LEUKEMIA2022

Rome, Hotel NH Collection - Vittorio Veneto

May 5-6, 2022

AIL President: P. Toro
Coordinators: A.M. Carella, S. Amadori

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ASSOCIAZIONE ITALIANA CONTRO LEUCEMIE LINFOMI E MIELOMA

UNDER THE AUSPICES OF:

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

GITMO

SIES Società Italiana Ematologia Sperimentale

SIE - Società Italiana di Ematologia

Re-assessing the treatment paradigm of PV

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Valerio De Stefano

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie					x		
Alexion					x		
Amgen					x		
AOP Health						x	
BMS Celgene					x	x	
Grifols						x	
GSK						x	
Novartis	x				x	x	
Sanofi					x		
SOBI						x	
Takeda					x	x	

Risk for Incident Arterial and Venous Thrombosis in Patients With Myeloproliferative Neoplasms

A Population-Based Cohort Study

Annals of Internal Medicine • Vol. 168 No. 5 • 6 March 2018

Setting: Population-based setting in Sweden from 1987 to 2009, **with follow-up to 2010.**

9429 MPN pts vs. 35820 matched controls

Arterial thrombosis

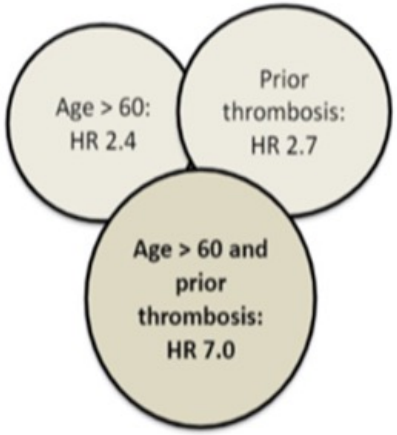
- HR 3.0, 2.0, and 1.5
  (3 months, 1 yr, and 5 yrs from dx)

Venous thrombosis

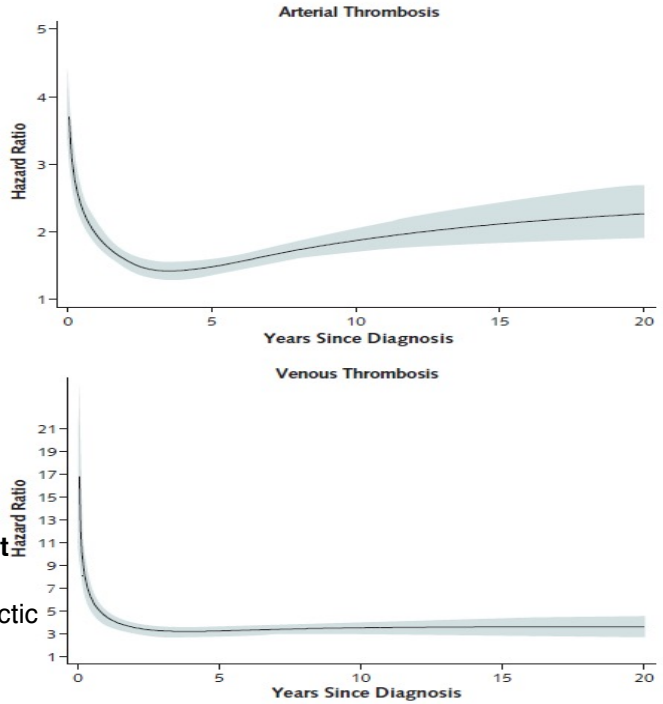
- HR 9.7, 4.7, and 3.2
  (3 months, 1 yr, and 5 yrs from dx)

Splanchnic vein thrombosis (SVT)

- HR 81.1 at 3m



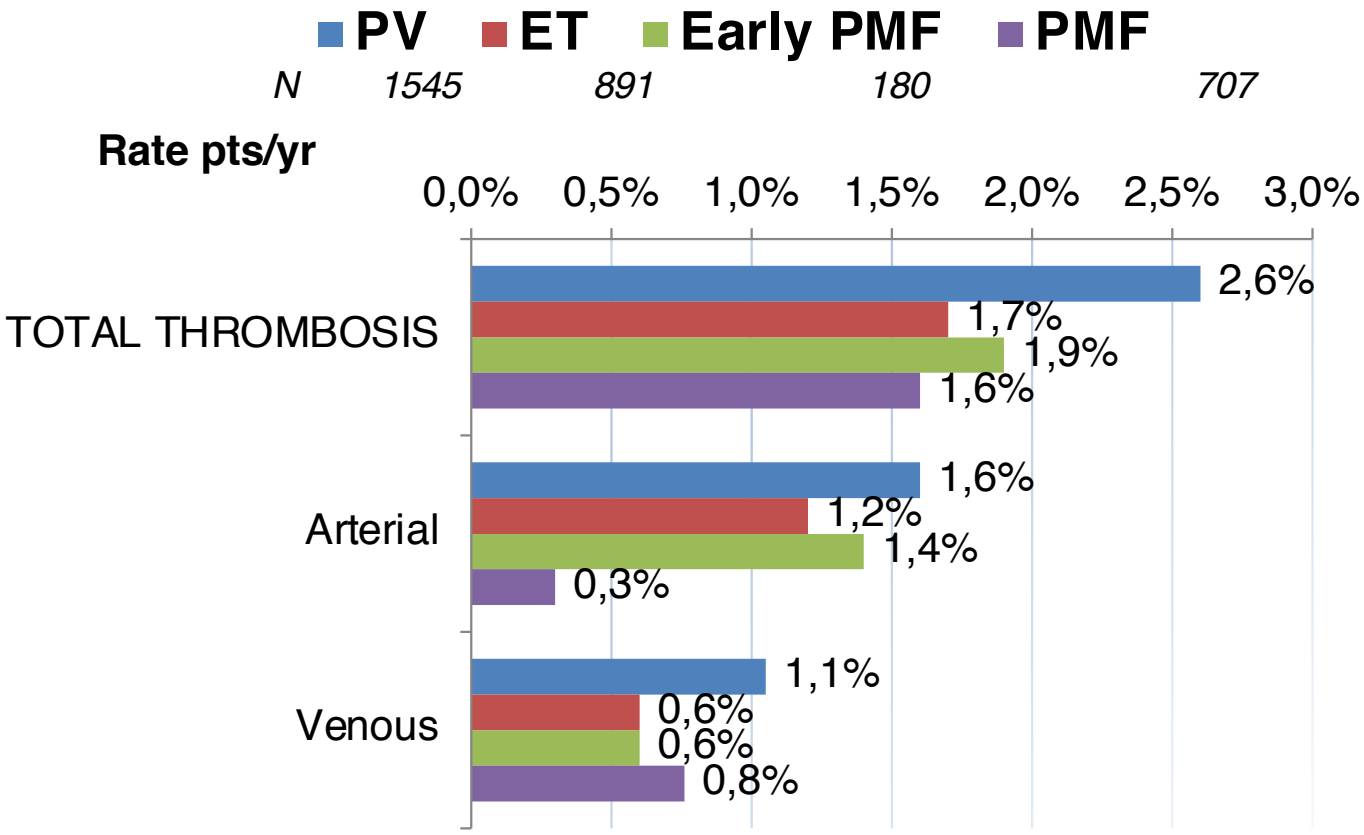
Arterial (*top*) and venous (*bottom*) thrombosis during follow-up in patients with MPNs versus matched control partecipants.



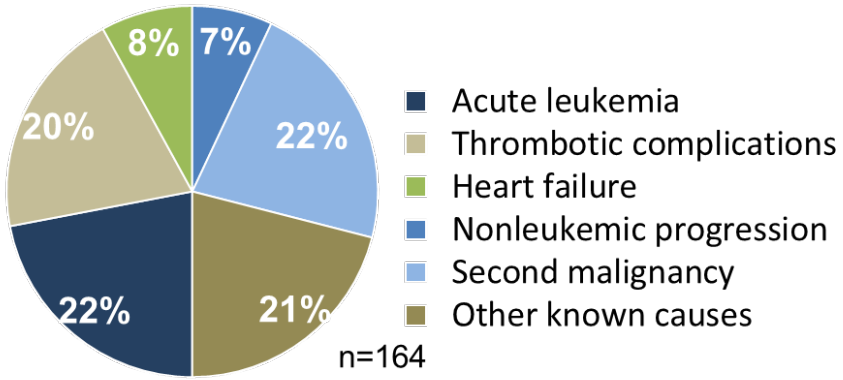
We conclude that the relative rate and risk for thrombosis in patients with MPNs is highest shortly after diagnosis and remains significantly elevated throughout follow-up.
This novel finding underlines the importance of initiating phlebotomy as well as thromboprophylactic and cytoreductive treatment, when indicated, as soon as the MPN is diagnosed.

Thrombosis rate in real-world clinical practice of MPN

(patient n= 3323; Rate % per year)



Known Causes of Death in PV

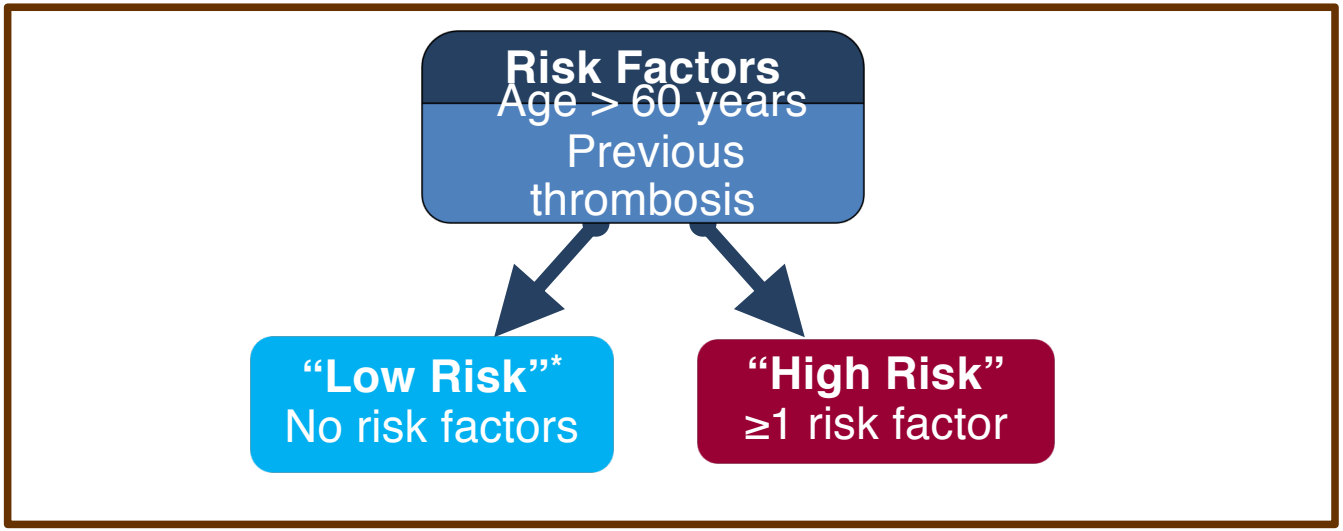


From the International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) – Study on PV

- International study of 1545 patients diagnosed based on 2008 WHO criteria
- Percentages derived from patients who had died at the time of the analysis (n=347) and for whom cause of death was known (n=164)

Tefferi A, et al. *Leukemia.* 2013;27:1874-1881.

Risk Stratification in PV



*Low-risk patients with extreme thrombocytosis (platelet count >1000 x 10^9/L) are considered separately.

- Risk stratification in PV (not yet validated prospectively in controlled randomized trials) estimates likelihood of thrombotic events and not survival or leukemic transformation[1]
- "Classic" cardiovascular risk factors (arterial hypertension, cigarette smoking, obesity, diabetes) should be corrected/prevented[2]

1. Tefferi A, et al. *Am J Hematol.* 2013;88:508-516.
2. Reikvam H, et al. *Leukemia.* 2012;26:563-571.

VOLUME 23 · NUMBER 10 · APRIL 1 2005

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Vascular and Neoplastic Risk in a Large Cohort of Patients With Polycythemia Vera

Roberto Marchioli, Guido Finazzi, Raffaele Landolfi, Jack Kutti, Heinz Gisslinger, Carlo Patrono, Raphael Marilus, Ana Villegas, Gianni Tognoni, and Tiziano Barbui

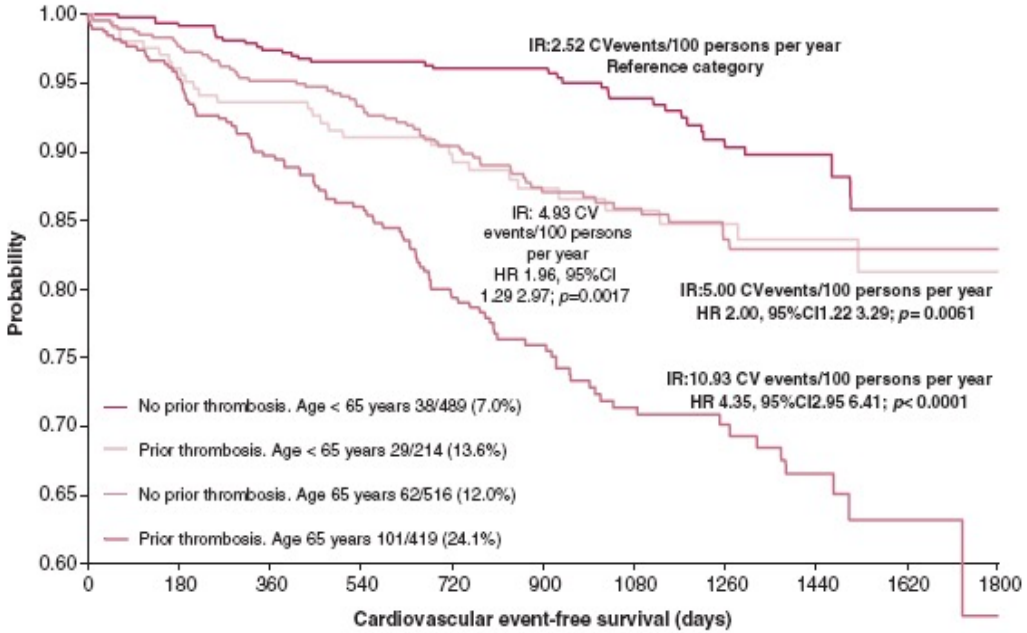


Figure 1. Incidence of thrombotic events by risk factors in the ECLAP study.[2]

