BOLOGNA
17 FEBBRAIO 2023
NH De La Gare

POLICITEMIA VERA NEL 2023:

qualcosa è cambiato

Quando il paziente a basso rischio trombotico merita una terapia citoriduttiva? E quale terapia va scelta?

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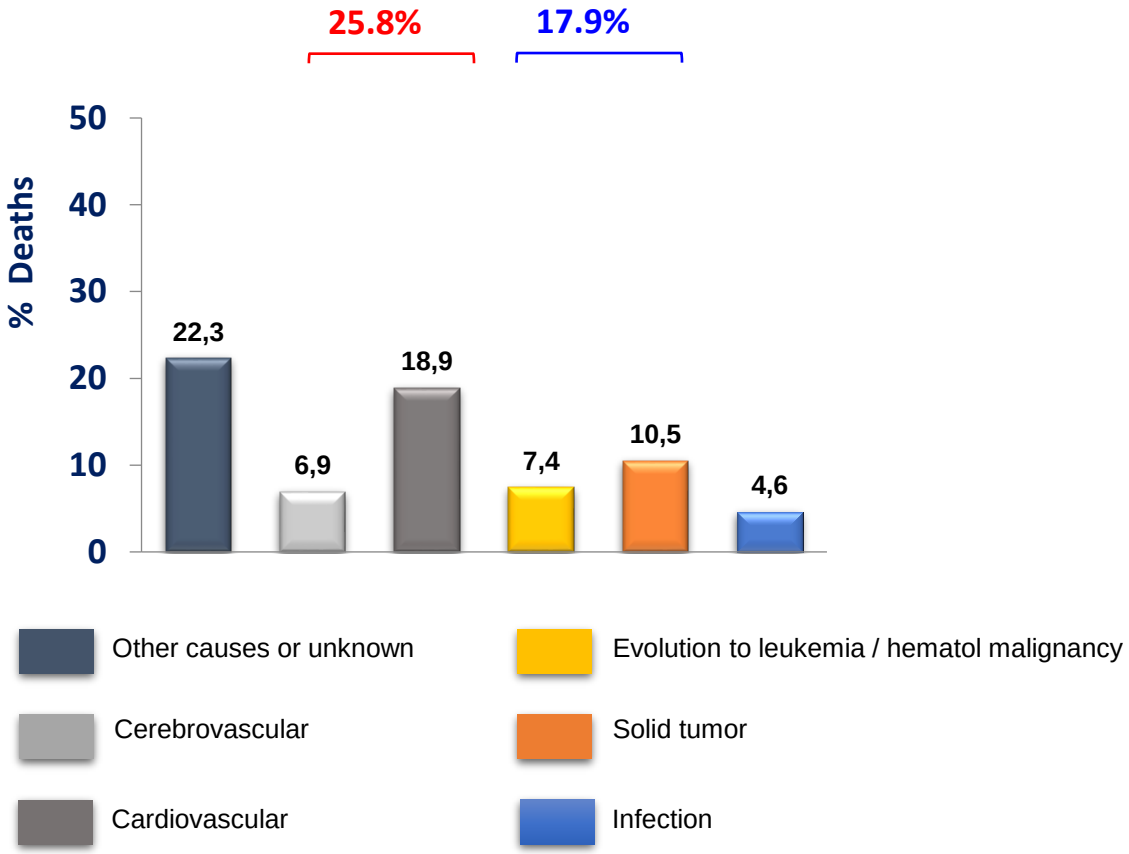
Disclosures of Massimiliano Bonifacio

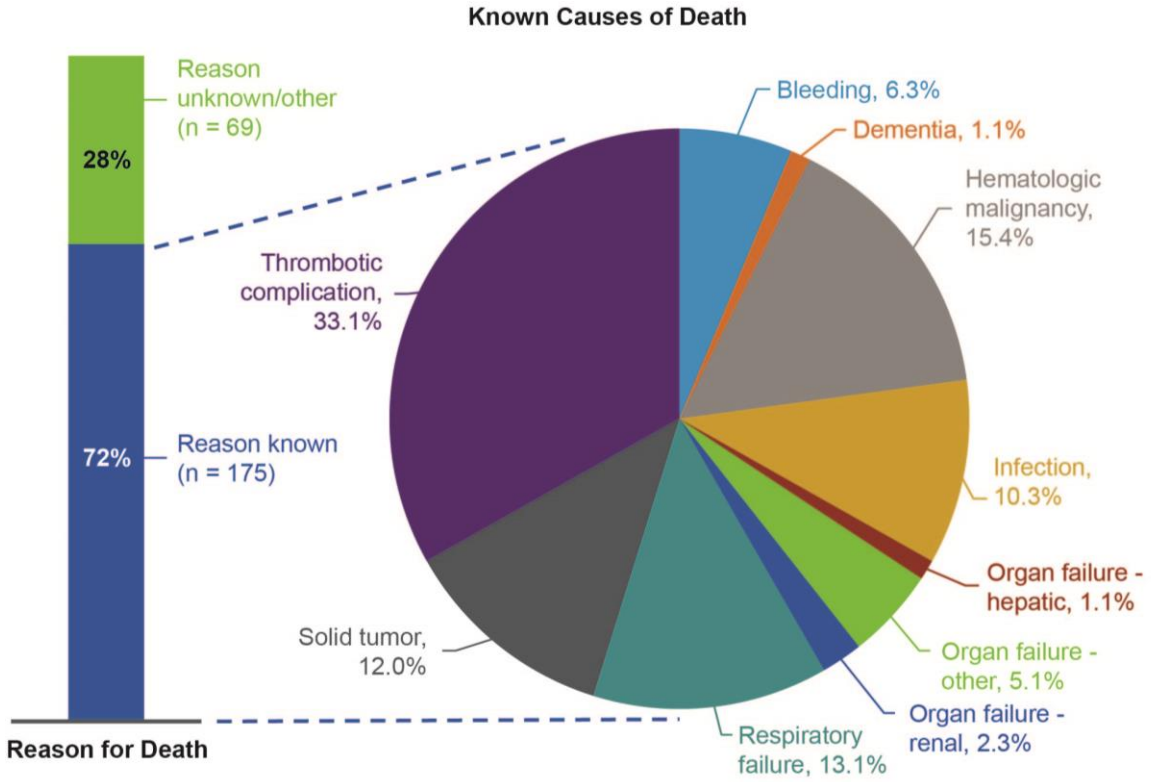
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis						x	
Bristol Myers Squibb						x	
Incyte						x	
Pfizer						x	
Amgen						x	
Clinigen						x	

Open issues in the management of Polycythemia Vera

- Reduce the rate of thromboembolic and hemorrhagic events
- Improve quality of life
- Prevent the evolution of the disease to post-PV myelofibrosis and acute leukemia

