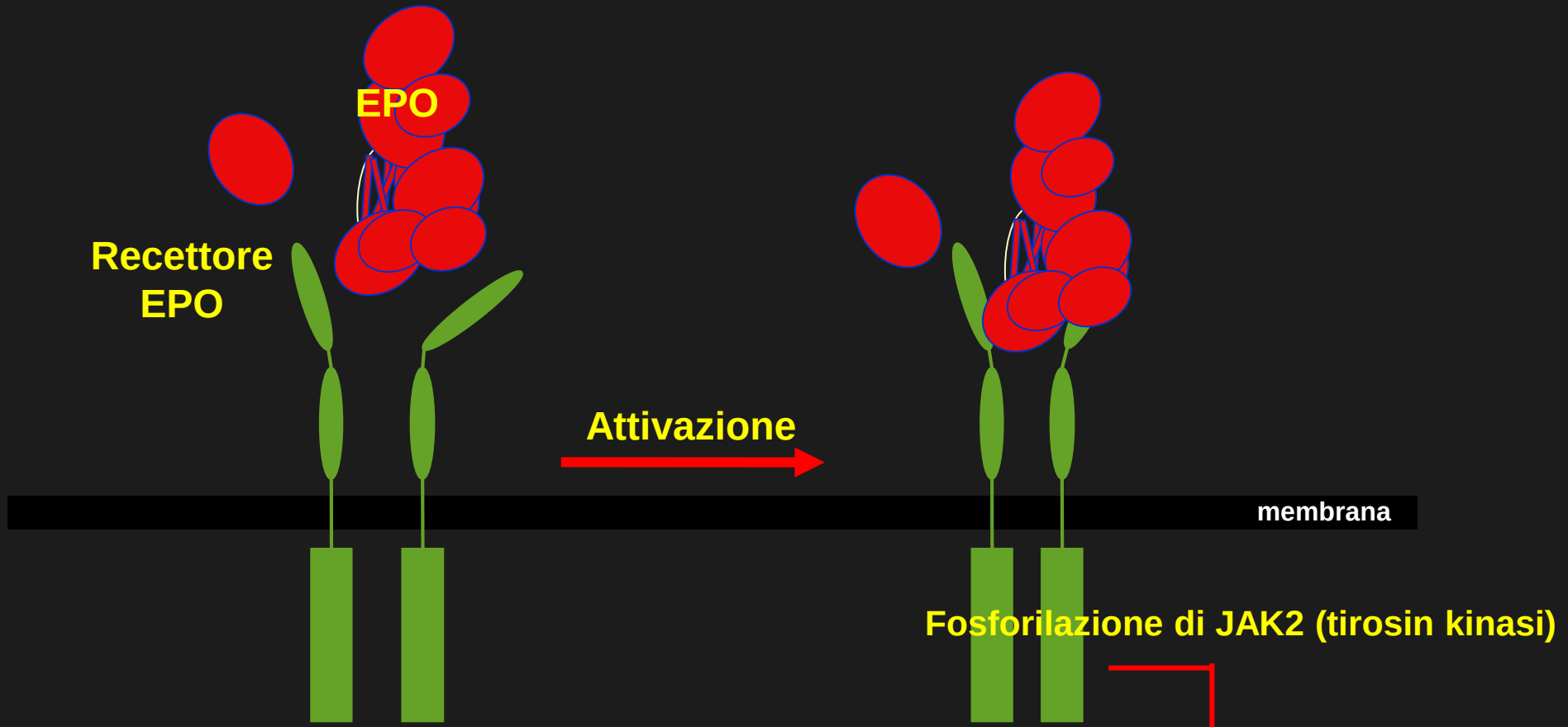
Iron is critical for heme synthesis
(O^2 carrier as part of hemoglobin)



haematologica
the hematology journal

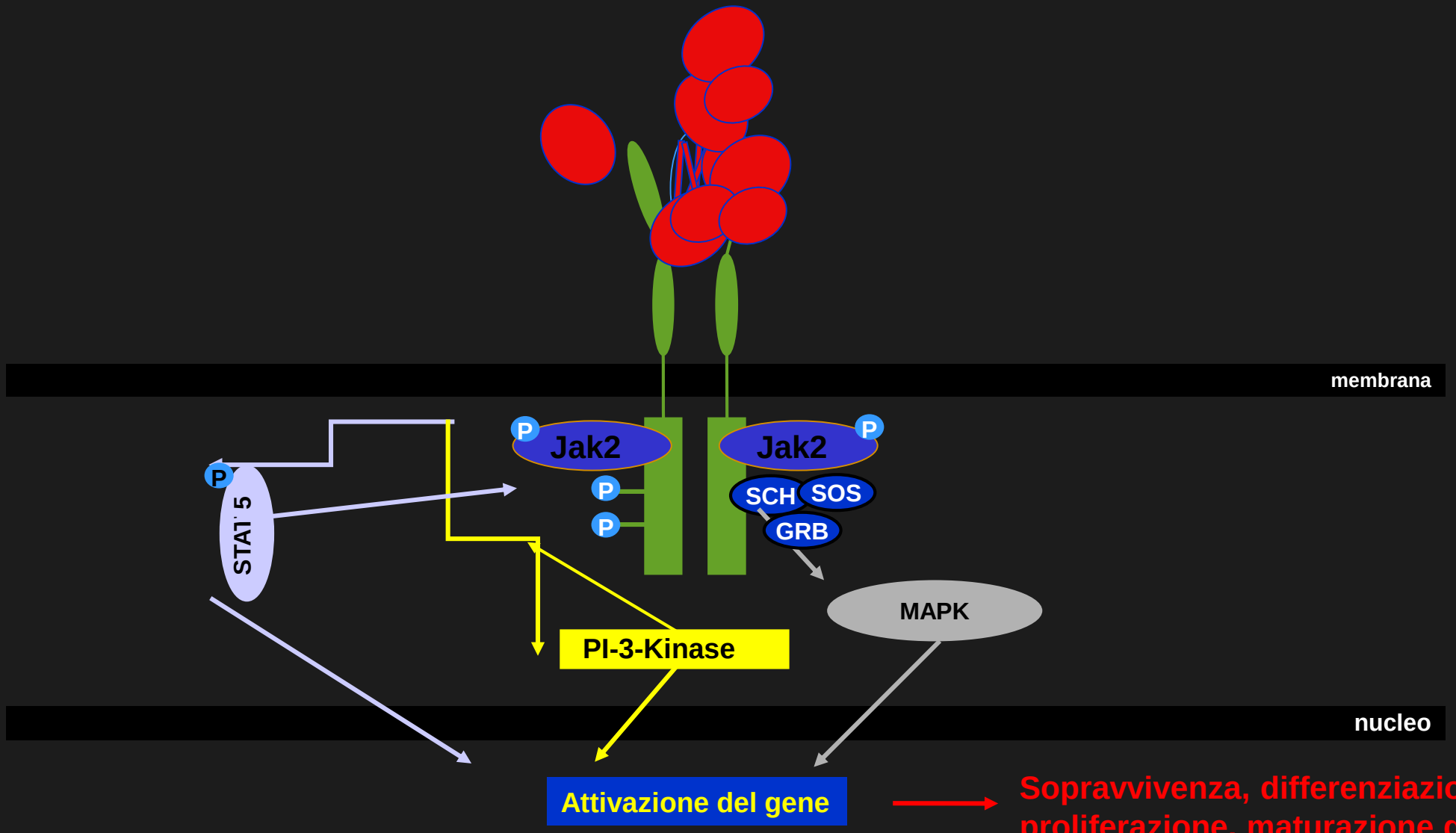
Haematologica 2003;88:601

EPO stimola l'eritropoiesi agendo sul recettore EPO



Papayannopoulou T, et al. In: Hoffman R, et al. eds. *Hematology Basic Principles and Practice*, 4th ed. Philadelphia, PA: Elsevier Churchill Livingstone. 2005:267-288. Watowich SS. *Int J Biochem Cell Biol*. 1999;20:1075-1088.

Il recettore EPO attiva il gene che promuove l'eritropoiesi



Sopravvivenza, differenziazione, proliferazione, maturazione dei progenitori e dei precursori dei GR

Constantinescu SN, et al. TEM. 1999;10:18-23.
Miura Y, et al. J Biol Chem. 1994;269:29962-29969.
Rossert J, et al. *Nehrol Dial Transplant*. 2005;20:1025-1028.

VALORI NORMALI

	♂	♀
Hb gr/dL	14 – 18	12 – 16
Hct %	42 – **52**	36 – **46**
	47± 5	41 ± 5

Fattori che possono variare il valore di Hb/Hct

- Età ↓ (non tutti d'accordo)
- Etnia ↓1-2% Afro-americani
- Altitudine ↑ 1 gr/dl ogni 3-4% ↓ Sat O2
- Fumo ↑ 0.5-1 gr/dl x ipossia
- Laccio ↑ 2,5-5% Hct
- Stress ↑ fino a 1 gr/dl x ansia e dolore
- Dieta (introito H2O)
- Attività fisica
- **Variabilità individuale**

Legge di Poiseville

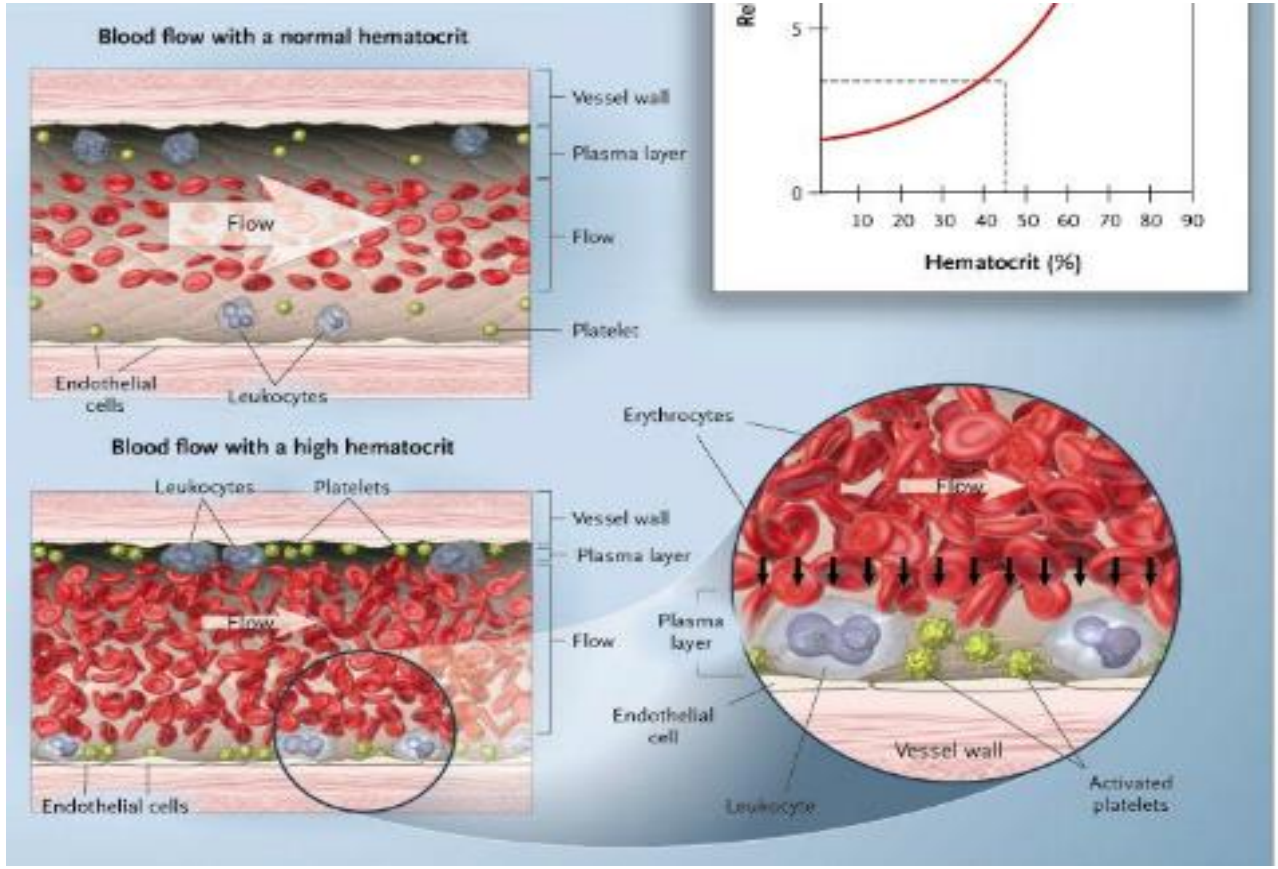
Fluidodinamica: lega la viscosità di un fluido alla sua conducibilità idraulica

$K = 8S / \pi\mu$

S = sezione della condotta

μ = viscosità del fluido considerato

Effects of elevated red cell mass in PV



- Red cell aggregation increases at high Hct level, favouring vascular stasis

- The resulting enhanced interplay between platelet, leukocytes and vessel wall might facilitate thrombosis

Spivak JNEJM. 2004 Jan 8; 350(2):99-101.