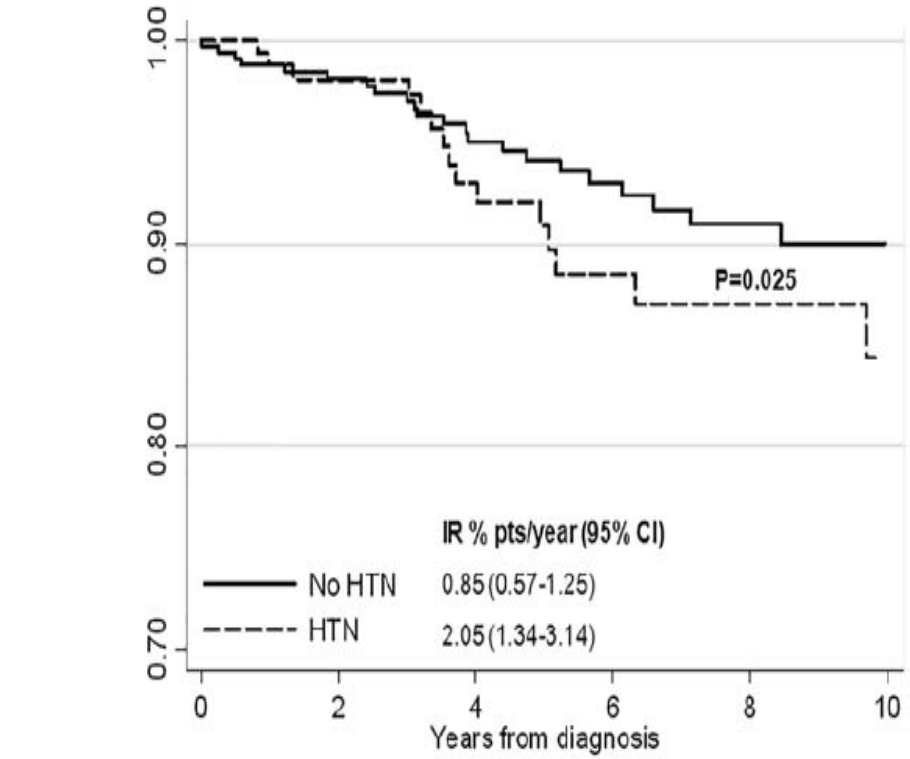


Figure 1. Arterial thrombosis-free survival in low-risk PV patients according to hypertension. Legend: HTN= Hypertension; IR=Incidence Rate; CI=Confidence Interval

Barbui T et al., Am J Hematol 2017

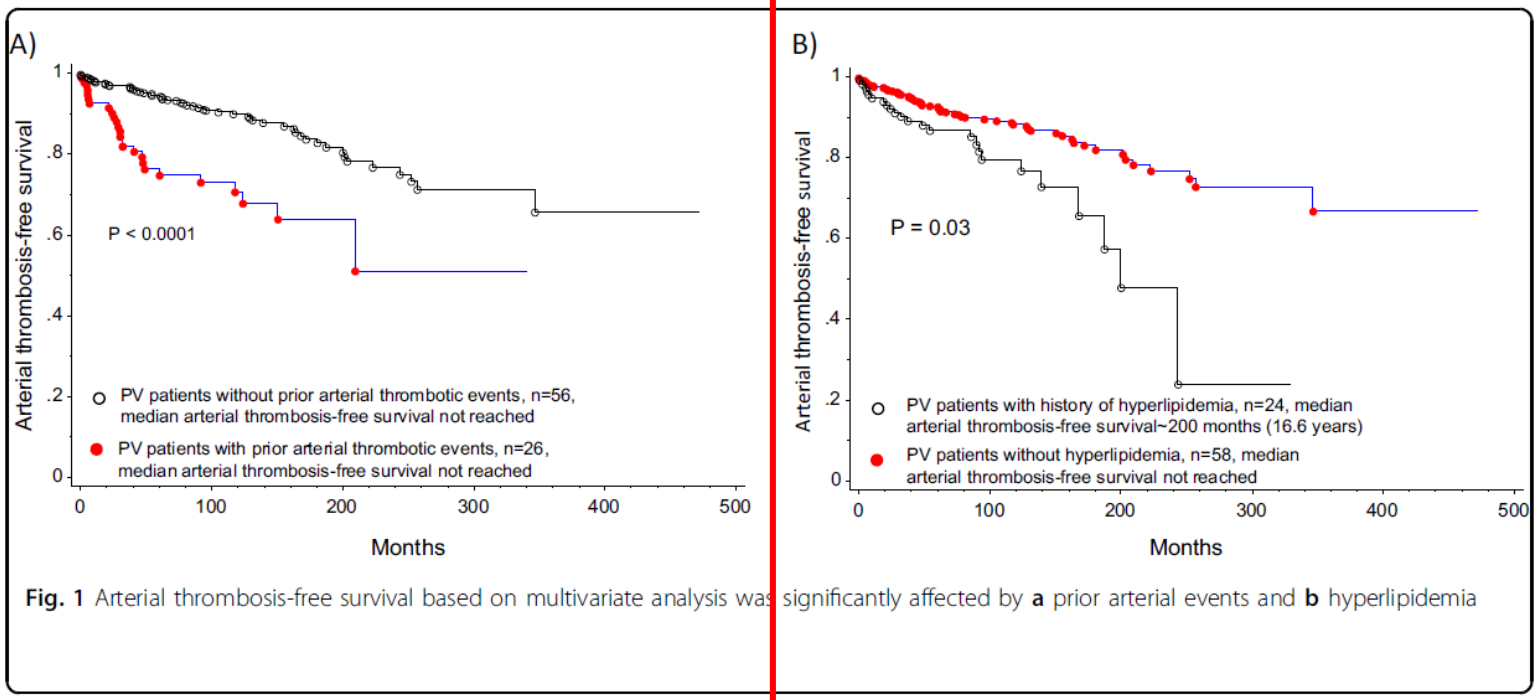


Fig. 1 Arterial thrombosis-free survival based on multivariate analysis was significantly affected by **a** prior arterial events and **b** hyperlipidemia

Cerquozzi et al, Blood Cancer J 2017 (PV pts n=587)

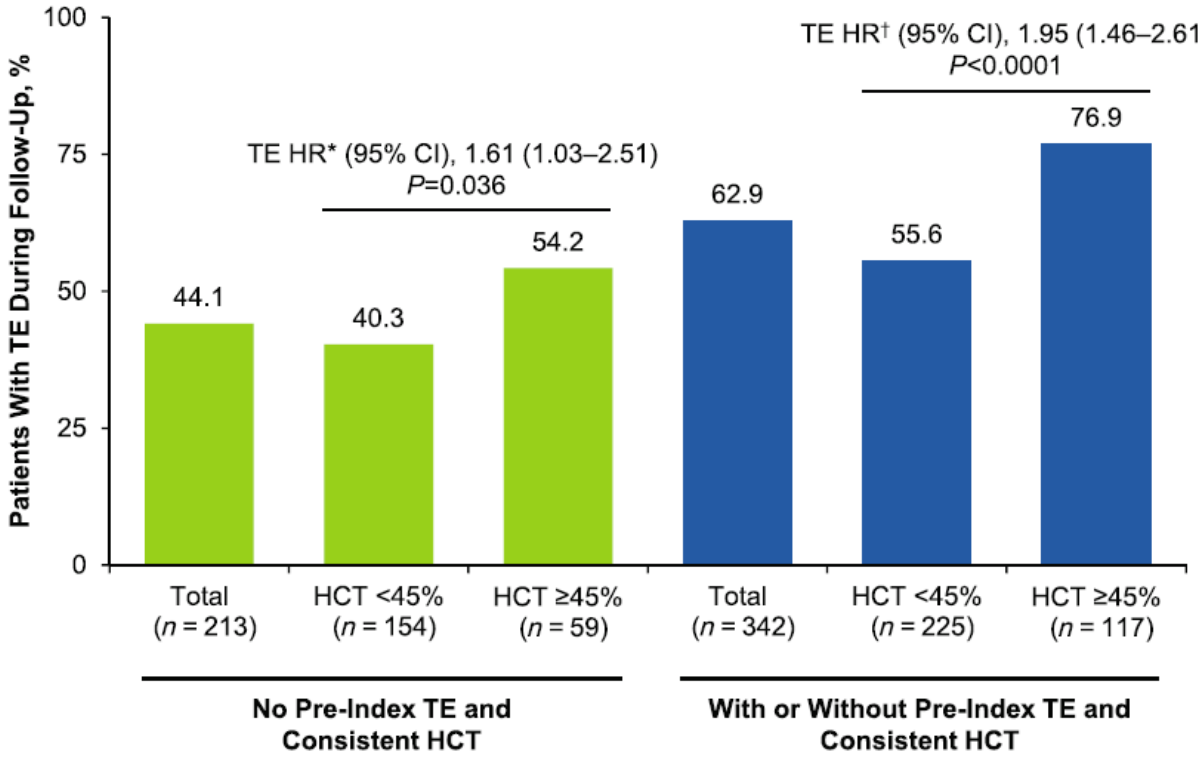
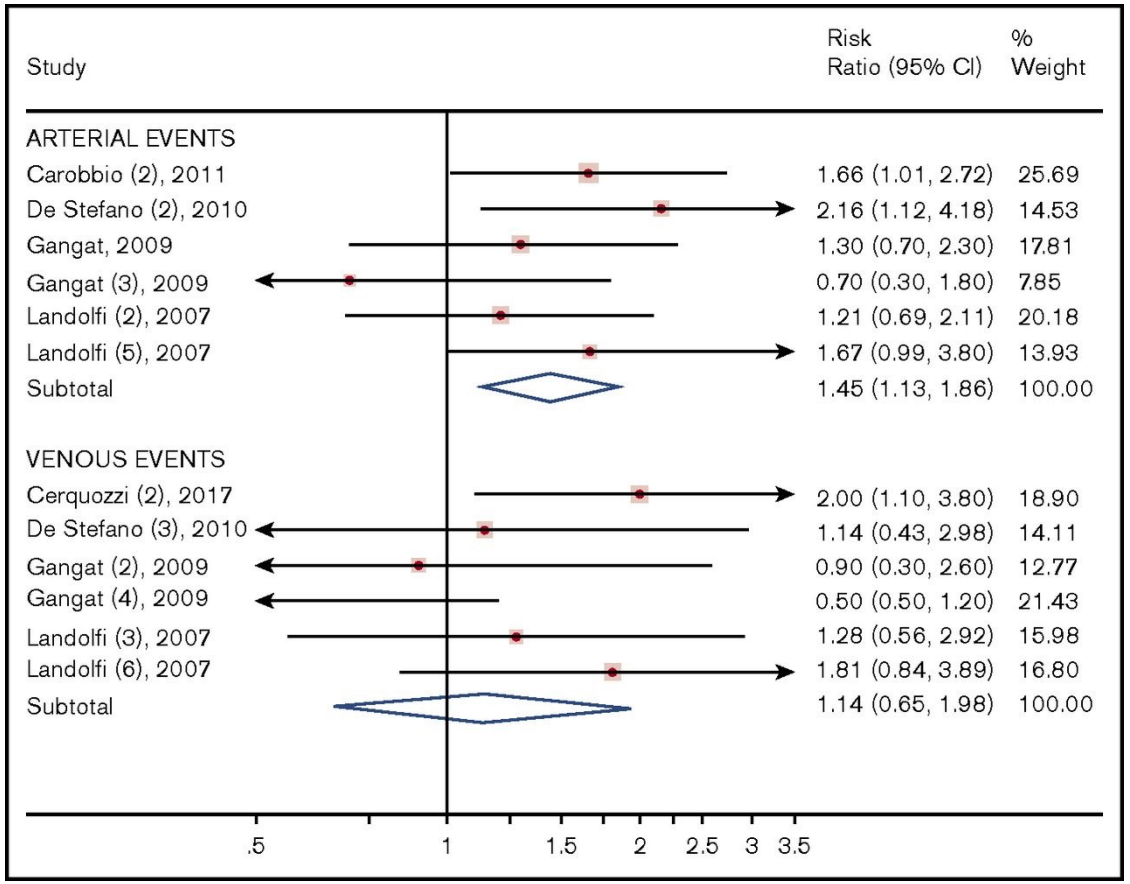


Fig. 3 TE during follow-up. HCT, hematocrit; HR, hazard ratio; TE, thrombotic event. *HR calculation based on patients with ≥ 1 HCT value before first TE ($n = 208$). †HR calculation based on patients with ≥ 1 HCT value before first TE ($n = 322$)

Parasuraman et al, Ann Hematol 2019

LEUKOCYTOSIS AND RISK OF THROMBOSIS

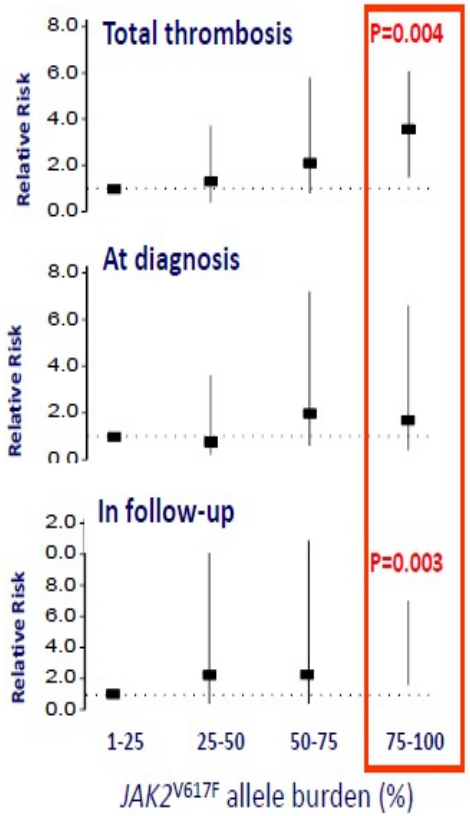
Forest plot of the subgroup analysis on primary outcome according to type of thrombosis.