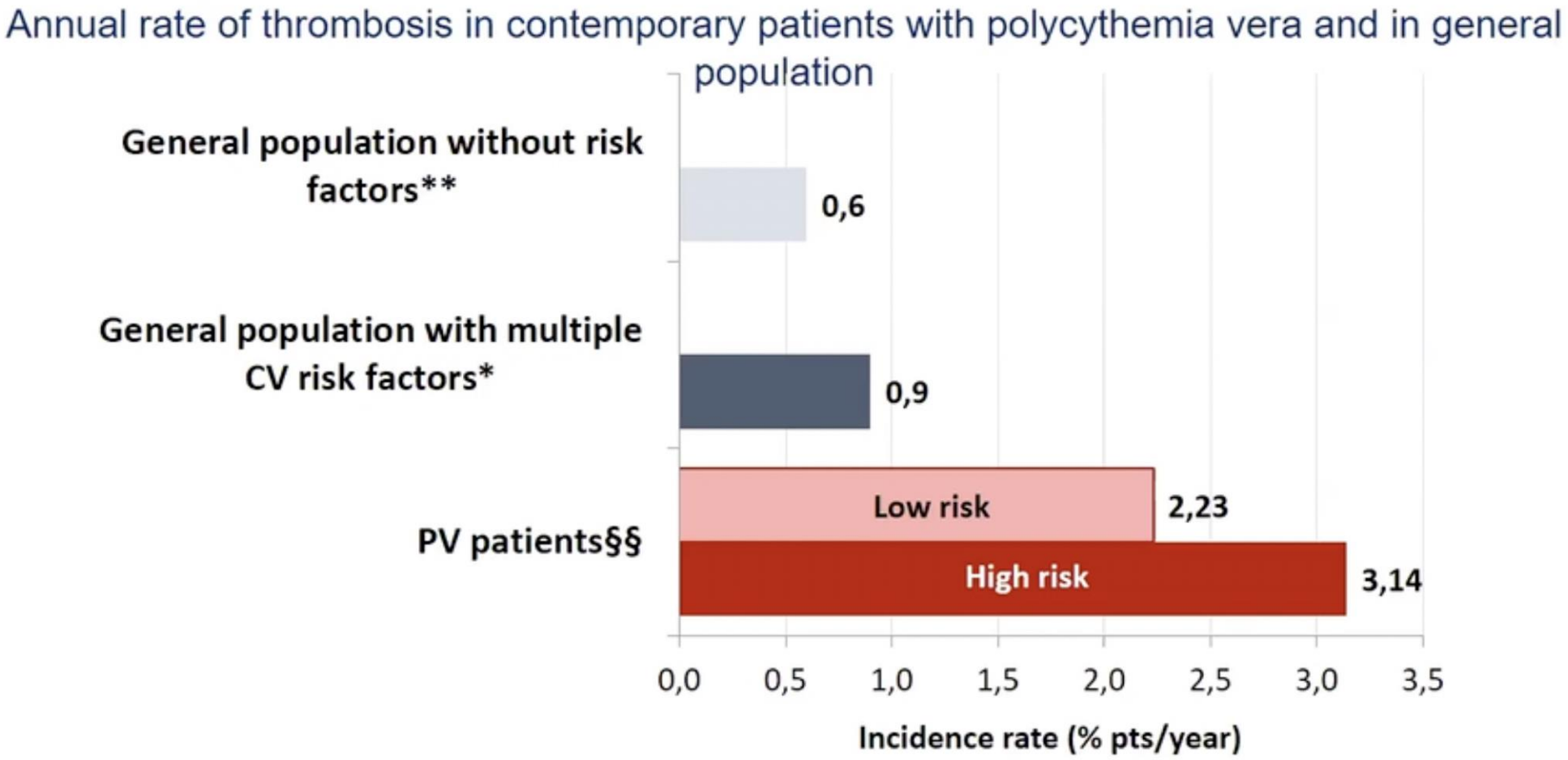
Causes of death in PV patients





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

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



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

Factors associated with thrombosis risk in PV

General factors

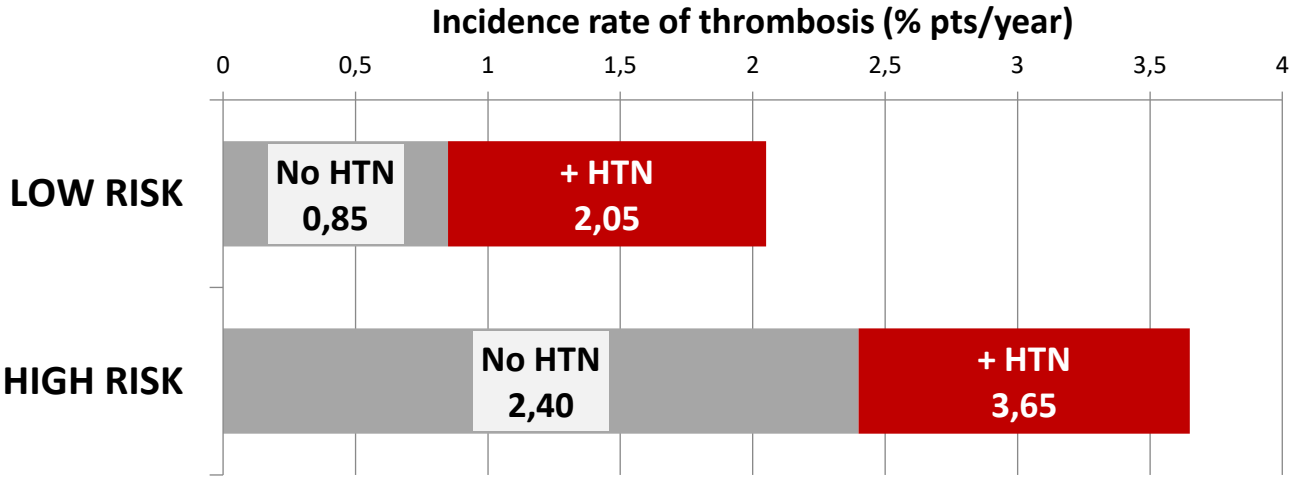
- Advanced age (> 60 years)
- History of thrombosis
- Cardiovascular risk factors (smoking, hypertension, dislypidemia, diabetes)
- Inherited or acquired thrombophilia

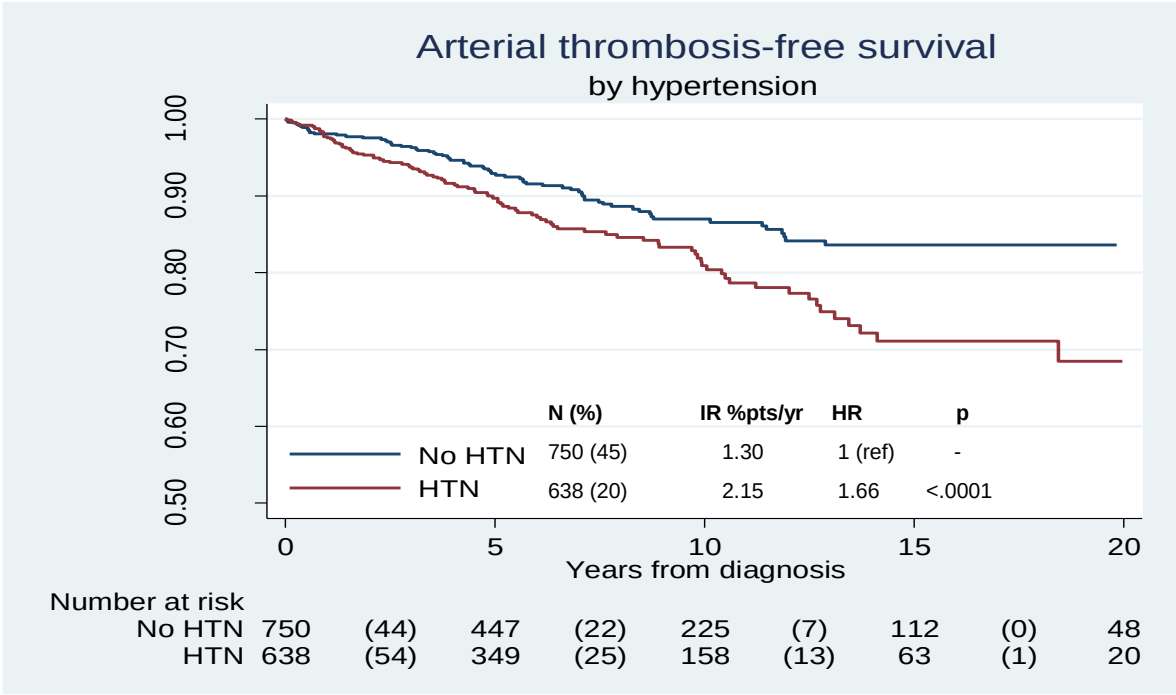
PV-specific factors

- Hypercythemia (high hematocrit, leukocytosis, *but not thrombocytosis*)
- Higher $JAK2^{V617F}$ mutation allele burden
- Platelet biochemical and functional abnormalities
- Coagulation activation
- Leukocyte and platelet activation

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.

Hypercythemia: the role of hematocrit

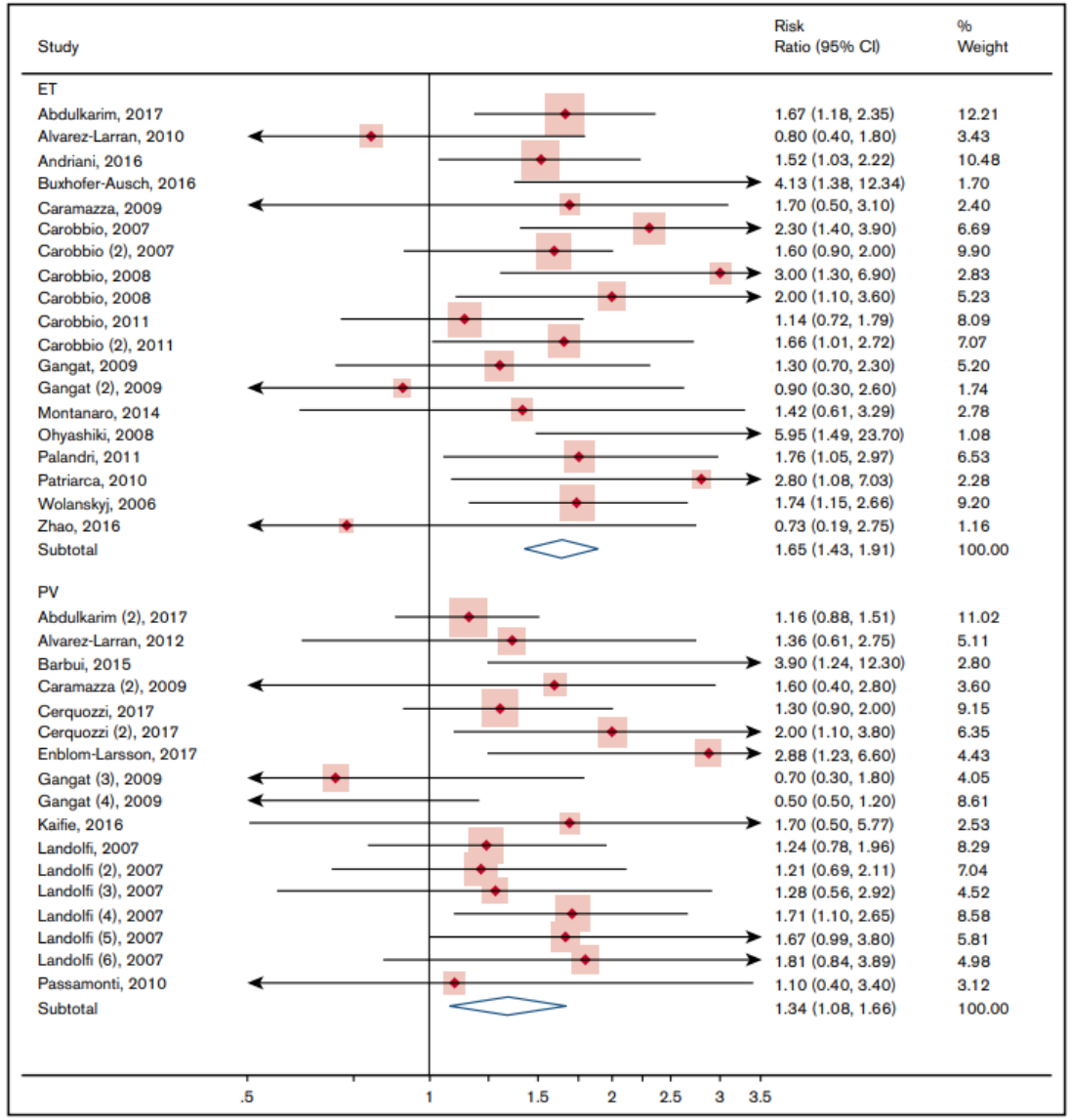
In PV patients with **Ht levels ≥45%**, the risk of CV-related **death or major thrombosis** was increased approximately **4 times** vs patients with Ht<45%