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- Diagnosi
- Clinica
- Terapia

ERITROCITOSI

♂ Hb > 165 g/L o Ht > 49%
♀ Hb > 160 g/L o Ht > 48%

Relative

- **EMOCONCENTRAZIONE** (sudorazione,vomito, diarrea, DM, D.Insipido, terapia diuretica, Ustioni)
- **STRESS** o M.di Gaisbok

Assolute

Acquisite

- **P. PRIMITIVA o Vera (PV)**
- **P. SECONDARIE**

1) > FISIOLOGICO produzione EPO

- Soggiorno in altura, Malattie polmonari croniche ostruttive, Shunt Dx-Sn, OSAS, Tabagismo (carbossiHb)

2) INAPPROPRIATA secrezione EPO

- Malattie renali (r.policistico,cisti, idronefrosi), Tumori (HCC, cerebellari, renali, fibromi), S.Cushing

3) ASSUNZIONE EPO

Congenite

ERITROCITOSI IDIOPATICA

AGENDA

- Fundamentals
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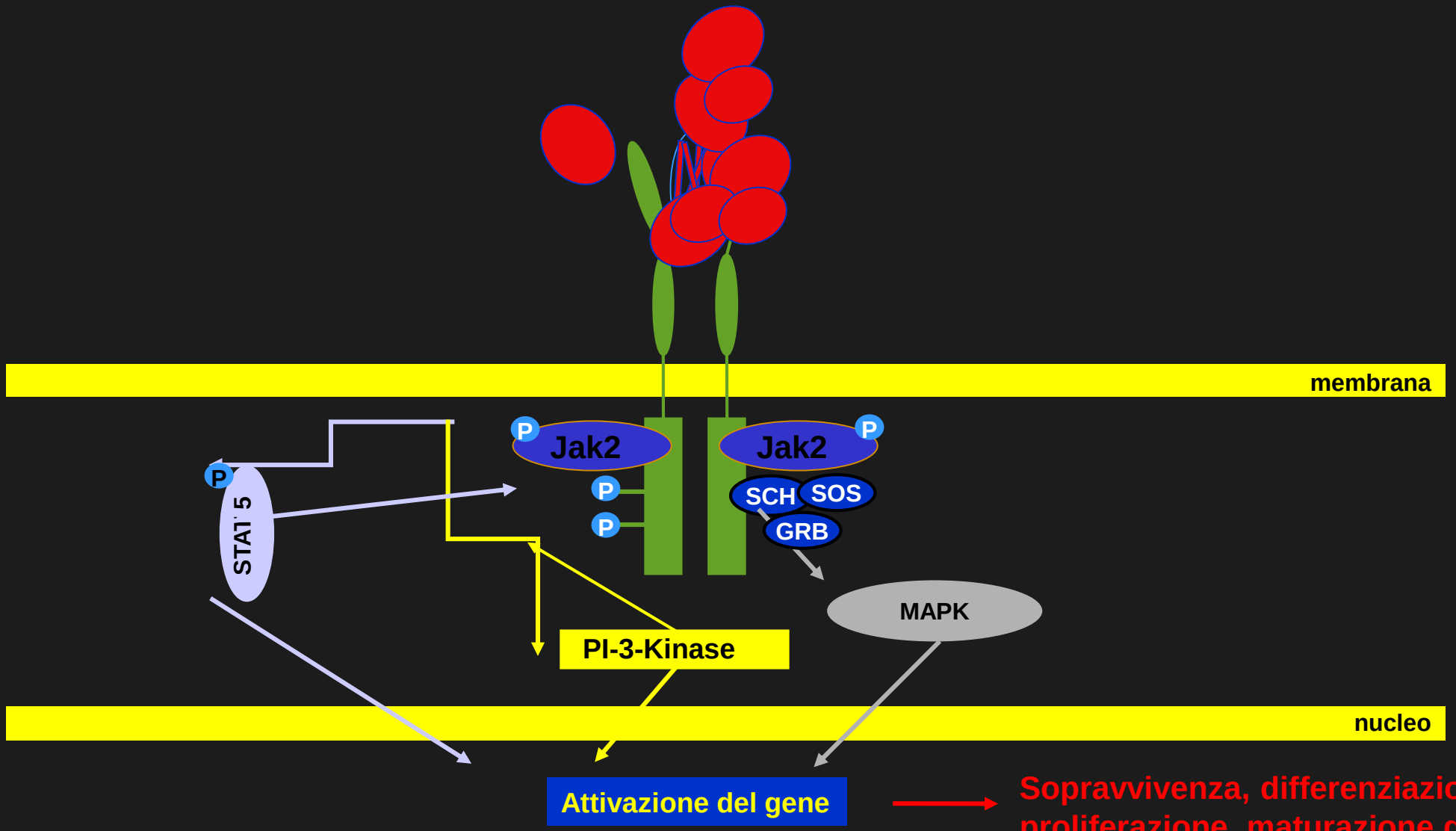
POLICITEMIA VERA

- Disordine clonale della cellula staminale emopoietica multipotente (WHO: Ph neg cMPN)
- Mediana età 60 aa
- M/F 1.2 : 1.0
- Incidenza 0.6 – 1.6 /100.000/anno

MUTAZIONE JAK2V617F

- Mutazione puntiforme in posizione 617 del Cr. 9, con sostituzione di Valina con Fenilalanina
- Avviene nell'esone 14 nel 95-96% dei casi; nell'esone 12 nel 2-3% = 98%
- Codifica per una tirosin kinasi (Janus Kinase 2) coinvolta nella via di segnalazione JAK-STAT

La mutazione JAK2 attiva il gene che promuove l'eritropoiesi



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Rossert J, et al. *Nehrol Dial Transplant*. 2005;20:1025-1028.

ORIGINAL ARTICLE Hematolymphoid Malignancies

Influence of JAK2V617F allele burden on clinical phenotype of polycythemia vera patients: A study from India

Sudha Sazawal, Kanwaljeet Singh, Sunita Chhikara, Rekha Chaubey, Manoranjan Mahapatra, Renu Saxena

Abstract

Background: Elevated JAK2V617F allele burden is associated with enhanced expression of downstream target genes in Philadelphia negative chronic myeloproliferative neoplasms (CMPNs) which include PV, ET & PMF. Previous studies have shown the impact of JAK2V617F allele burden on clinical phenotype of CMPNs. However, there is no data from India regarding the association between JAK2V617F allele burden and clinical phenotype in PV. **Aims/Settings and Design:** We aimed to investigate the effect of allele burden on clinical phenotype in 90 JAK2V617F positive PV patients and to see its influence on disease related complications. **Material and Methods:** Allele burden of 90 JAK2V617F positive PV patients was quantified by Real-time polymerase chain reaction (RQ-PCR). **Results:** 74/90 (82.22%) were males and 16/90 (17.78%) were females (median 45 years, range 35-78). Patients with age >50 years had significantly higher JAK2V617F allele burden (median 40.15%, range 0.49–91.62 %) than patients with ≤ 50 years age (median 48.59 %, range 0.56–86.74 %; $P < 0.032$). Patients with splenomegaly had significantly higher JAK2V617F allele burden (mean 50.24%, range 6.91–84.17%) than patients without splenomegaly (mean 33.82 %, range 0.49–71.83 %; $P < 0.017$). Patients with higher allele burden (median 57.20, range 43.4–72.03%) had significantly raised thrombotic events than the patients with lower allele burden (median 37.38, range 0.49–84.17%; $P < 0.043$). 49/90 (54%) were homozygous and 41/90 (46%) were heterozygous. **Conclusions:** Higher JAK2V617F allele burden showed association with increased age, splenomegaly and thrombotic events. Thus, it may be considered for prognostication and setting up the treatment protocol in PV patients.

Key words: JAK2V617F allele burden, polycythemia vera, real-time polymerase chain reaction

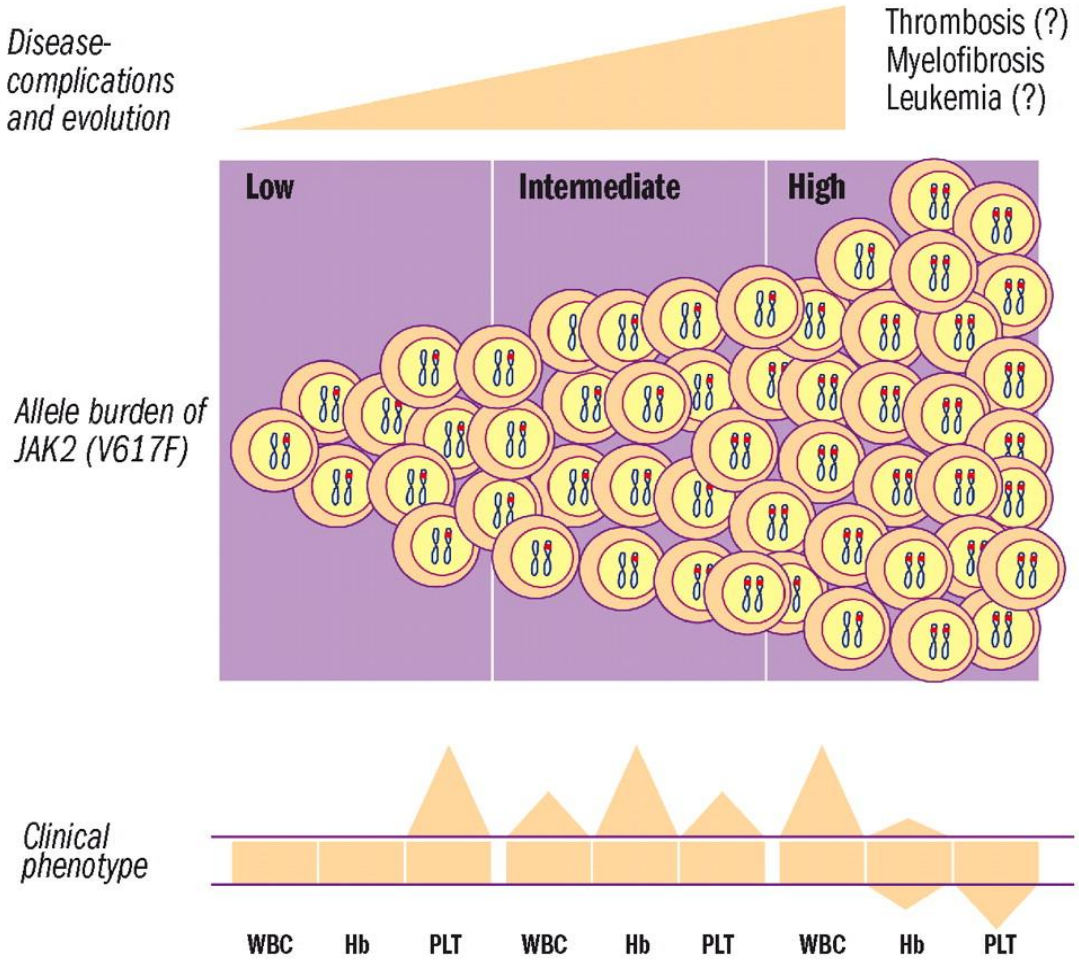
Therapeutic Advances in Hematology *Review*

JAK2 allele burden in the myeloproliferative neoplasms: effects on phenotype, prognosis and change with treatment

Ther Adv Hematol
(2011) 2(1) 21–32
DOI: 10.1177/2040620710394474

Alessandro M. Vannucchi, Lisa Pieri and Paola Guglielmelli

Abstract: The field of Philadelphia-chromosome-negative chronic myeloproliferative neoplasms (MPNs) has recently witnessed tremendous advances in the basic knowledge of disease pathophysiology that followed the identification of mutations in *JAK2* and *MPL*. These discoveries led to a revision of the criteria employed for diagnosis by the World Health Organization. The prognostic role of the *JAK2*V617F mutation and of its allelic burden has been the objective of intensive research using a variety of cellular and animal models as well as in large series of patients. While a definitive position cannot yet been taken on all of the issues, there is a consensus that the presence of higher V617F allele burden, that is on the basis of a stronger activation of intracellular signalling pathways, is associated with the clinical phenotype of polycythemia vera and with defined haematological and clinical markers indicative of a more aggressive phenotype. On the other hand, a low allele burden in myelofibrosis is associated with reduced survival. Finally, a significant reduction of *JAK2*V617F allele burden has been demonstrated in patients treated with interferon, while the effects of novel JAK1 and JAK2 inhibitors have not yet been fully ascertained.


Disease-complications and evolution
Thrombosis (?)
Myelofibrosis
Leukemia (?)
Low
Intermediate
High
Allele burden of JAK2 (V617F)
Clinical phenotype
WBC
Hb
PLT
WBC
Hb
PLT
WBC
Hb
PLT
Cells heterozygous for JAK2 (V617F)
Cells homozygous for JAK2 (V617F)
Normal range
Above normal range
Below normal range

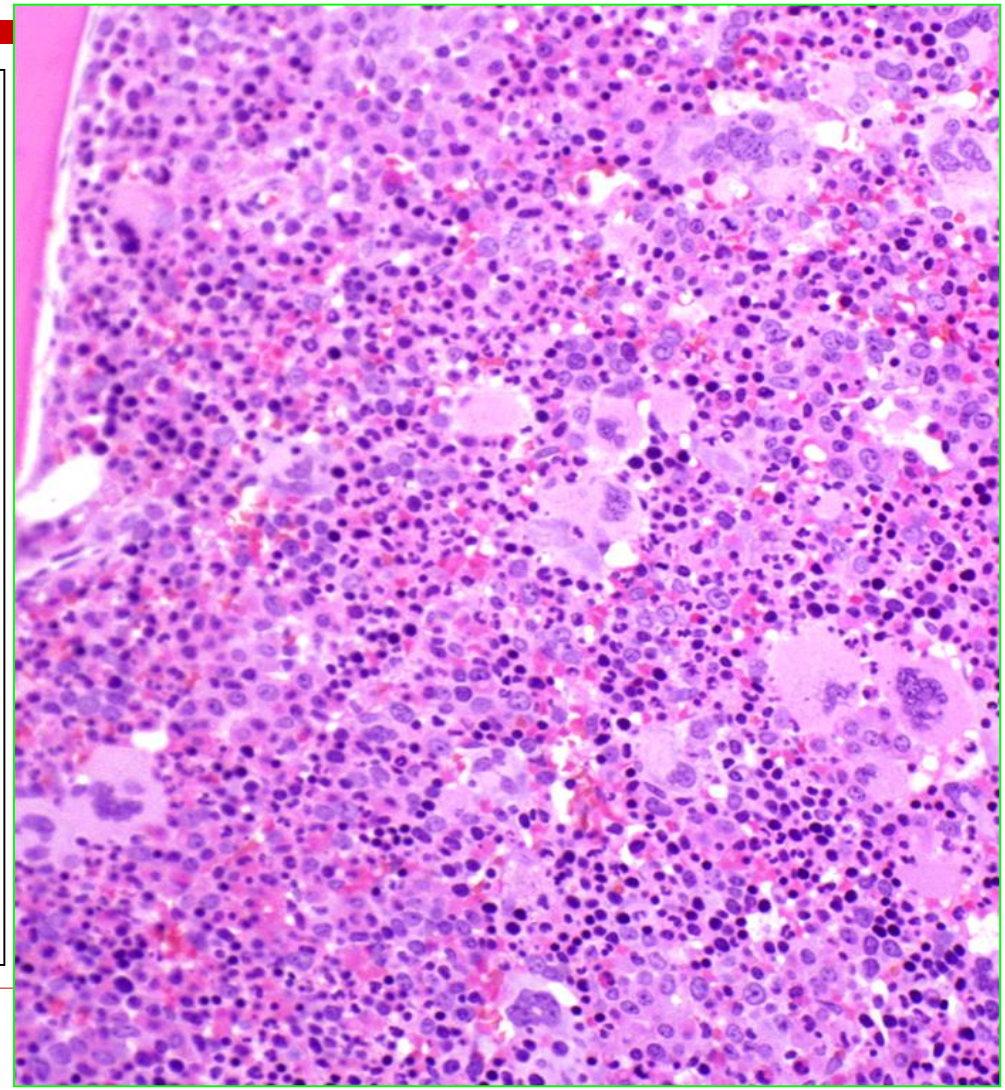
WHO (2008) criteria for polycytemia vera (PV): diagnosis requires the presence **of both major criteria and one minor criterion**, or the presence of the first major criterion together with two minor criteria