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

blood advances

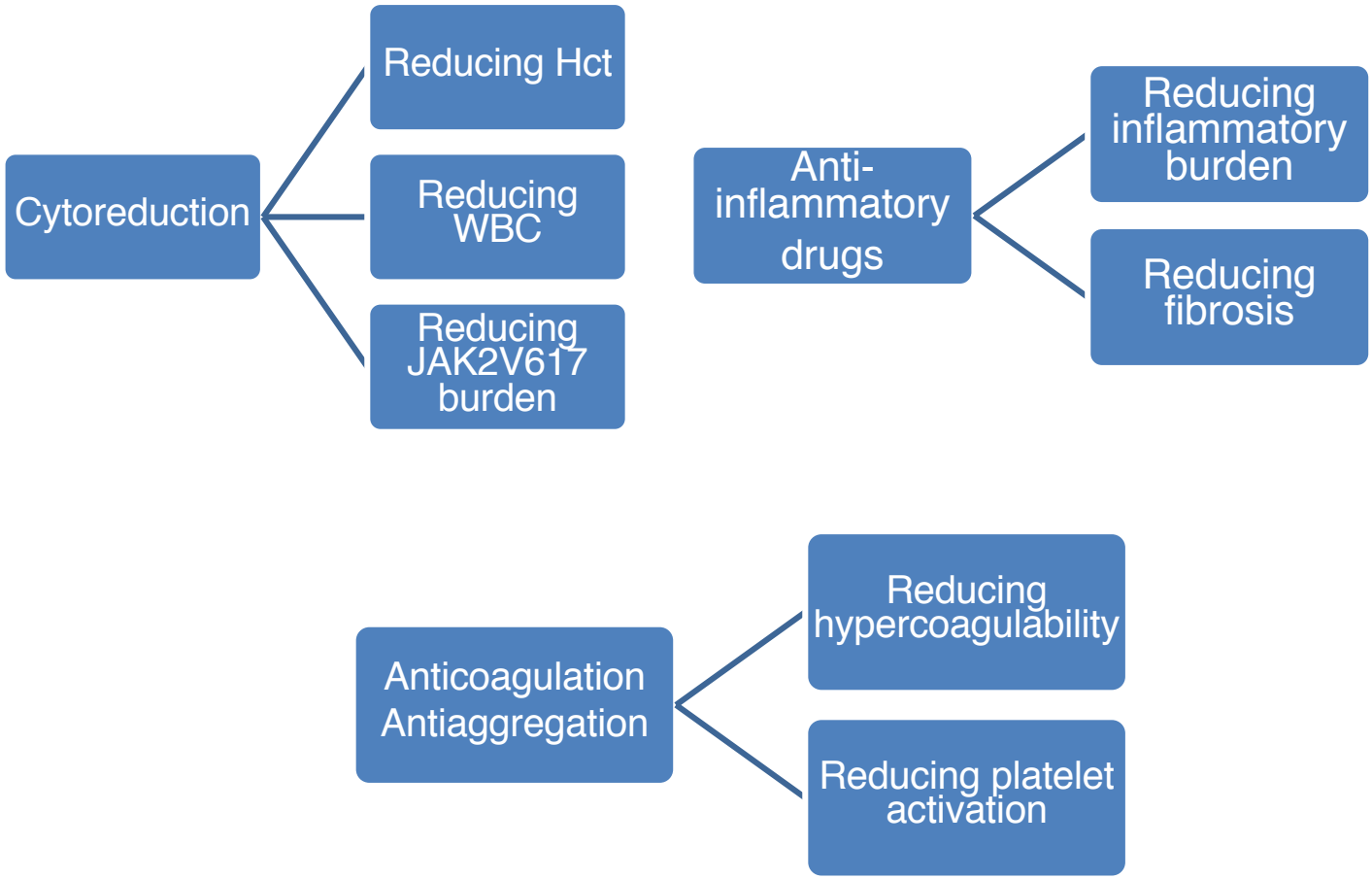
JAK2 V617F Burden and Thrombosis in PV



V617F burden (%)	Rate of total thrombosis	HR (95%CI)	P
1-25	10 %	1	
25-50	14 %	1.2 (0.6-3.7)	NS
50-75	24 %	1.7 (0.8-5.5)	NS
75-100	37 %	3.56 (1.4-7.1)	0.004

Vannucchi AM et al, Leukemia 2007; 21:1952

Targets of antithrombotic treatment

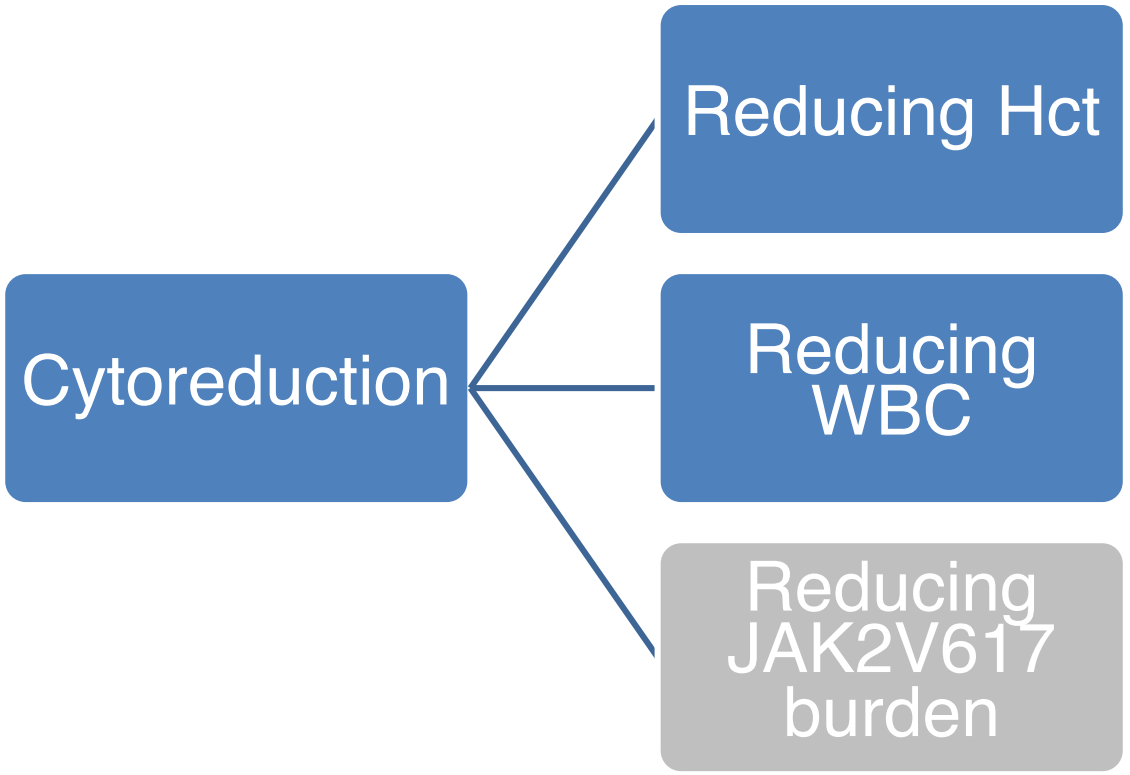


Key International PV Treatment Guidelines

ELN[1]	ESMO[2]	BCSH[3]
▪ Phlebotomy and low dose aspirin (all pts)	▪ Phlebotomy and low dose aspirin (all pts)	▪ Phlebotomy and low dose aspirin (all patients)
▪ HU or IFN for high-risk pts	▪ HU or IFN for high-risk pts	▪ HU or IFN for high-risk pts
▪ Ruxolitinib or interferon-α in patients who are intolerant or resistant/refractory to HU	▪ Ruxolitinib may be considered as second line therapy for pts who are resistant/refractory to HU	▪ Ruxolitinib or interferon-α in patients who are intolerant or resistant/refractory to HU
▪ Intermittent busulphan can be considered in very elderly	▪ Busulphan in select pts when other options contraindicated	▪ Busulfan or ^{32}P or pipobroman
	▪ Consider clinical trials	

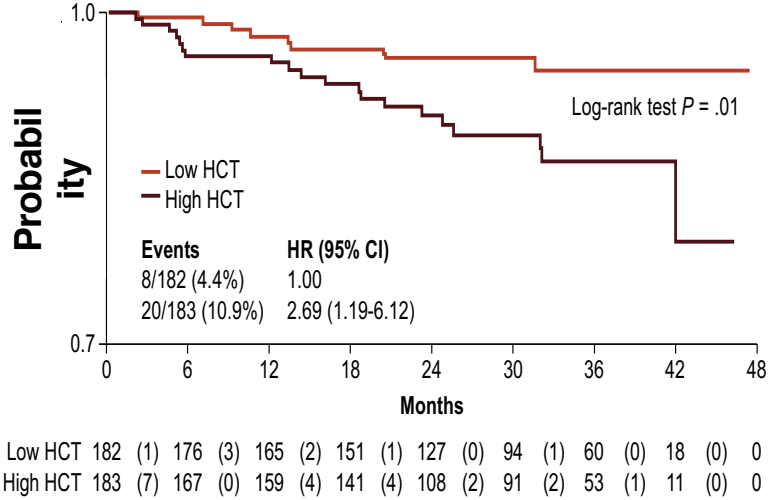
1. Barbui. Leukemia. 2018;32:1057. 2. Vannucchi. Ann Oncol. 2015;26:v85. 3. McMullin. Br J Haematol. 2019;184:176.

Targets of antithrombotic treatment



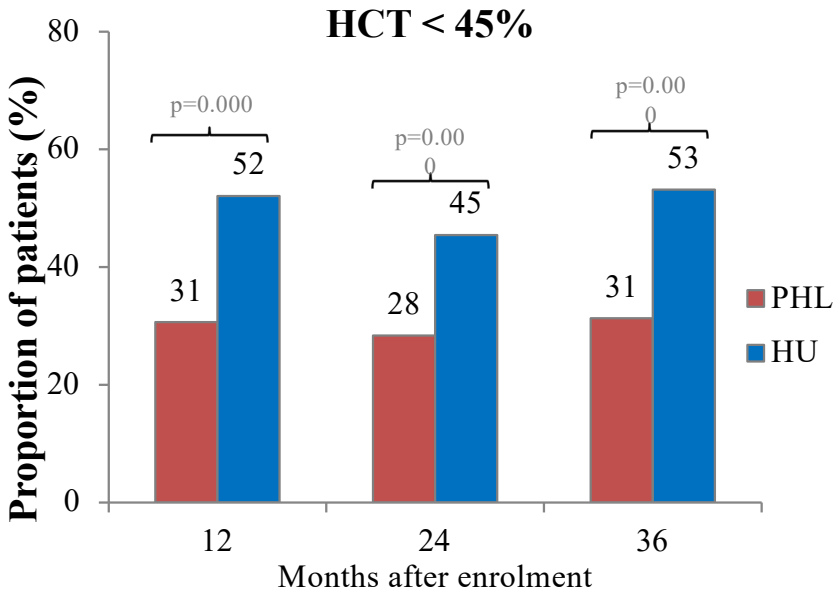
Phlebotomy-alone is currently the only cytoreductive therapy in low-risk patients (ELN* and NCCN**) *Questions: Is it adequate to reduce the incidence of thrombosis? How to keep HCT on target in real-world clinical practice?*

*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.

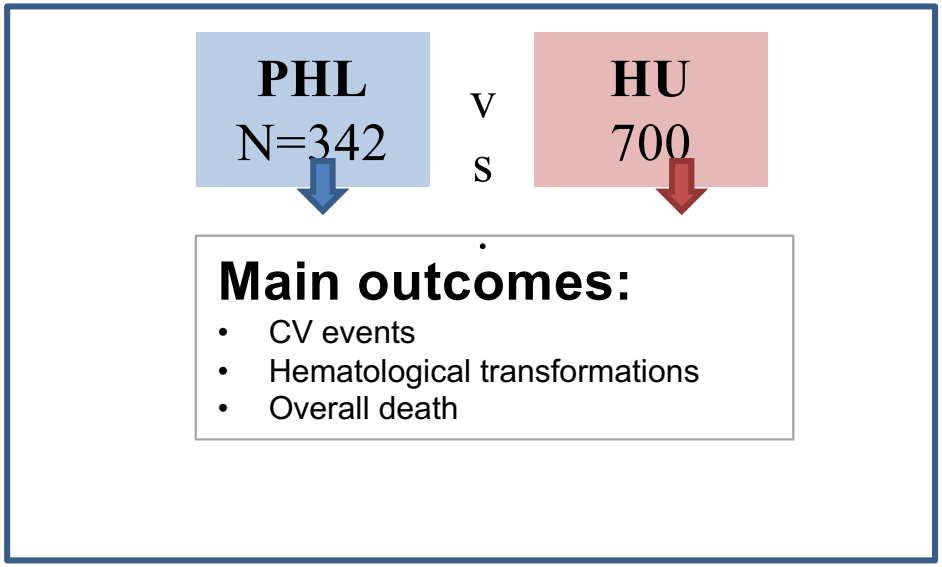
***How to reach HCT target:** Only phlebotomy or Citoreduction drugs with phlebotomy supplement?*



Barbui et al, AJH 2017

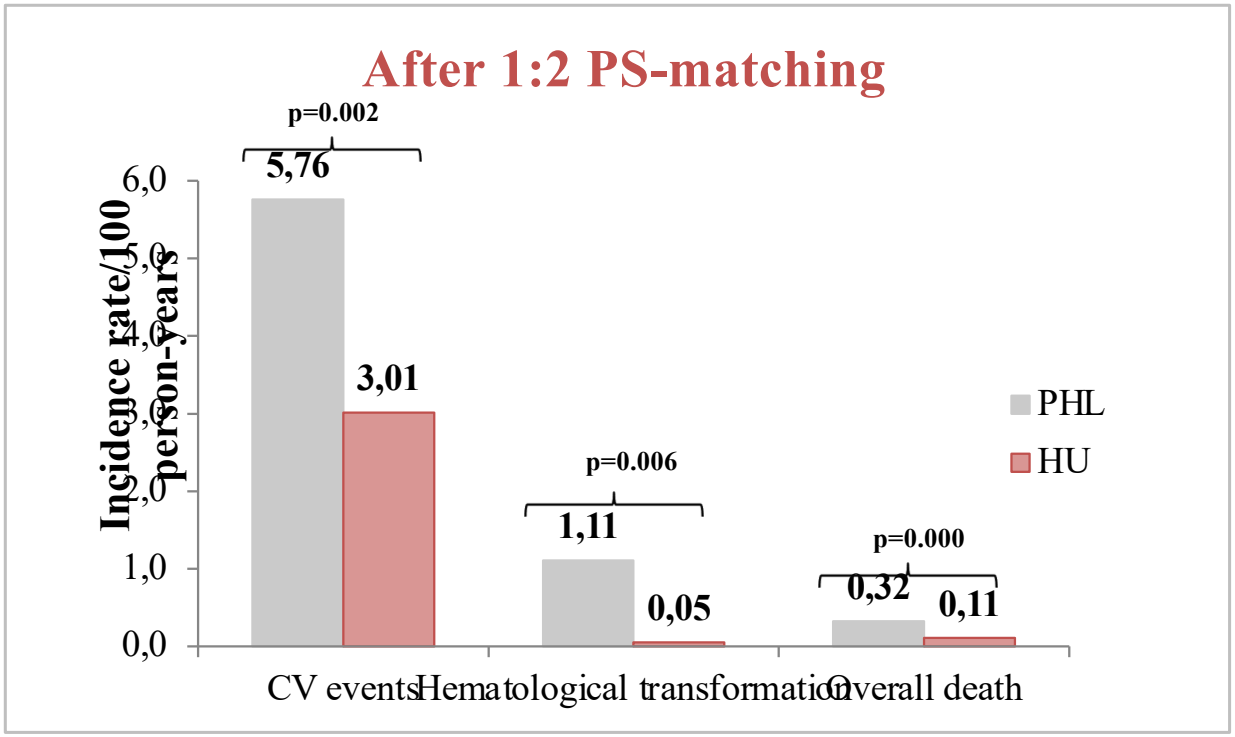
Risk-benefit profile of Hydroxyurea in Polycytemia Vera (ECLAP)

We identified 1,042 patients treated with PHL (n=342) alone or HU (n=700) to compare the outcomes of the two groups:



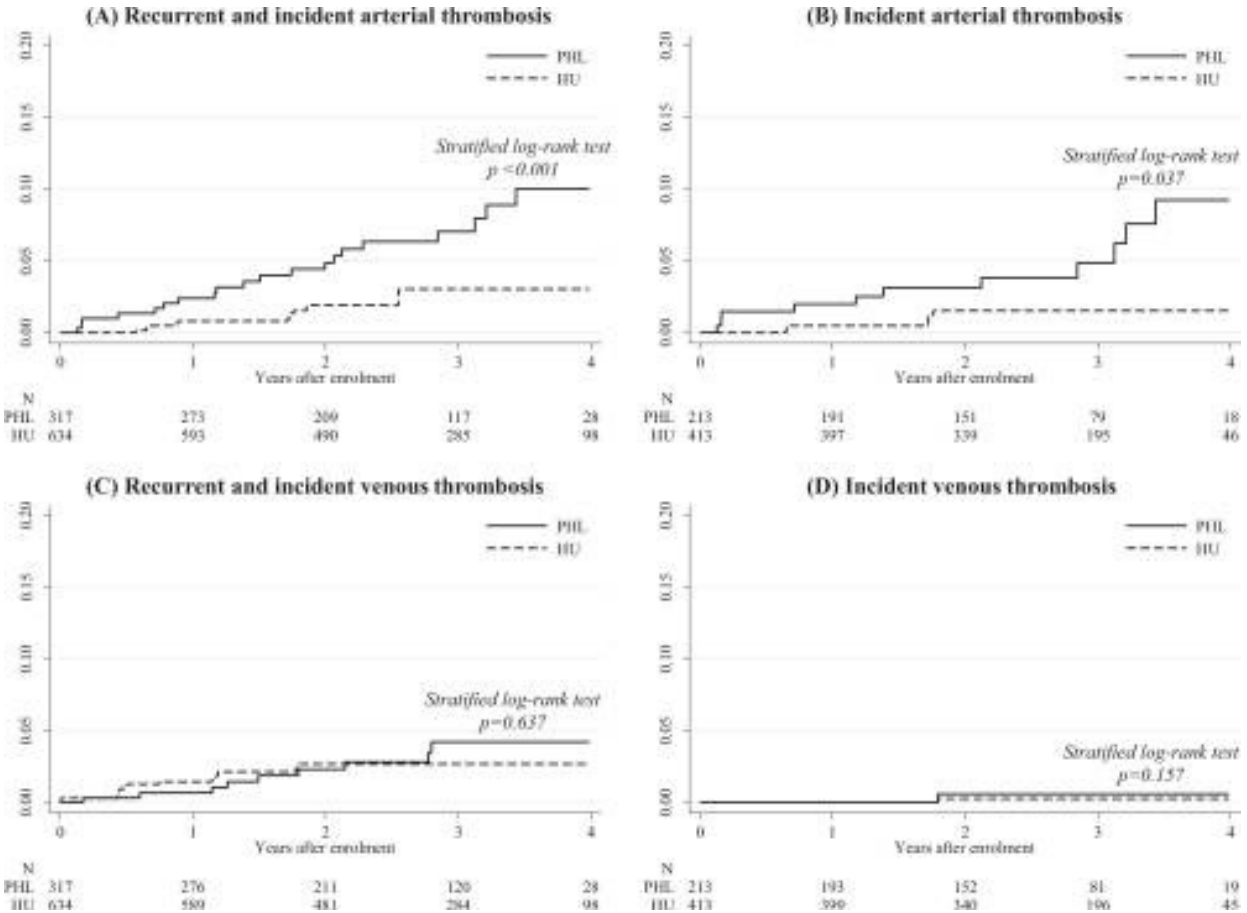
Risk-benefit profile of Hydroxyurea in Polycytemia Vera

Main outcome during follow-up



PHL-patients had an **higher incidence** of CV events, hematological transformation and death.

Barbui T et al. Am J Hematol 2017 [Epub ahead of print]

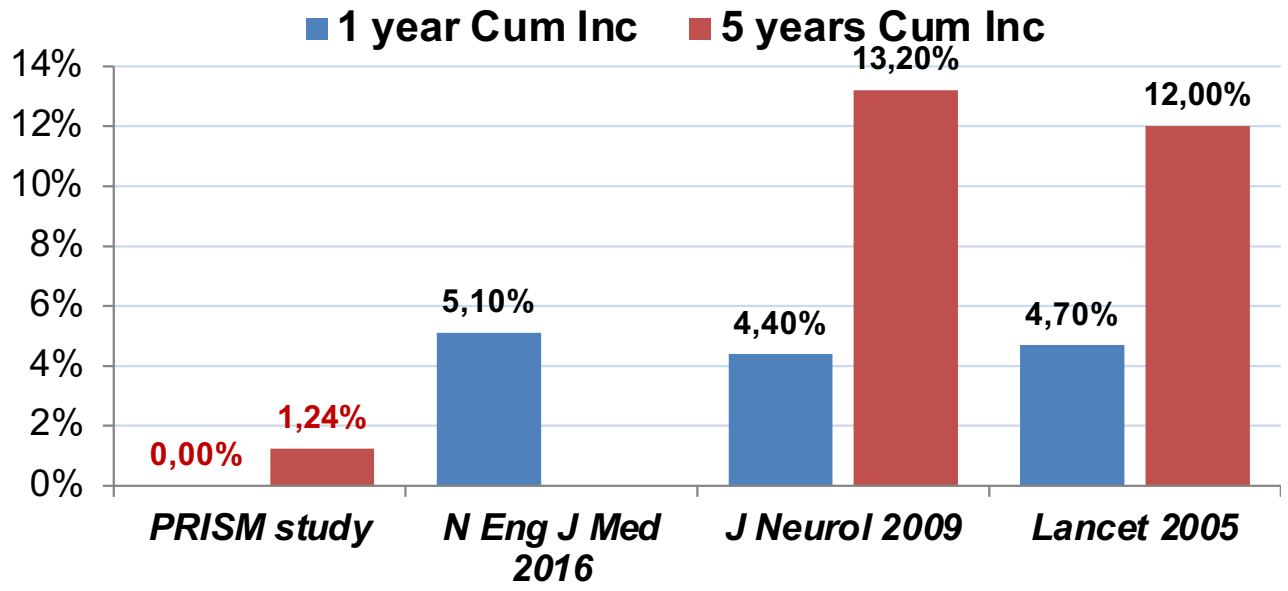


Barbui T et al, Blood Cancer J 2018

ELN-WP9 project
Thrombosis recurrences in MPN.
Analysis of 1032 index events

Index event	No. Centers	Design	No. Pts
Cerebral vein thrombosis *Martinelli et al, Am J Hematol 2014*	11	**Case-control study** • Cases: MPN with CVT • Controls: MPN and DVT	135 48 87
Deep vein thrombosis *De Stefano et al, Leukemia 2016* Splanchnic vein thrombosis *De Stefano et al, Blood Cancer J 2016*	23	**Retrospective cohort study** **Retrospective cohort study**	206 181
Cerebral arterial thrombosis *De Stefano et al, Blood Cancer J 2018*	22	**Retrospective cohort study** • TIA or • Ischemic Stroke	597 270 327

Estimates of **stroke after TIA** are lower than in contemporary non MPN patients

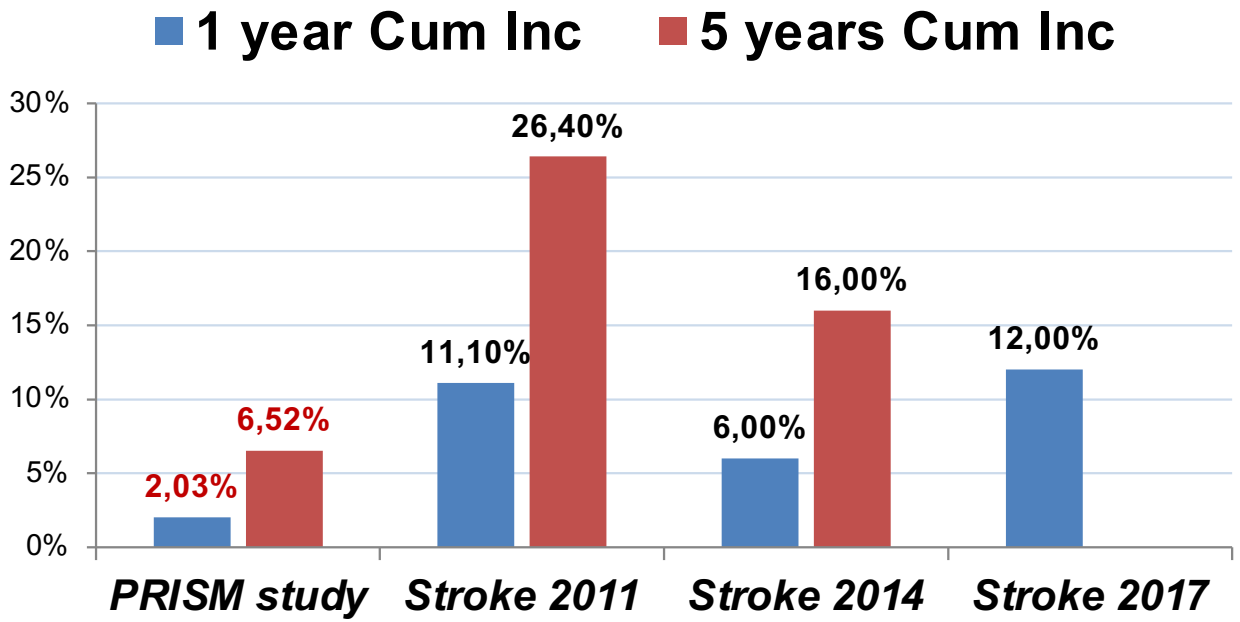


Amarenco P, et al. One-year risk of stroke after transient ischemic attack or minor stroke. ***N Engl J Med 2016****; 374: 1533-42*

Weimar C, et al. Long-term mortality and risk of stroke after transient ischemic attack: a hospital-based cohort study. ***J Neurol 2009****; 256: 639-44*

van Wijk I, et al. Long-term survival and vascular event risk after transient ischaemic attack or minor ischaemic stroke: a cohort study. ***Lancet 2005****; 365: 2098-104*

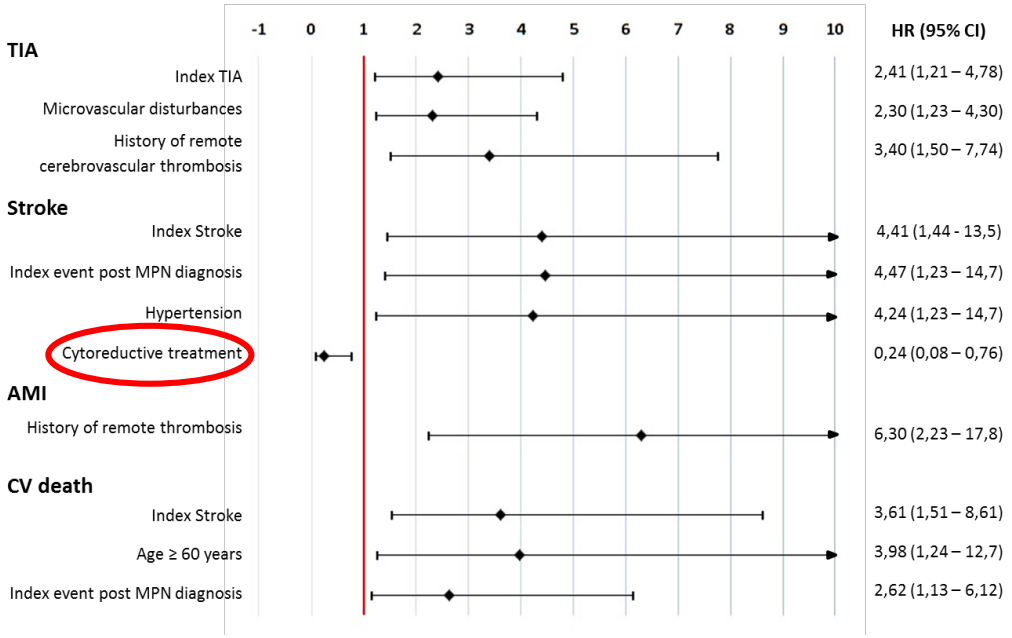
Estimates of **stroke recurrence after the first episode** are lower than in contemporary non MPN patients



Mohan KM, et al. Risk and cumulative risk of stroke recurrence: a systematic review and meta-analysis. ***Stroke 2011****; 42: 1489-94*

Pennlert J, et al. Long-term risk and predictors of recurrent stroke beyond the acute phase. ***Stroke 2014****; 45: 1839-41*

Bergström L, et al. One-year incidence, time trends, and predictors of recurrent ischemic stroke in Sweden from 1998 to 2010: an observational study. ***Stroke 2017****; 48: 2046-2051.*



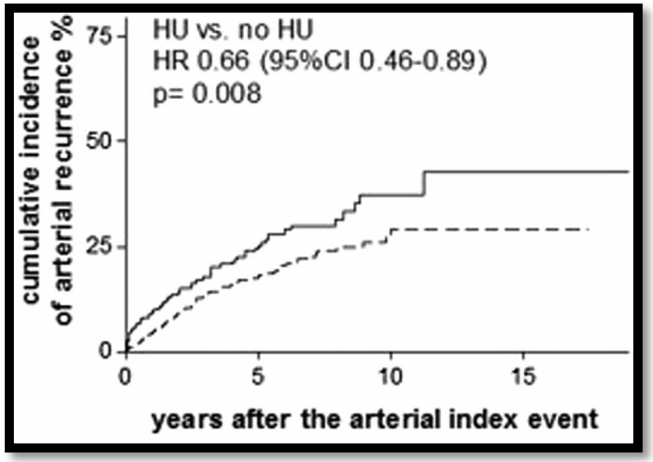
De Stefano V et al, Blood Cancer Journal 2018; 8: 25

Recurrent thrombosis

- Pooled analysis of **1500 MPN pts*** (761 ET [51%]; 590 PV [39%]; 149 PMF [10%])
- 935 **index arterial** thrombosis [62%], 565 **index venous** thrombosis [38%]
- **Recurrences n= 348** corresponding to **5.7% pts-year**

Effects of treatments on recurrences (multivariable model):

	Arterial (HR, 95% CI, p-value)	**Venous** (HR, 95% CI, p-value)
Antiplatelet treatment	**0.52 (0.35-0.82), 0.003**	0.64 (0.40-1.03), 0.07
Oral anticoagulation (VKA or DOACs)	**0.58 (0.35-0.82), 0.03**	**0.60 (0.37-0.95), 0.03**
Hydroxyurea	**0.67 (0.46-0.98), 0.04**	0.87 (0.56-1.33), 0.52



Favorable cumulative incidence of recurrent thrombosis after the first arterial event in patients receiving HU and no effect of this drug after the first splanchnic venous thrombosis.