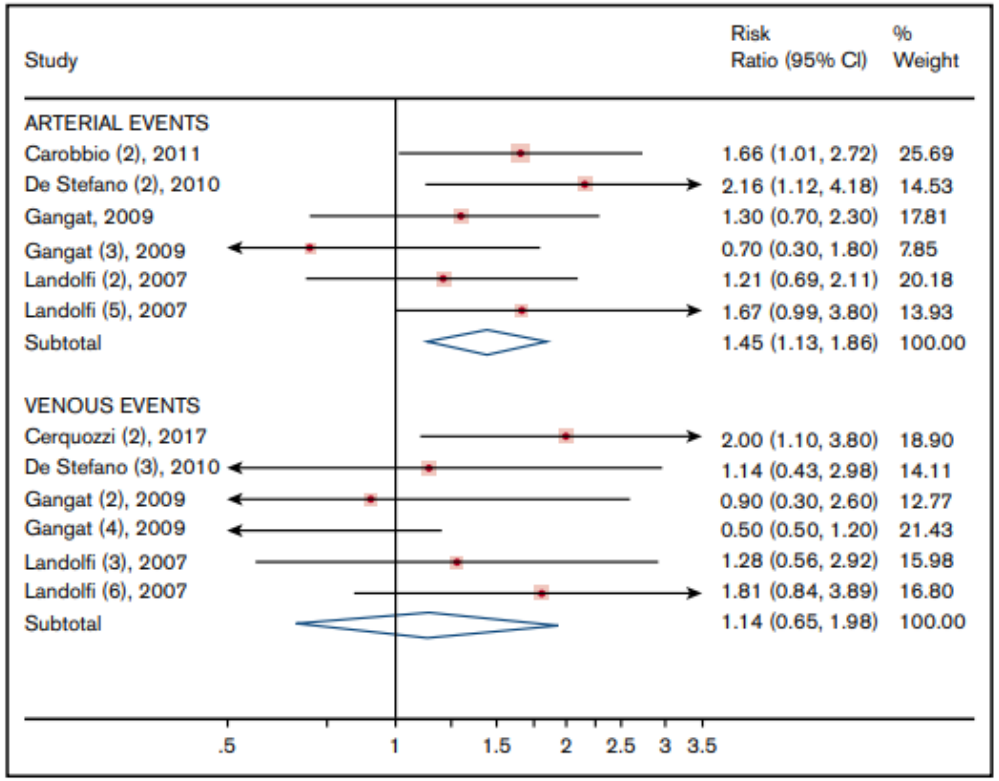
	HCT< 45% *n* = 182	HCT 45-50% *n* = 183	Total *n* = 365	HR (95% CI)	*p*
Primary Endpoint*, *n* (%) (CV death, MI, stroke, PAT, DVT, PE, TIA and abdominal thrombosis)	**5 (2.8)**	**19 (10.4)**	24 (6.6)	4.12 (1.54-11.0)	0.005
IR person/year	**1.1**	**4.7**	2.9		
Total CV events*, *n* (%) (Primary Endpoint 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. *N Engl J Med* **2013**;368:22-33.