Major criteria

1. **Hemoglobin >18.5 g /dL in men, 16.5 g/dL in women** or other evidence of increased red cell volume
2. Presence of **JAK2 V617F** or other functionally similar mutation such **as JAK2 exon 12 mutation**

Minor criteria

1. **Bone marrow biopsy** showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic and megakaryocytic proliferation
2. **Serum eryhtropoietin level** below the reference range from normal
3. Endogenous erythroid colony formation in vitro

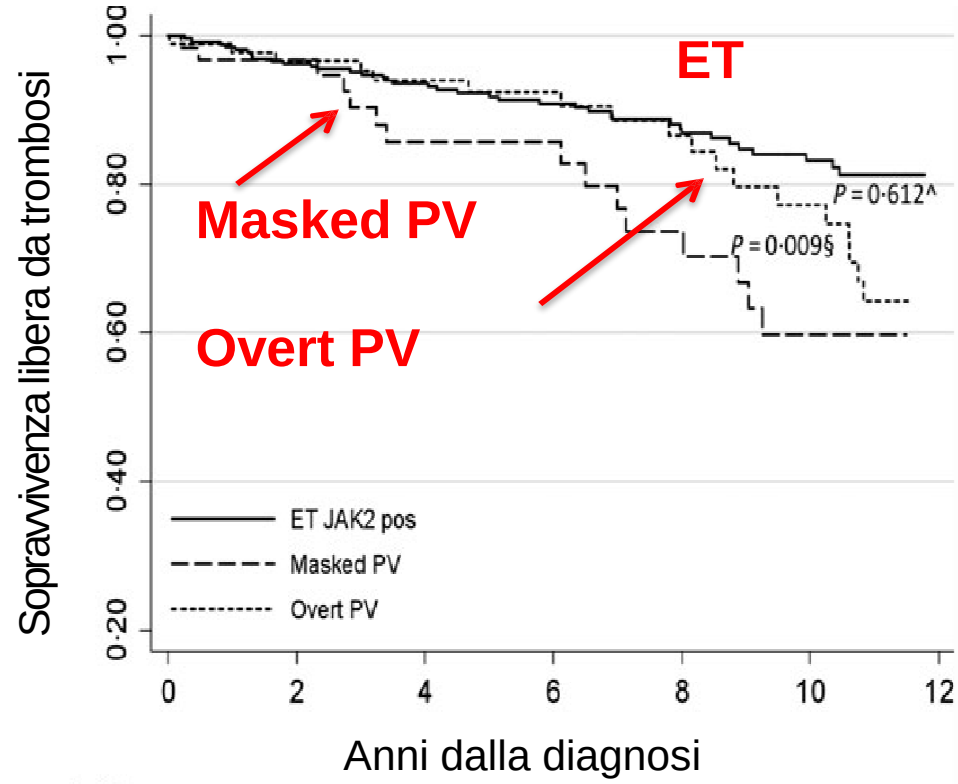


Revisione dei Criteri Diagnostici della WHO per la Policitemia Vera nel 2016

- **Perché?**
  - **Sottostima** della diagnosi sec. criteri del 2008 nel 30-65% dei soggetti nei quali si dimostrava un aumento della massa eritrocitaria
  - Dimostrazione dell'elevata sensibilità e specificità della **biopsia osteomidollare**
  - Dimostrazione dell'esistenza di una forma iniziale ("**mascherata**") di PV
  - Necessità di distinguere le forme "mascherate" di PV dalla **Trombocitemia Essenziale**

Implicazioni dei nuovi criteri diagnostici

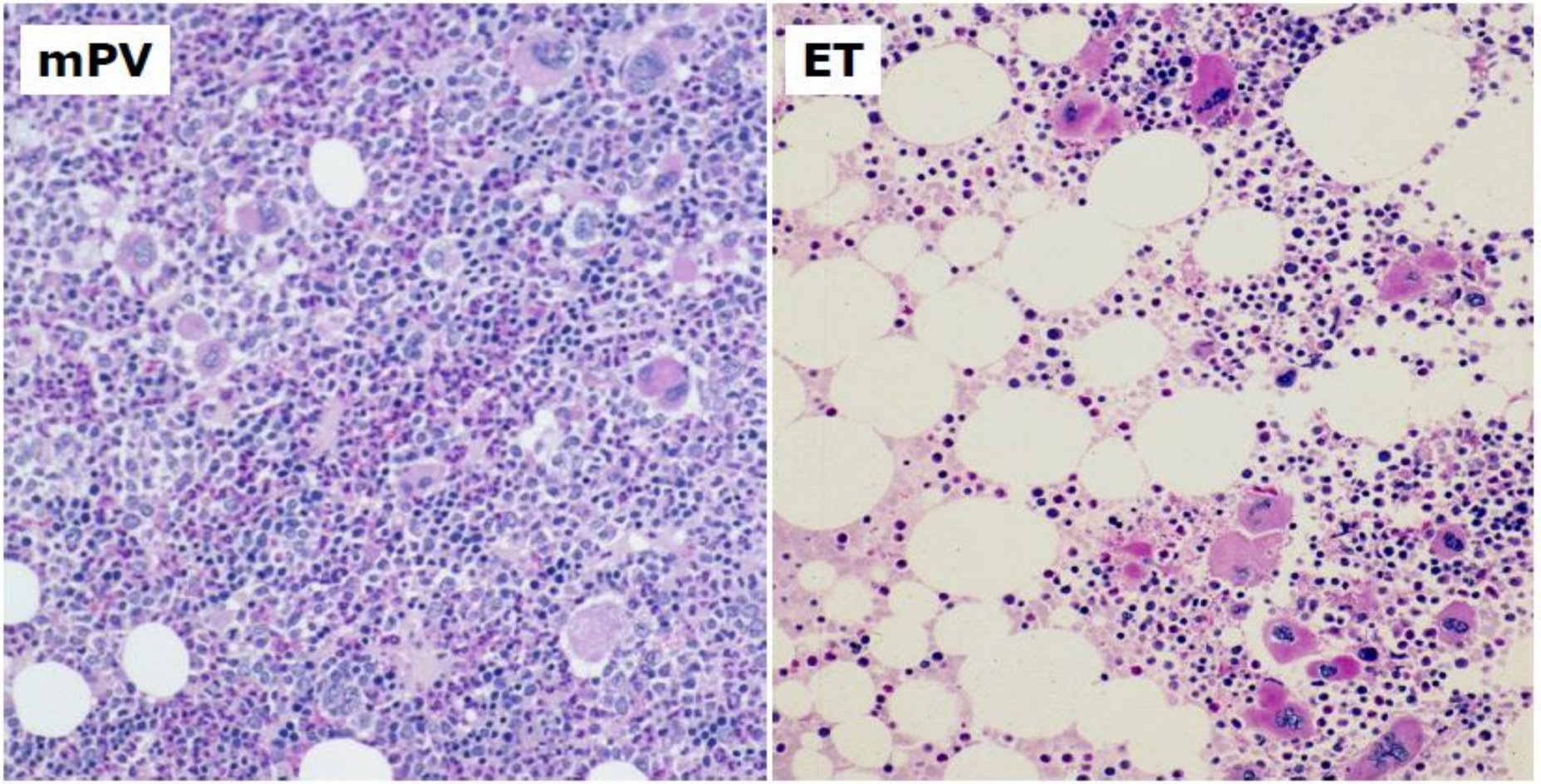
- I “nuovi” livelli di emoglobina ed ematocrito si riscontrano in almeno il 5% della popolazione sana
- I “nuovi” criteri potrebbero risultare in un numero eccessivo di esami non diagnostici
- I “nuovi” criteri devono essere utilizzati ed interpretati da ematologi esperti



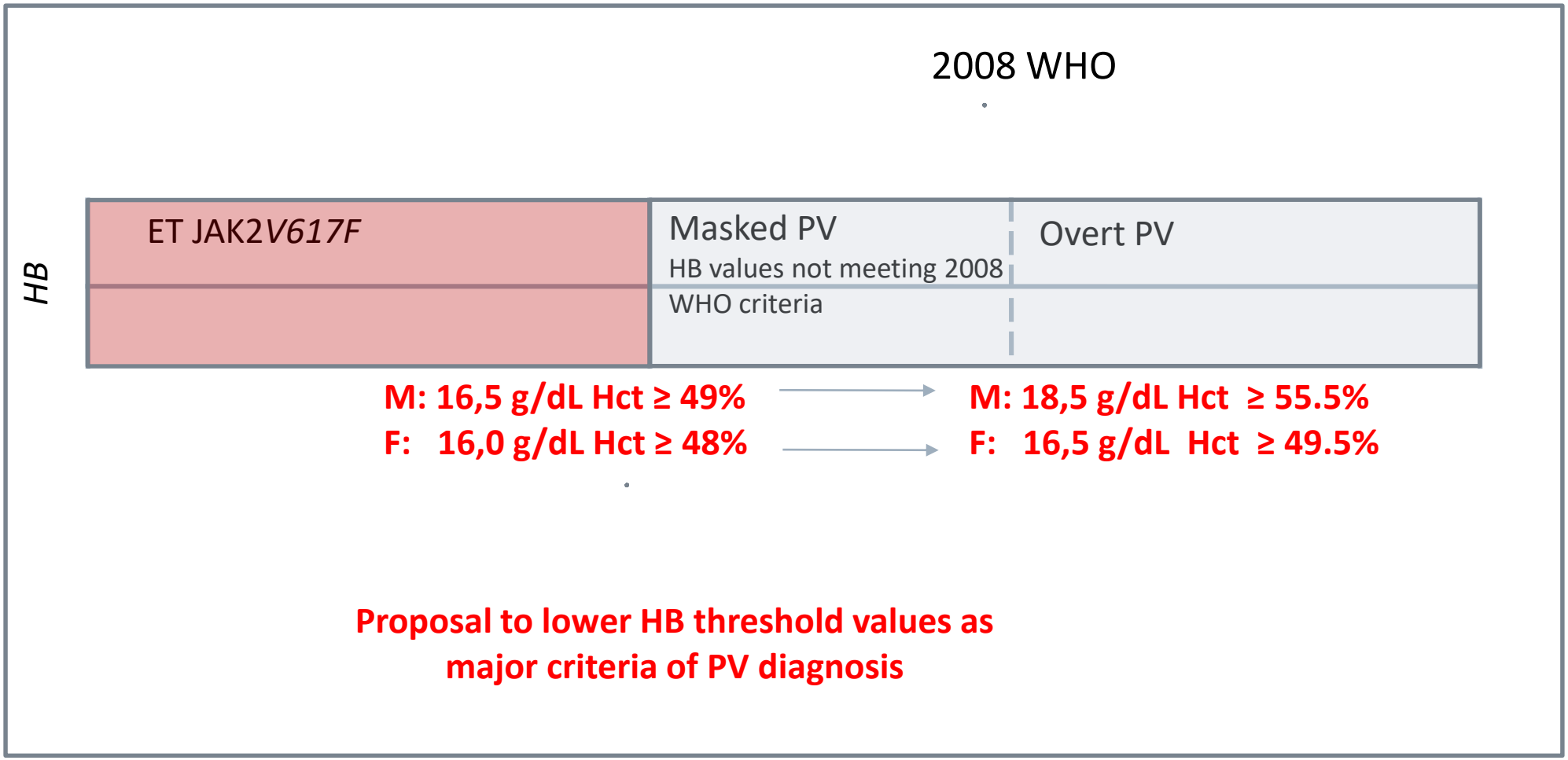
•I pazienti con PV mascherata presentavano un più elevato numero di eventi trombotici, dovuto ad un trattamento meno intensivo

Impact of BM morphology in masked PV

I. Discrimination from ET



Discrimination of ET and PV in JAK2 *V617F* patients by hemoglobin levels



Barbui et al, Leukemia 2014, Barbui et al. AJH 2013, 2014

WHO 2016 - Diagnostic criteria for PV

Major criteria:

1. **Hb > 16.5** g/dL in men , Hb **> 16.0** g/dL in women OR,
   Hct > 49% in men, Hct **>48%** in women OR increased red cell mass

2. **Bone marrow biopsy** showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic and megakaryocytic proliferation with pleomorphic megakaryocytes

3. Presence of **JAK2 mutation**

Minor criterion:

Subnormal serum **EPO level**

Diagnosis of PV requires meeting either all three major criteria, or the first two major criteria and the minor criterion

WHO 2016 – Revised criteria for PV

- In **cases with sustained absolute erythrocytosis** (Hb levels >18.5 g/dL, Hct > 55.5 % in men or >16.5 g/dL, 49.5% in women, **bone marrow biopsy may not be necessary for diagnosis if major criterion 3 and the minor criterion are present.**

- However, only by performing a bone marrow biopsy an **initial myelofibrosis** (up to 20%) may be detected that indicates a more rapid progression to overt myelofibrosis (post-PV MF).

