45° Convegno Nazionale di Studi di Medicina Trasfusionale
Rimini | 29-31 maggio 2024
SIMTI

Policitemia e poliglobulia: salasso, eritroriduzione, farmacoterapia

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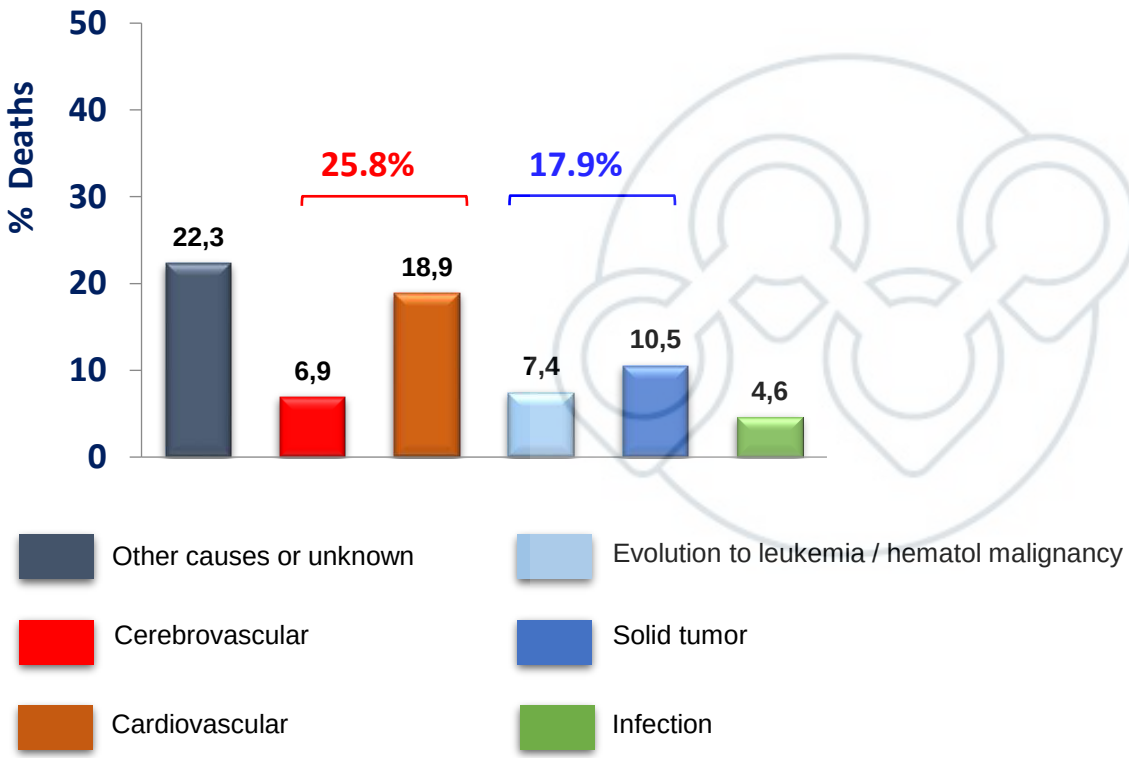
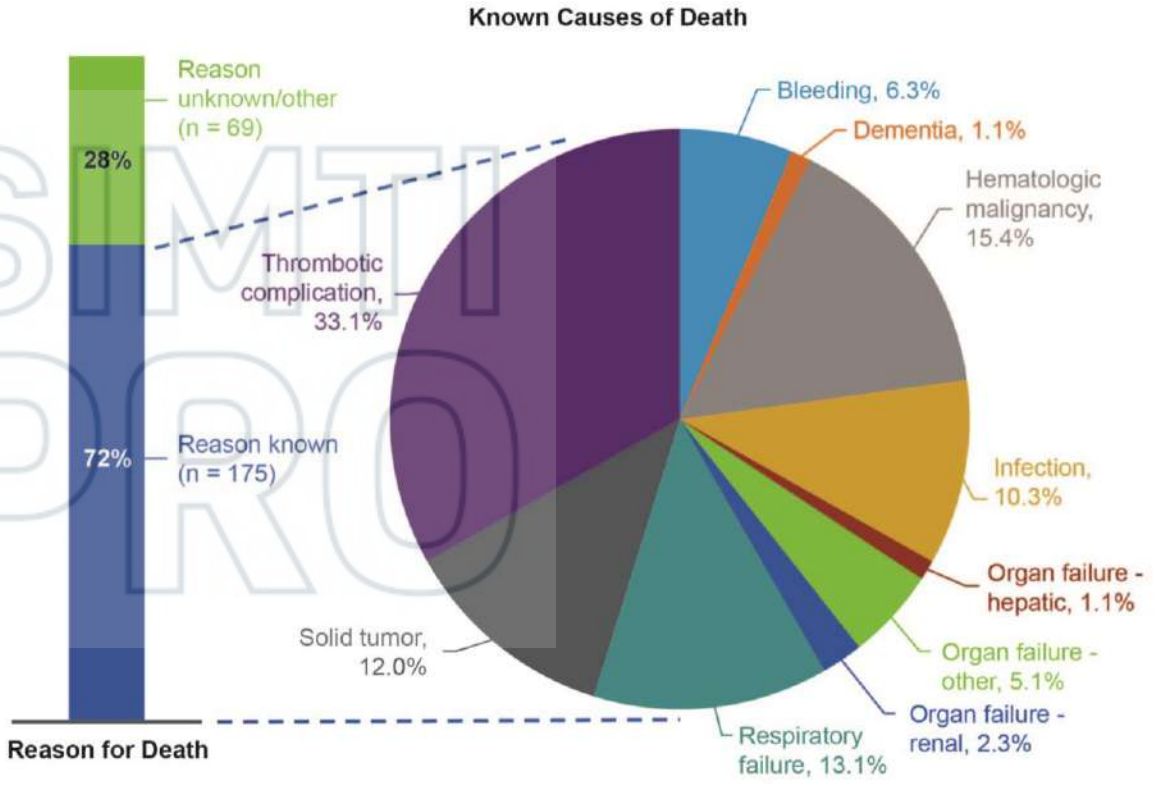
Il sottoscritto, in qualità di Relatore

dichiara che

nell'esercizio della Sua funzione e per l'evento in oggetto, NON È in alcun modo portatore di interessi commerciali propri o di terzi; e che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali non sono tali da permettere a tali soggetti di influenzare le sue funzioni al fine di trarne vantaggio.

Causes of morbility and death in PV patients

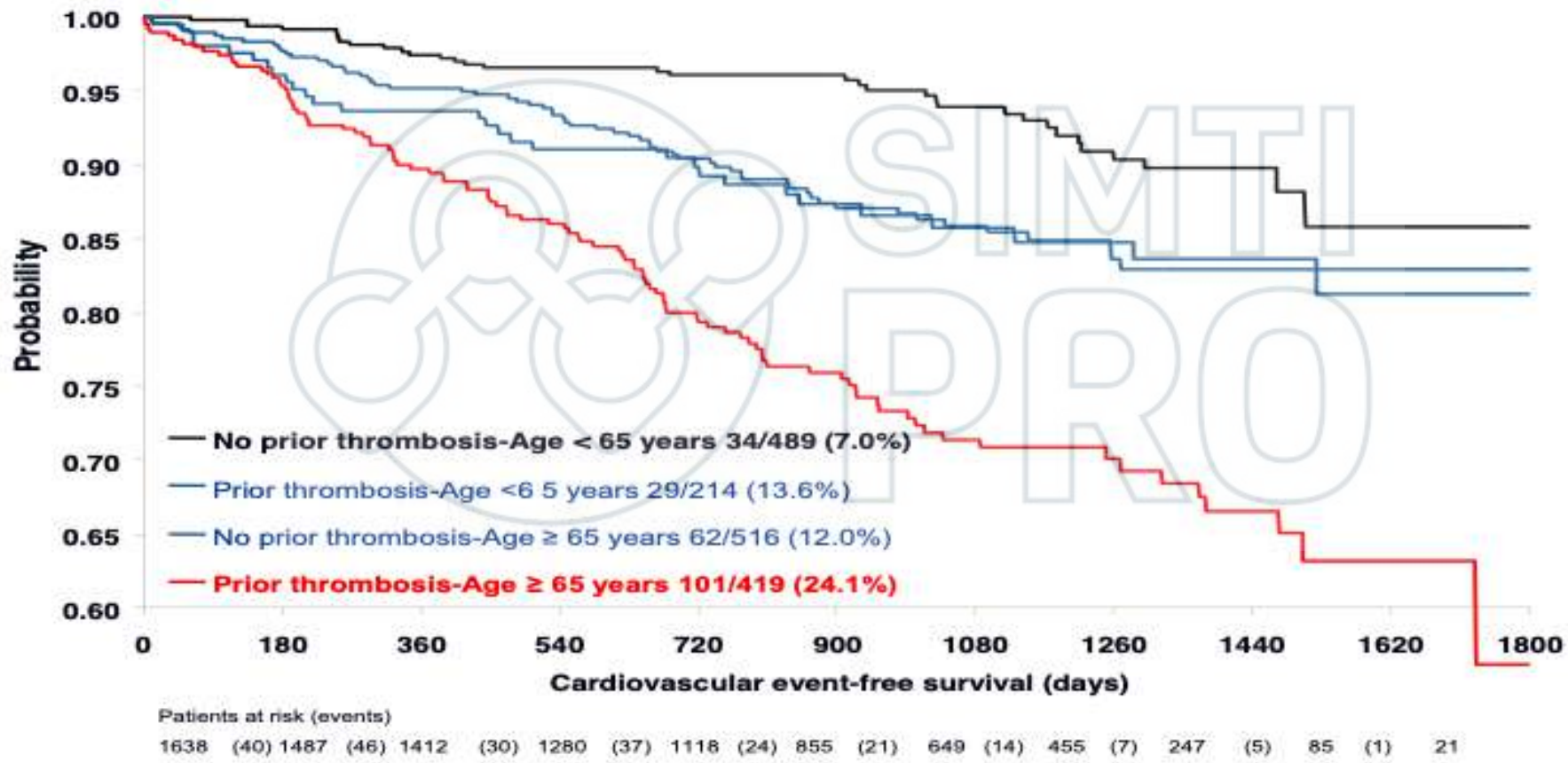




[1] Hultcrantz et al. *J Clin Oncol.* **2015**;33:2288-2295. [2] Stein et al. *ASH annual meeting* **2020**;abs#484.