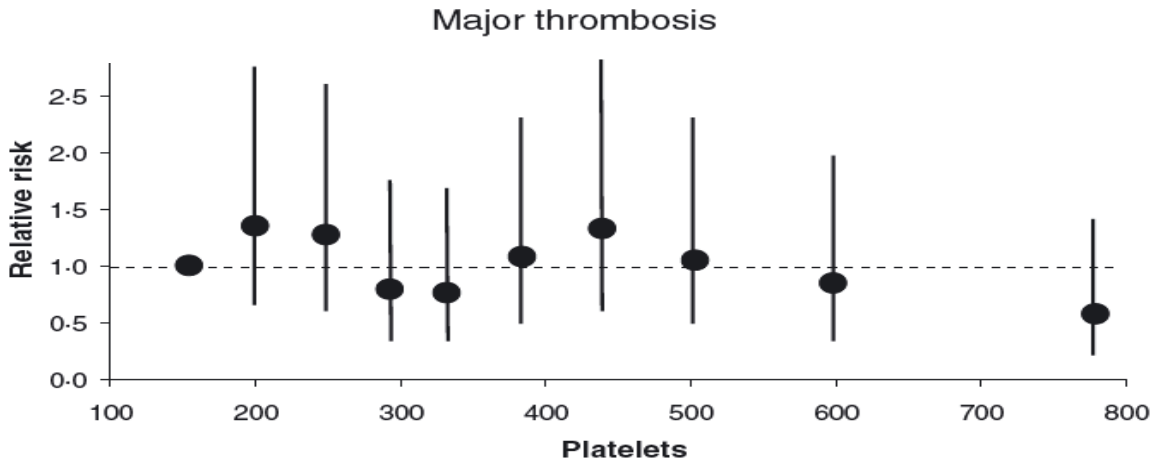
Hypercythemia: the role of WBC

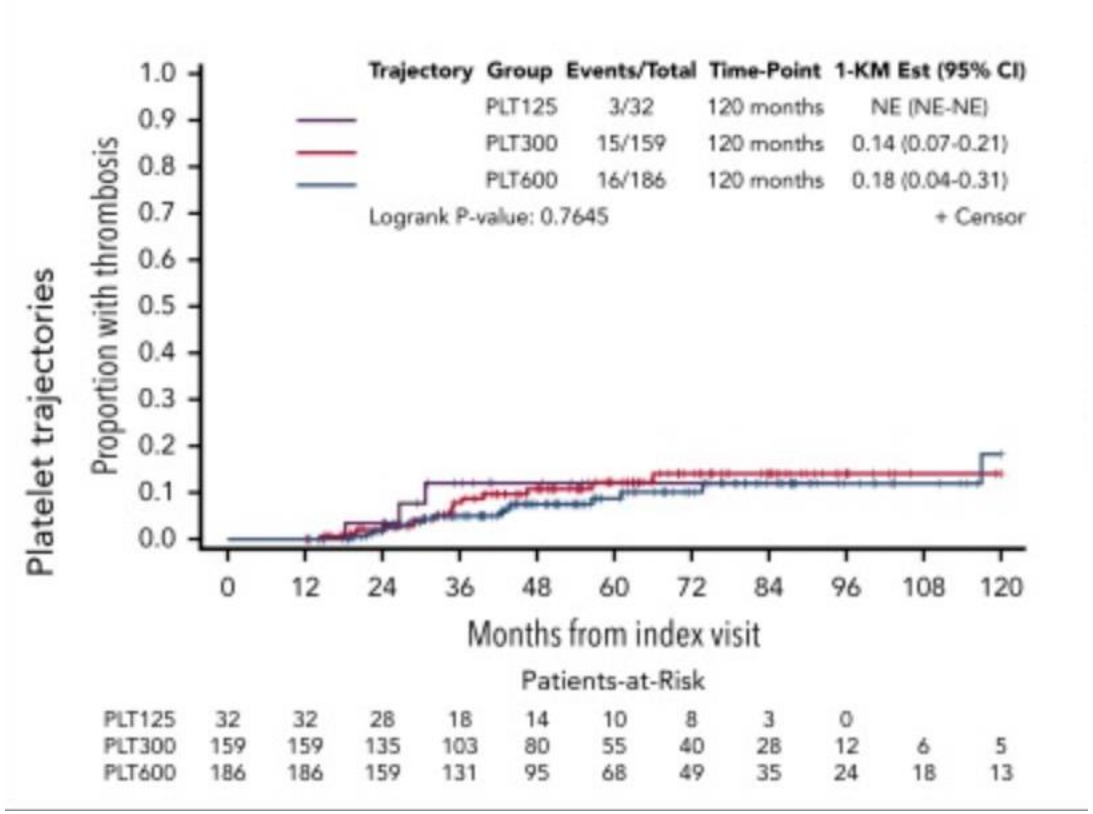




Carobbio et al. *Blood Adv* **2019**;3:1729-1737

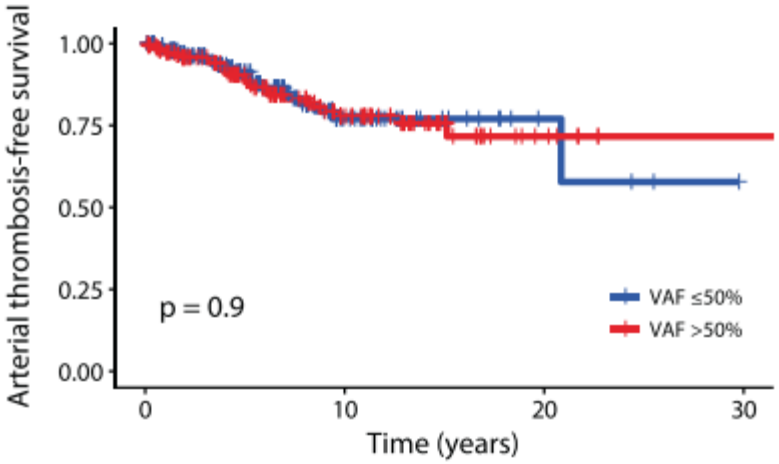
Hypercythemia: the role of platelets

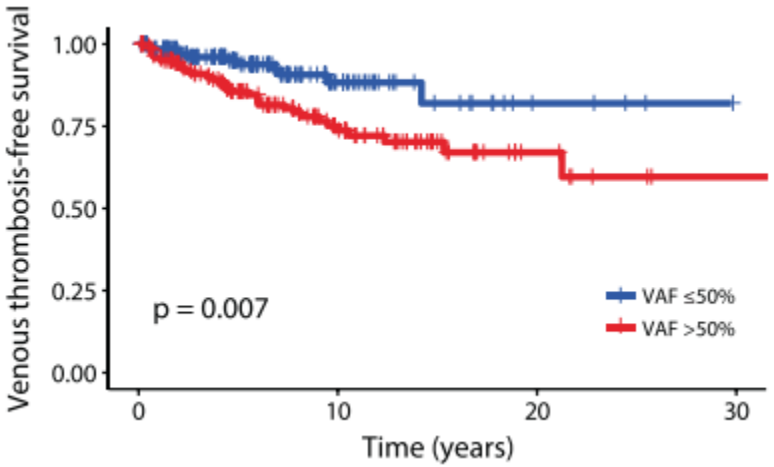




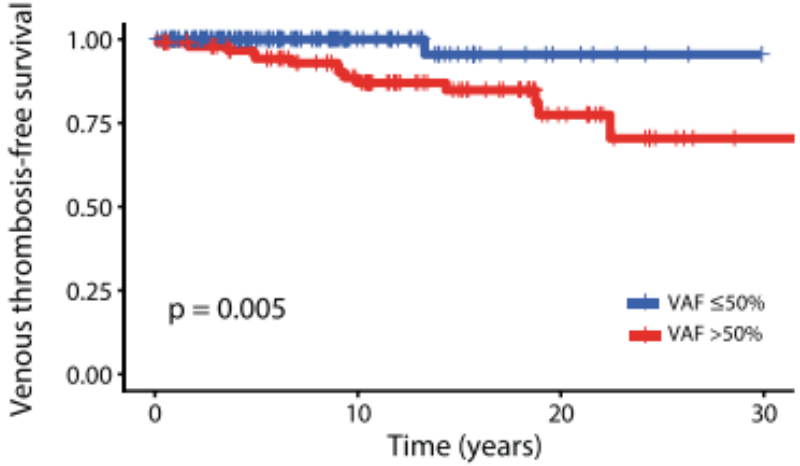
[1] Di Nisio et al. *Br J Haematol* **2007**;136:249-259. [2] Ronner et al. *Blood* **2020**;135:1696-1703.

JAK2 allele burden and thrombotic risk





Low-risk patients



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

Cytoreduction therapy in PV: ELN guidelines

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

European LeukemiaNet Indications for Cytoreduction

- **High-risk PV**, but also in **low-risk** in specific situations:
  - Frequent phlebotomy requirement or poor tolerance to phlebotomy
  - Severe disease-related symptoms
  - PLT >1,500 x 10^9/L
  - Progressive leukocytosis
  - Symptomatic and progressive splenomegaly

Options for first-line cytoreduction include HU and IFN (and busulfan for very eldely patients)

Barbui et al. *Leukemia* **2018**;32:1057-1069.

Recommendations for cytoreduction in LOW-RISK patients

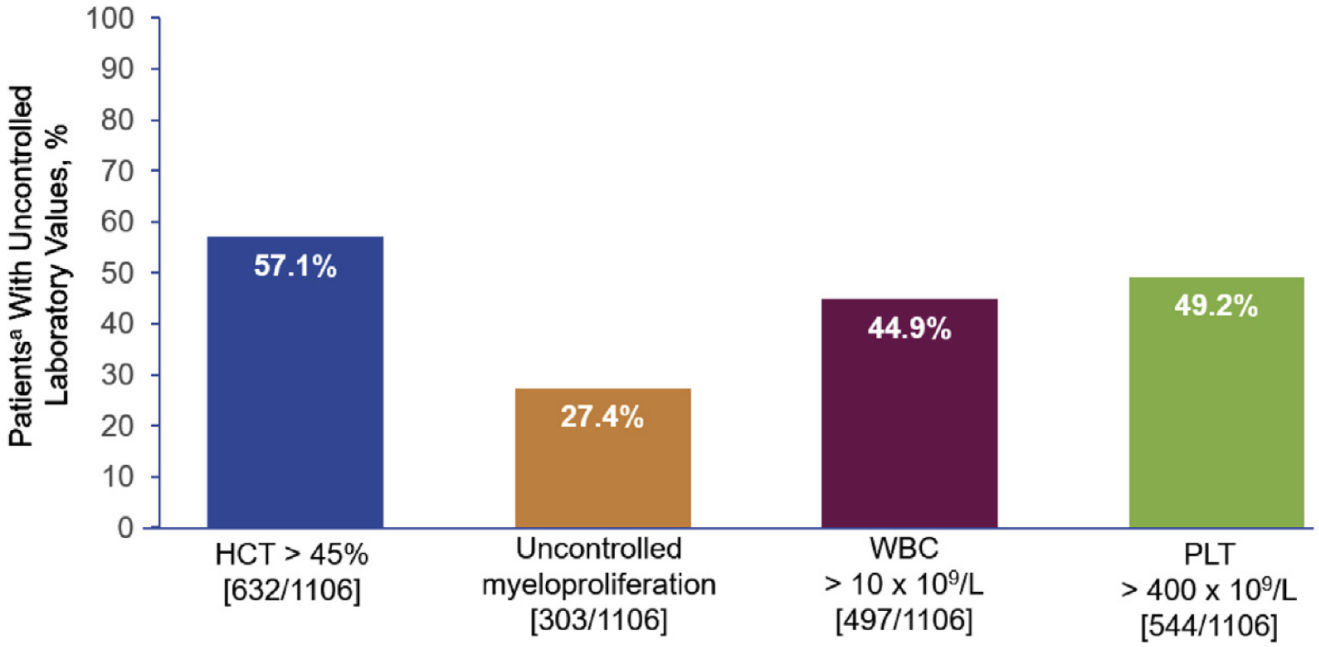
Cytoreduction is recommended	• poor tolerance to **phlebotomy**, strictly defined • symptomatic progressive **splenomegaly** (increase by >5 cm in the past year) • persistent **leukocytosis** (leukocyte count >20 × 10^9 cells per L confirmed at 3 months
Cytoreduction should be considered	• progressive (at least 100% increase if baseline count is <10 × 10^9 cells per L or at least 50% increase if baseline count is >10 × 10^9 cells per L) and persistent (leukocyte count >15 × 10^9 cells per L confirmed at 3 months) **leukocytosis** • extreme **thrombocytosis** (>1500 × 10^9 platelets per L), bleeding manifestations related to the disease irrespective of the platelet count, or both • **inadequate haematocrit control** with phlebotomies, i.e. a need for at least six phlebotomies per year for at least 2 years in the maintenance phase
Cytoreduction can be considered	• high **symptom burden** (total symptom score ≥20) or severe itching (itching score ≥5) that are not ameliorated by phlebotomy, antiplatelet therapy, or antihistamines • on an individual basis in patients reporting a **relevant cardiovascular risk**, provided that primary prevention strategies have been implemented

Marchetti et al. *Lancet Haematol* **2022**;9:e301-311.

Dose intensity and efficacy of hydroxyurea in the real world (REVEAL study)

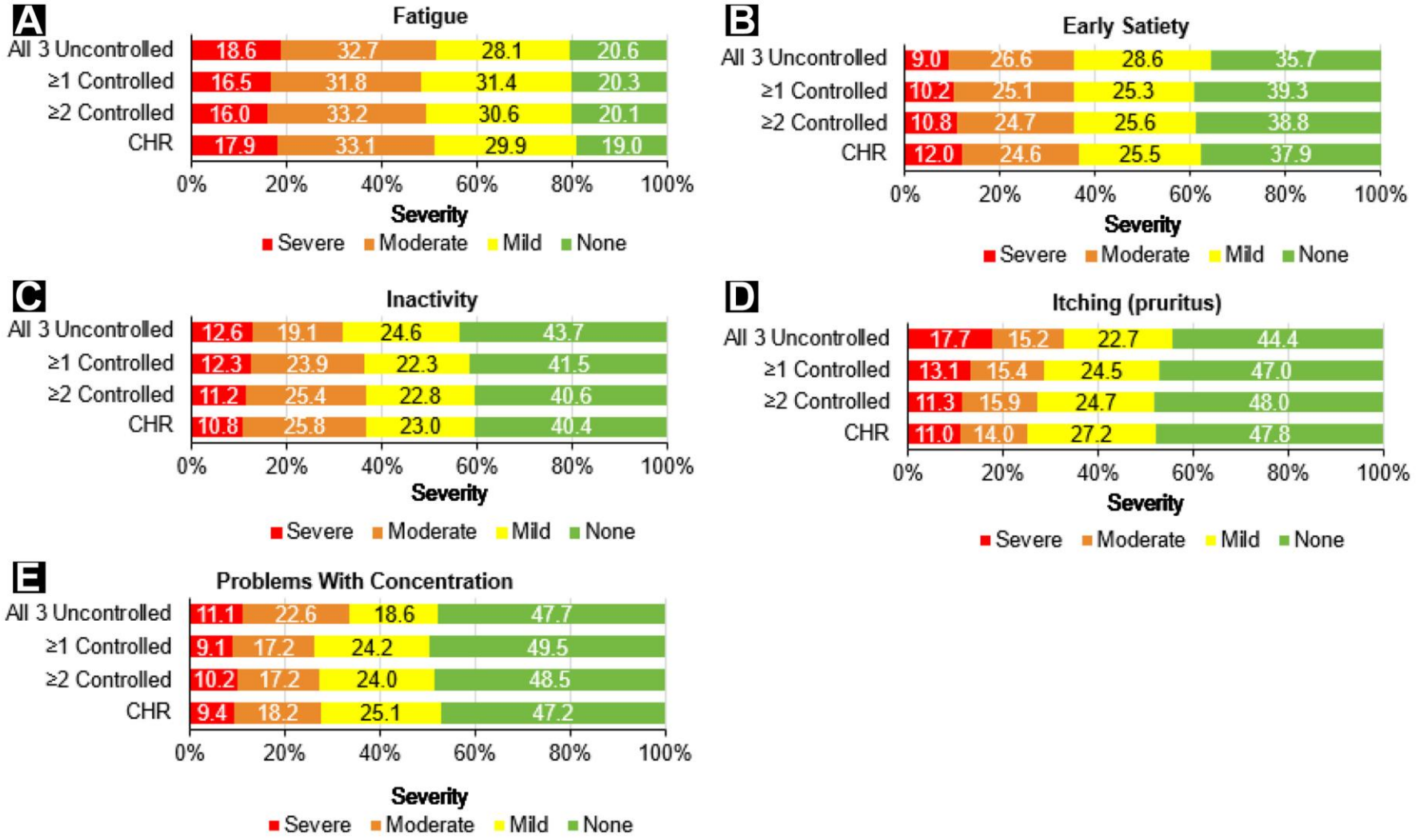
Table 3 HU Dose Intensity and Exposure

	Received HU for ≥ 3 Months (n = 1381)
Median maximum daily dose (range), mg/d	1000.0 (71.4-5571.4)
Maximum daily dose, mg/d, n (%)	
< 400	91 (6.6)
500	415 (30.1)
750	159 (11.5)
1000	423 (30.6)
1500	204 (14.8)
2000	61 (4.4)
> 2000	28 (2.0)
Median duration of maximum daily dose, (range), mos	19.6 (0.0-38.5)
Median HU exposure post-index (range), mos	23.6 (3.1-38.5)



Grunwald et al. *Clin Lymphoma Myeloma Leuk* **2020**;20:219-225.