Work-up diagnostico

- Ricerca Mutazione JAK2 + esone 12
- Dosaggio EPO circolante
- (Saturazione O2)
- (Ecografia addome)

REGIONE AUTONOMA FRIULI VENEZIA GIULIA

PRESIDIO OSPEDALIERO UNIVERSITARIO
Santa Maria della Misericordia di Udine

azienda sanitaria universitaria integrata di udine

I.M.F.R.

SOC Istituto di Genetica Medica
Direttore: prof. Giuseppe Damante

Tel.: +39 0432 554321 – Fax: +39 0432 554359
e-mail: giuseppe.damante@asuiud.sanita.fvg.it

Cognome.....Nome.....Sesso.....

Data di nascita.....

Reparto di provenienza e/o medico inviante.....

Sospetto diagnostico.....

Data della diagnosi.....

Fase della malattia.....

Precedenti campioni analizzati per la stessa indicazione [ ] no [ ] si

Se si, data.....risultato.....

MALATTIA MIELOPROLIFERATIVA sospetta (poliglobulie, piastrinosi...)

Fase della malattia.....

Precedenti campioni analizzati per la stessa indicazione [ ] no [ ] si

Se si, data.....risultato.....

MALATTIA MIELOPROLIFERATIVA sospetta (poliglobulie, piastrinosi...)

[ ] mutazione **V617F JAK2**

Se JAK2 V617F neg, [ ] ricerca mutazioni **CALR**

se CALR neg, [ ] ricerca mutazioni **MPL W515L/K**

MALATTIA MIELOPROLIFERATIVA nota (TE, MF, PV) JAK2 V617F negati

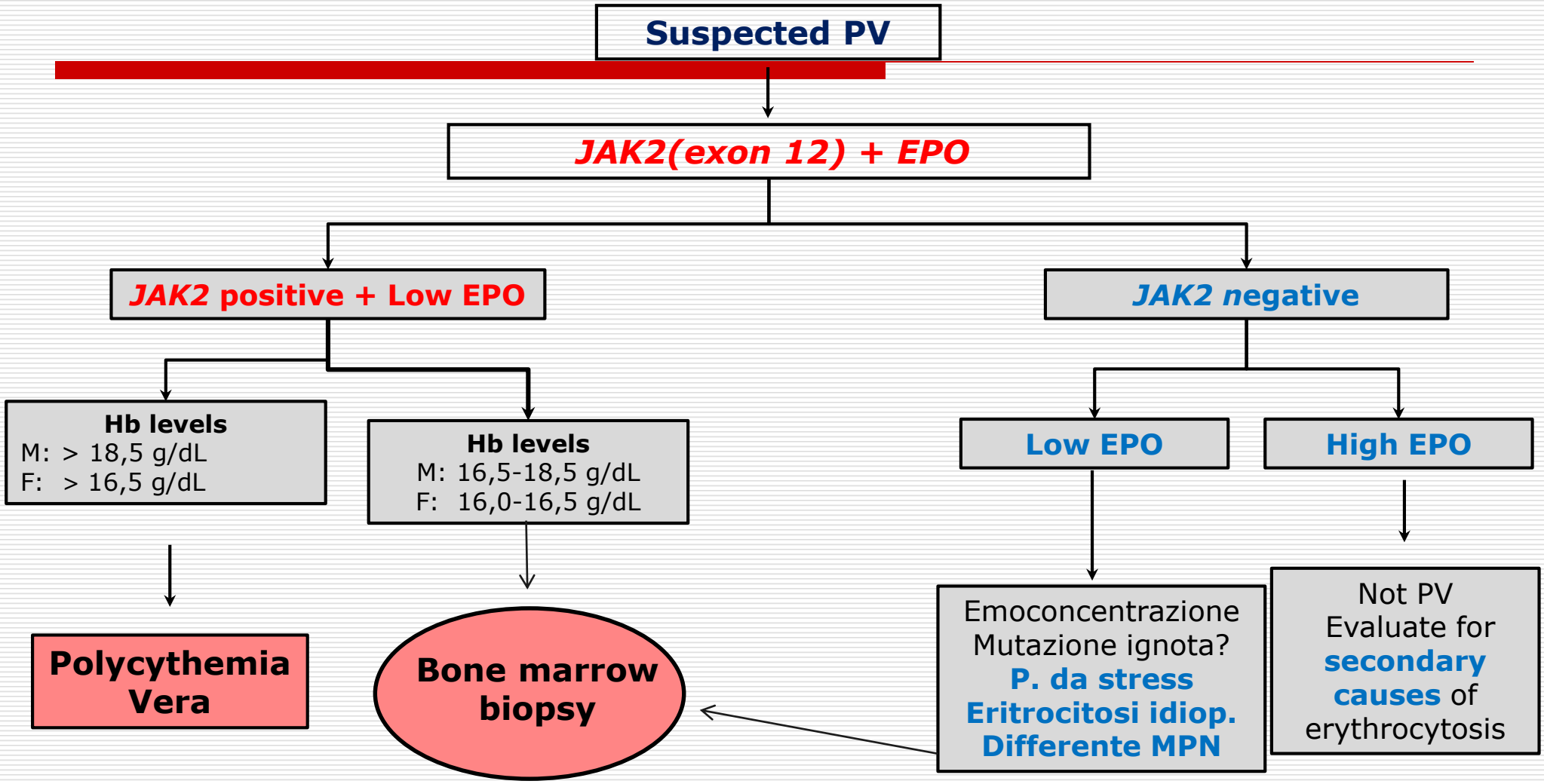
[ ] mutazione **CALR**

se CALR neg , [ ] ricerca mutazioni **MPL W515L/K**

[ ] ricerca mutazioni **JAK2 esone 12**

Materiale inviato [ ] midollo osseo [ ] sangue periferico

Algorithm for diagnosis of PV



Indicazioni alla BO

- casi JAK2 neg (PMF > ET)
- casi con Hb borderline (DD MPN)
- fibrosi midollare (indice prognostico)
- cambio quadro clinico

The role of erythropoietin

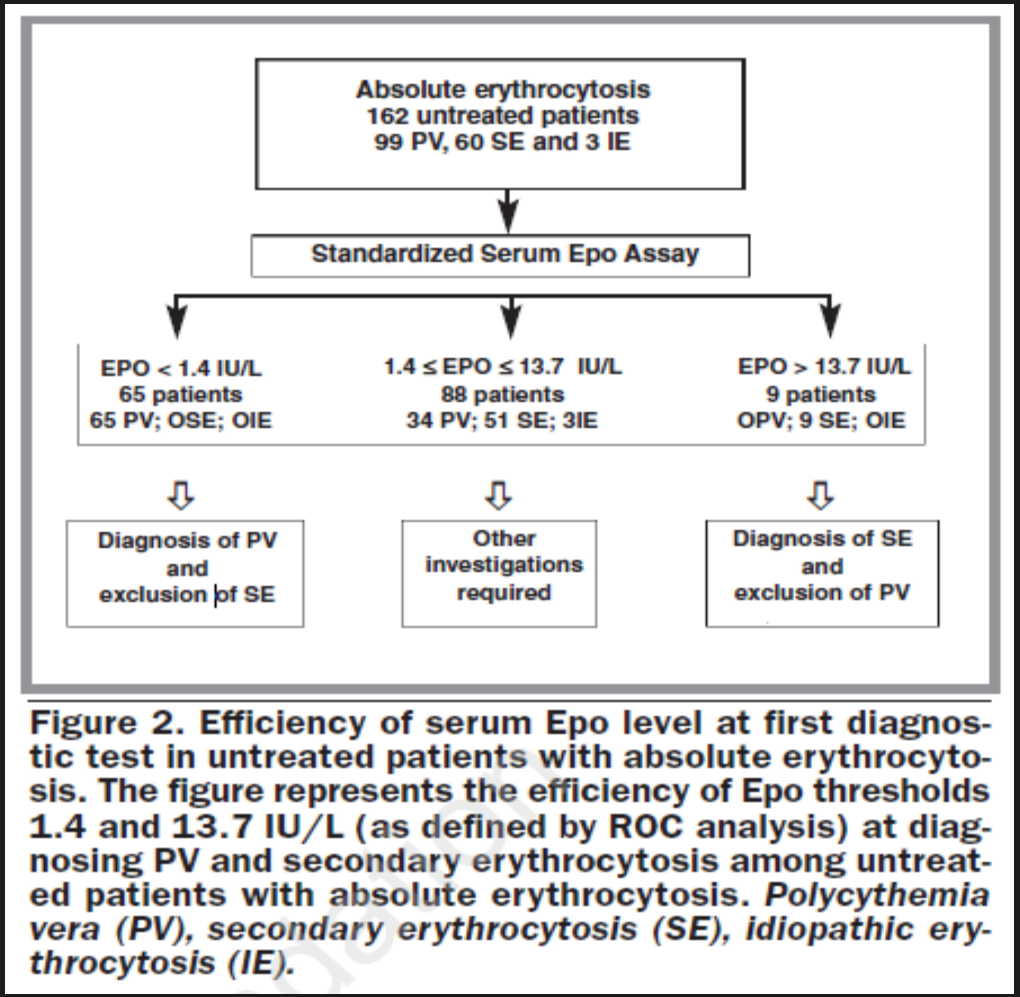


Figure 2. Efficiency of serum Epo level at first diagnostic test in untreated patients with absolute erythrocytosis. The figure represents the efficiency of Epo thresholds 1.4 and 13.7 IU/L (as defined by ROC analysis) at diagnosing PV and secondary erythrocytosis among untreated patients with absolute erythrocytosis. *Polycythemia vera (PV), secondary erythrocytosis (SE), idiopathic erythrocytosis (IE).*

The evaluation of serum erythropoietin is an easy, fast and cheap parameter that aims the physician in the diagnostic evaluation of the patient with polyglobulia

Mossuz P et al. Haematologica 2004 Oct;89(10):1194-8
Tefferi A. Mayo Clin Proc 1999 Feb;74(2):159-62

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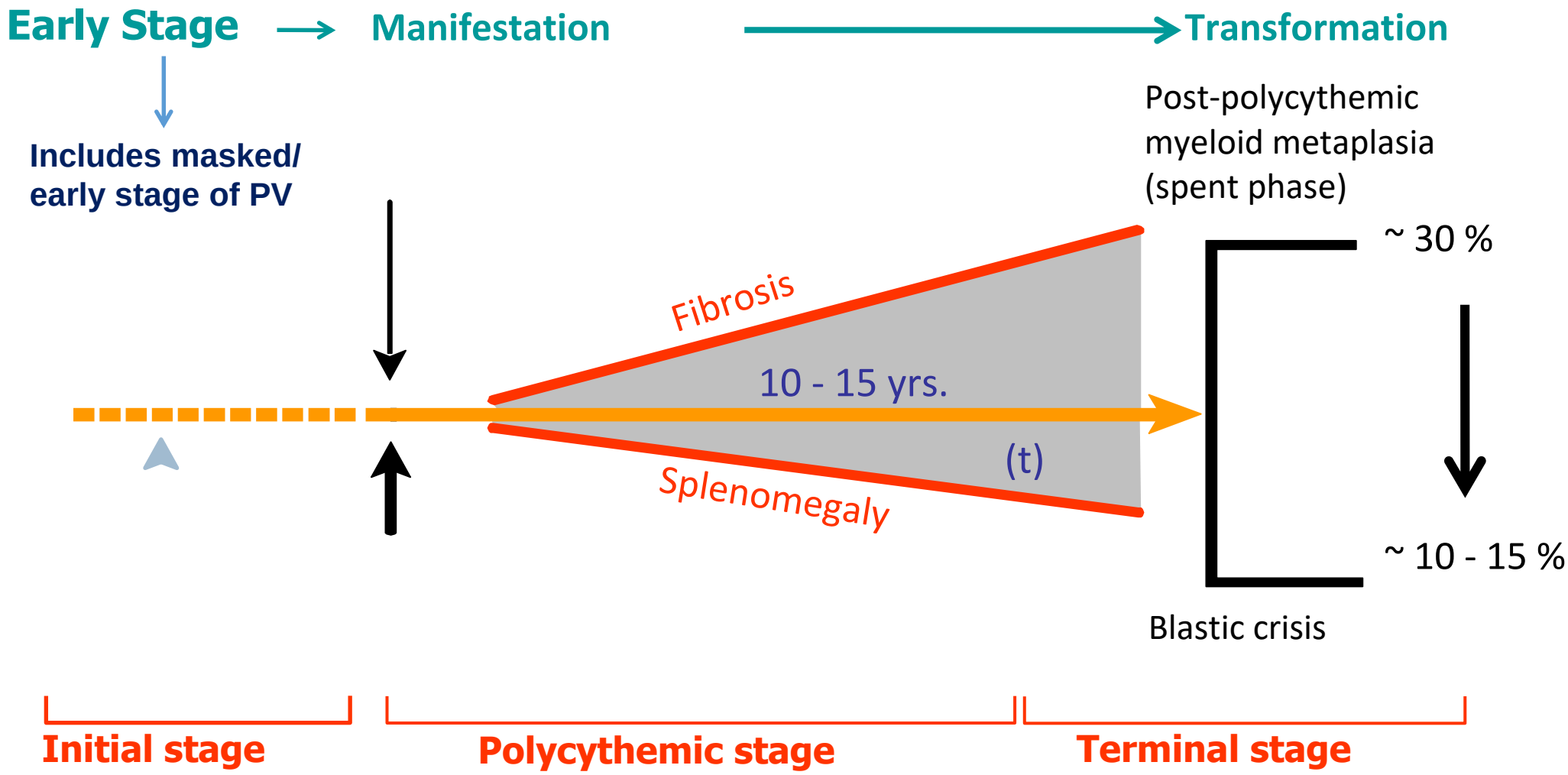
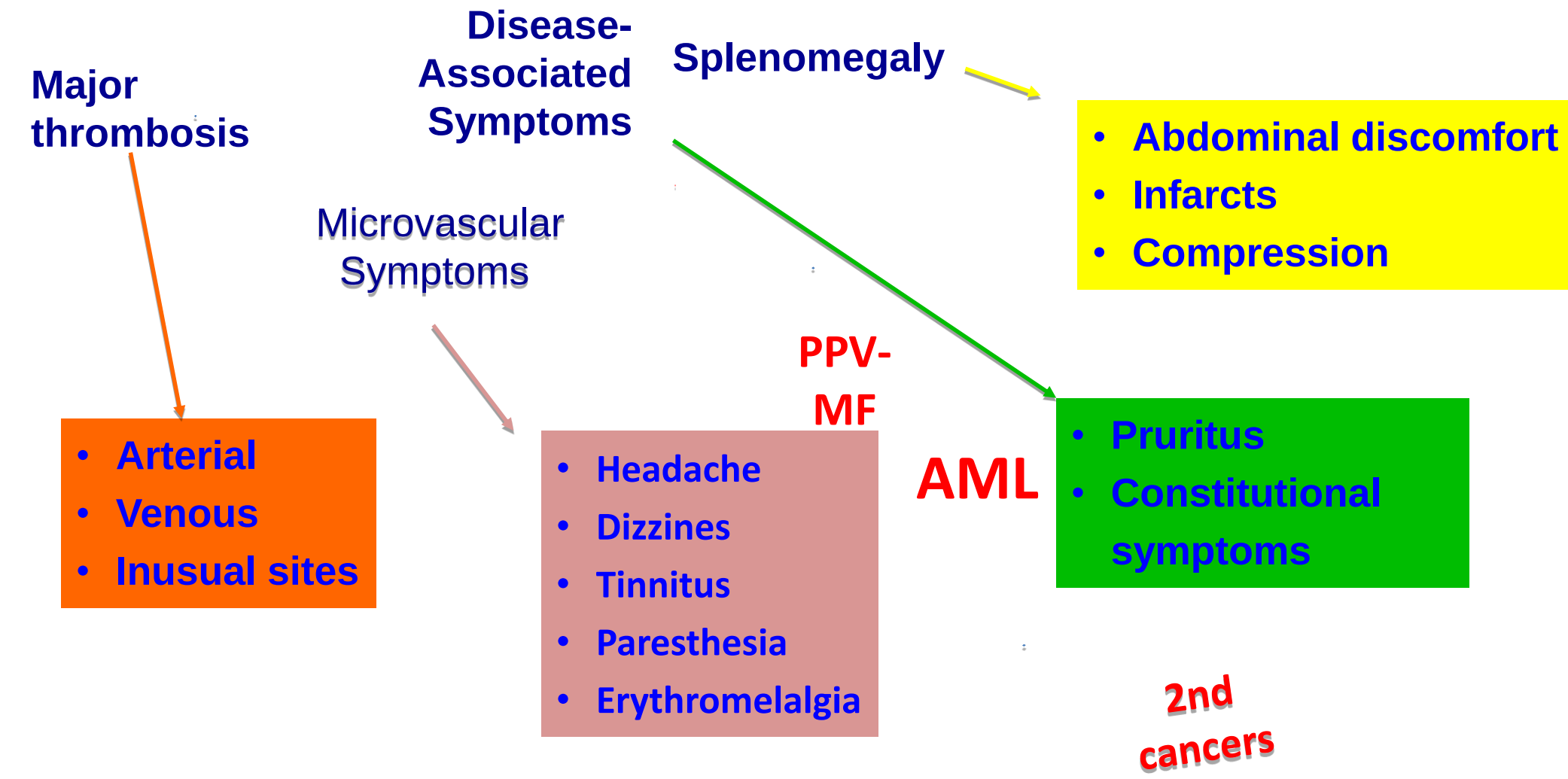
Evolution of the Disease Progress in PV