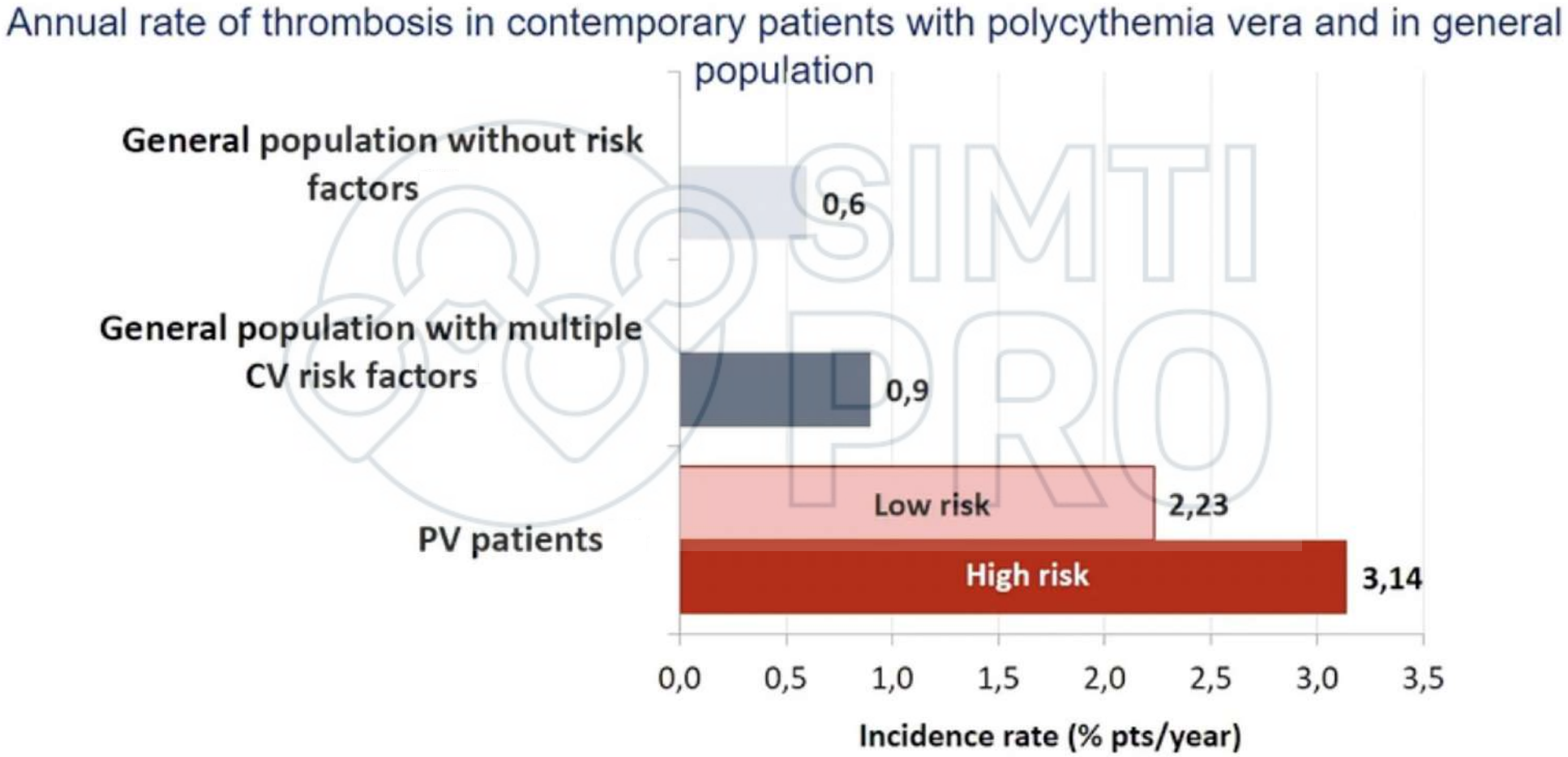
«Classic» risk factors: age and history of thrombosis

Determinant of thrombosis in 1,638 patients enrolled in the ECLAP study



Marchioli et al. *J Clin Oncol.* **2005**;23:2224-2232.

Rates of thrombosis in low-risk PV are higher than in non-MPN population

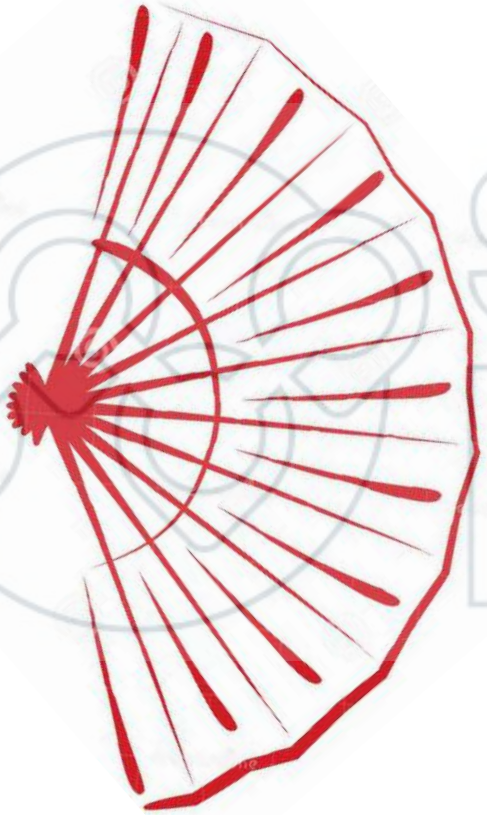


Barbui et al. *Blood.* **2014**;124:3021-3023.

New insights for the assessment of thrombotic risk in PV

MILESTONES

- Age > 60 years
- History of thrombosis



RISK OF ARTERIAL EVENTS

- History of arterial thrombosys
- Hypertension[1]
- Diabetes[1]
- Dyslipidemia[1]
- Leukocytosis[1]

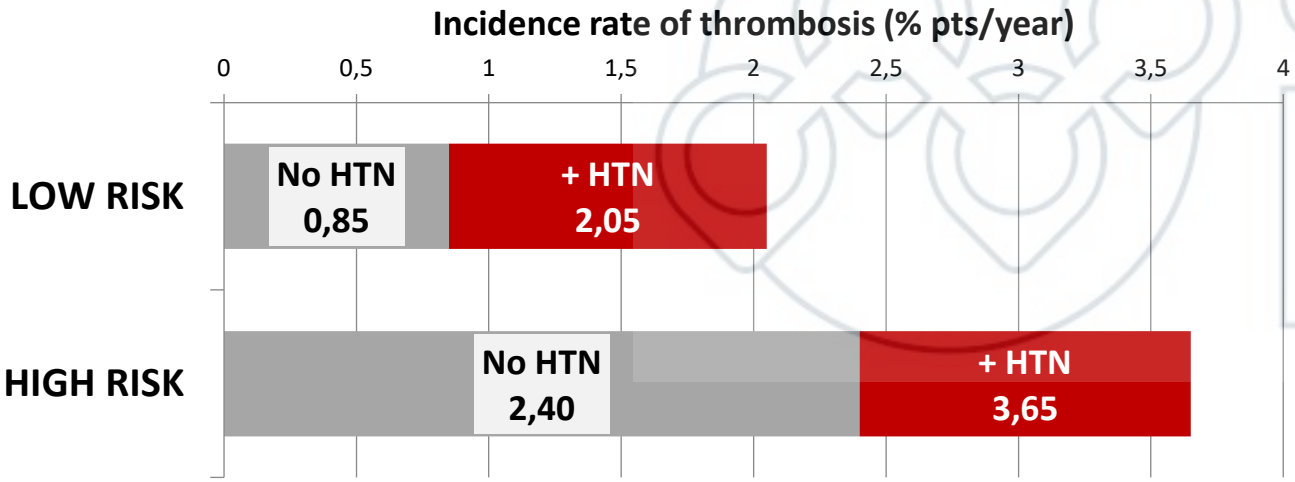
RISK OF VENOUS EVENTS

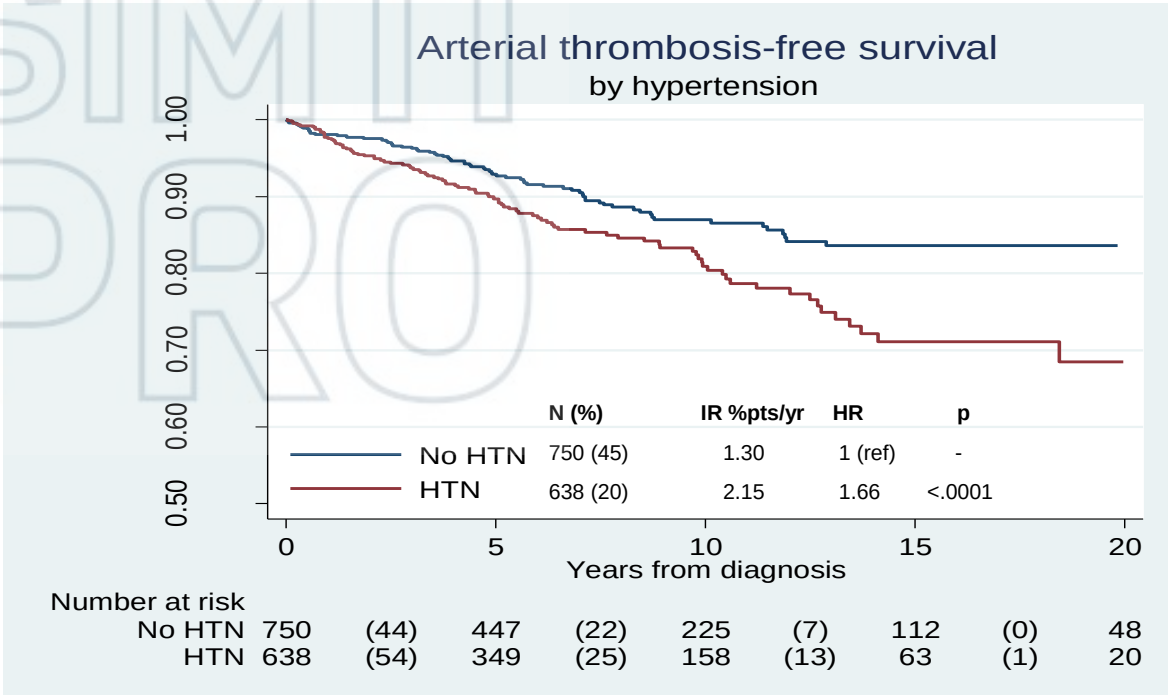
- Age ≥ 65 years
- History of venous thrombosys
- Neutrophil/lymphocyte ratio ≥5 [2]
- JAK2^{V617F} VAF >50% [3]

[1] Cerquozzi et al. *Blood Cancer J.* **2017**;7:662. [2] Carobbio et al. *Blood Cancer J.* **2022**;12:28. [3] Guglielmelli et al. *Blood Cancer J.* **2021**;11:199.