Blood count control does not imply symptom control



Grunwald et al. *Clin Lymphoma Myeloma Leuk* **2019**;19:579-584.

Predictors of complete response to hydroxyurea

Characteristics before treatment	CR (n. 195)	SubOR (n. 467)	p value
Age, median (range), years	71 (43-89)	65 (21-89)	**<0.001**
Male sex, %	43.1%	55.7%	**0.003**
JAK2^{V617F}≥50%, % on 426 evaluable	39.0%	54.1%	**0.004**
Platelet count, median (range), x 10^9/L	497 (159-1279)	457 (138-1209)	0.03
Leukocytes, median (range), x 10^9/L	10 (3.3-30)	10 (1-38)	0.93
Hemoglobin, median (range), g/dL			
Male	18.6 (12-23.6)	18.6 (12-24.8)	0.93
Female	17.8 (15.3-22)	17.5 (13.2-21.9)	0.05
Hematocrit, median (range), %			
Male	55.5 (38-72.5)	56.3 (38-73)	0.94
Female	54 (47.6-71.7)	54 (39-72)	0.81
Palpable spleen, % of 645 evaluable	16.6%	40%	**<0.001**
Spleen palpable at ≥5 cm BLCM	1.0%	7.7%	**0.001**
Symptoms, no. (%)	92 (47.1%)	315 (67.5%)	**<0.001**
Pruritus, no. (%)	31 (16.0%)	188 (40.3%)	**<0.001**
BMI ≥25, % of 398 evaluable	43.8%	49.9%	0.35
At least one CVRF, no. (%)	154 (79.0%)	362 (77.5%)	0.68
Thromboses pre-/at diagnosis, no. (%)	47 (24.1%)	122 (26.1%)	0.59

Compared to SubOR patients, at diagnosis CR patients were characterized by:

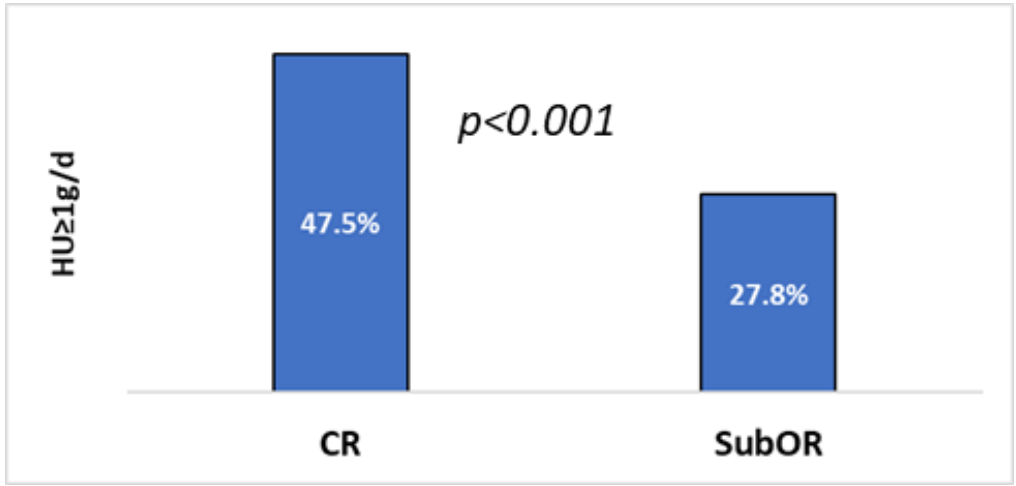
- Older age
- Female sex
- Less frequent occurrence of
  - *JAK2*^{V617F} ≥50%
  - palpable spleen, spleen ≥5 cm BLCM
  - symptoms and pruritus

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

Palandri et al. *SIE* **2021**;abs#C097.

Hydroxyurea dose is associated with response

- In 593 patients, median HU dose was reported
- Median dose was 0.5 g/d (range, 0.2-2) and was ≥2 g/d in 3.1% of patients. 192 patients (32.4%) received median HU doses ≥1 g/d
- CR patients received more frequently HU ≥1 g/d compared to SubOR patients, with no significant difference between PR and NR patients (p=0.08).



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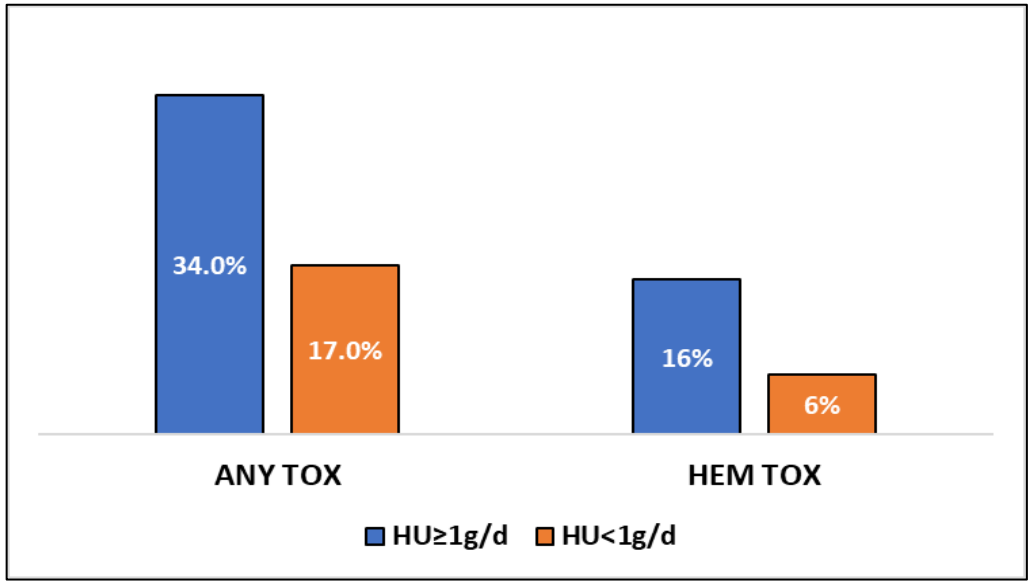
- In the 192 patients who received HU ≥1 g/d, $JAK2^{V617F}$ <50% & absence of palpable spleen/symptoms confirmed their association with CR

Palandri et al. *SIE* **2021**;abs#C097.

Hydroxyurea dose is associated with toxicity

- At least one HU-related AE occurred in 152/662 patients (23%) and was hematological in 59 patients (8.9%).
- HU dose ≥1 g/d was associated with increased incidence of HU-related AEs