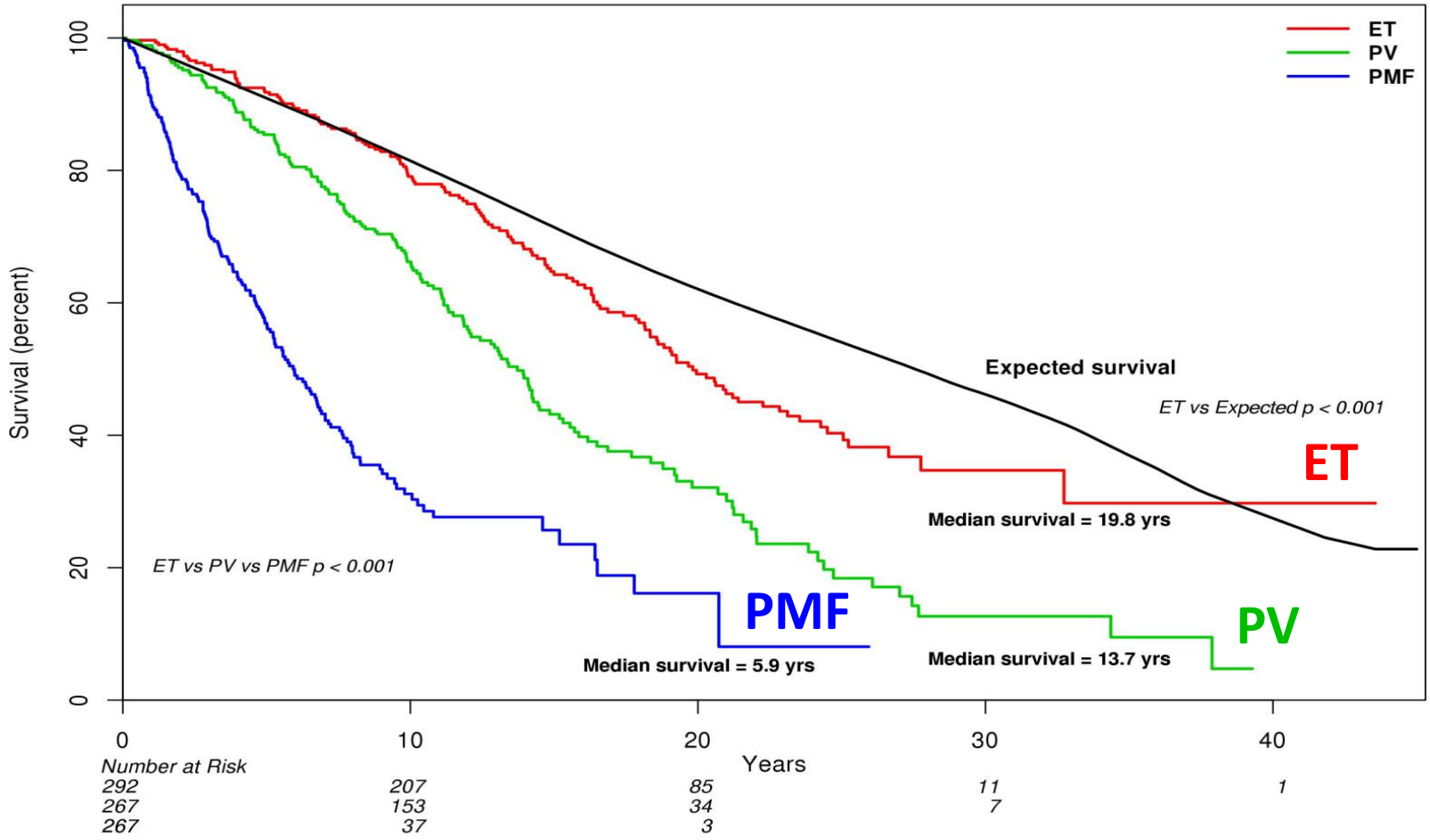


Barbui T et al, Leukemia 2014; 28:1191-5

Burden of PV


Major thrombosis
Disease-Associated Symptoms
Splenomegaly
Microvascular Symptoms
• Abdominal discomfort
• Infarcts
• Compression
PPV-MF
AML
• Arterial
• Venous
• Inusual sites
• Headache
• Dizzines
• Tinnitus
• Paresthesia
• Erythromelalgia
• Pruritus
• Constitutional symptoms
2nd cancers

Overall Survival in PV

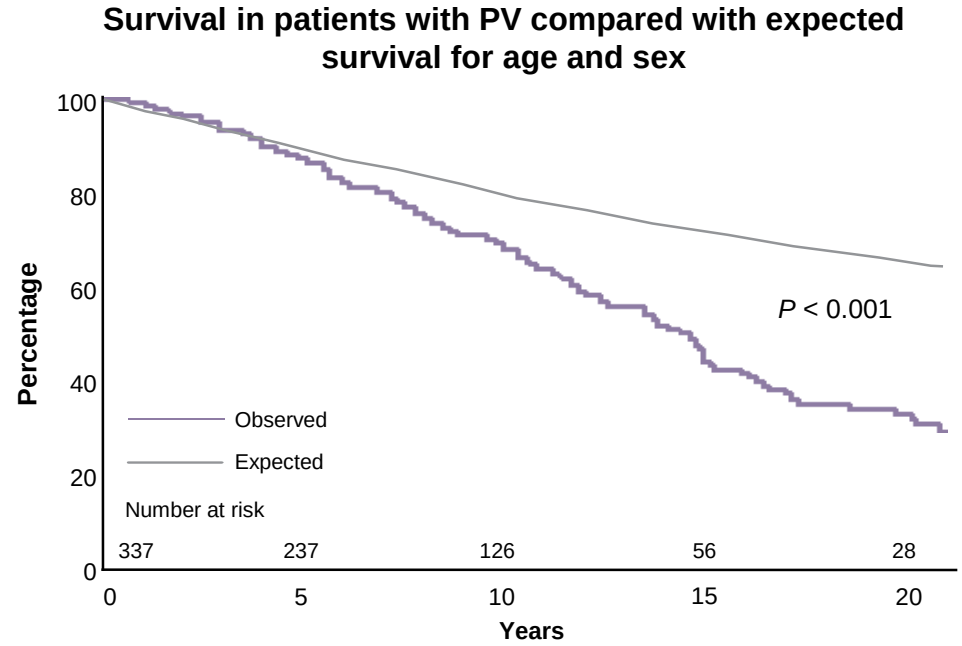


Survival in 337 Mayo Clinic patients with PV (44% followed to death) compared with expected survival based on individuals of the same age and gender from the US population

Tefferi A et al, Blood 2014; 124: 2507-13

PV patients mortality rate is about 1.6 times higher vs. general population[4]

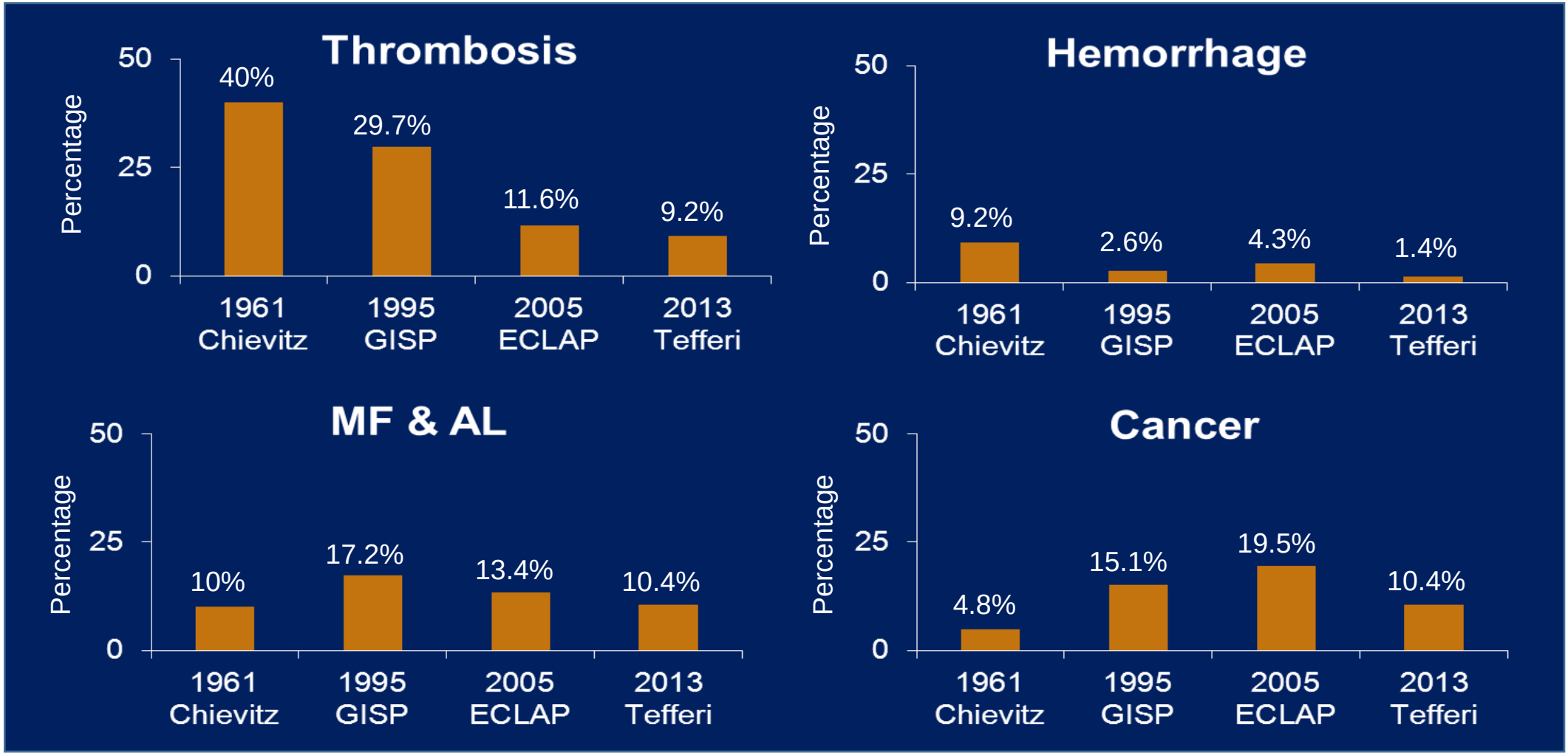
- Patients can live with PV for many years but life expectancy is shorter than the average population of the same age[1]
- **If not treated, PV can lead to death within 18 months (median)[1]**
- **If treated, PV patients median overall survival (OS) is approximately 14.1 years[2]**
- **46% of PV Patients are classified as high risk Patients* with a median OS of 8.3 years[2]**



Survival in 337 Mayo Clinic patients with PV (44% followed to death; median survival, 14.1 years) compared with expected survival based on individuals of the same age and sex from the total US population.