Cardiovascular risk factors

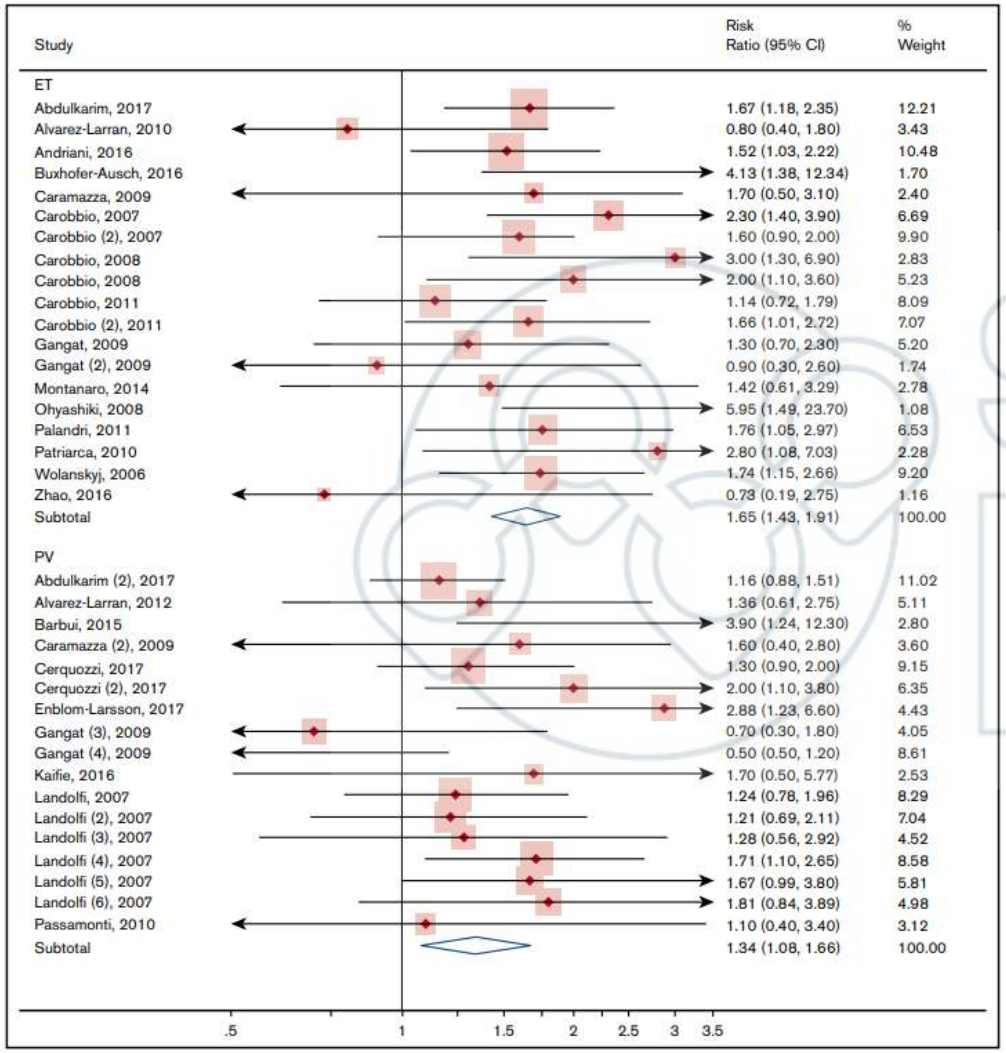
Additional effect of hypertension (HTN) in Low and High risk PV cases enrolled in ECLAP trial

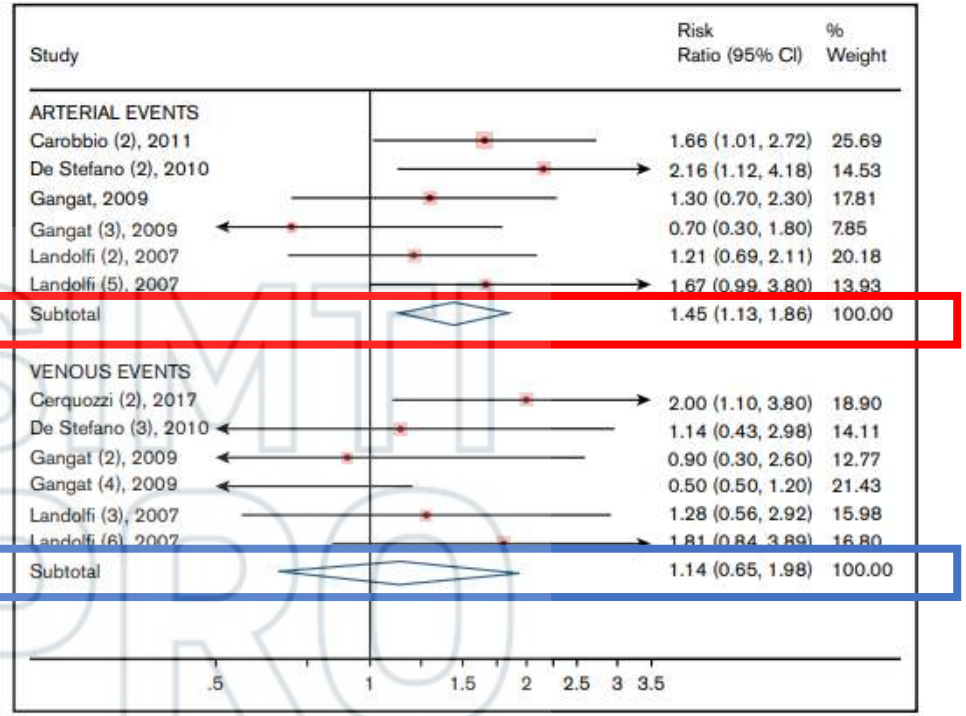




Barbui et al. *Am J Hematol.* **2017**;92:e5.

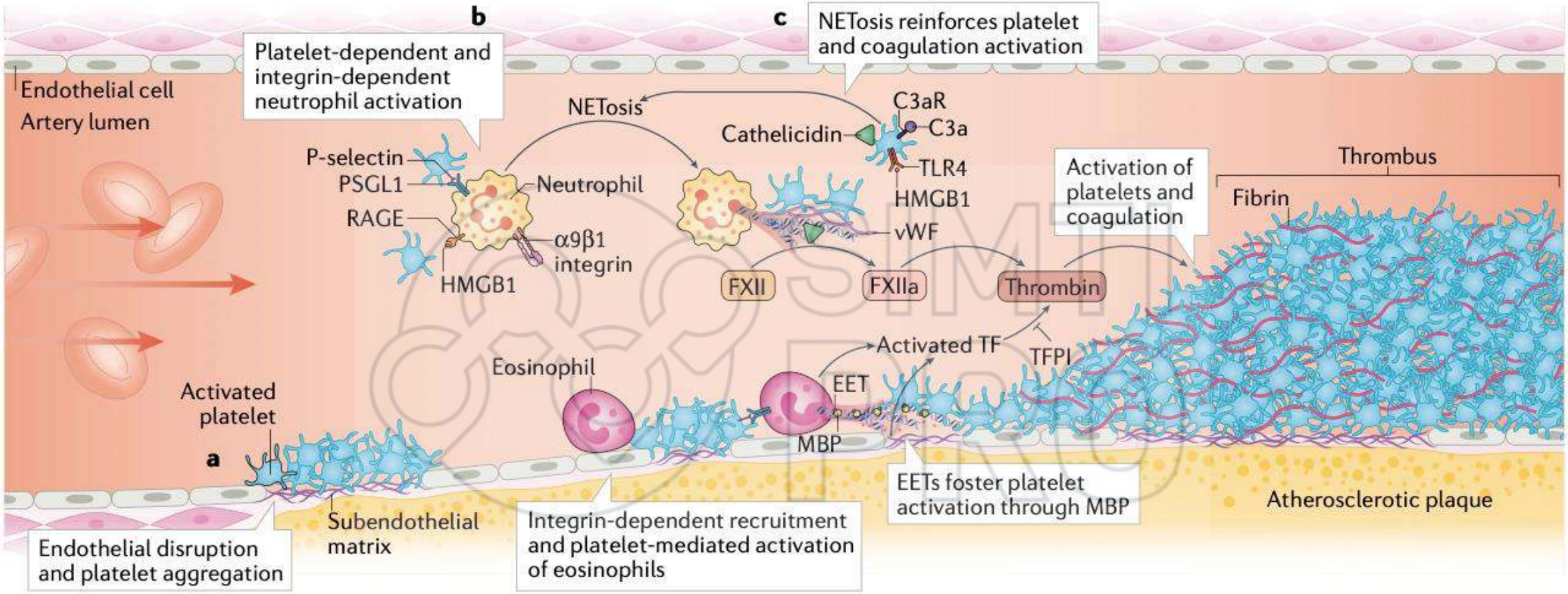
Leukocytosis is an established risk factor for arterial thrombosis in PV





Carobbio et al. *Blood Adv.* **2019**;3:1729-1737

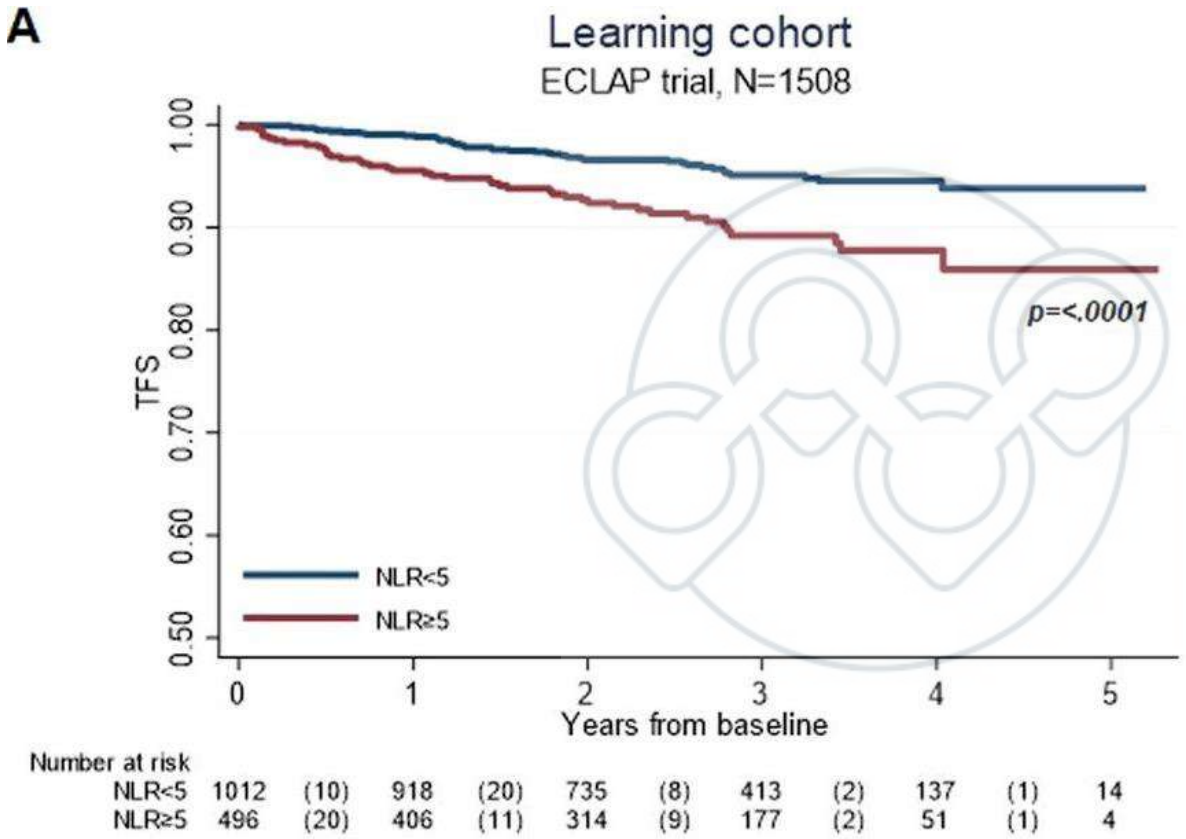
The good and the bad: immunothrombosis and thromboinflammation