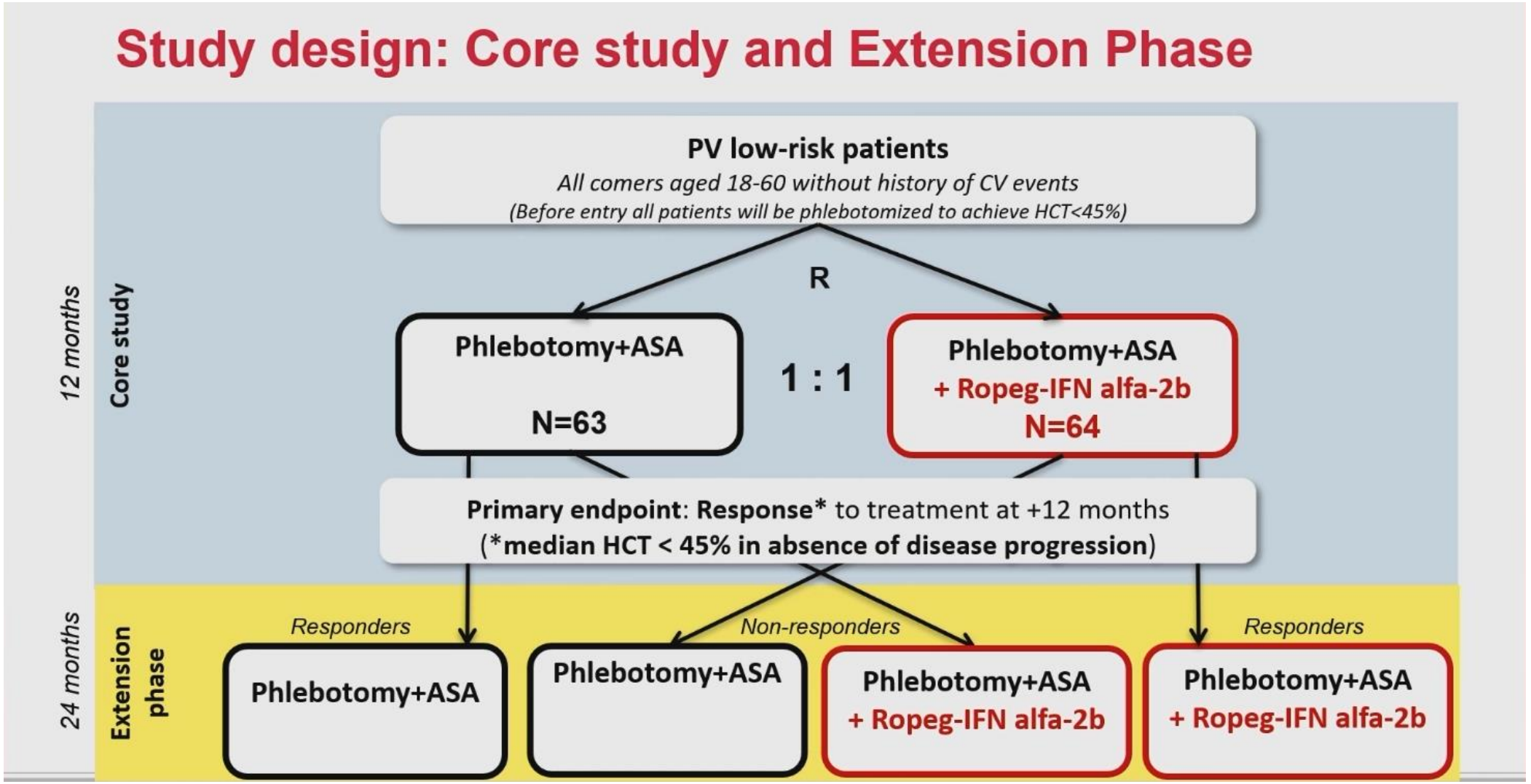


Toxicity	HU <1 g/d (n. 401)	HU ≥1 g/d (n. 192)
Anemia/thrombocytopenia	24 (6.0%)	30 (15.6%)
Skin ulcers	21 (5.2%)	24 (12.5%)
Oral aftosis	11 (2.7%)	5 (2.6%)
Gastrointestinal disturbances	6 (1.5%)	4 (2.1%)
Fever	2 (0.5%)	1 (0.5%)
Mialgia	3 (0.7%)	0
Zoster reactivations	1 (0.2%)	1 (0.5%)

- Among non hematological adverse events, there was a significant excess of skin ulcers in HU ≥1 g/d (p=0.002).
- A total of 14 NMSC occurred during or after HU, with no impact of HU dose (p=0.22)

Palandri et al. *SIE* **2021**;abs#C097.

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



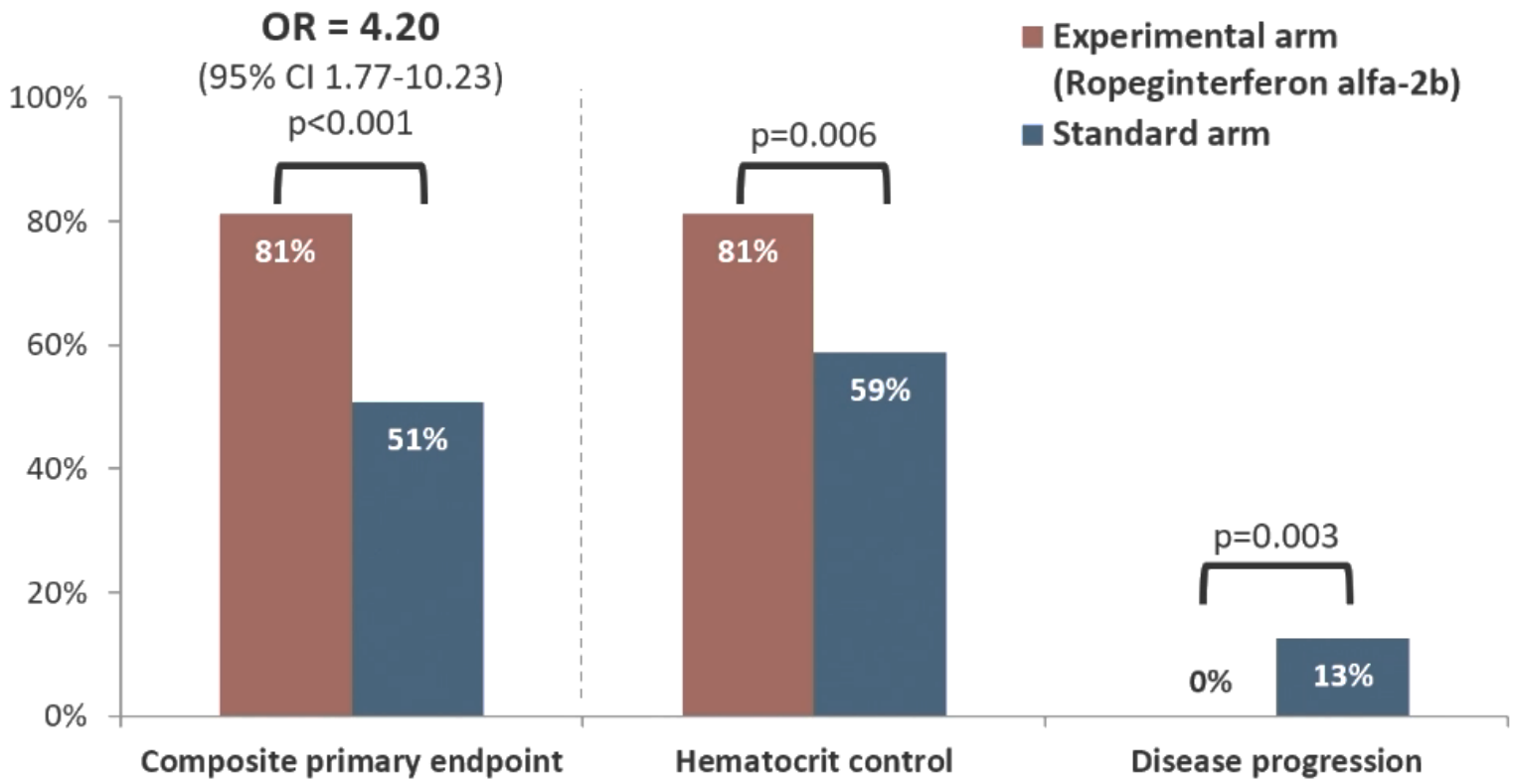
Barbui et al. *Lancet Hematol* **2021**;8:e175.

Low-PV: study population

	Ropeg arm N=64	Phlebotomy arm N=63
Age, years	51.7 (45.5-55.3)	48.2 (43.7-57.4)
Male sex	47 (73.4%)	39 (61.9%)
Palpable splenomegaly	21 (33.3%)	18 (28.6%)
Symptoms None/mild Moderate/severe	 38 (61.3%) 24 (38.7%)	 34 (56.7%) 26 (43.4%)
Hematocrit, %	44.2 (42.4-45.0)	44.0 (42.3-45.8)
White blood cells, x 10^9/L	10.4 (8.6-13.8)	10.3 (7.5-13.7)
Platelets, x 10^9/L	632.0 (489.5-738.0)	657.0 (460.0-803.0)
JAK2 V617F allele burden, %	38.0 (17.5-59.0)	34.5 (15.0-74.0)

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

Low-PV: primary endpoint



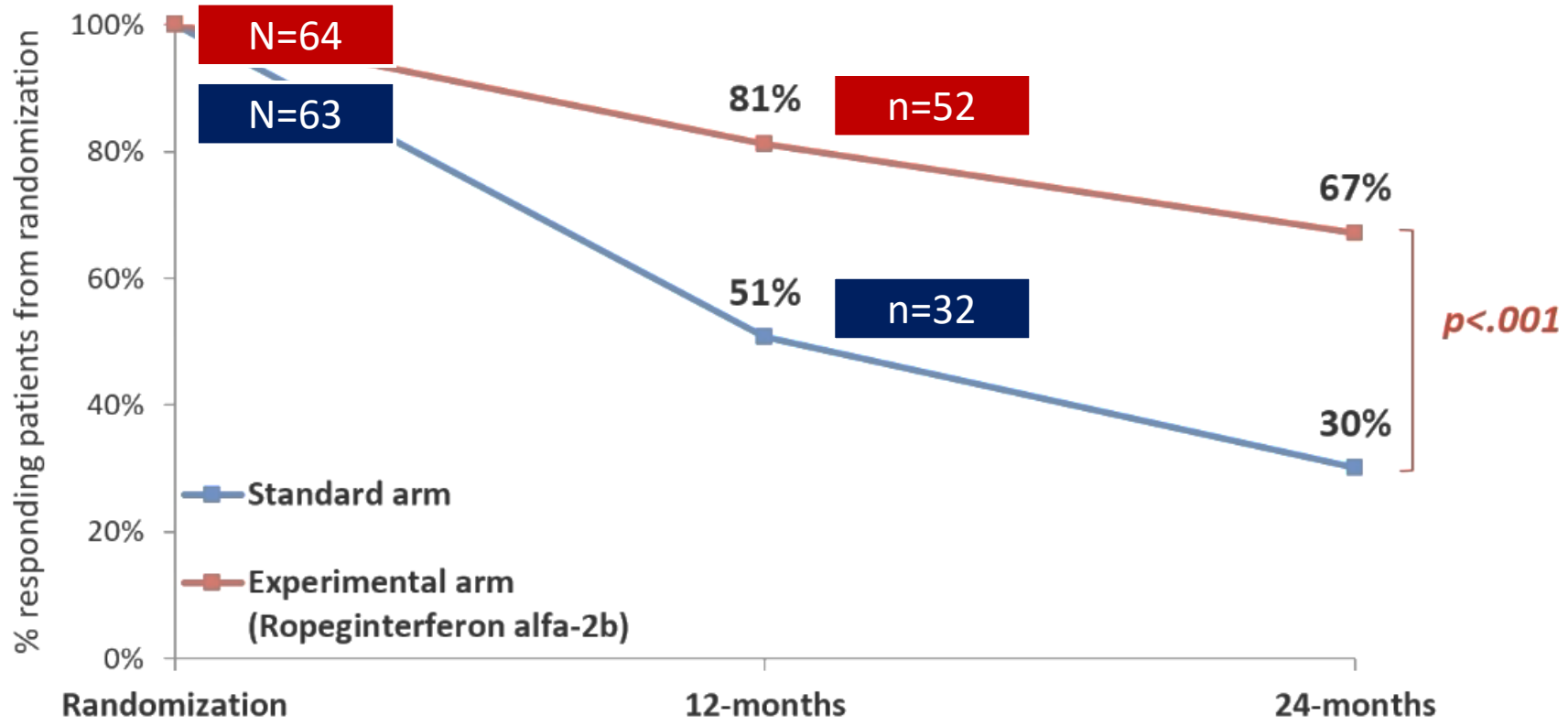
Disease progression was observed in **8 patients** (all in standard arm):

- **In 6**, platelet count progression to >1000x10^9/L in pts with baseline values lower than 600x10^9/L
- **In 2**, splenic infarction and transient ischemic attack, respectively

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

Low-PV: treatment response maintenance according to ITT

- *All randomized patients included.*
- *Patients crossed-over were censored at 12 months as non-responders of the orginal arm*



Barbui et al. *ASH* **2022**;abs#744.