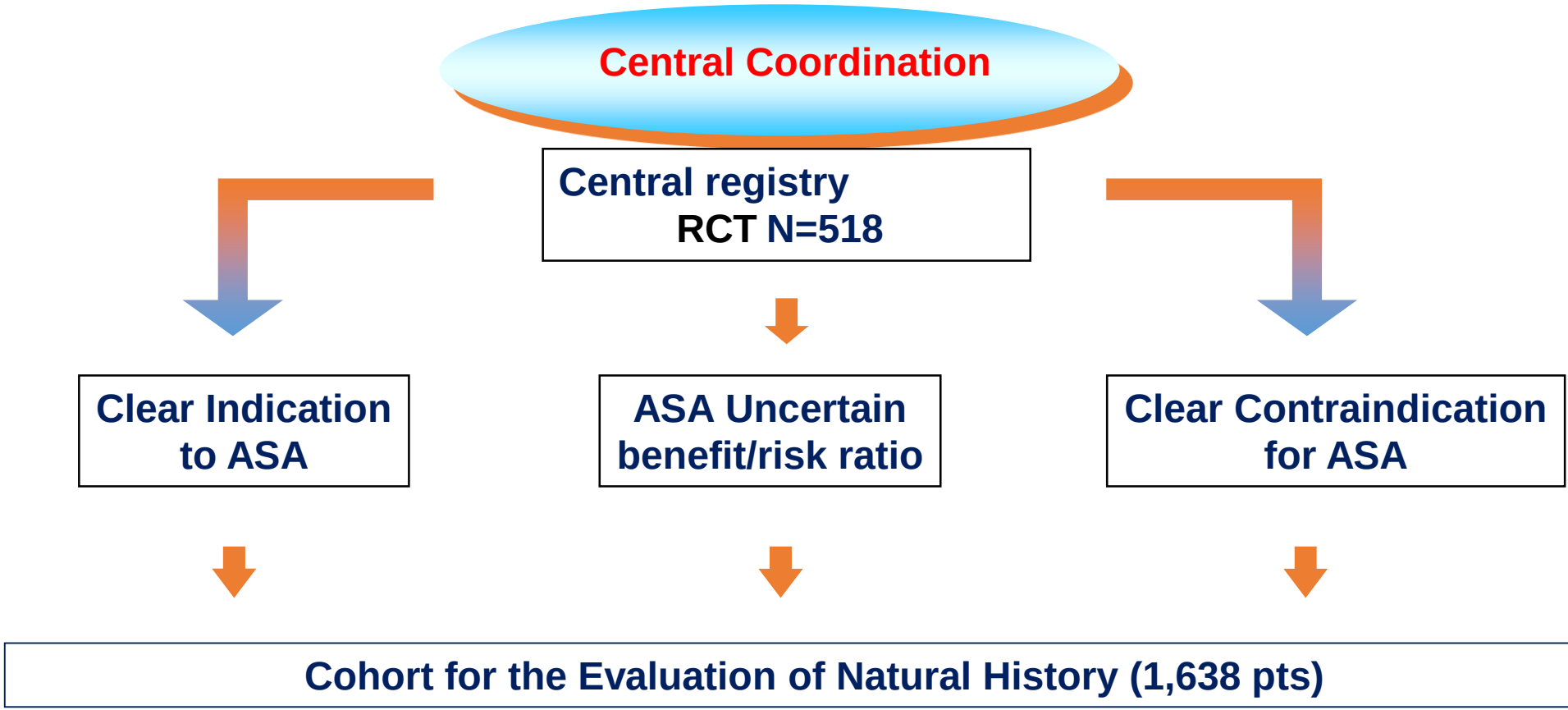
1. Tefferi A, et al. *Leukemia*. 2013;27:1874-1881; 2. Alvarez-Larrán A, et al. *Blood.* 2012;119:1363-1369.
3. Marchioli R, et al. *N Engl J Med.* 2013; 368:22-33.
4 Passamonti et al., 2014

Causes of Death in PV Patients



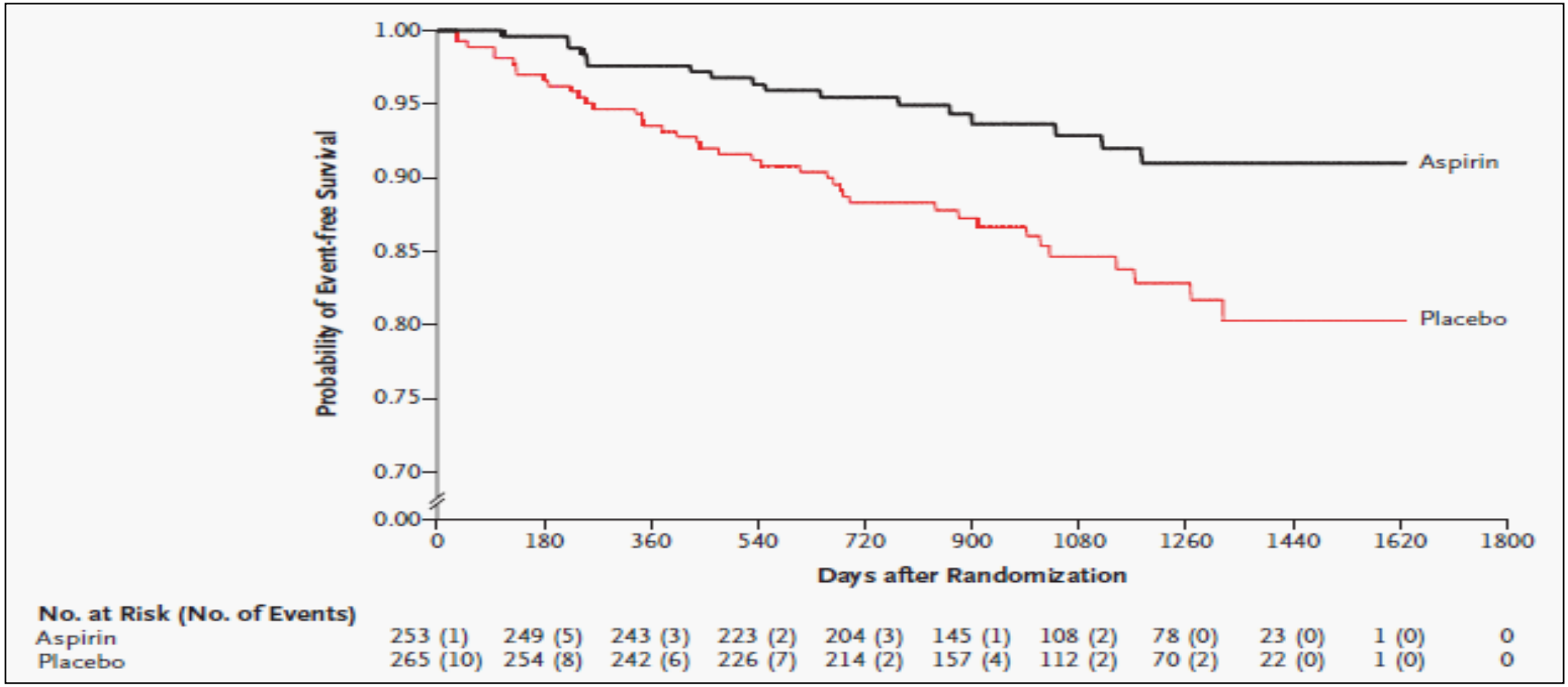
Thiede T, et al. *Acta Med Scand.* 1961;170:443-448. Gruppo Italiano Studio Policitemia. *Ann Intern Med.* 1995;123(9):656-664. Marchioli R, et al, *J Clin Oncol.* 2005;23(10):2224-2232. Tefferi A, et al, *Leukemia.* 2013;27(9):1874-1881.

ECLAP: European Collaboration on Low-Dose Aspirin in PV



Landolfi R et al, NEJM 2004;350:114-24.

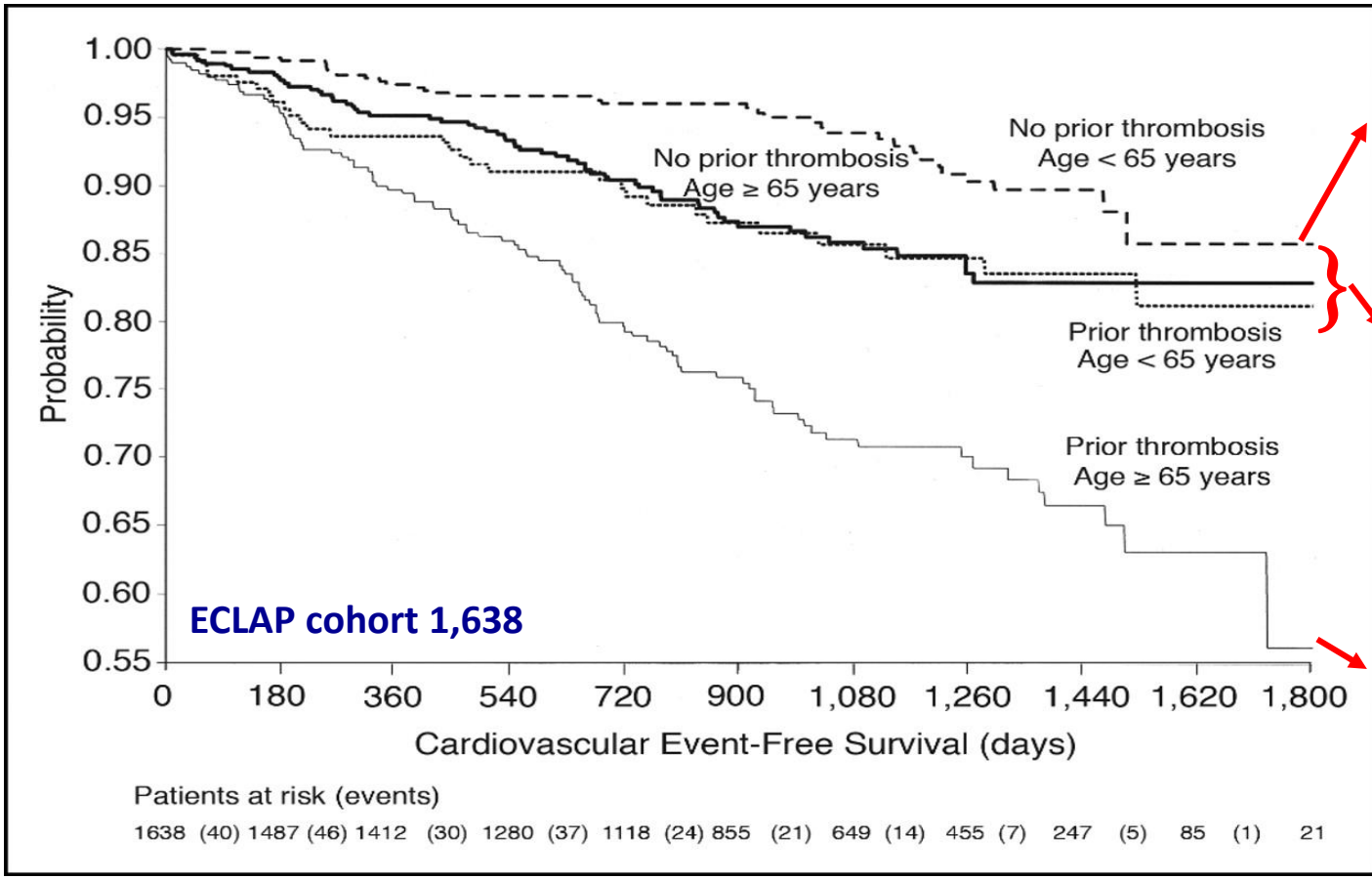
Superiority of Low Dose Aspirin to Placebo in the ECLAP Study



- **Probability of survival free** of myocardial infarction, stroke, and death from cardiovascular causes, pulmonary embolism and DVT. HR: 0.40 (95% CI, 0.18 to 0.91)
- A trend for more frequent minor bleeding was observed

Landolfi R et al, NEJM 2004;350:114-24.