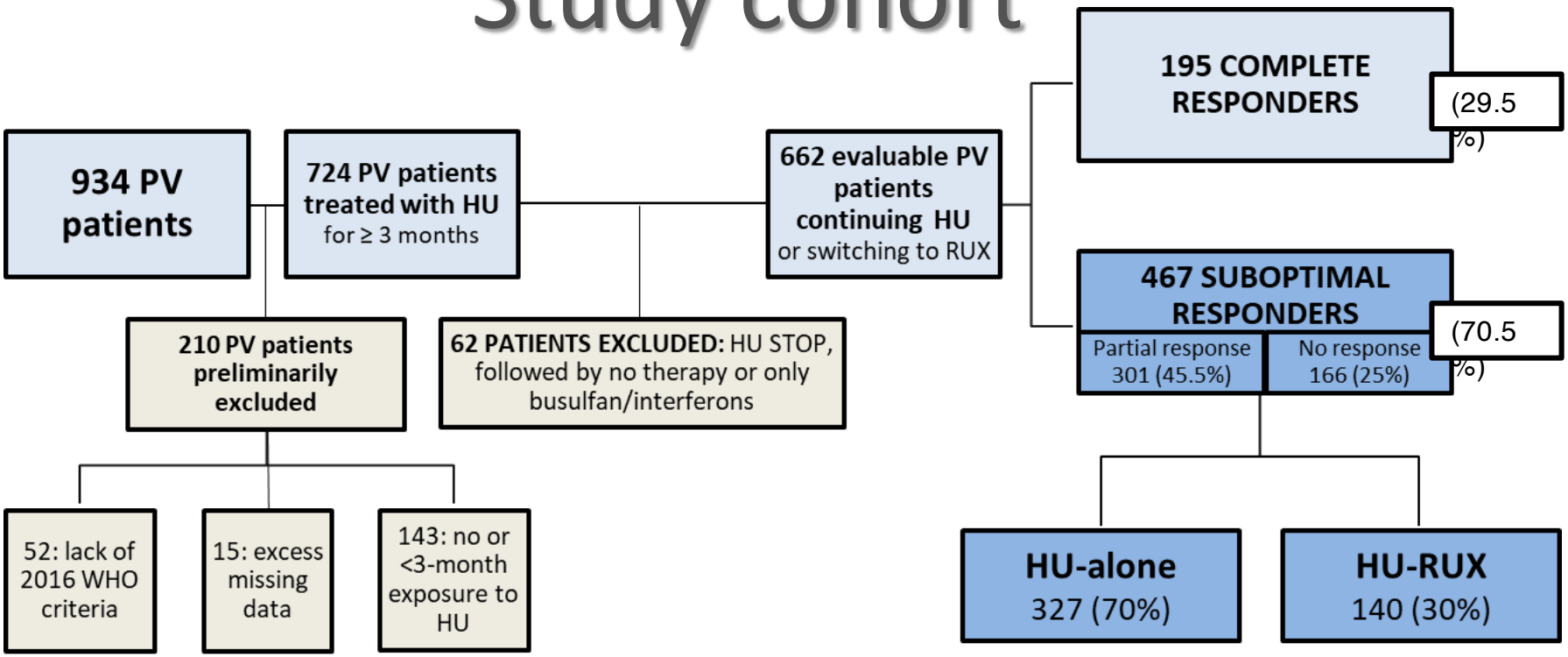
*De Stefano V et al, Blood Cancer J, 2018

Differential Treatment Strategy in Polycythemia Vera Patients with Stable Suboptimal Response to Hydroxyurea: Clinical Correlations and Impact on Survival

Francesca Palandri, Daniela Bartoletti, Elena Rossi, Giulia Benevolo Elena Maria Elli, Giuseppe Auteri, Francesco Cavazzini, Gianni Binotto, Alessia Tieghi, Mario Tiribelli, Massimiliano Bonifacio, Massimo Breccia, Novella Pugliese, Giovanni Caocci, Monica Crugnola, Francesco Mendicino, Alessandra D'Addio, Simona Tomassetti, Bruno Martino, Christian Di Pietro, Nicola Polverelli, Sara Ceglie, Rossella Stella, Ivan Civettini, Fabrizio Pane, Antonio Cuneo, Mauro Krampera, Gianpietro Semenzato, Roberto Massimo Lemoli, Michele Cavo, Nicola Vianelli, Giuseppe Alberto Palumbo, Valerio De Stefano, Alessandro Andriani, Roberto Latagliata

Program section: *Malattie Mieloproliferative Croniche 1*

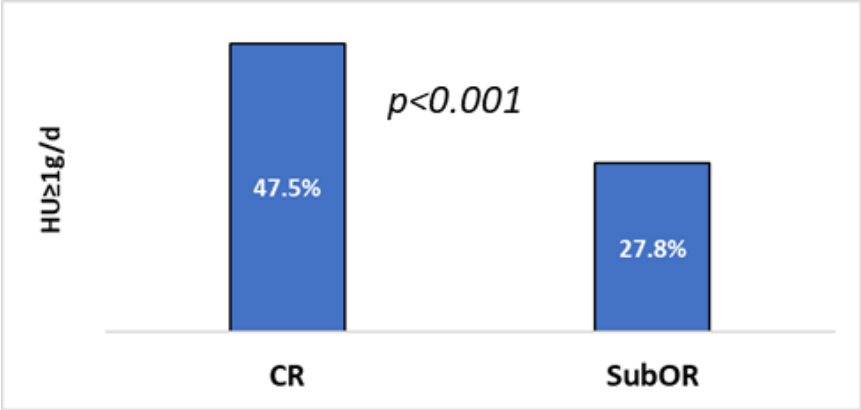
Study cohort



- Among the 662 pts who received HU for ≥3 months, 195 had a stable CR; 467 never achieved a CR and were defined as stable suboptimal responders, including 301 patients with PR and 166 patients with NR
- RUX switch was performed in 140/467 suboptimal responders, while 327 (70%) continued HU until last contact
- Median follow-up after HU start: 4.8 yrs (0.3-27.6)

HU 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).

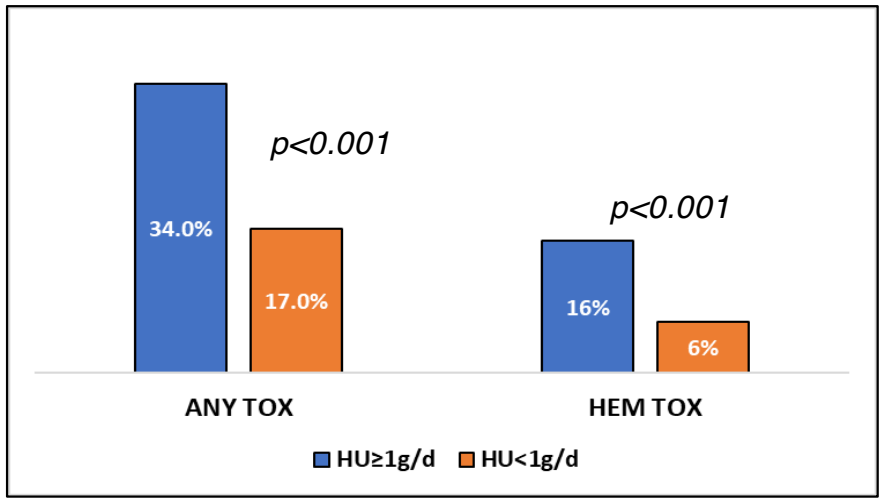


- In the 192 patients who received HU ≥1 g/d, *JAK2*^{V617F} <50% & absence of palpable spleen/symptoms confirmed their association with CR

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

HU 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

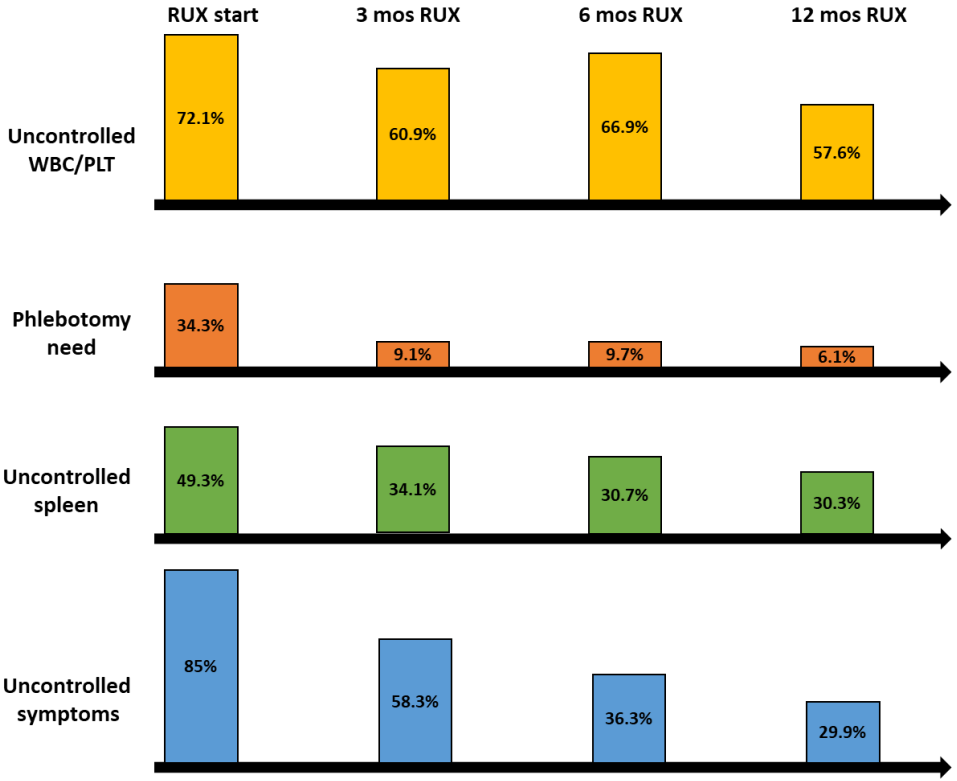


Toxicity	HU <1 g/d (n. 401)	HU ≥1 g/d (n. 192)
Anemia/thrombocytopenia	24 (6.0%)	30 (15.6%)
Skin ulcers	21 (5.2%)	24 (12.5%)
Oral aftosis	11 (2.7%)	5 (2.6%)
Gastrointestinal disturbances	6 (1.5%)	4 (2.1%)
Fever	2 (0.5%)	1 (0.5%)
Mialgia	3 (0.7%)	0
Zoster reactivations	1 (0.2%)	1 (0.5%)

- 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)

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

Response to RUX

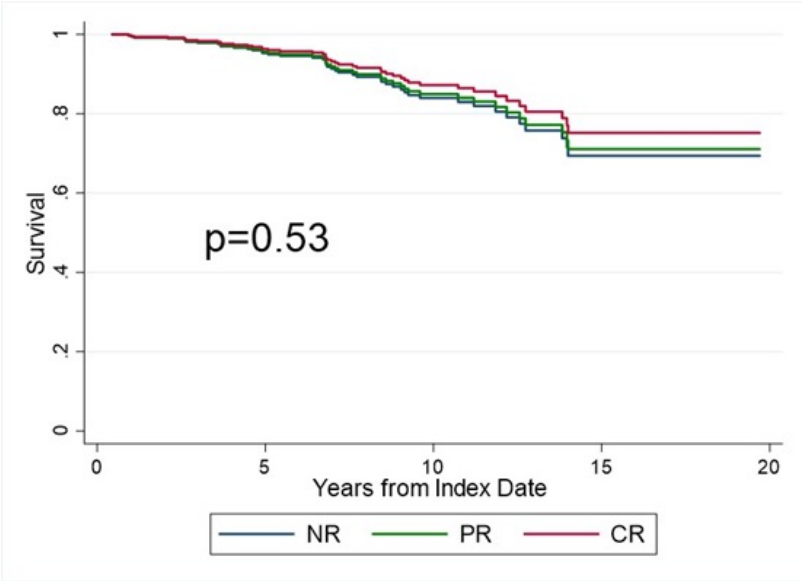


- A significant reduction of patients with the suboptimal criteria was observed over time during RUX therapy

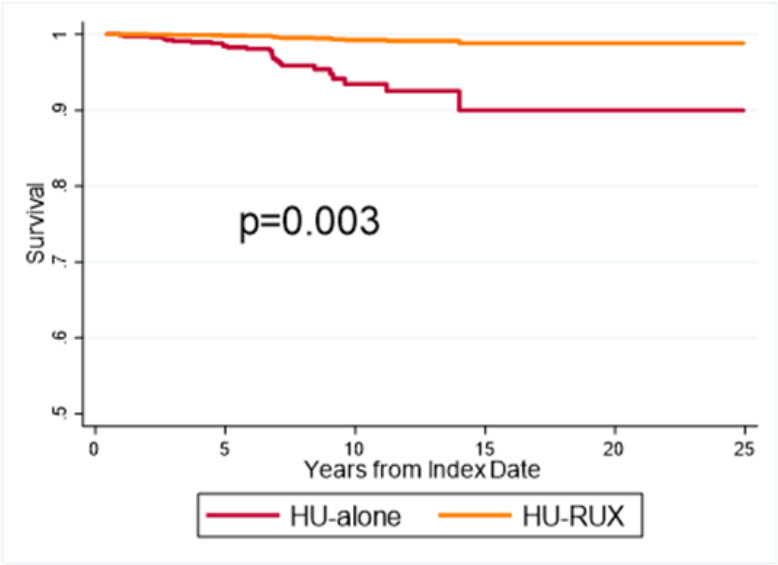
- Overall, 10.6%, 15.3% and 22.2% achieved a complete response at 3, 6 and 12 months from RUX start, respectively

Overall survival

In the 522 patients receiving only HU, overall survival was not influenced by response



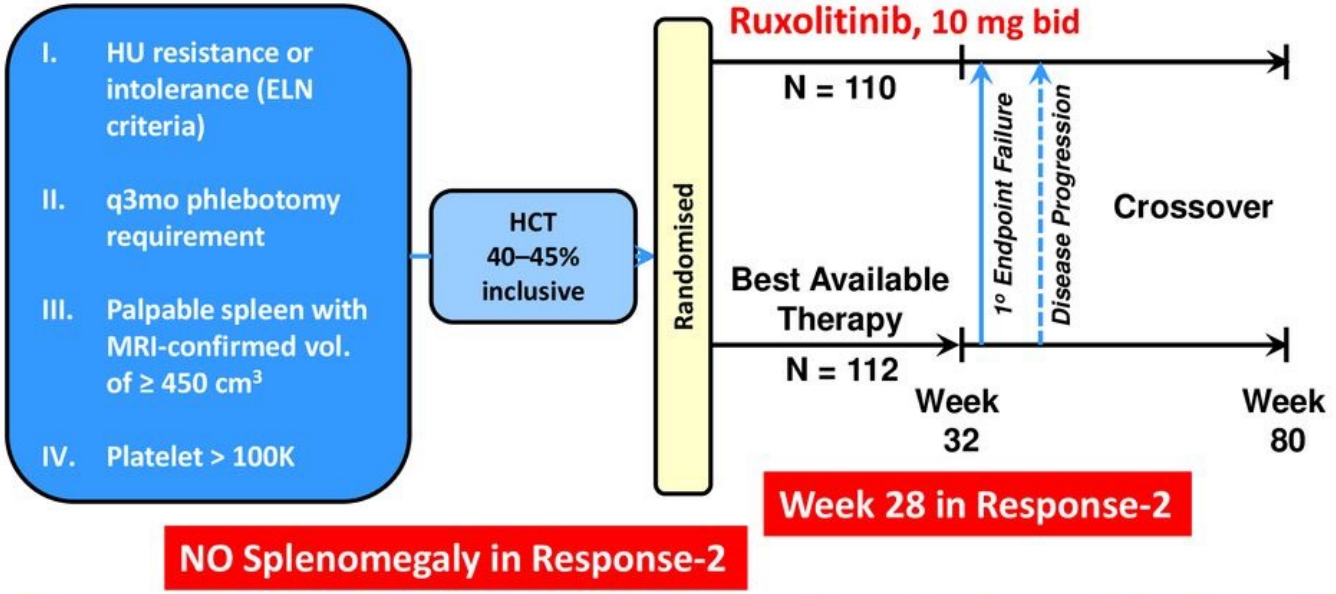
In the 467 SubOR patients, RUX switch was associated with improved OS compared to HU-alone



Number at risk:						
HU-alone	327	136	30	7	1	1
HU-RUX	140	87	32	10	5	1

Survivor functions of CR, PR and NR patients were plotted after the Cox proportional hazards multivariable regression model adjusting for age
Survivor functions of HU-RUX and HU-alone SubOR patients were plotted after the Cox proportional hazards multivariable regression model adjusting for age and splenomegaly.