Low-PV: characteristics of responders at entry to the extension phase

	Patients maintaining treatment	
	Standard (n=32)	**Ropeg (n=52)**
At randomization		
Age	48.2 (45.0-57.4)	52.0 (47.0-55.7)
Male sex	16 (50.0%)	36 (69.2%)
BMI	23.0 (21.1-27.4)	24.7 (22.2-26.1)
12 months		
Hematocrit, %	44.1 (42.4-45.2)	43.0 (41.3-44.3)
Phlebotomy no. per pat-yr	2.0 (1.5-4.0)	2.0 (1.0-4.0)
White blood cells, $x10^9$/L	**9.8** (8.8-14.9)	**5.3** (4.2-7.2)
Platelets, $x10^9$/L	**682.0** (542.0-883.0)	**317.5** (225.0-409.0)
JAK2V617F VAF, %	**35.0** (17.0-64.0)	**18.0** (8.0-35.0)

Statistically significant differences (i.e., $p<0.05$) in bold

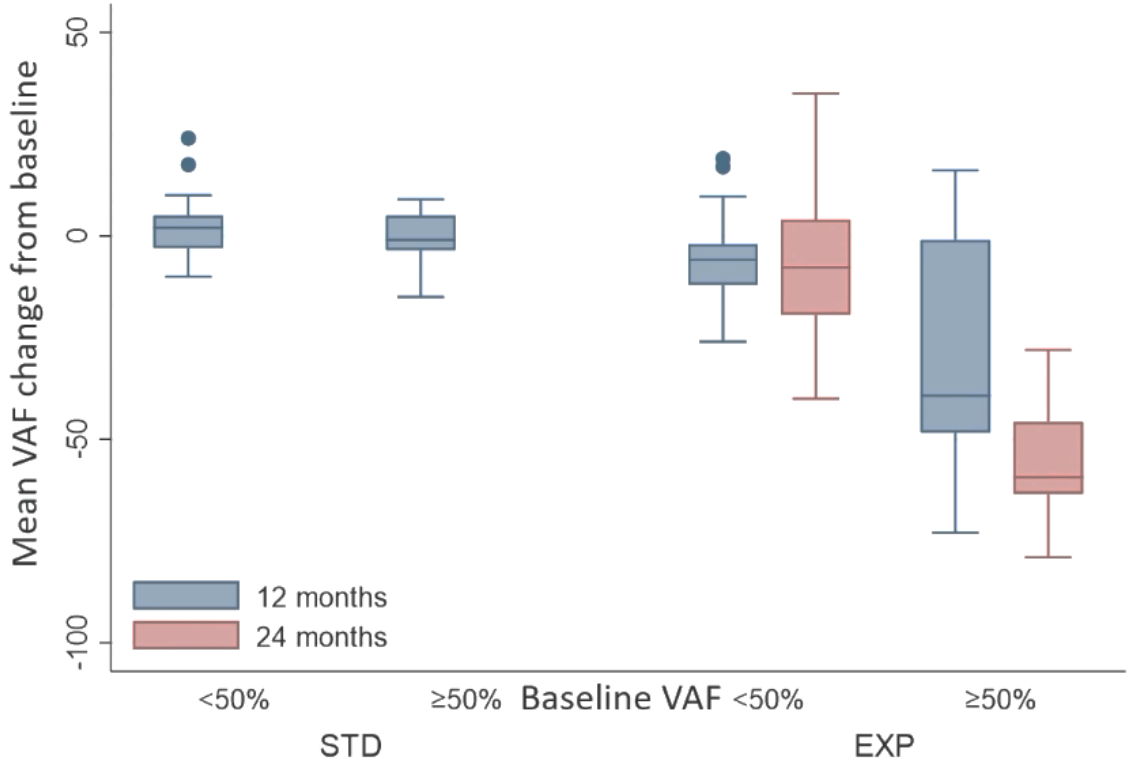
Barbui et al. *ASH* **2022**;abs#744.

Low-PV: trend of *JAK2* V617F allele burden in responders

All responders

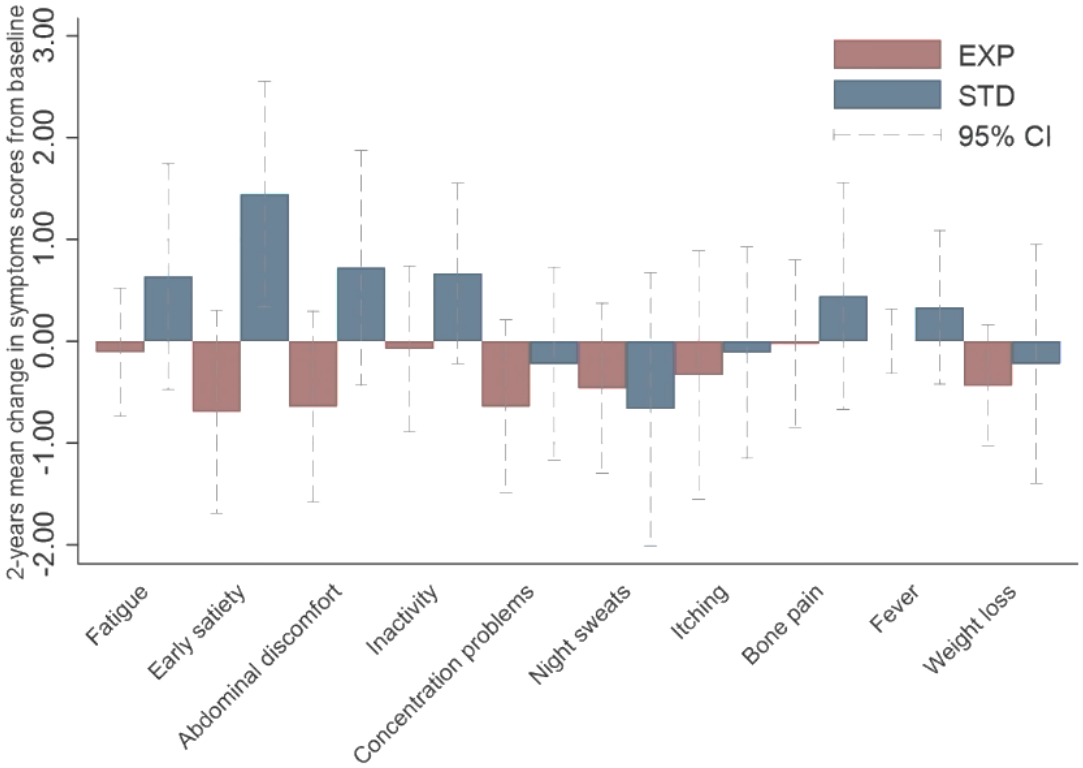
* *Statistical differences from baseline (paired t-test)*

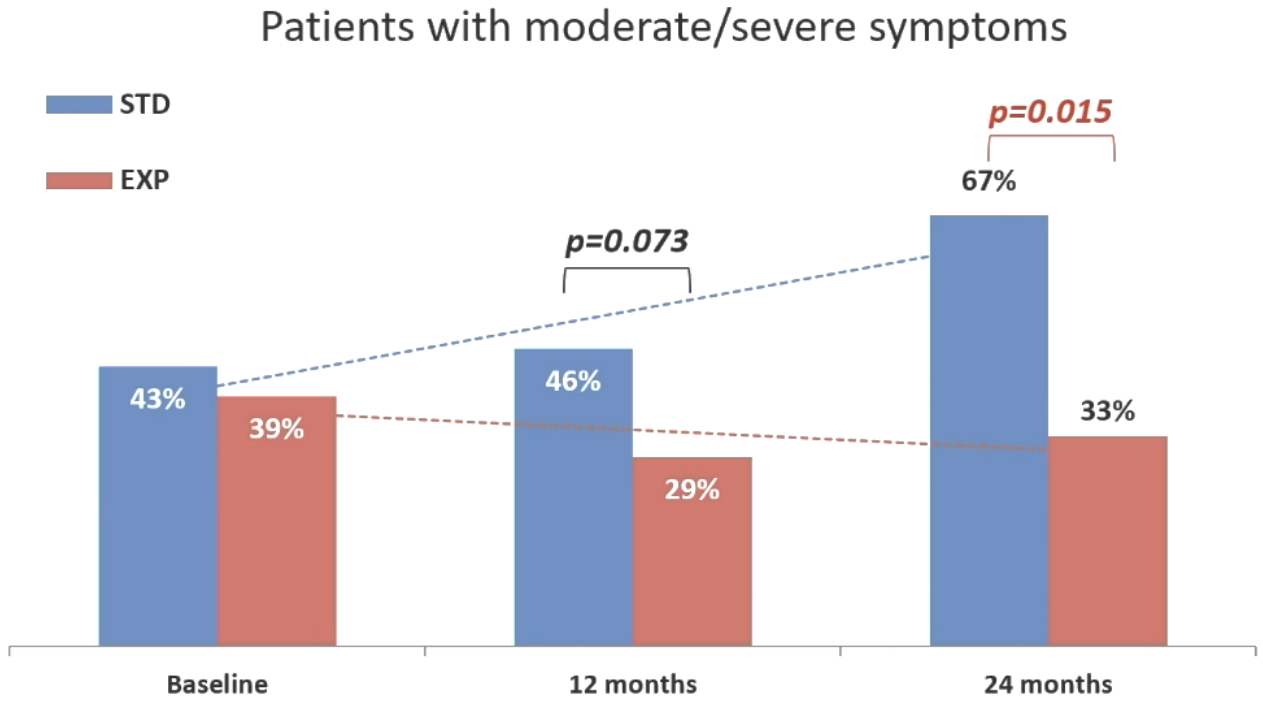
By baseline allele burden



Barbui et al. *ASH* **2022**;abs#744.