Risk Factors for Thrombosis: Results of the ECLAP Observational Study



Low-risk

Events/100 persons/yr	HR
2.5	1

Intermediate-risk

Events/100 persons/yr	HR
5.0	2.00
4.9	1.96

High-risk

Events/100 persons/yr	HR
10.9	4.35

Marchioli R et al., JCO 2005, Apr 1;23(10):2224-32

Rate of Major Thrombosis by Risk Group in PV and Calendar Period of Diagnosis

	LOW RISK	HIGH RISK
Dx before 2005 IR per 100 person/yrs	IR: 2.03 % pts/yr; 95% CI: 1.58-2.61	**IR: 4.01 %** pts/yr; 95% CI: 3.28-4.90
Dx after 2005 IR per 100 person/yrs	IR: 2.24 % pts/yr; 95% CI: 1.33-3.78	**IR: 2.93 %** pts/yr; 95% CI: 1.89-4.54

- AMI, stroke, PAT, DVT, PE, TIA, SVT

DVT = deep-vein thrombosis, IR = incidence rate, AMI = acute myocardial infarction, , PAT = peripheral arterial thrombosis), PE = pulmonary embolism, TIA = transient ischemic attack

Barbui T et al, Am J Hematol 2015; 90:934-7

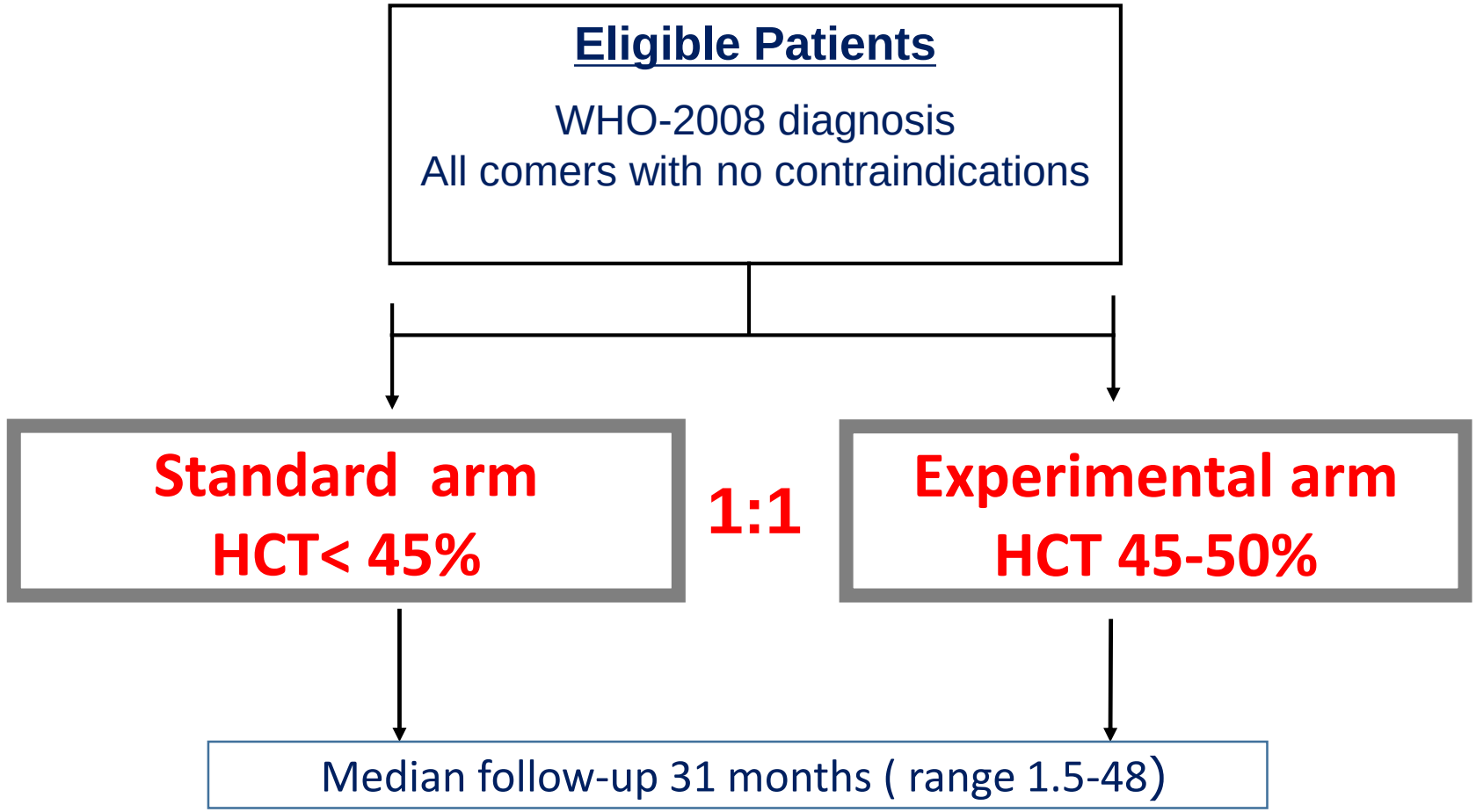
Thrombotic risk stratification in PV

Risk Category	Age > 60 Years or History of Thrombosis
Low	**NO**
High	**YES**

High hematocrit, hypertension, leukocytosis, *JAK2V617F* allele burden, and other risk factors for thrombosis (smoking, DM, hypercholesterolemia, thrombophilia), are not formally integrated into current scores.

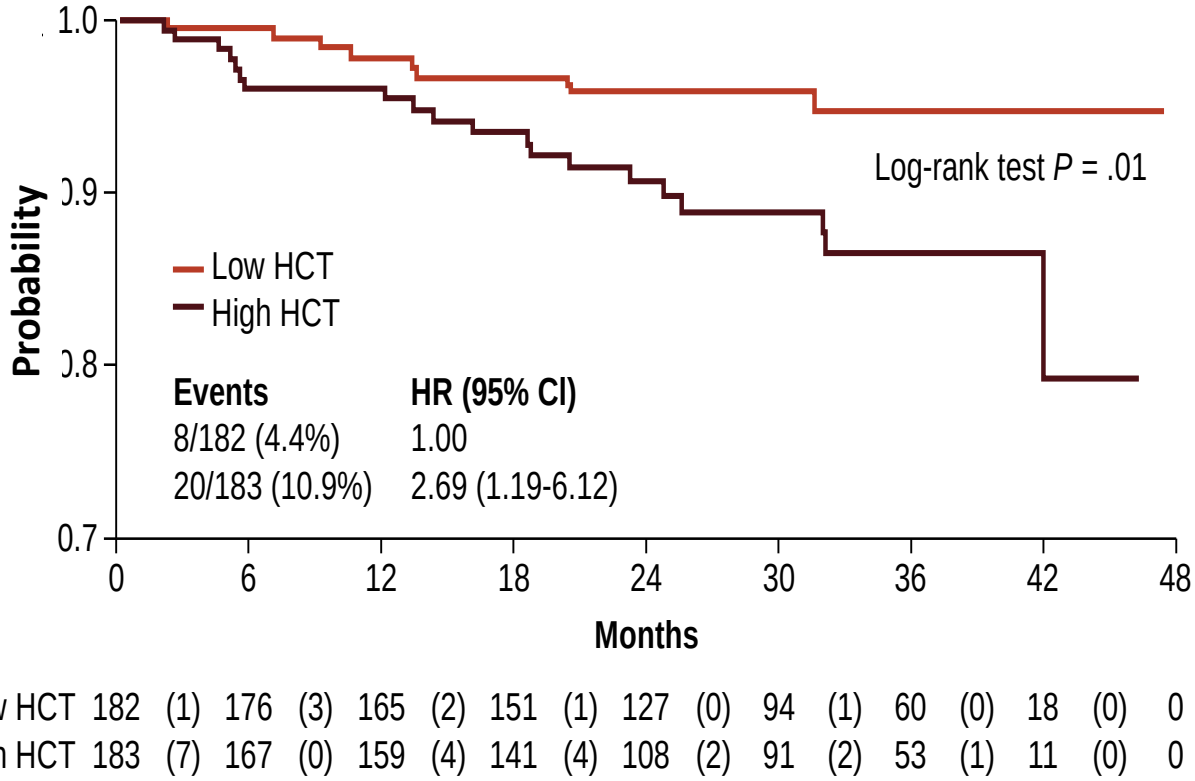
Barbui et al. J Clin Oncol. 2011; 29:761
Vannucchi AM Haematologica 2017; 102:18

Optimal Target Level of Hematocrit in the Management of PV: the CYTO-PV Study



Marchioli R, et al. NEJM. 2013; 368:22-33

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



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.

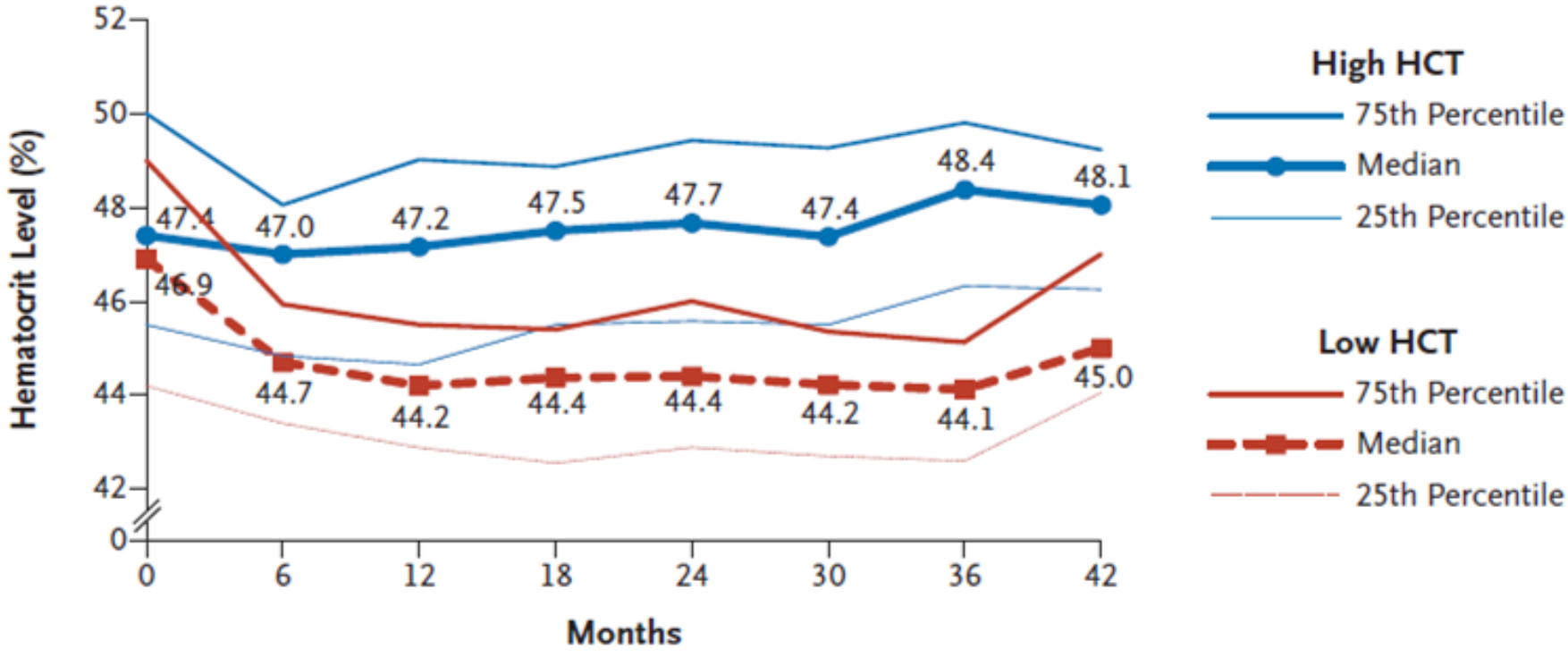
Hematocrit is a risk factor for thrombosis in PV

	HCT< 45% *n* = 182	HCT 45-50% *n* = 183	Total *n* = 365	HR (95% CI)	*p*
Primary Endpoint*, *n* (%) (CV death, MI, stroke, PAT, DVT, PE, TIA and abdominal thrombosis)	**5 (2.8)**	**19 (10.4)**	24 (6.6)	**4.12** (1.54-11.0)	0.005
IR person/year	**1.1**	**4.7**	2.9		
Total CV events*, *n* (%) (Primary Endpoint plus superficial thrombosis)	**8 (4.4)**	**21 (11.5)**	29 (8.0)	**2.83** (1.25-6.38)	0.012
IR person/year	**1.9**	**5.2**	3.5		

* After a median of 31 months of follow-up.

Marchioli et al. NEJM 2013;368:22

Hematocrit Level During the Cyto-PV Study



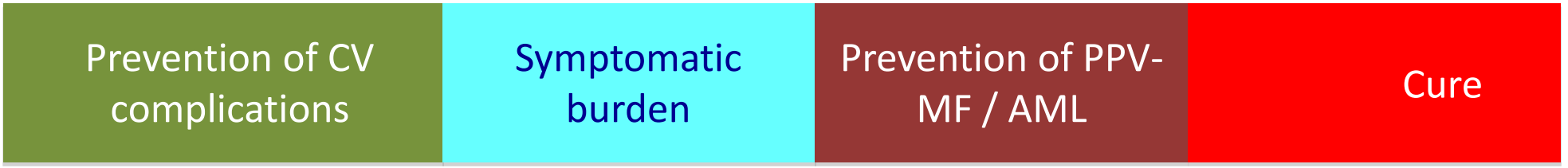
No. of Patients								
Low HCT	182	179	171	157	135	103	64	26
High HCT	183	178	166	145	127	97	63	22

Marchioli R, et al. NEJM. 2013; 368:22-33

AGENDA

- Fundamentals
- Inquadramento nosologico
- Diagnosi
- Clinica
- Terapia

Goals of Therapy in Patients with PV



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

Management of the disease is tailored to individual patients on the basis of their risk for thrombotic events and age

PV Population

Low risk patients
- < 60 years old **AND**
- No history of thrombosis

High risk patients
- ≥ 60 years old **AND / OR**
- History of thrombosis

Treatment

Phlebotomy
+

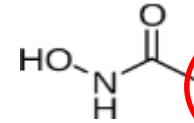
Aspirin low dose

In case of:
- Frequent **phlebotomy** requirements/intolerance
- Symptomatic **splenomegaly**
- Severe disease related **symptoms**
- **Plt count** > 1,500 x 109 / L
- Progressive **leukocytosis**

Add cytoreductive therapies

Treatment

Phlebotomy
+

Aspirin low dose
+


Cytoreductive therapy, mainly hydroxyurea[1]

% of PV patients are not fully responders because they become resistant or intolerant to HU

Not fully respondent patients
Resistant or intolerant to hydroxyurea

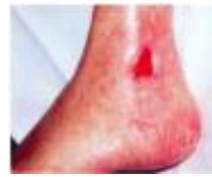
1.Alvarez Larran BLOOD, 9 FEBRUARY 2012 VOLUME 119, NUMBER 6; 2.ELN guidelines

ELN criteria for resistance and intolerance to HU in PV

Not fully respondent patients

Resistant or intolerant to hydroxyurea

INTOLERANT PATIENTS



Non hematologic toxicities

- Leg ulcers
- other unacceptable HU-related non-hematological toxicities, gastrointestinal symptoms, pneumonitis or fever at any dose of hydroxycarbamide