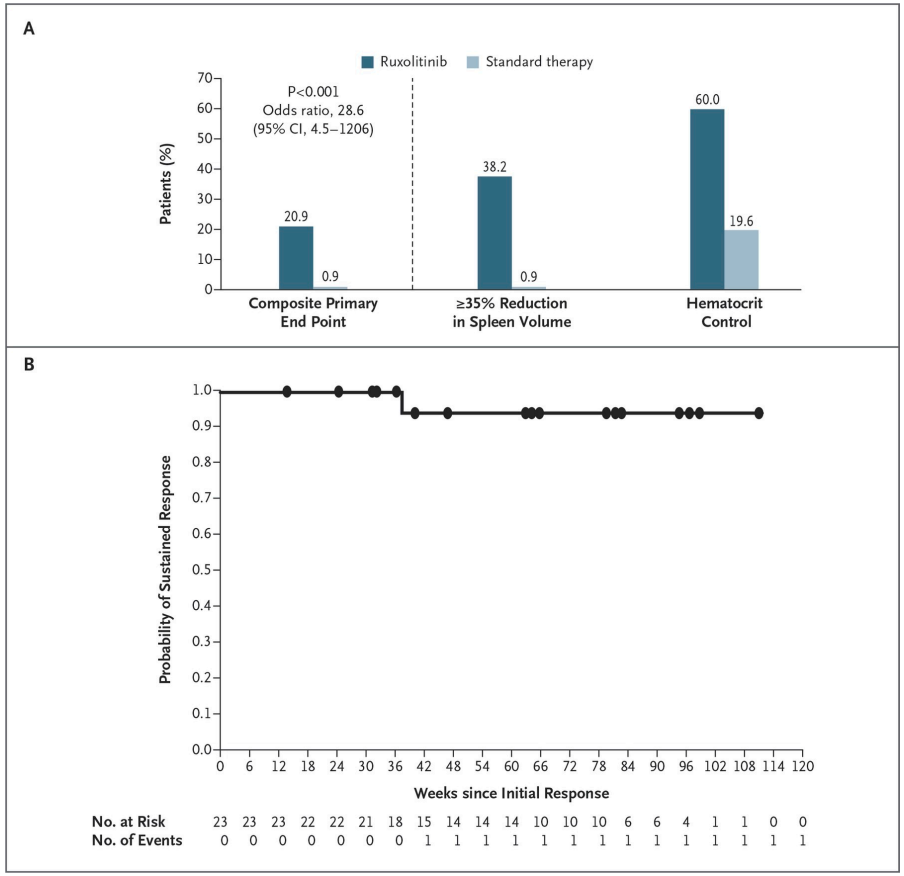
Ruxolitinib in PV: Phase 3 trials *RESPONSE and RESPONSE 2*



- Primary composite endpoint: haematocrit control (phlebotomy independence from week 8 to 32, with ≤ 1 phlebotomy post randomization) in the absence of phlebotomy and 35% reduction in spleen volume at week 32 (this latter absent in Response 2)
- Secondary endpoints: complete haematological remission at week 32 (absence of phlebotomy requirement, PLT count ≤ 400 x 10^9/L, and WBC count ≤ 10 × 10^9/L); % of patients who maintain primary endpoint response for ≥ 48 weeks; Symptom improvement (MPN-SAF diary) and quality of life (EORTC QLQ-C30; PGIC).

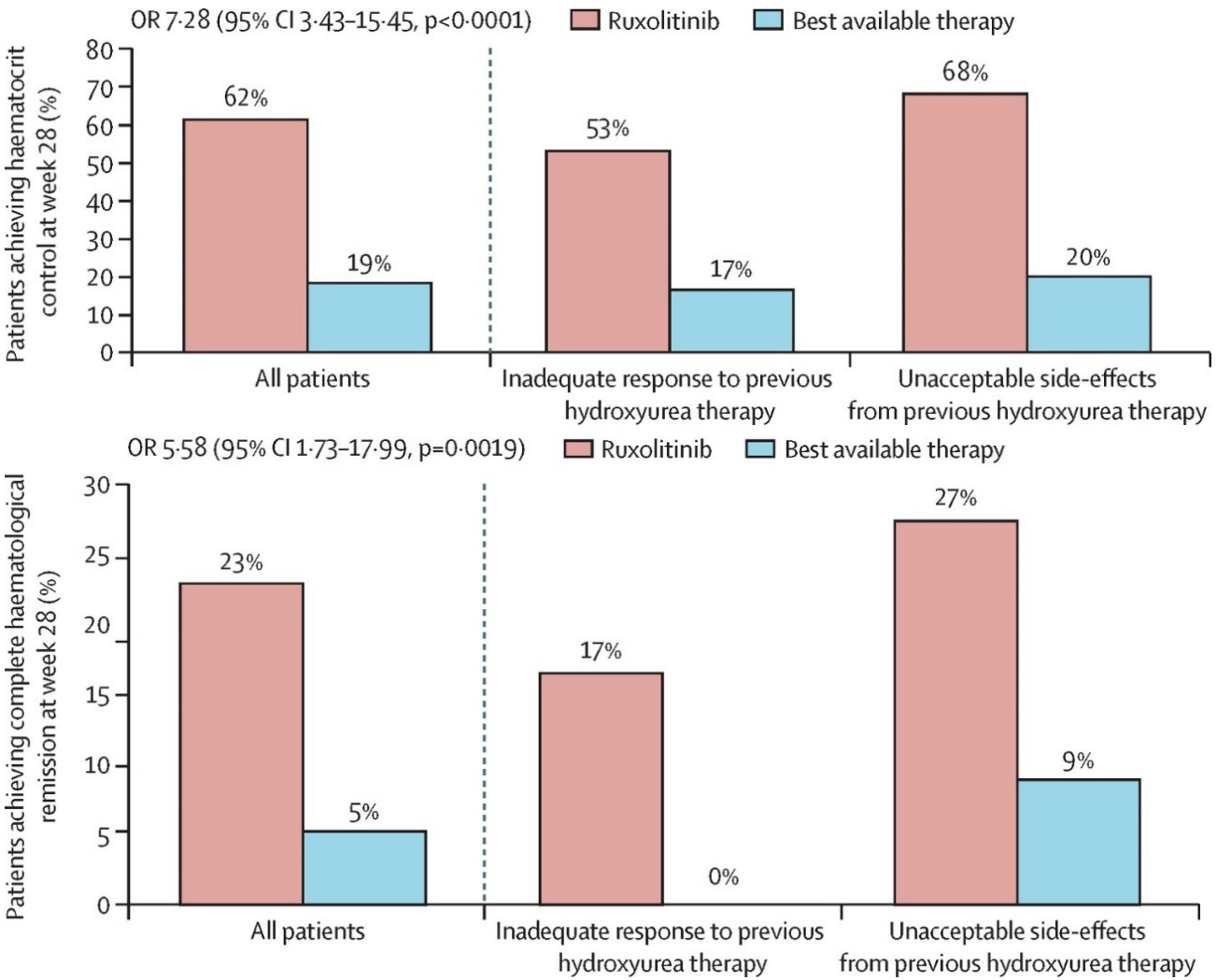
Vannucchi et al, N Engl J Med. 2015 Jan 29;372(5):426-35;
Passamonti et al, Lancet Oncol. 2016 Dec 1. pii: S1470-2045(16)30558-7.

RESPONSE STUDY



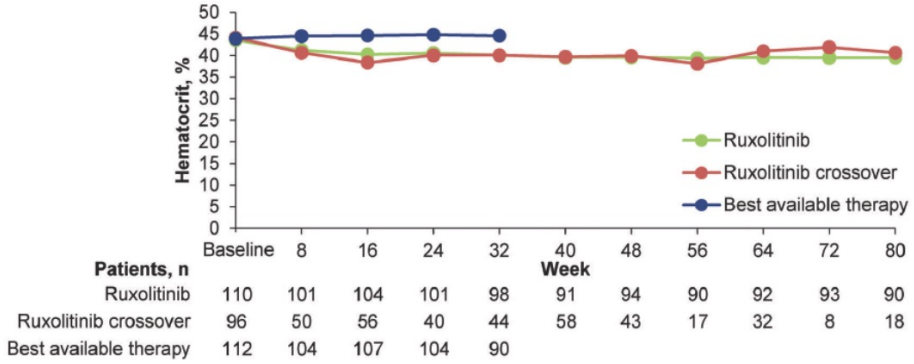
Vannucchi AM et al. N Engl J Med 2015;372:426-435

RESPONSE-2 STUDY



Passamonti F et al, Lancet Oncology 2017; 18: 88-99

Ruxolitinib provide more consistent control of HCT to ≤ 45% than those who received BAT over time

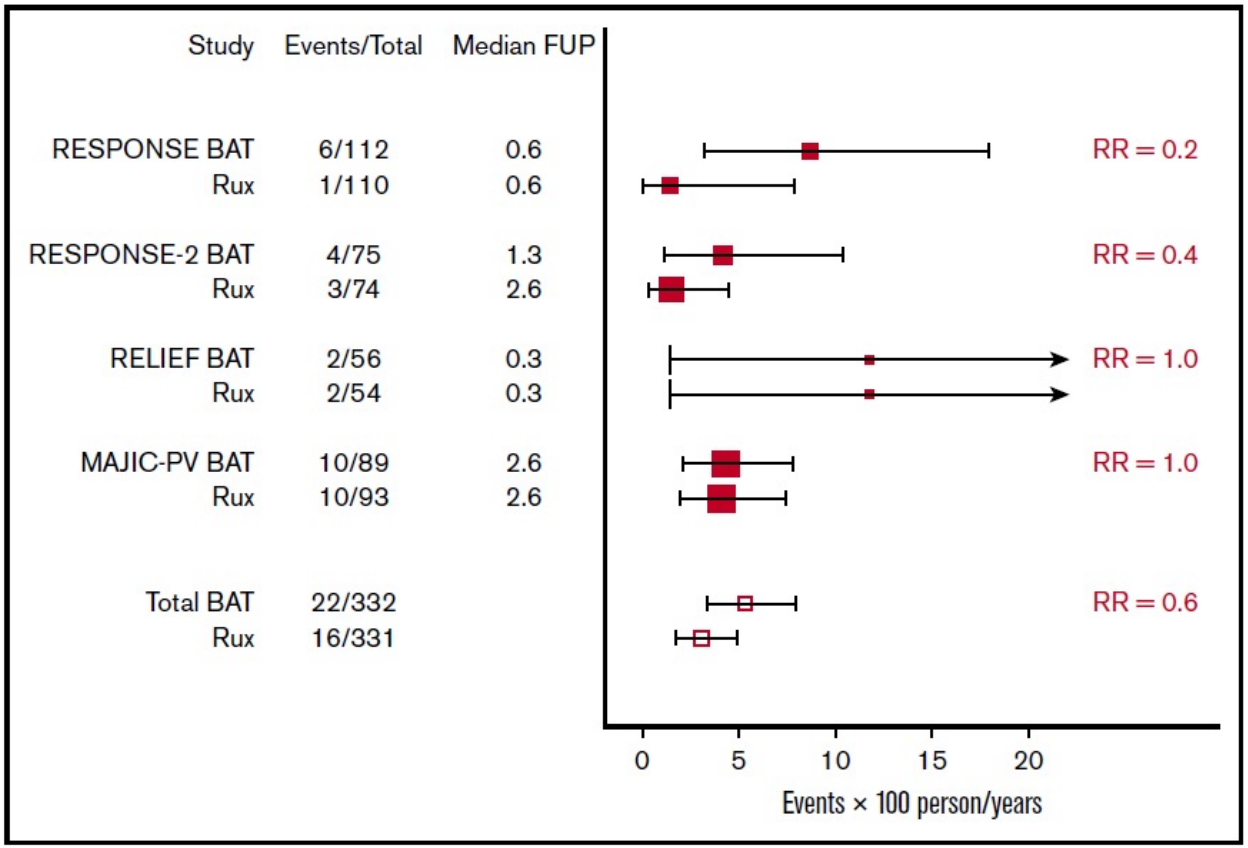


- **Patients in the BAT arm spent 12 times more time (in percentage of time) with an HCT > 45% than patients in the ruxolitinib arm** (median, 39.1% [quartile (Q) 1-Q3, 12.9%-65.9%] vs 3.0% [Q1-Q3, 0.0%-16.7%])

Verstovsek et al. Haematologica 2016 Volume 101(7):821-829

RCTs on ruxolitinib (Rux) in patients with PV (n= 663)

A systematic review and meta-analysis



Thrombosis annual incidence rate

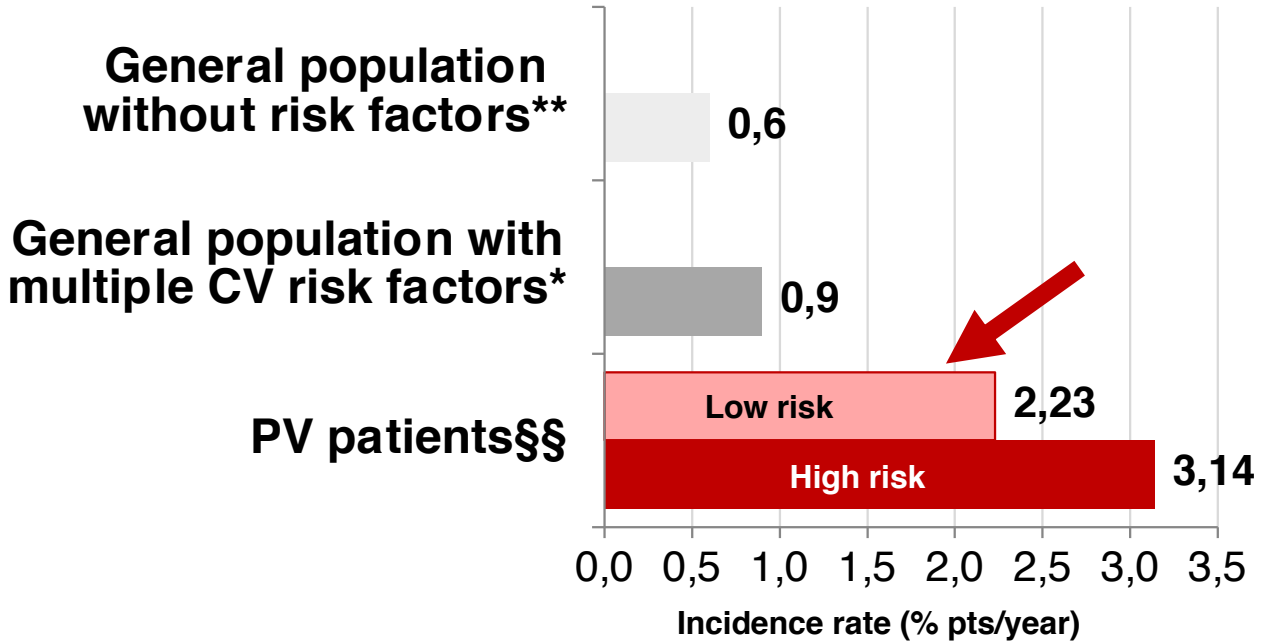
- **BAT** : 5.51 (95% CI, 3.72- 7.30);
- **Ruxo**: 4.30 (95% CI, 3.00-5.60)
- **RR** for ruxolitinib vs BAT of 0.56.