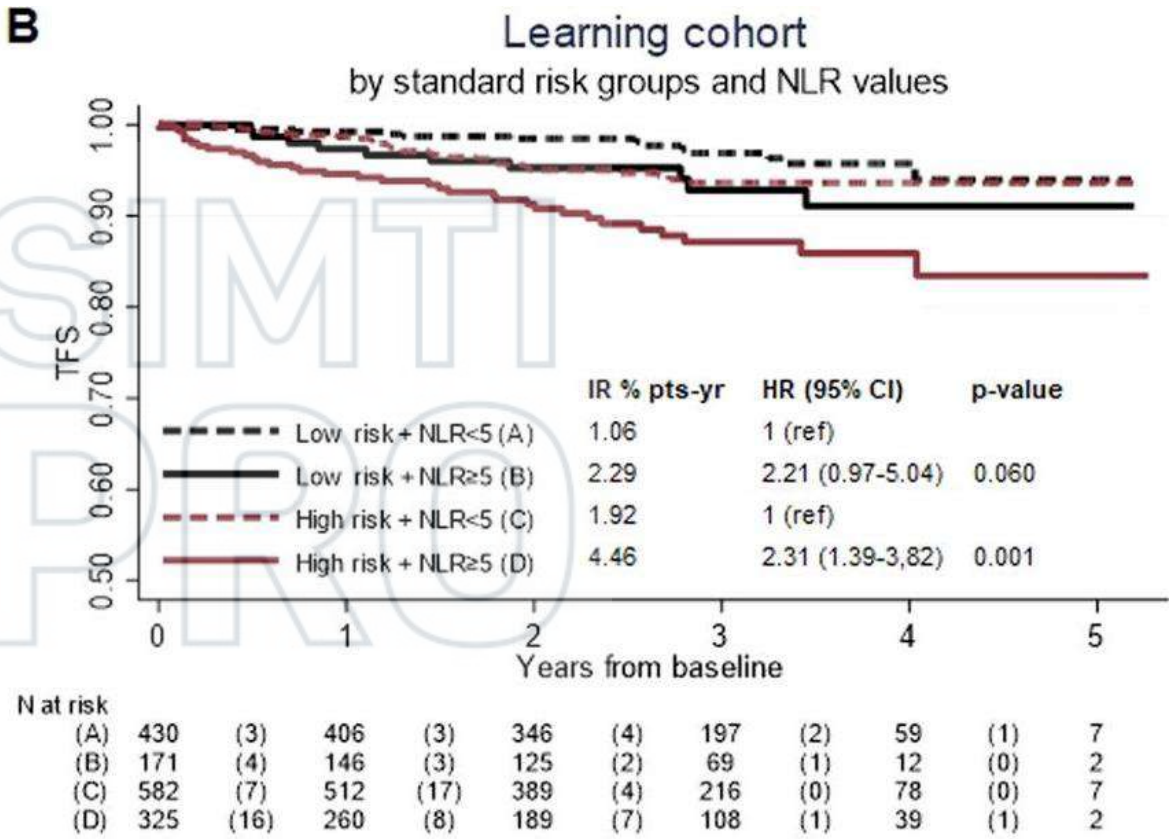


- Platelet-induced activation of neutrophils results in the formation of neutrophil extracellular traps (NETs), which promote the activation of the coagulation system.[1]
- Neutrophils from patients with JAK2^{V617F} mutation are primed for NET formation.[2]

[1] Stark and Massberg. *Nat Rev Cardiol.* **2021**;18:666-682. 2 Wolach et al. *Sci Transl Med.* **2018**;10:eaan8292.

Neutrophil-to-lymphocyte ratio predicts for the risk of thrombosis in PV

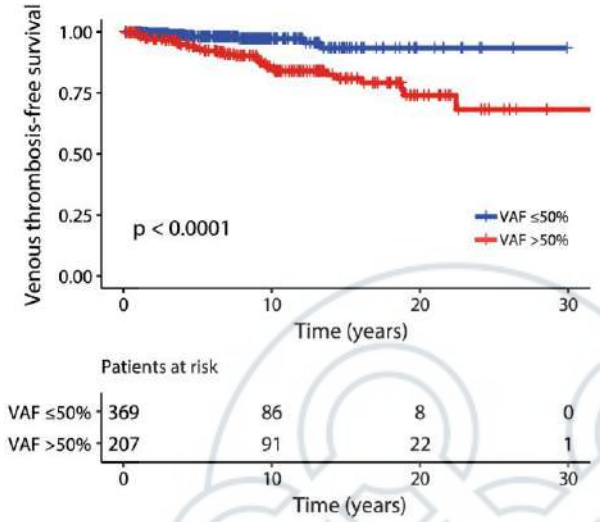




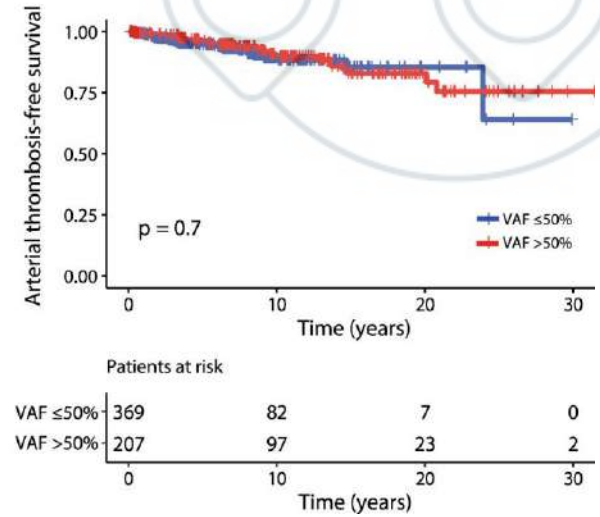
Carobbio et al. *Blood Cancer J.* **2022**;12:28.

JAK2^{V617F} allele burden and thrombosis risk

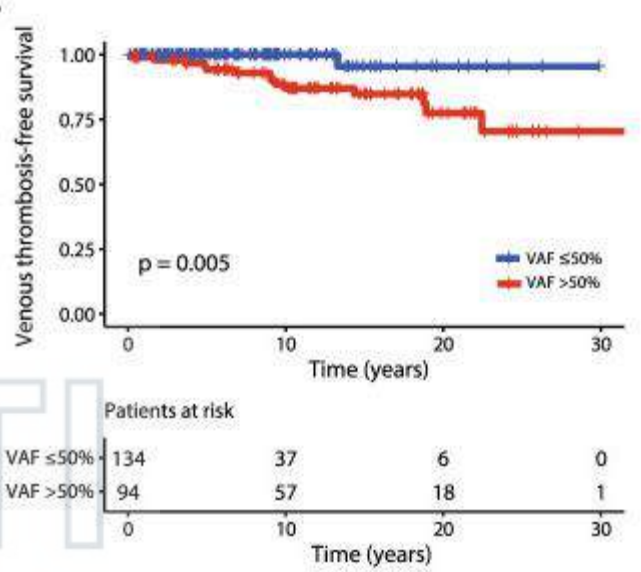
Venous events



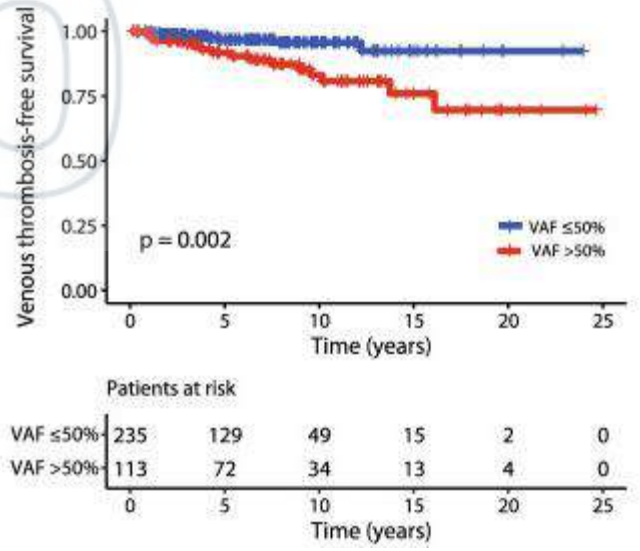
Arterial events



Low-risk patients



High-risk patients



Guglielmelli et al. *Blood Cancer J.* **2021**;11:199.

JAK2^{V617F} allele burden is predictive of disease progression

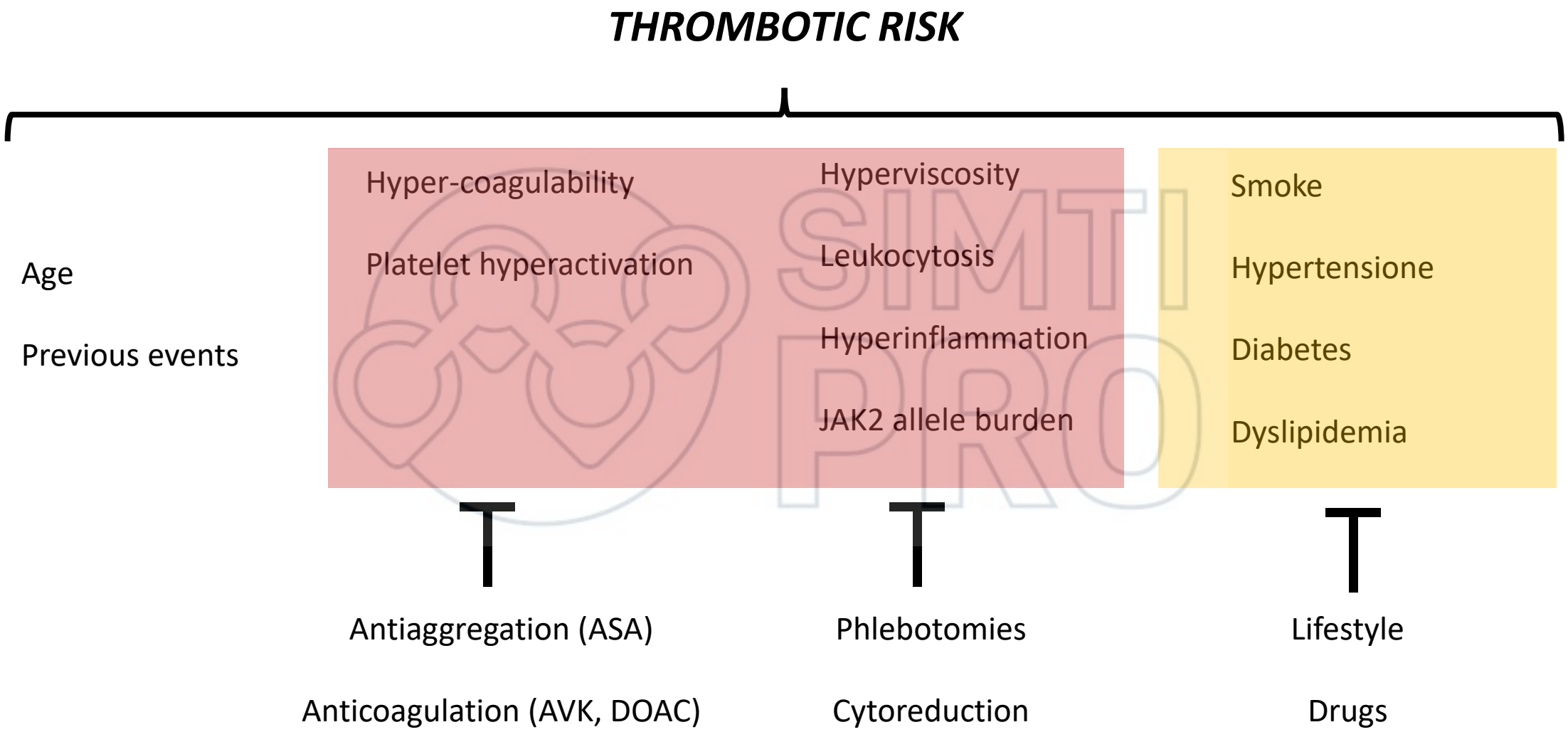
In PV, increased *JAK2*^{V617F} allele fraction is correlated with:

- increased WBC
- venous thrombosis risk
- presence of splenomegaly
- risk of progression to myelofibrosis

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

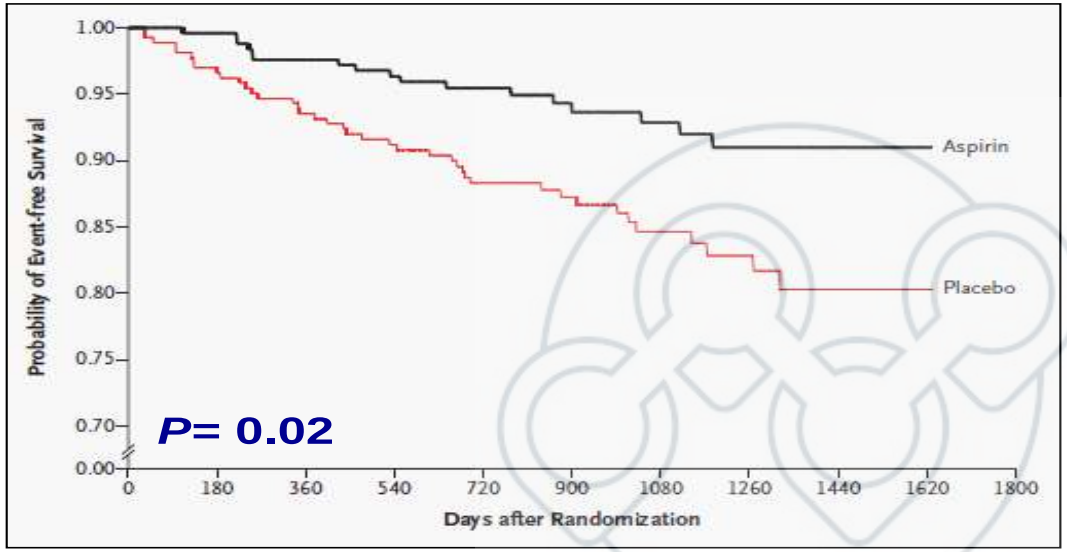
Moliterno et al. *Blood.* **2023**;141:1934-1942.

How to address risk factors in PV patients?



Treatment backbones: low dose aspirin and hematocrit level <45%

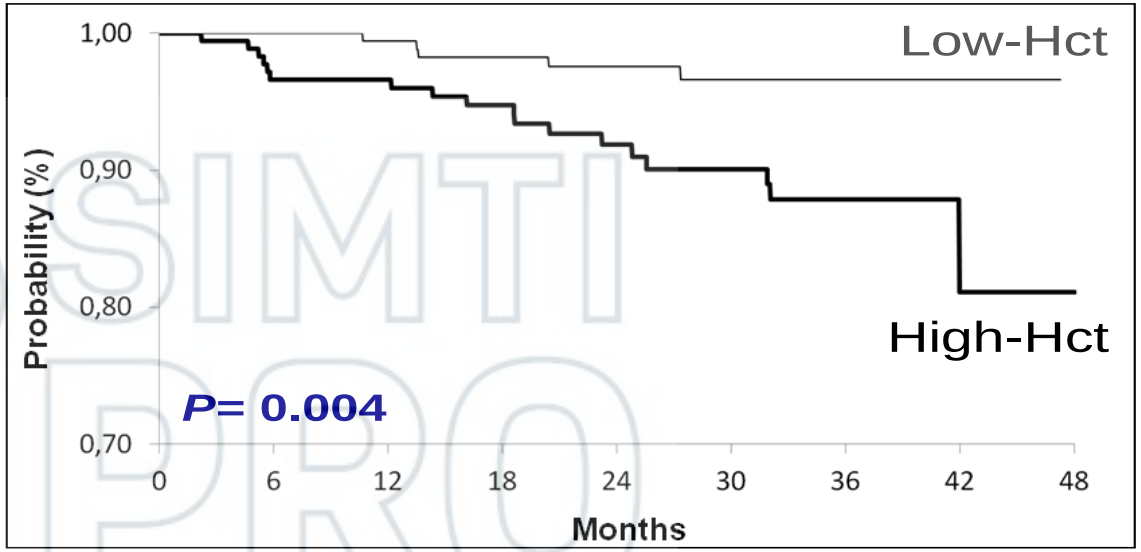
ECLAP Trial



- **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)

Cyto-PV Trial



Hct target level	Low Hct <45%	High Hct 45-50%
IR %person/year	1.1	4.4

P< 0.005

Primary Endpoint
(CV death, MI, stroke, PAT, DVT, PE, TIA, SVT)

Landolfi et al. *N Engl J Med.* **2004**;350:114-124. Marchioli et al. *N Engl J Med.* **2013**;365:22-33.

Expert recommendations for phlebotomy in PV (SIE, SIMTI, SIDEM)

Target hematocrit

The target of phlebotomy in PV should be maintaining a **stable hematocrit < 45%.**
A lower target hematocrit (40–42%) is appropriate in persons with persistent or recurrent symptoms of hyperviscosity such as erythromelalgia, transient ocular attacks, headache, dizziness, and/or amaurosis fugax at a target hematocrit of 45% and when a benefit is documented.

Phlebotomy strategy

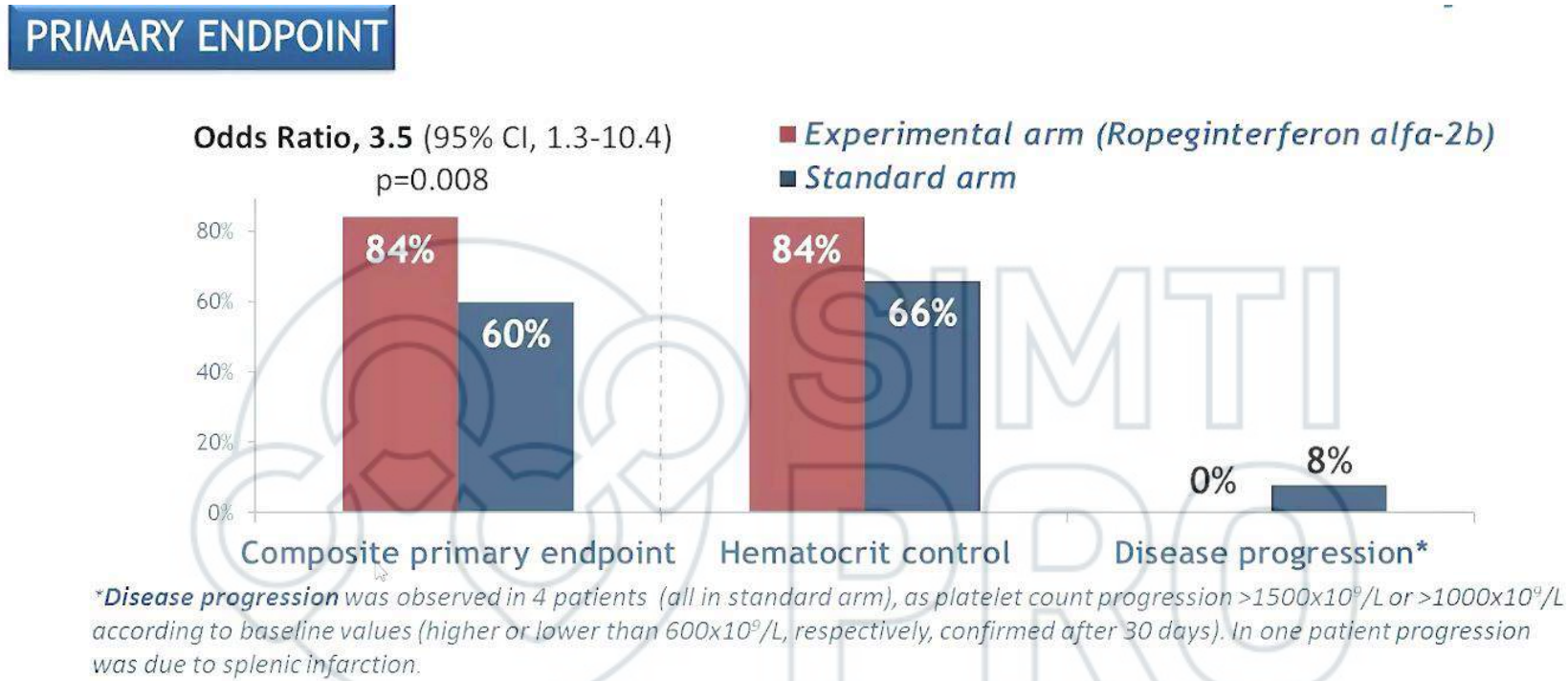
In the **induction phase**, the phlebotomy regimen should consider a person's weight and should remove 300–450 mL of blood every other day or twice a week until the target hematocrit is achieved. The **maintenance phase** should have the same volume of blood removed as in the induction phase.
Phlebotomy intervals should be determined by measuring hematocrit levels monthly in the first 6 months and ≤2 months thereafter.

RBC apheresis

RBC-apheresis is an alternative to phlebotomy in persons with severe vascular complications when rapid attainment of a target hematocrit is needed, or before emergency surgery in persons with an extremely high hematocrit value to reduce the risk of peri-operative vascular complications.

Barbui et al. *Leukemia.* **2018**;32:2077-2081.