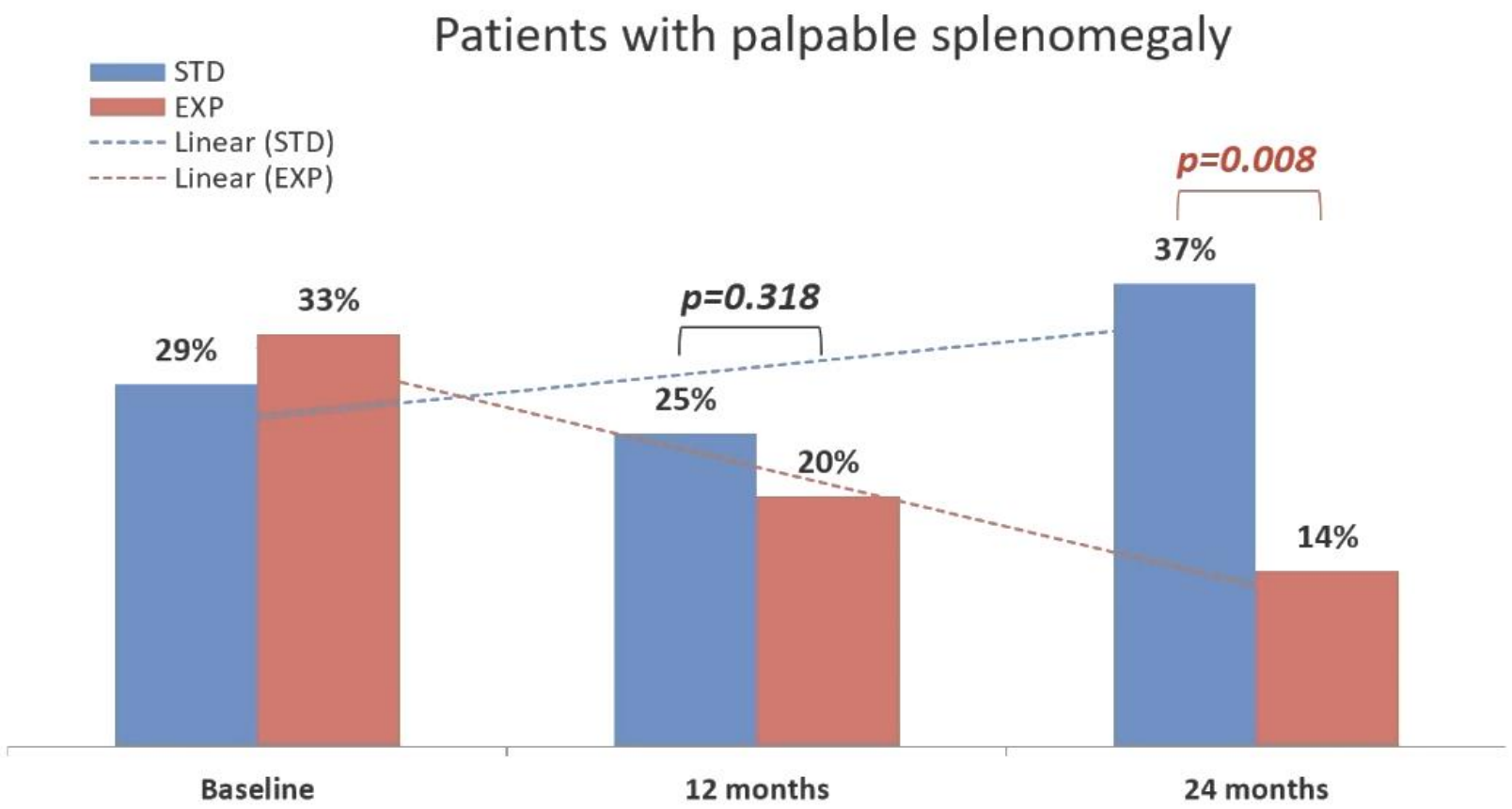
Low-PV: symptoms and overall quality of life





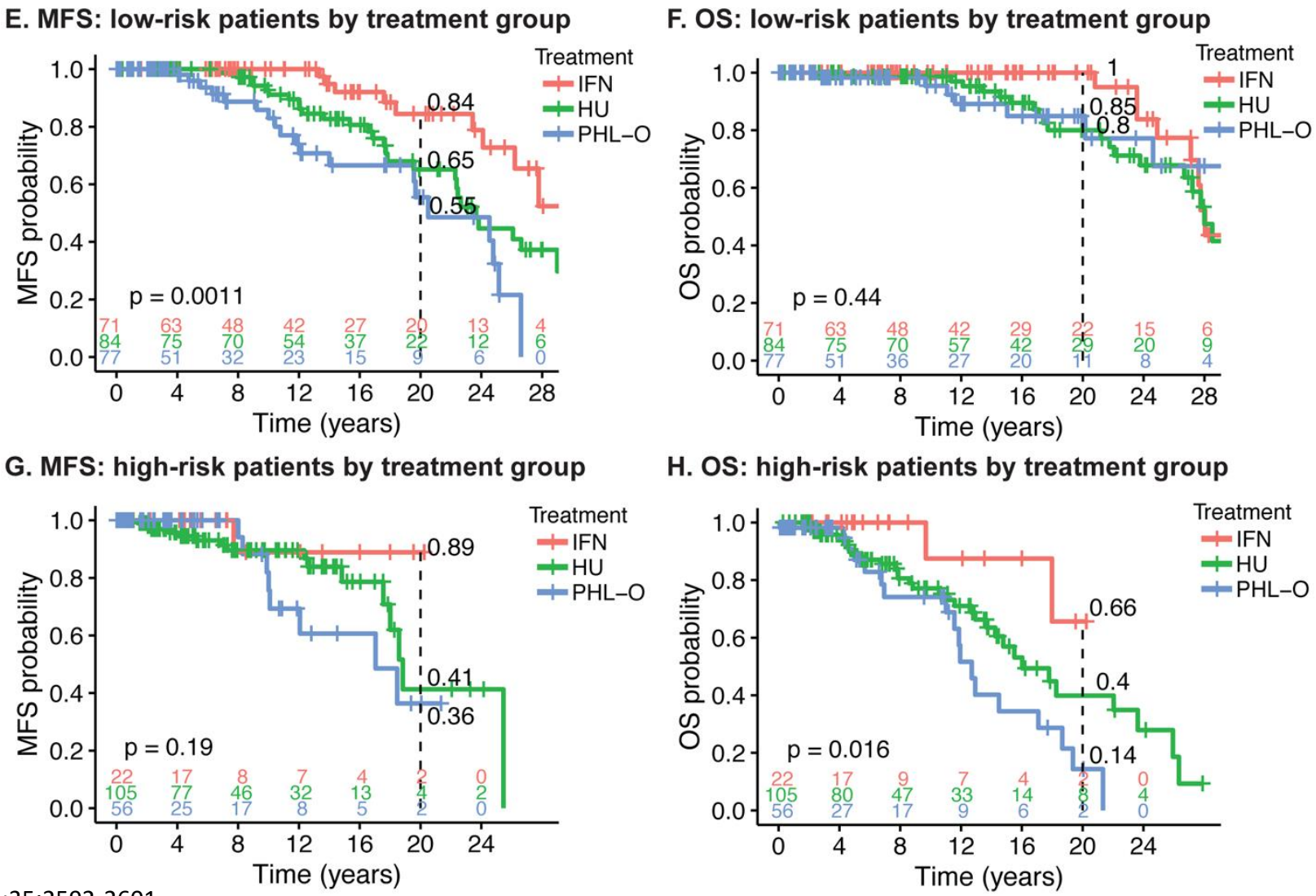
Barbui et al. *ASH* **2022**;abs#744.

Low-PV: splenomegaly



Barbui et al. *ASH* **2022**;abs#744.

IFN treatment is associated with improved MFS and OS in PV



Abu-Zeinah et al. *Leukemia* **2021**;35:2592-2601.

Take home messages

- Arterial and/or venous thromboses represent the main cause of morbidity and mortality in PV and may be prevented by pharmacological cytoreduction, on the top of ASA and phlebotomies.
- In low-risk patients cytoreduction is recommended or should be considered in specific situations, including poor tolerance/high frequency of phlebotomies, leukocytosis, extreme thrombocytosis, or high symptom burden.
- Hydroxyurea and interferons are suitable options for the front-line treatment of PV; prolonged treatment with interferon is associated to a progressive reduction of *JAK2* V617F allele burden.
- Low-dose (100 μg every 2 weeks) Ropeginterferon alfa 2-b is safe, well tolerated and more efficacious in comparison to a strict therapeutic phlebotomy policy in steadily keeping the hematocrit at target levels without disease progression in low-risk PV patients.
- The drug has a significant effect in reducing blood counts, reducing splenomegaly and improving quality of life. These benefits may translate in a favorable modification of the natural history of PV in low-risk patients.