- *The evidence of an advantage of ruxolitinib is suspect (P=.098) but not significant.*

Masciulli A et al, Blood advances, 2020

Treatment of low-risk patients

Annual rate of thrombosis in contemporary patients with polycythemia vera and in general population



** Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual partecipant data from randomized trials, Lancet 2009; 373:1849-1860..* Yusef S et al Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease NEJM 2016

***The Risk and Prevention Study Collaborative Group. N−3 Fatty Acids in Patients with Multiple Cardiovascular Risk Factors. N Engl J Med 2013;368:1800-8.*

§ Barbui T, et al. Practice-relevant revision of IPSET-thrombosis based on 1019 patients with WHO-defined essential thrombocythemia. Blood Cancer Journal. In press

§§ Barbui T, et al. In contemporary patients with polycythemia vera, rates of thrombosis and risk factors delineate a new clinical epidemiology. Blood 2014 124: 3021-3023

Leukemia
https://doi.org/10.1038/s41375-018-0077-1

REVIEW ARTICLE

Chronic myeloproliferative neoplasms

Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet

Tiziano Barbui[1] · Ayalew Tefferi[2] · Alessandro M. Vannucchi[3] · Francesco Passamonti[4] · Richard T. Silver[5] · Ronald Hoffman[6] · Srdan Verstovsek[7] · Ruben Mesa[8] · Jean-Jacques Kiladjian[9] · Rüdiger Hehlmann[10] · Andreas Reiter[10] · Francisco Cervantes[11] · Claire Harrison[12] · Mary Frances Mc Mullin[13] · Hans Carl Hasselbalch[14] · Steffen Koschmieder[15] · Monia Marchetti[16] · Andrea Bacigalupo[17] · Guido Finazzi[1] · Nicolaus Kroeger[18] · Martin Griesshammer[19] · Gunnar Birgegard[20] · Giovanni Barosi[21]

Received: 27 November 2017 / Revised: 16 January 2018 / Accepted: 26 January 2018

Recommendations

The Panel strongly recommended that all patients with PV should be managed with phlebotomy to maintain the hematocrit below 45%, together with daily low-dose acetyl salicylic acid.

Cytoreduction is strongly recommended in high-risk cases, i.e., patients with an age older than 60 years, or those with a previous thrombotic event.

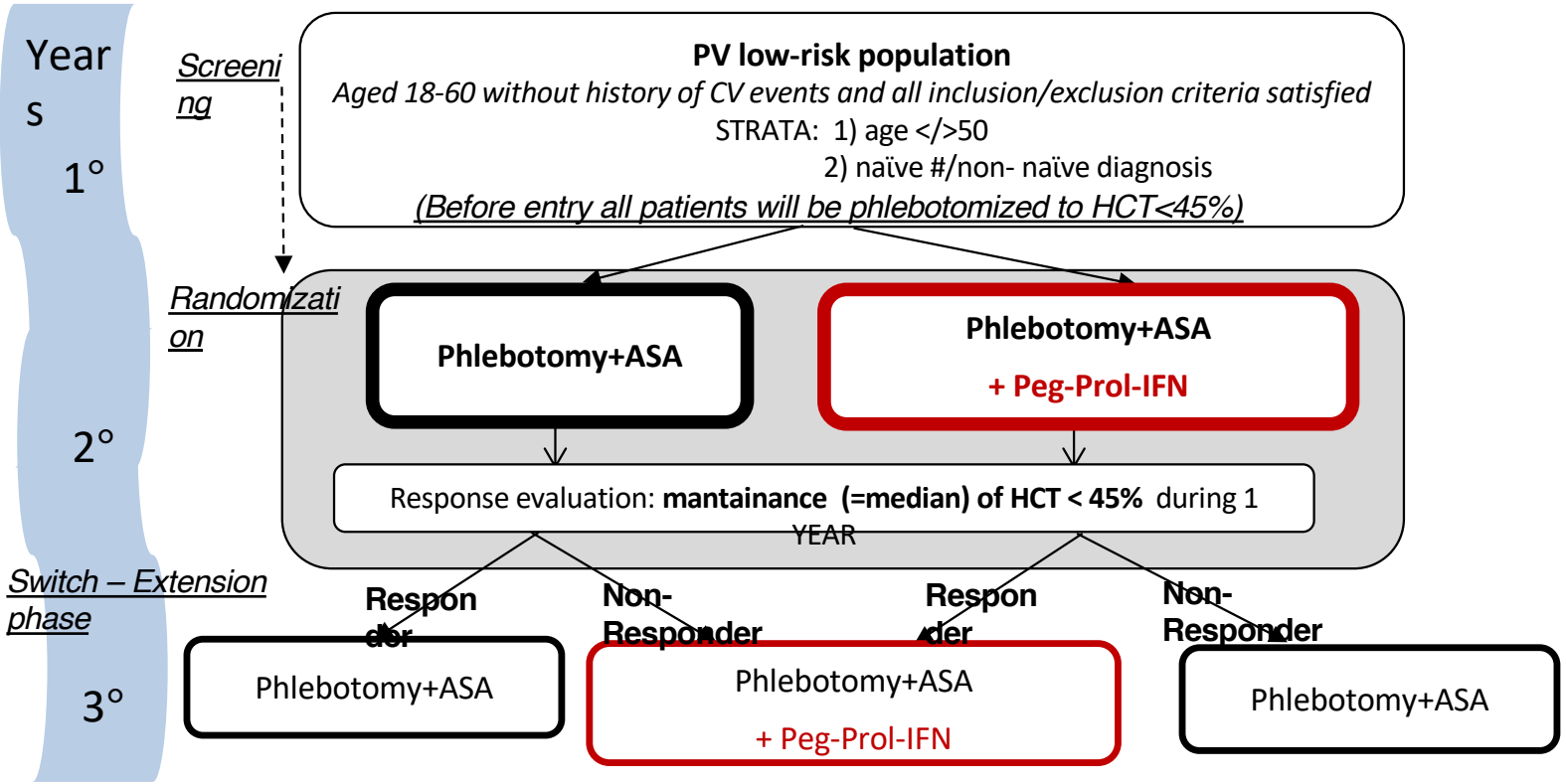
The Panel convened that poor tolerance to phlebotomy is an additional indication to cytoreductive therapy.

Symptomatic or progressive splenomegaly, severe disease-related symptoms, platelet counts greater than 1500×10^9/l or leukocyte count higher than 15×10^9/l, are further indications to start cytoreductive therapy.

Either hydroxyurea or rIFNα is the first-line cytoreductive therapy at any age. However, the Panel agreed it is wise to adopt a cautionary principle and carefully consider the use of hydroxyurea in young patients.

All patients should be managed aggressively for their cardiovascular risk factors.

Study design



#new cases coming to observation, diagnosed for the first time just before study entry (within 90 days) and never treated

The Benefit/Risk Profile of Pegylated Proline-Interferon Alpha-2b (AOP2014) Added to the Best Available Strategy Based on Phlebotomies in Low-risk Patients With Polycythemia Vera (PV). The Low-PV Randomized Trial

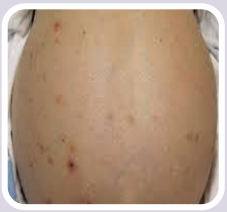
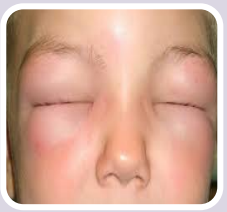
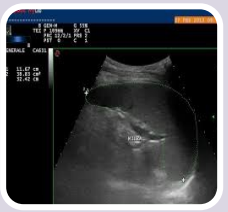
POINT-C

POlycythemia **INT**erferon **C**onsensus

a European LeukemiaNet project

26th Jan 2021 – Kickoff meeting




Need of cyto-reduction	Naiive patients	HU intolerant or resistant patients	Contrain dications (&AE manag)	Response evaluation	Pregnant women

In which low-risk PV patients should cytoreduction be considered?

Should all low-risk PV patients be treated with IFN? If not, which ones?

Appropriate management of polycythaemia vera with cytoreductive drug therapy: European LeukemiaNet 2021 recommendations

Monia Marchetti, Alessandro Maria Vannucchi, Martin Griesshammer, Claire Harrison, Steffen Koschmieder, Heinz Gisslinger, Alberto Álvarez-Larrán, Valerio De Stefano, Paola Guglielmelli, Francesca Palandri, Francesco Passamonti, Giovanni Barosi, Richard T Silver, Rüdiger Hehlmann, Jean-Jacques Kiladjian, Tiziano Barbui

Polycythaemia vera is associated with a reduced quality of life, a high rate of vascular events, and an intrinsic risk of disease evolution. The results of several randomised trials for the treatment of this disorder are now available, and Lancet Haematol 20; 9: e301-11

Panel 1: Recommendations for cytoreductive drug therapy in patients with low-risk polycythaemia vera

In patients with low thrombotic risk (younger than 60 years and without previous vascular events), cytoreductive drugs should be considered only in specific clinical subgroups (consensus, 85%; strength of the recommendation, weak negative).

Cytoreductive drugs are recommended in patients reporting:

- A poor tolerance to phlebotomy, strictly defined as recurrent episodes of post-phlebotomy syncope despite appropriate preventive interventions or blood phobia leading to avoidance behaviour despite counselling, or severe difficulties in venous access (consensus: 100%)
- Symptomatic progressive splenomegaly (increase by >5 cm in the past year), provided that transformation to myelofibrosis has been ruled out (consensus: 85%)
- Persistent leukocytosis (leukocyte count $>20\times10^9$ cells per L confirmed at 3 months (without therapy; consensus: 85%)

Cytoreductive drugs should be considered in patients reporting:

- Progressive (at least 100% increase if baseline count is $<10\times10^9$ cells per L or at least 50% increase if baseline count is $>10\times10^9$ cells per L) and persistent (leukocyte count $>15\times10^9$ cells per L confirmed at 3 months) leukocytosis (consensus: 80%)
- Extreme thrombocytosis ($>1500\times10^9$ platelets per L), bleeding manifestations related to the disease irrespective of the platelet count, or both (consensus: 85%)
- Inadequate haematocrit control with phlebotomies—ie, a need for at least six phlebotomies per year for at least 2 years in the maintenance phase after reaching haematocrit concentrations below 45% in the induction phase (consensus: 80%)

A trial of cytoreductive drugs can be considered:

- In patients reporting a high symptom burden (total symptom score ≥20) or severe itching (itching score ≥5) that are not ameliorated by phlebotomy, antiplatelet therapy, or antihistamines (consensus: 93%)
- On an individual basis in patients reporting a relevant cardiovascular risk (appendix p 4), provided that primary prevention strategies have been implemented (appendix p 5; consensus: 85%)

In treatment-naive patients with polycythaemia vera who are younger than 60 years and have had no previous vascular events but need cytoreductive drug therapy, the first cytoreductive drug to be considered should be ropeginterferon alfa-2b or pegylated interferon alfa-2a, unless clinically contraindicated (consensus: 85%; strength of the recommendation: weak in favour of interferon alfa).

Low-PV

The benefit/risk profile of Pegylated proline-Interferon alpha-2b (AOP2014) added to the best available strategy based on phlebotomies in low-risk patients with Polycythemia Vera (PV).

The Low-PV randomized trial

Results of the 2nd pre-planned interim analysis

Ropeginterferon alfa-2b versus phlebotomy in low-risk patients with polycythaemia vera (Low-PV study): a multicentre, randomised phase 2 trial

Lancet Haematol 2021

This online publication has been corrected. The corrected version first appeared at thelancet.com/haematology on January 27, 2021

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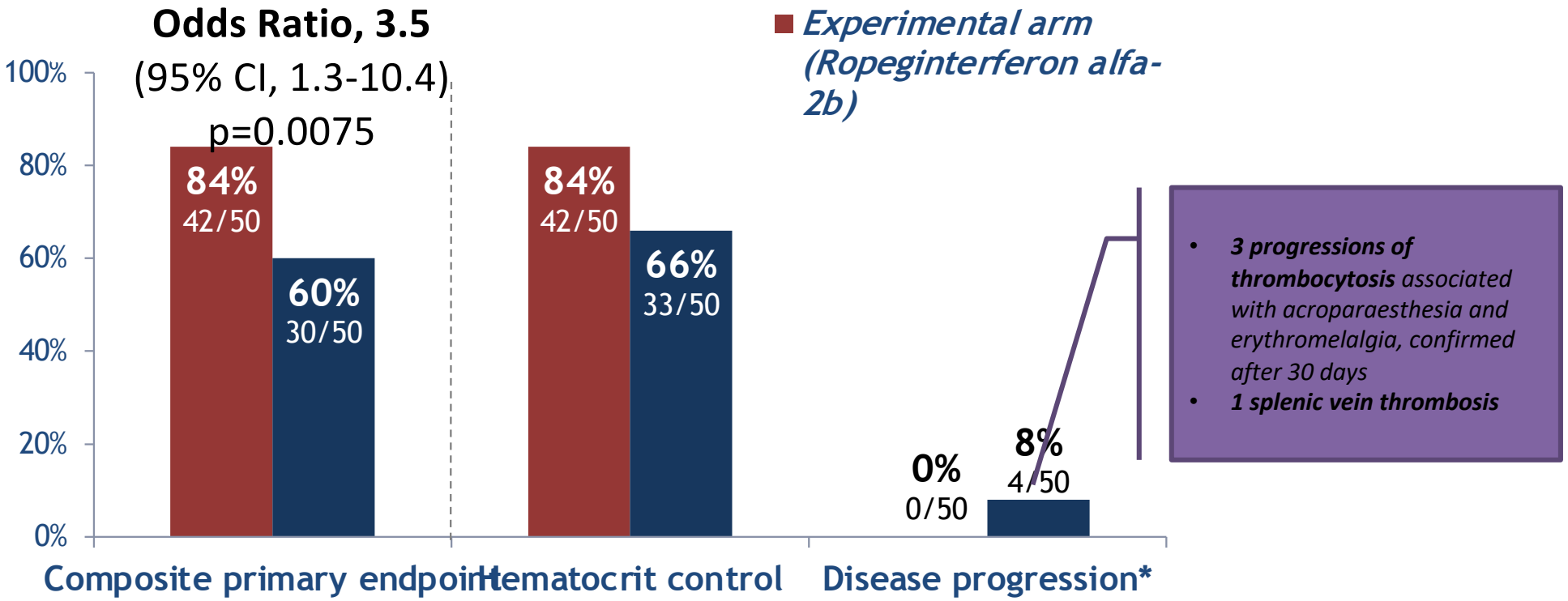
Tiziano Barbui, Alessandro Maria Vannucchi, Valerio De Stefano, Arianna Masciulli, Alessandra Carobbio, Alberto Ferrari, Arianna Ghirardi, Elena Rossi, Fabio Ciceri, Massimiliano Bonifacio, Alessandra Iurlo, Francesca Palandri, Giulia Benevolo, Fabrizio Pane, Alessandra Ricco, Giuseppe Carli, Marianna Caramella, Davide Rapezzi, Caterina Musolino, Sergio Siragusa, Elisa Rumi, Andrea Patriarca, Nicola Cascavilla, Barbara Mora, Emma Cacciola, Carmela Mannarelli, Giuseppe Gaetano Loscocco, Paola Guglielmelli, Silvia Betti, Francesca Lunghi, Luigi Scaffidi, Cristina Bucelli, Nicola Vianelli, Marta Bellini, Maria Chiara Finazzi, Gianni Tognoni, Alessandro Rambaldi