Low-PV: Ro-PEG-IFN α2b vs phlebotomies only in low-risk PV patients



Additional efficacy	▪ **10% allele burden reduction in experimental group (vs 1% in standard)** ▪ **8/37 were molecular responders**
Safety	▪ No difference in rate of grade ≥3 toxicities ▪ Neutropenia (4/50) in experimental group noted ▪ "Skin symptoms" (2/50) in standard group ▪ 1 thrombotic event (splenic vein) in standard group

Barbui et al. *Lancet Hematol.* **2021**;8:e175.

Cytoreduction therapy in PV: ELN recommendations

Category	Characteristics
Low risk	Age <60 years and no history of thrombosis
High risk	Age ≥60 years or history of thrombosis

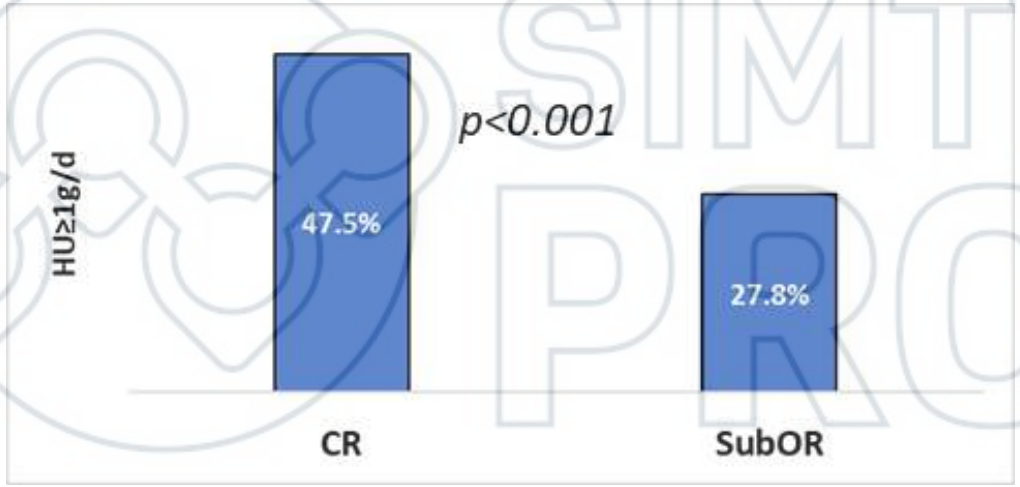
European LeukemiaNet[1,2] Indications for Cytoreduction

- All **high-risk PV**, but also **low-risk patients** if:
  - Poor tolerance to phlebotomy
  - Inadequate haematocrit control with phlebotomies (i.e. ≥ 6 procedures per year)
  - Severe disease-related symptoms (TSS ≥ 20) or severe itching
  - Progressive (WBC >15-20 x 10^9/L) and persistent (≥ 3 months) leukocytosis
  - Extreme thrombocytosis (>1500 × 10^9/L), or bleeding manifestations
  - Symptomatic and progressive splenomegaly

Barbui et al. *Leukemia.* **2018**;32:1057-1069. Marchetti et al. *Lancet Haematol.* **2022**;9:e301-311.

Hydroxyurea dose is associated with response

- In 506 PV patients, median HU dose was 0.5 g/d (range, 0.2-2) and was ≥2 g/d in 3.1% of patients.
- 160 patients (31.6%) received median HU doses ≥1 g/d
- CR patients received more frequently HU ≥1 g/d compared to SubOR patients.



Suboptimal response (SubOR) included ≥1 of the following criteria after at least 3 months of HU: leukocyte count >10 x10^9/l and platelet count 400 x10^9/l; need for phlebotomy to keep HCT<45%; persistence/occurrence of palpable splenomegaly; failure to completely relieve PV-related symptoms

- Predictors of CR included also: $JAK2^{V617F}$ <50%, absence of palpable spleen, absence of symptoms/pruritus at treatment start.

Palandri et al. *Cancers.* **2023**;15:3706.

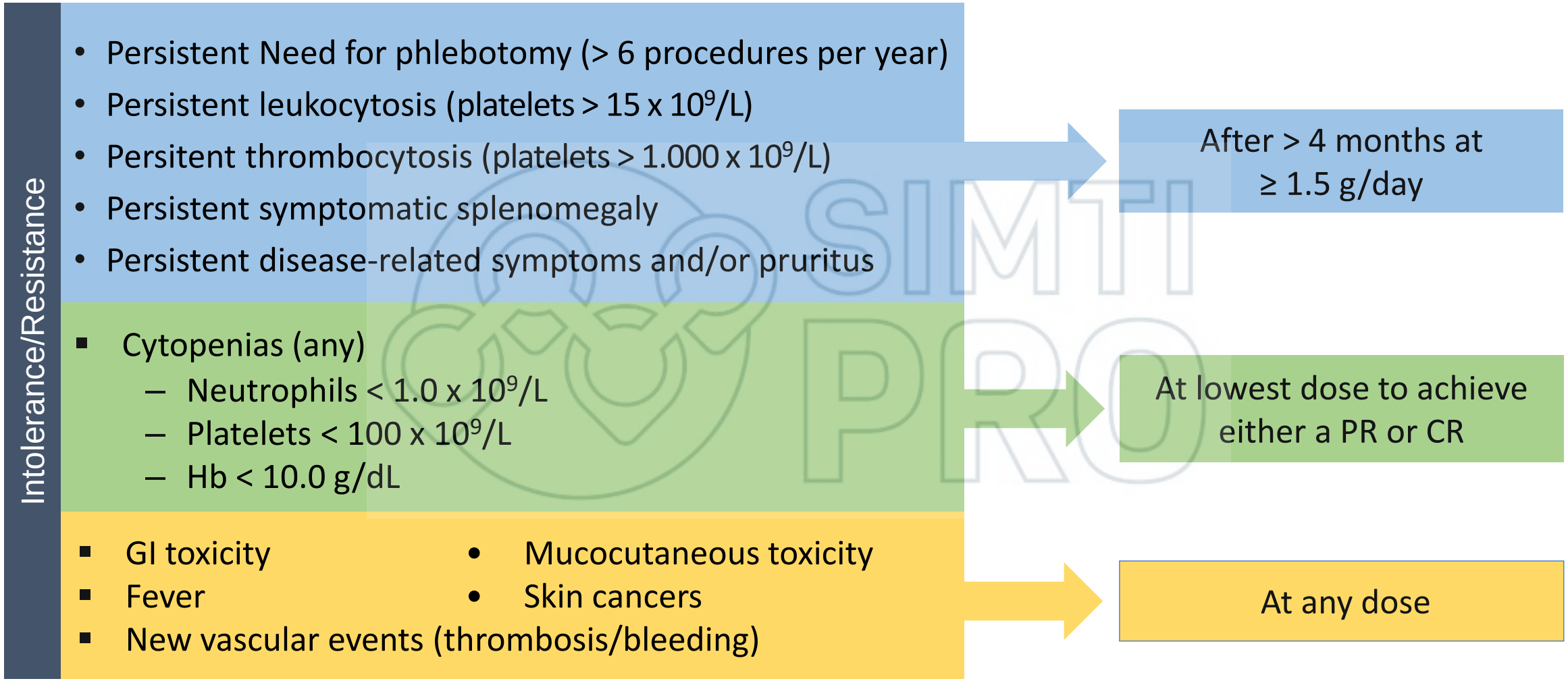
Hydroxyurea dose is associated with toxicity

- At least one HU-related AE occurred in 128/563 patients (22.7%) with an overall incidence rate of 5.8 per 100 patient-years.
- HU dose ≥1 g/d was associated with increased incidence of HU-related AEs

Toxicities	HU < 1 g/d (n. 346)		HU ≥ 1 g/d (n. 160)		*p*
	n. (%)	Incidence Rate (per 100 Patient-Years)	n. (%)	Incidence Rate (per 100 Patient-Years)	
Hematological toxicity	22 (6.4%)	1.7	26 (16.3%)	4.0	**0.003**
Anemia	5 (1.5%)	0.4	9 (5.7%)	1.3	**0.03**
Thrombocytopenia	15 (4.3%)	1.2	16 (10%)	2.5	0.09
Neutropenia	2 (0.6%)	0.1	1 (0.6%)	0.2	1.0
Extra-hematological toxicity	42 (12.1%)	3.1	33 (20.6%)	4.7	0.11
Skin ulcers	18 (5.2%)	1.4	20 (12.5%)	2.9	**0.02**
Oral aftosis	9 (2.6%)	0.7	4 (2.5%)	0.6	0.81
Gastro-intestinal disturbances	4 (1.1%)	0.3	3 (1.9%)	0.4	0.65
Fever	2 (0.6%)	0.1	0	0	0.43
Myalgia	2 (0.6%)	0.1	0	0	0.43
Zoster reactivations	1 (0.3%)	0.1	1 (0.6%)	0.2	0.69
Non-melanoma skin cancer	6 (1.7%)	0.4	5 (3.1%)	0.6	0.53
Overall toxicity	64 (18.5%)	4.8	59 (36.9%)	8.7	**0.002**

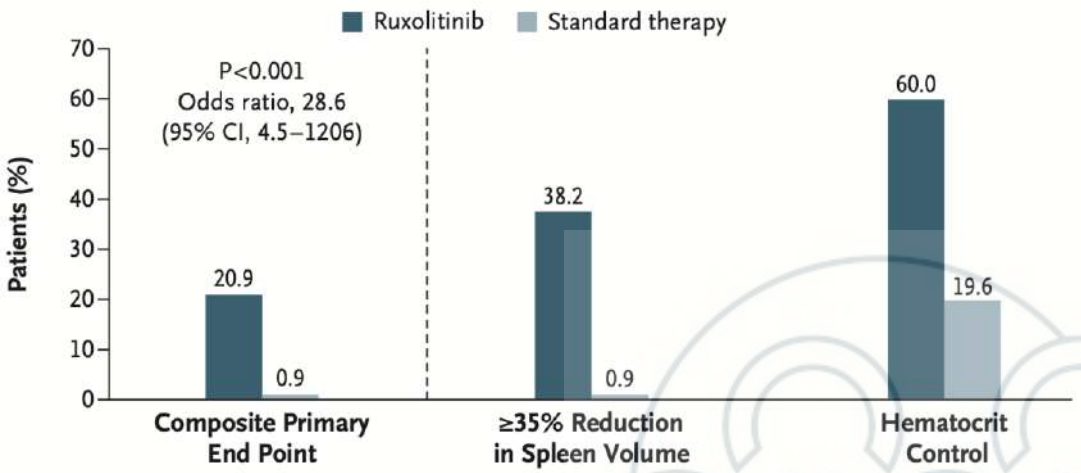
Palandri et al. *Cancers.* **2023**;15:3706.