Hematologic toxicities

- Neutrophil count <1,000/mL
- platelet count <100,000/mL
- Hb <10 g/dL

RESISTANT PATIENTS

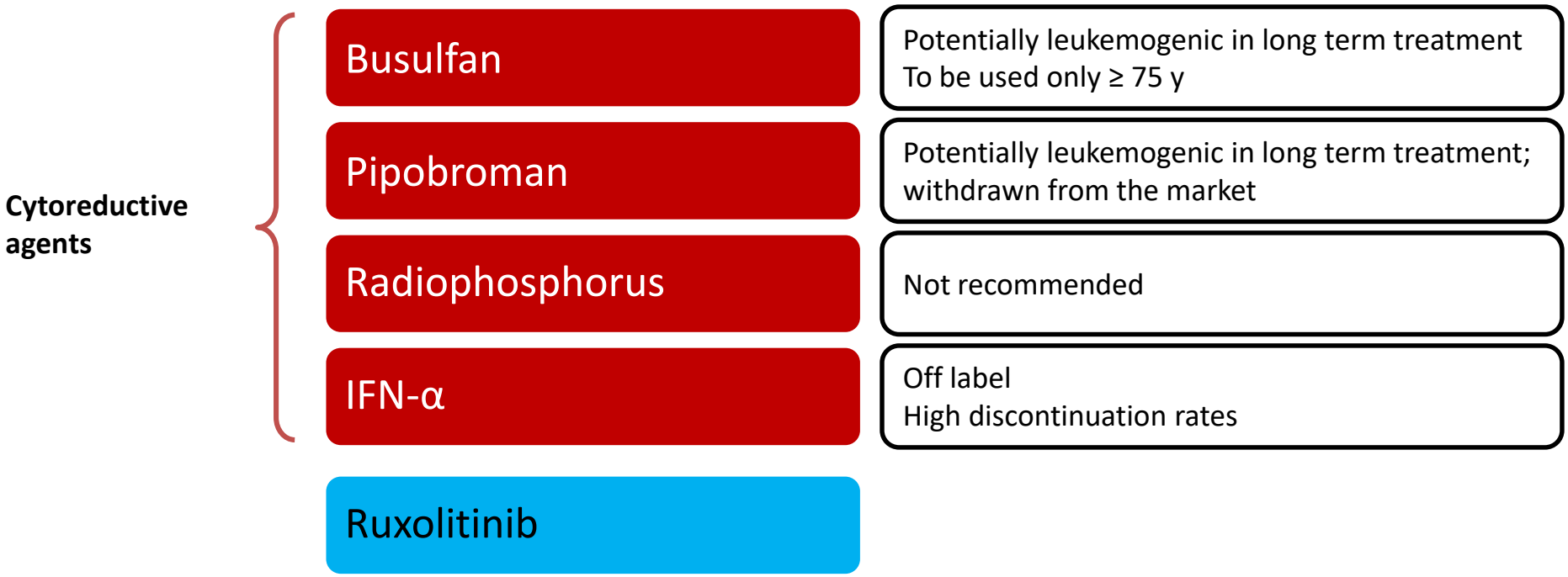
R is defined after 3 months HU ≥ 2 g/day by:

inability to adequately control blood counts without phlebotomies or symptoms:

- Need for phlebotomy to keep Ht <45%
- Uncontrolled myeloproliferation:
  - platelet count >400,000/mL
  - blood cell count >10,000/mL
- Failure to reduce massive splenomegaly by more than 50% as measured by palpation OR Failure to relieve symptoms related to splenomegaly[2]

Barosi et al 2010

Development of resistance or intolerance to HU in a real life setting represents a therapeutic challenge



Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Ropeginterferon alfa-2b, a novel IFNα-2b, induces high response rates with low toxicity in patients with polycythemia vera

Heinz Gisslinger,[1] Oleh Zagrijtschuk,[2] Veronika Buxhofer-Ausch,[3,4] Josef Thaler,[5] Ernst Schloegl,[6] Guenther A. Gastl,[7] Dominik Wolf,[7,8] Robert Kralovics,[1,9] Bettina Gisslinger,[1] Karin Strecker,[3] Alexander Egle,[10] Thomas Melchardt,[10] Sonja Burgstaller,[5] Ella Willenbacher,[7] Martin Schalling,[1] Nicole C. Them,[9] Pavla Kadlecova,[11] Christoph Klade,[2] and Richard Greil[10]

[1]Department of Internal Medicine I, Division of Hematology and Blood Coagulation, Medical University of Vienna, Vienna, Austria; [2]AOP Orphan Pharmaceuticals AG, Vienna, Austria; [3]Sozialmedizinisches Zentrum Ost - Donauspital, Vienna, Austria; [4]Krankenhaus der Elisabethinen Linz, Linz, Austria; [5]Department of Internal Medicine IV, Wels-Grieskirchen Hospital, Wels, Austria; [6]Third Medical Department, Hanusch Hospital, Vienna, Austria; [7]Department of Internal Medicine V, Hematology & Oncology, Innsbruck Medical University, Innsbruck, Austria; [8]Medical Clinic 3, Oncology, Hematology and Rheumatology, University Hospital of Bonn, Bonn, Germany; [9]Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria [10]Laboratory for Immunological and Molecular Cancer Research, Department of Internal Medicine III with Hematology, Medical Oncology, Hemostaseology, Infectious Diseases, Rheumatology, Oncologic Center, Paracelsus Medical University, Salzburg, Austria; and [11]Advanced Drug and Device Services SA, Brno, Czech Republic

Key Points

- The novel IFNα-2b, ropeginterferon alfa-2b, administered once every 2 weeks has low toxicity and

In this prospective, open-label, multicenter phase 1/2 dose escalation study, w a next-generation, mono-pegylated interferon (IFN) α-2b isoform, ropeginterferon The unique feature of ropeginterferon alfa-2b is a longer elimination half-life, whic administration every 2 weeks. We present data from 51 polycythemia vera patie main goal was to define the maximum tolerated dose and to assess safety and A dose range of 50 to 540 μg was tested without the appearance of dose-limi known toxicities associated with I

Interferon Alpha in Polycythemia Vera

- **IFN-α has shown evidence of**
  - **Molecular responses** in patients with early stages of PV
  - **Relieving pruritus in some patients**
  - **Use in pregnancy**
  - Inducing **complete hematologic responses**
  - Based upon phase 2 studies in a limited number of patients, IFN-α affects rates of thrombosis, the evolution to AML or secondary MF, and the development of bone marrow fibrosis[1]
  - However, **15–25%** of the patients have to discontinue treatment with pegylated IFN because of **toxicities**

Eventi avversi associati al trattamento con oncocarbide o interferone

	ONCO	Peg-IFN	
Adverse Event	HU (n=36)	PEG (n=36)	P Value*
Abdominal pain	2 (6%)	7 (19%)	0.07
Anemia	6 (17%)	7 (19%)	0.76
Depression	-	10 (28%)	<0.001
Diarrhea	5 (14%)	7 (19%)	0.53
Dyspnea	1 (3%)	7 (19%)	0.02
Fatigue	10 (28%)	18 (50%)	0.05
Flu-like symptoms	1 (3%)	12 (33%)	<0.001
Headache	4 (11%)	7 (19%)	0.33
Injection site reaction	-	9 (25%)	0.001
Leukopenia	3 (8%)	8 (22%)	0.10
Nausea	7 (19%)	7 (19%)	0.99
Pain	9 (25%)	11 (31%)	0.60
Pruritus	3 (8%)	10 (28%)	0.03
Thrombocytopenia	7 (19%)	6 (17%)	0.76
Overall (grade 1+)	32 (89%)	36 (100%)	0.04
Overall (grade 3+)	5 (14%)	17 (47%)	0.002

bjh research paper

A pilot study of the Histone-Deacetylase inhibitor Givinostat in patients with JAK2V617F positive chronic myeloproliferative neoplasms

ssandro Rambaldi,[1] Chiara Maria
lacasa,[1] Guido Finazzi,[1] Alessandra
bbio,[1] Maria Luisa Ferrari,[1] Paola
ielmelli,[2] Elisabetta Gattoni,[3] Silvia
piraghi,[1] Maria Chiara Finazzi,[1]
Di Tollo,[4] Carmine D'Urzo,[4]
ndro M. Vannucchi,[2] Giovanni
and Tiziano Barbui[1]

Summary

A phase II A study was conducted to evaluate the safety and effi
Givinostat, a novel Histone-Deacetylases inhibitor, in patien
Polycythaemia Vera (PV, $n = 12$), Essential Thrombocythaem
$n = 1$) and Myelofibrosis ($n = 16$), bearing the JAK2V617F muta
study was approved by the local ethics committees and
participants gave written informed consent. Givinostat was give
24 weeks at a starting dose of 50 mg twice daily. The media
discontinuation

bjh research paper

A phase II study of Givinostat in combination with hydroxycarbamide in patients with polycythaemia vera unresponsive to hydroxycarbamide monotherapy

Guido Finazzi,[1] Alessandro M. Vannuc-
hi,[2] Vincenzo Martinelli,[3] Marco
ggeri,[4] Francesco Nobile,[5] Giorgina
ecchia,[6] Enrico Maria Pogliani,[7]
oardo Maria Olimpieri,[8] Giuseppe
itoni,[9] Caterina Musolino,[10] Daniela
ni,[11] Piera Sivera,[12] Giovanni
si,[13] Maria Chiara Finazzi,[1] Silvia
lle,[14] Tim Demuth,[14] Tiziano

Summary

Givinostat, a histone-deacetylase inhibitor (HDACi),
of cells bearing the JAK2 V617F mutation and has sh
ity with good tolerability in patients with chronic m
plasms (MPN). In this multicentre, open-label, phas
with polycythaemia vera (PV), unresponsive to t
doses (MTD) of hydroxycarbamide (HC), were
(50 or 100 mg/d) in combination with MTD of H

blood

MENU

634. MYELOPROLIFERATIVE SYNDROMES: CLINICAL: POSTER I | DECEMBER 7, 2017

A Long-Term Safety and Efficacy Study of Givinostat in Patients with Polycythemia Vera: The First 4 Years of Treatment

Guido Finazzi, MD, Alessandra Iurlo, MD PhD, Bruno Martino, Giuseppe Carli, MD, Attilio Guarini, MD, Richard Noble, MD, Alessandro M. Vannucchi, Nikolas von Bubnoff, MD, Marianna De Muro, MD, Paolo Di Bartolomeo, MD, Mary Frances McMullin, MB,Bch BAO, MD FRCPath, Vincenzo Martinelli, MD, Antonio Pezzutto, MD PhD, Vittorio Rosti, MD, Giorgina Specchia, MD, Paolo Bettica, MD PhD, Sara Manzoni, DHSC, BSc, Silvia DI Tollo, DHSC, BSc, Alessandro Rambaldi, MD Prof

Blood (2017) 130 (Supplement 1): 1648.

https://doi.org/10.1182/blood.V130.Suppl_1.1648.

blood

MENU

634. MYELOPROLIFERATIVE SYNDROMES: CLINICAL: PHASE I/II TRIALS OF NOVEL AGENTS IN MPNS | DECEMBER 7, 2017

A Two-Part Study of Givinostat in Patients with Polycythemia Vera: The Maximum Tolerated Dose Selection and the Proof of Concept Final Results

Alessandro Rambaldi, MD Prof, Alessandra Iurlo, MD PhD, Alessandro M. Vannucchi, Richard Noble, MD, Nikolas von Bubnoff, MD, Attilio Guarini, MD, Andrzej Hellmann, MD, Bruno Martino, Antonio Pezzutto, MD PhD, Giuseppe Carli, MD, Marianna De Muro, MD, Paolo Di Bartolomeo, MD, Mary Frances Frances McMullin, MB,Bch BAO, MD FRCPath, halie Cambier, MD, Jean-Pierre Marolleau, MD PhD, Ruben A Mesa, MD, Raoul Tibes, MD Paolo Bettica, MD PhD, Sara Manzoni, DHSC, BSc, Silvia DI Tollo, DHSC, BSc

Blood (2017) 130 (Supplement 1): 253.

https://doi.org/10.1182/blood.V130.Supp

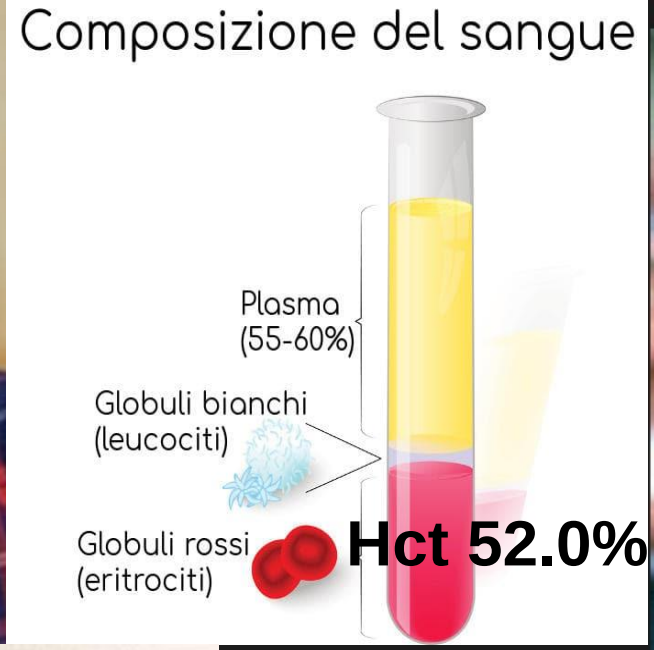
Perspectives for Therapy Improvement in the Management of PV

Strategies to Reduce the Residual Risk of Thrombosis

- Earlier diagnosis
- Aggressive control of **CV risk factors**
- Personalized use of **prophylactic ASA**
- New anti-thrombotic strategies?
- More **stringent criteria of phlebotomy**
- Appropriate and more timely use of **cytoreductive drugs**
- **New drugs (ruxolitinib)**

Strategies to Reduce the Risk of PPV-MF & sMDS/sLAM

- ????


Composizione del sangue
Plasma
(55-60%)
Globuli bianchi
(leucociti)
Globuli rossi
(eritrociti)
Hct 52.0%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