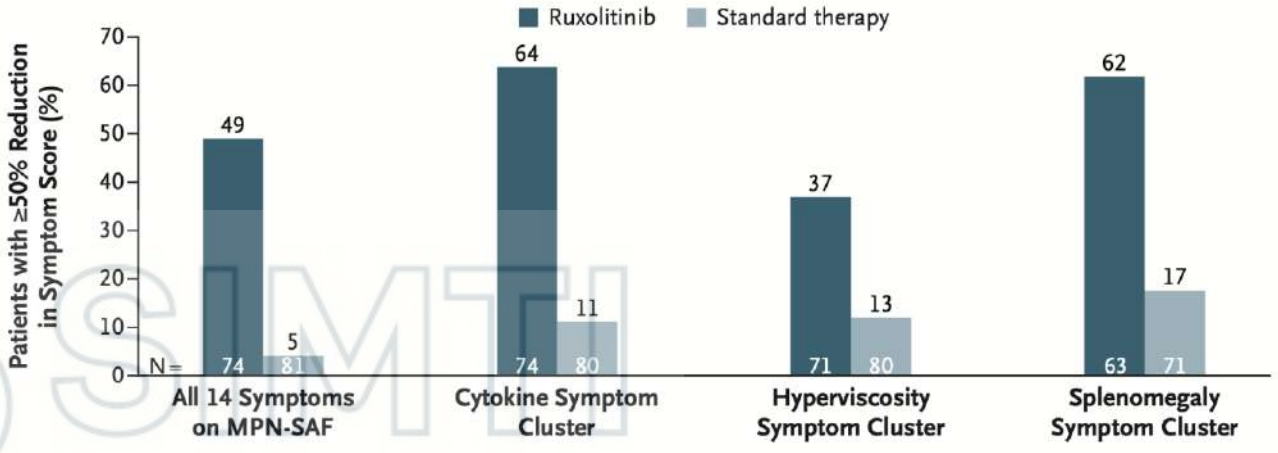
Inadequately controlled PV: when switching to a second-line therapy?

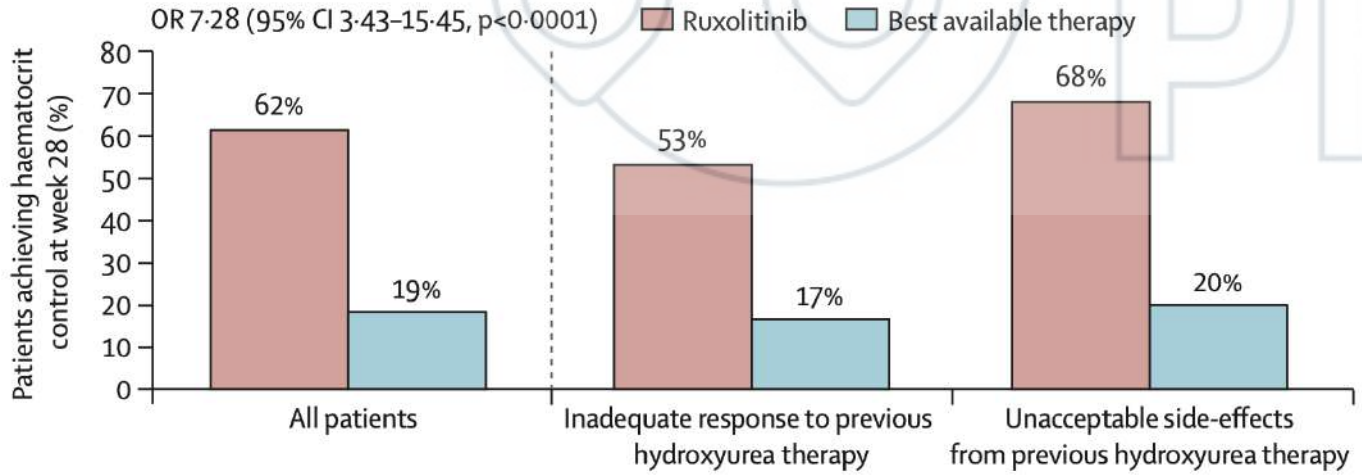


Barosi et al. *Br J Haematol.* **2010**;148:961-963. Marchetti et al. *Lancet Haematol.* **2022**;9:e301-311.

Ruxolitinib vs best available treatment in resistant/intolerant PV patients

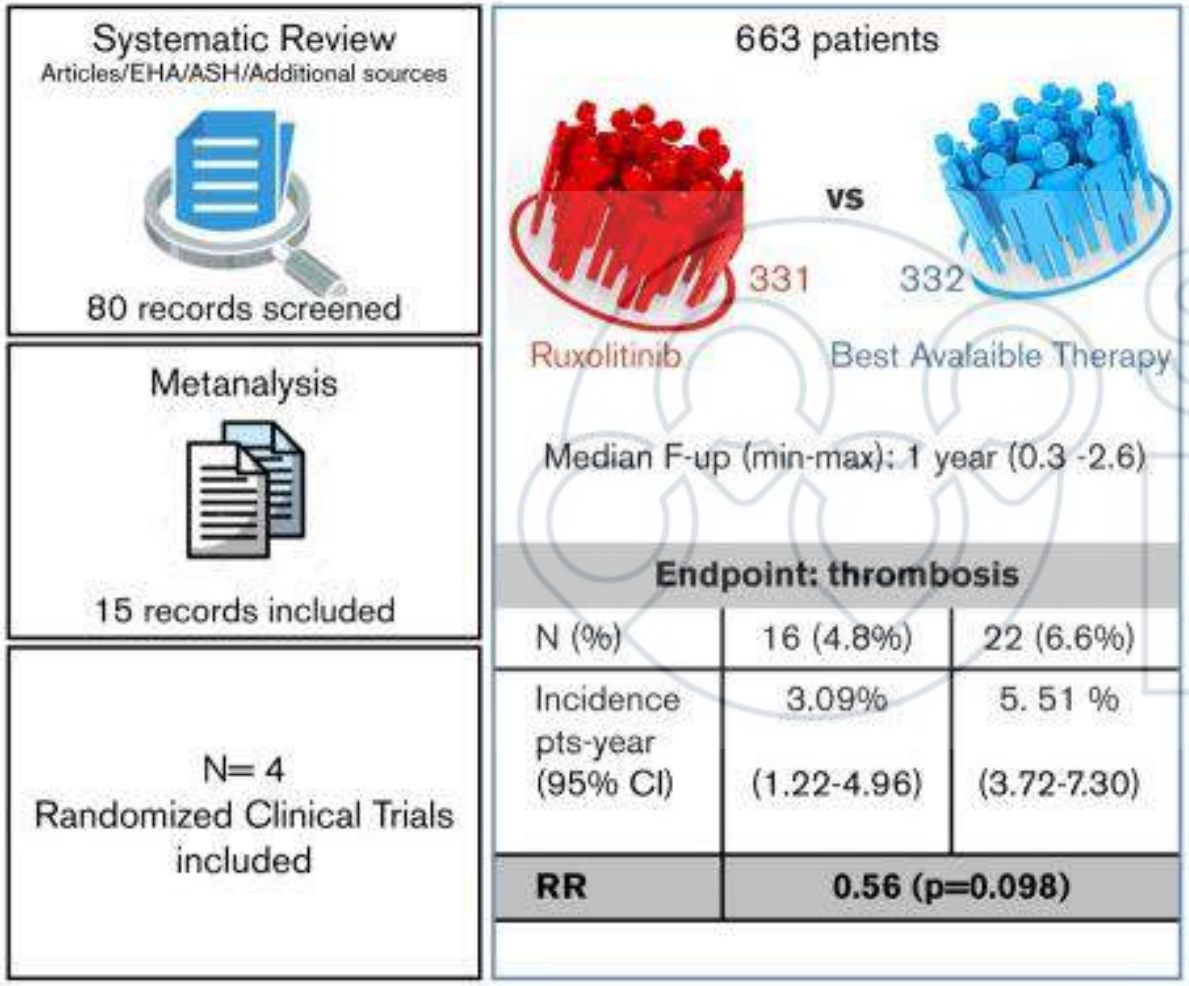






[1] Vannucchi et al. *N Engl J Med.* **2015**;372:426-435. [2] Passamonti et al. *Lancet Oncol.* **2017**;18:88-98.

Reduction of thrombosis risk with ruxolitinib



Endpoint: thrombosis		
N (%)	16 (4.8%)	22 (6.6%)
Incidence pts-year (95% CI)	3.09% (1.22-4.96)	5. 51 % (3.72-7.30)
RR	**0.56 (p=0.098)**	

Potential determinants of reduction of thrombosis risk with ruxolitinib

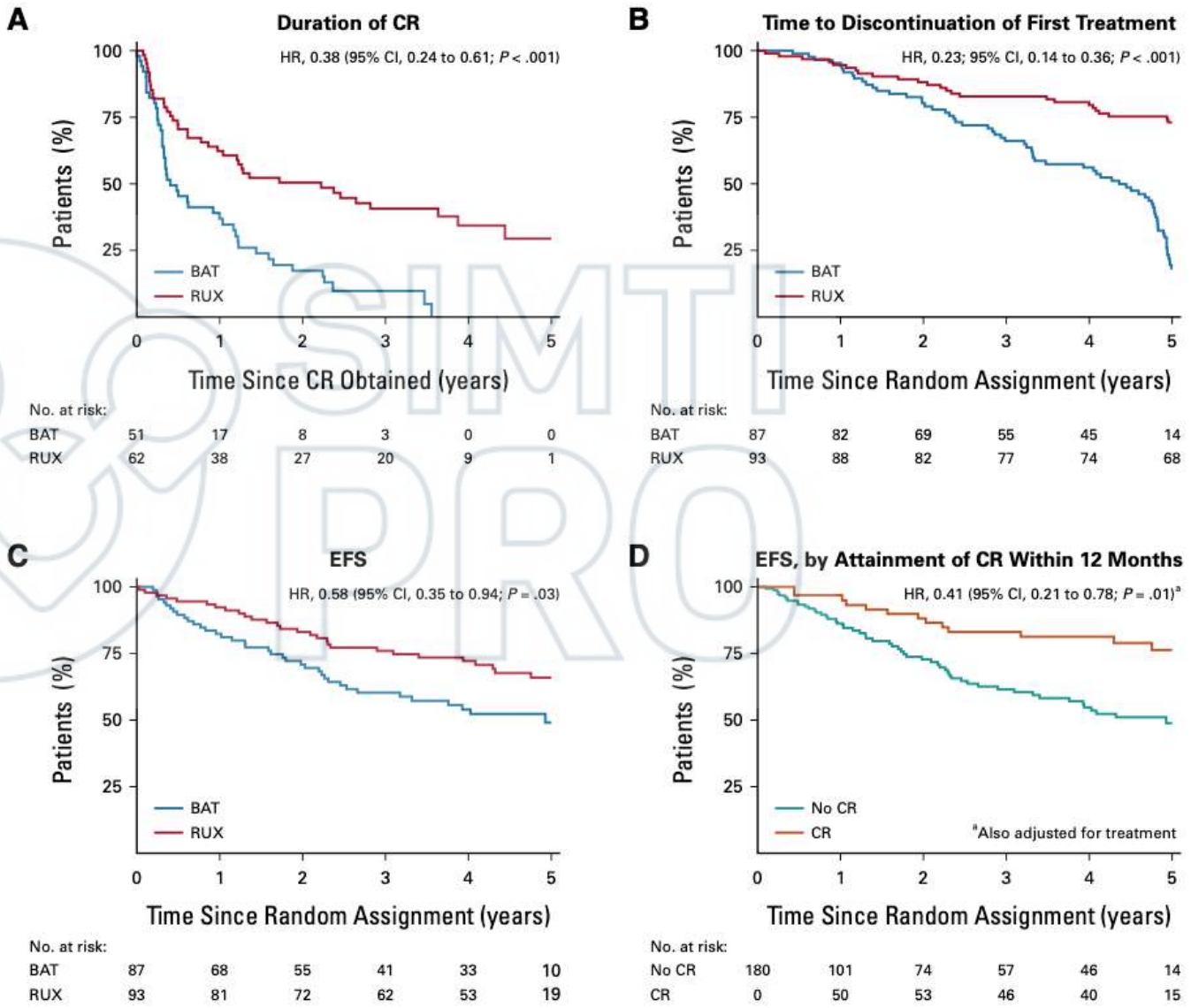
- Steady control of Hct at target level
- Control of leukocytosis
- Anti-inflammatory effect
- Reduction of *JAK2*^{V617F} allele burden
- Impact on JAK2-mutated endothelium

Masciulli et al. *Blood Adv.* **2020**;4:380-386.

MAJIC-PV trial: ruxolitinib vs best available treatment in PV after HU failure

Endpoint	Rux (n = 93)	BAT (n = 87)
CR within< 12 mo, n (%)	40 (43)	23 (26)
OR (90% CI), adjusted for sex (stratification factor)	2.12 (1.25-3.60) P = .02	
OR (90% CI), adjusted for sex, treatment arm, and baseline characteristics*	2.03 (1.09-3.78) P = .06	
Thrombolic EFS, HR (95% CI)	0.56 (0.32-1.00) P = .05	
Hemorrhagic EFS, HR (95% CI)	0.66 (0.34-1.28) P = .22	
3-yr PFS, % (95% CI)	84 (74-90)	75 (63-83)
3-yr OS, % (95% CI)	88 (79-93)	87 (77-93)

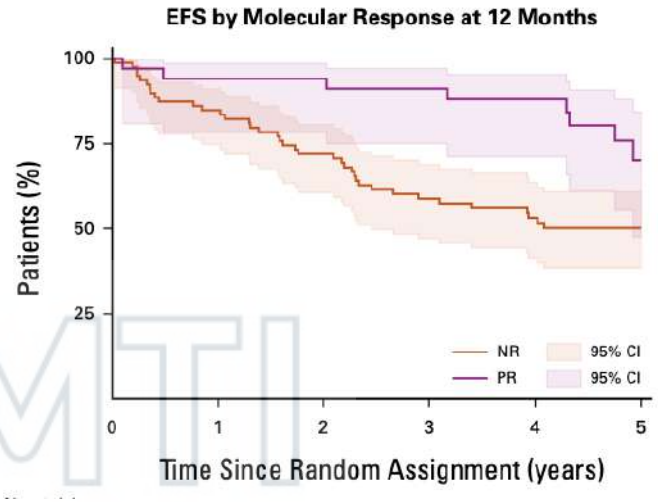
*Hgb, number of prior therapies, history of thrombosis, resistance or intolerance to HU, and splenomegaly.



Harrison et al. *J Clin Oncol.* **2023**;41:3534-3544.

Is the achievement of molecular response the true goal of treatment in PV?

- Molecular Response at 1 yr correlated with superior EFS
- Those with durable MR at last time point had significant improvements in EFS, PFS, and OS regardless of treatment arm
  - Correlation of clinical improvement with MR was driven by the ruxolitinib arm



	Any Treatment				Ruxolitinib			BAT		
Outcome	Whole Trial (n = 127), No. Events, (%)	NR[a] (n = 74), No. Events, (%)	PR[b] (n = 53), No. Events, (%)	*P*	NR[a] (n = 31), No. Events, (%)	PR[b] (n = 39), No. Events, (%)	*P*	NR[a] (n = 43), No. Events, (%)	PR[b] (n = 14), No. Events, (%)	*P*
Thromboembolic event[c]	38 (30)	28 (38)	10 (19)	.02	10 (32)	7 (18)	.17	18 (42)	3 (21)	.17
Hemorrhagic event[c]	28 (22)	23 (31)	5 (9)	.004	9 (29)	4 (10)	.04	14 (33)	1 (7)	.06
Progression-free survival[c]	35 (28)	29 (39)	6 (11)	.001	13 (42)	3 (8)	.001	16 (37)	3 (21)	.28
EFS[c]	53 (42)	40 (54)	13 (25)	.001	16 (52)	8 (21)	.006	24 (56)	5 (36)	.19
OS[c]	22 (17)	18 (24)	4 (8)	.01	8 (26)	3 (8)	.04	10 (23)	1 (7)	.18
CR achieved at 1 year	49 (39)	22 (30)	27 (51)	.02	10 (32)	22 (56)	.04	12 (28)	5 (36)	.58

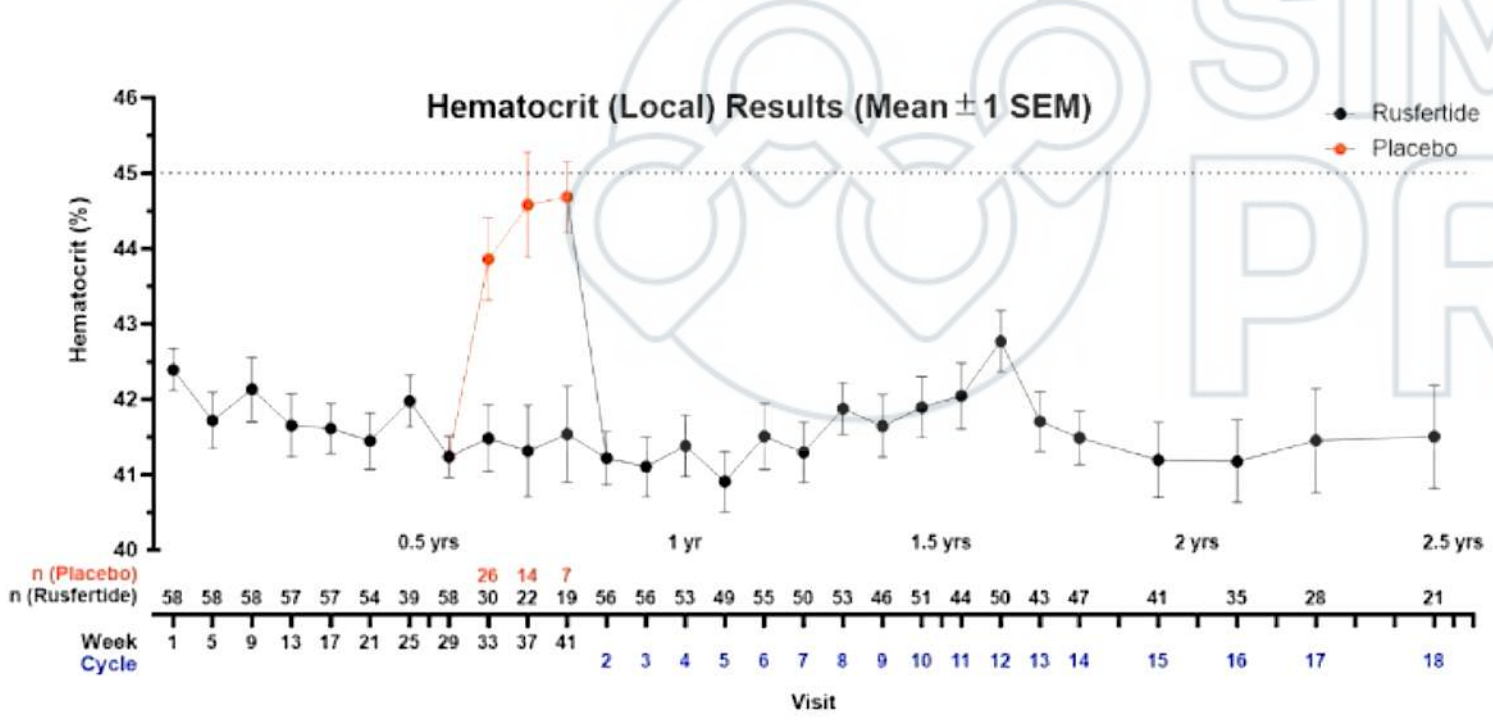
[a] No molecular response defined as <50% reduction in JAK2 variant allele fraction.
[b] Partial molecular response defined as ≥50% response in JAK2 variant allele fraction.

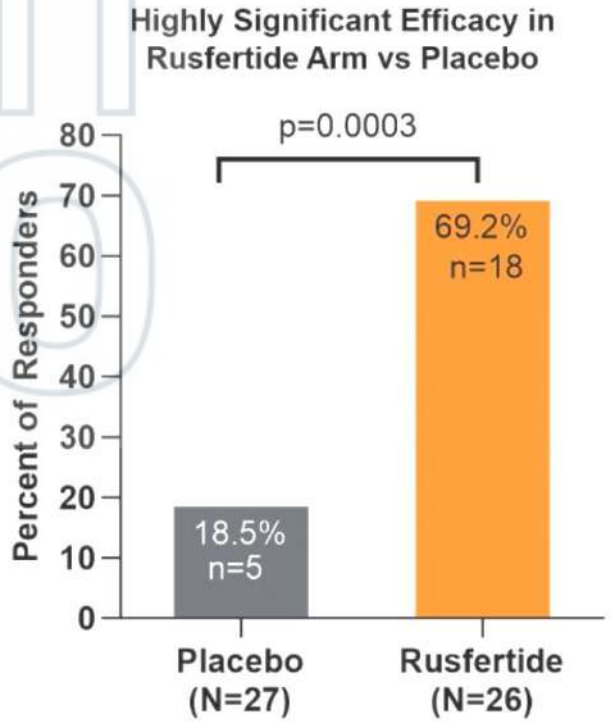
Harrison et al. *J Clin Oncol.* **2023**;41:3534-3544.

Rusfertide, a hepcidin mimetic, enables durable hematocrit control in PV

Rusfertide is a hepcidin mimetic that controls red blood cell production in PV patients by limiting iron availability.

Eligible patients were required to have ≥ 3 therapeutic phlebotomies in the 28-week period prior to enrollment with or without concurrent cytoreductive therapy.





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Conclusions

- Treatment of PV should be mainly focused on reduction of thrombotic risk, myeloproliferation control, improvement of symptomatic burden, and management of disease-associated complications.
- Along with conventional risk factors (age, history of thrombosis), many other determinants of thrombotic risk exist and should be addressed (e.g. leukocytosis, JAK2 allele burden)
- The target of phlebotomy is keeping strictly Ht < 45%.
- Hydroxyurea and interferons are suitable options for the front-line treatment of PV: all high-risk and many low-risk patients should be treated with cytoreductive agents.
- Ruxolitinib is approved as second-line treatment in patients with resistance and/or intolerance to hydroxyurea and is more effective than best available treatments (including interferons) in inducing hematological responses and improving the EFS.