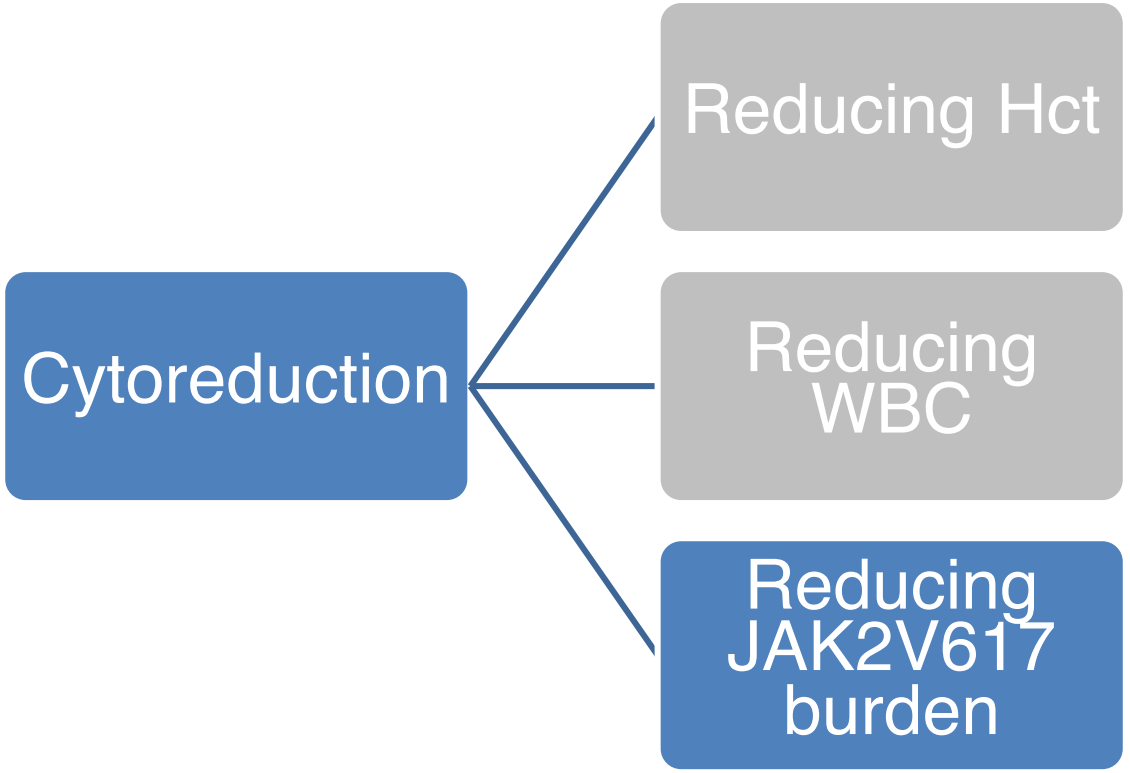
Primary Endpoint - 1

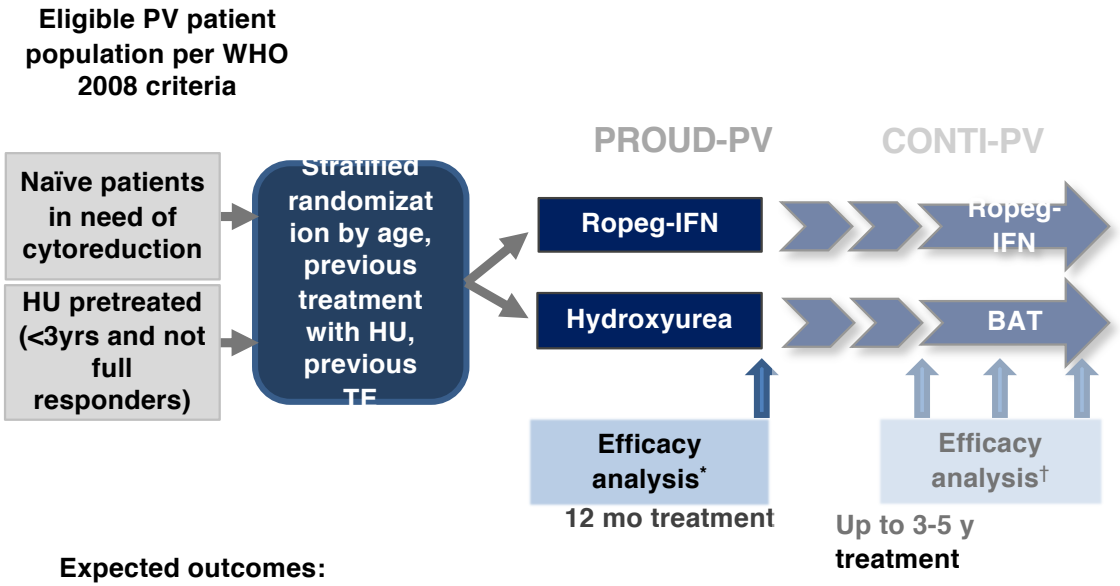
Definition: patients maintaining the median HCT values <45% during 12 months in the absence of progressive disease*



Barbui et al, Lancet Haematol, 2021

Targets of antithrombotic treatment





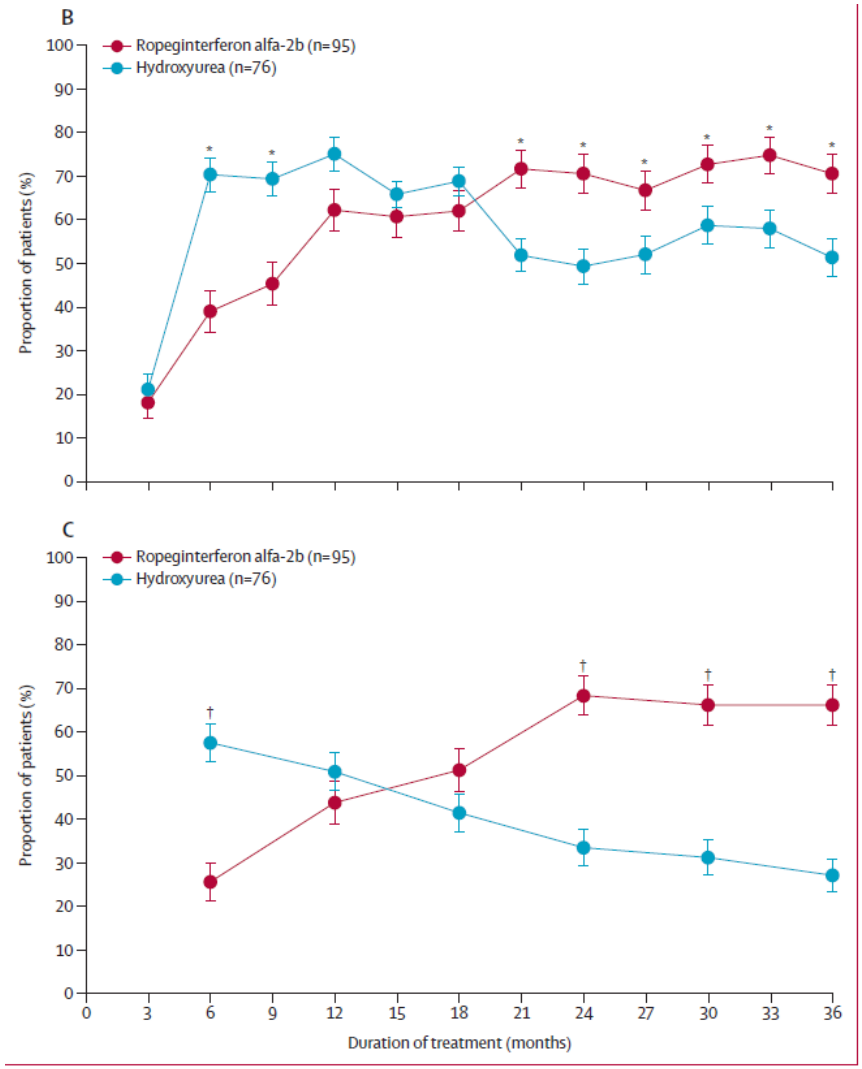
Expected outcomes:

*Non-inferiority: hematologic response

†Benefit: durable hematologic response, progression-free survival, PV symptom relief

Gisslinger H, et al. Proceedings from the 2016 Annual Meeting of the American Society of Hematology. Abstract #475.

CONTINUATION PV

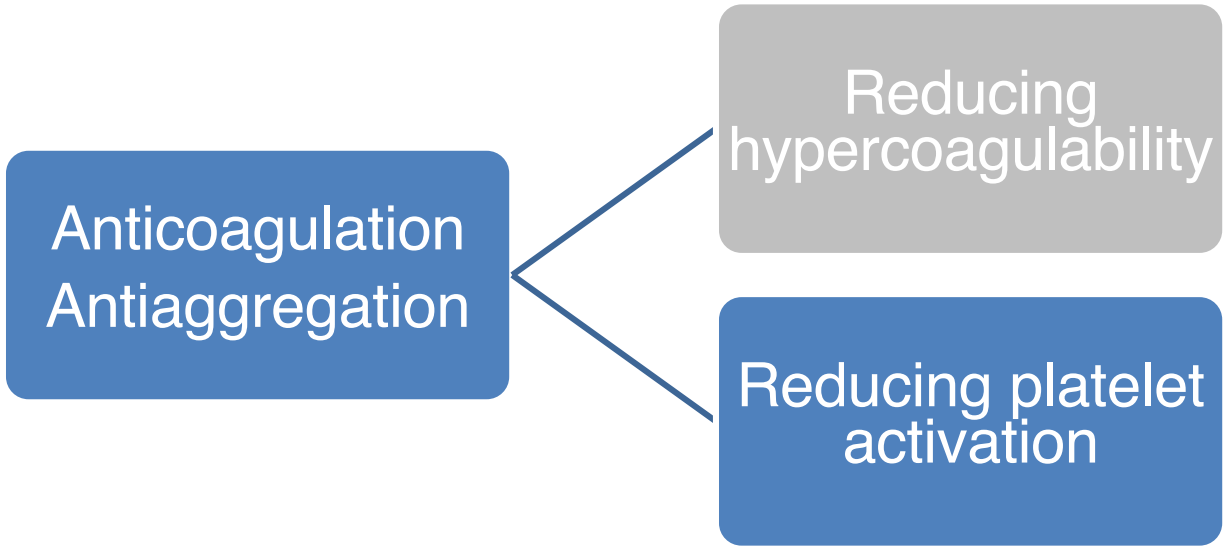


Complete Hematological Response

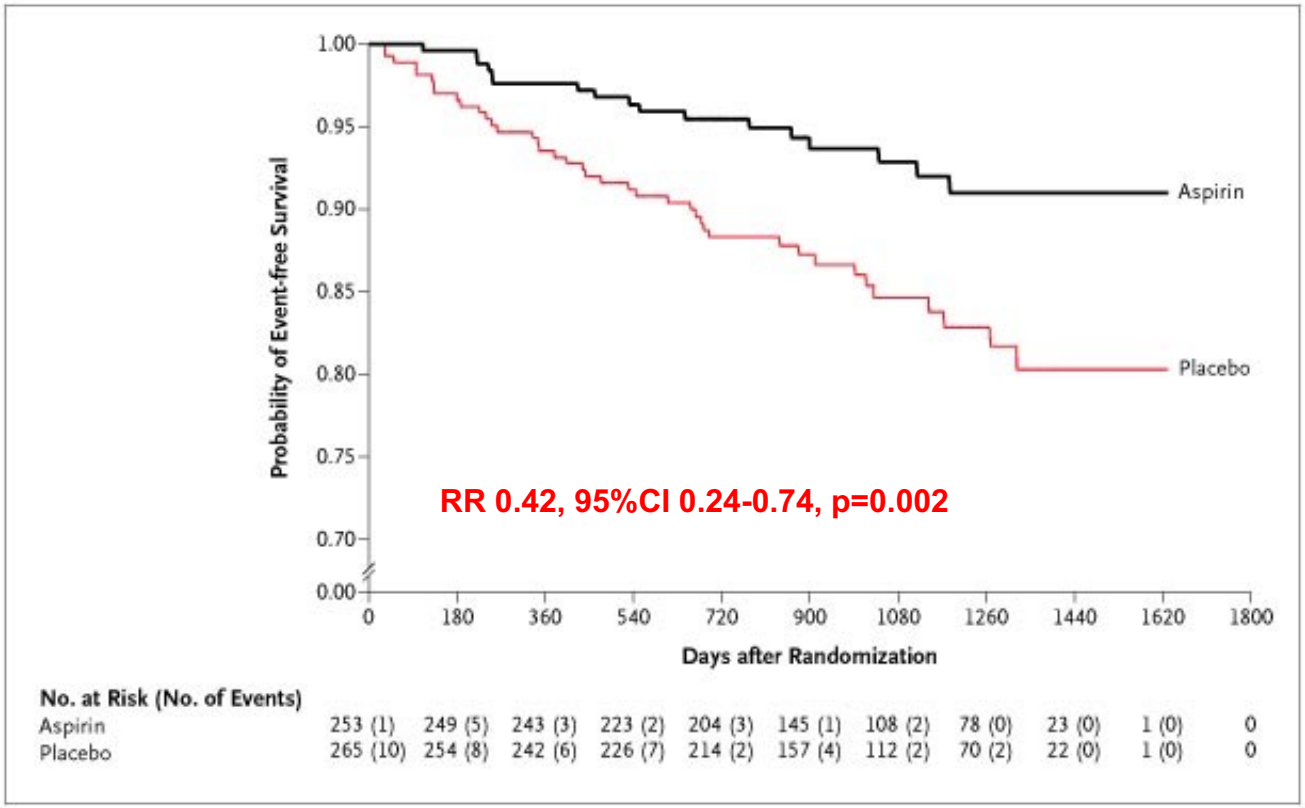
Molecular Response

Gisslinger H et al, Lancet Hematology 2020

Targets of antithrombotic treatment



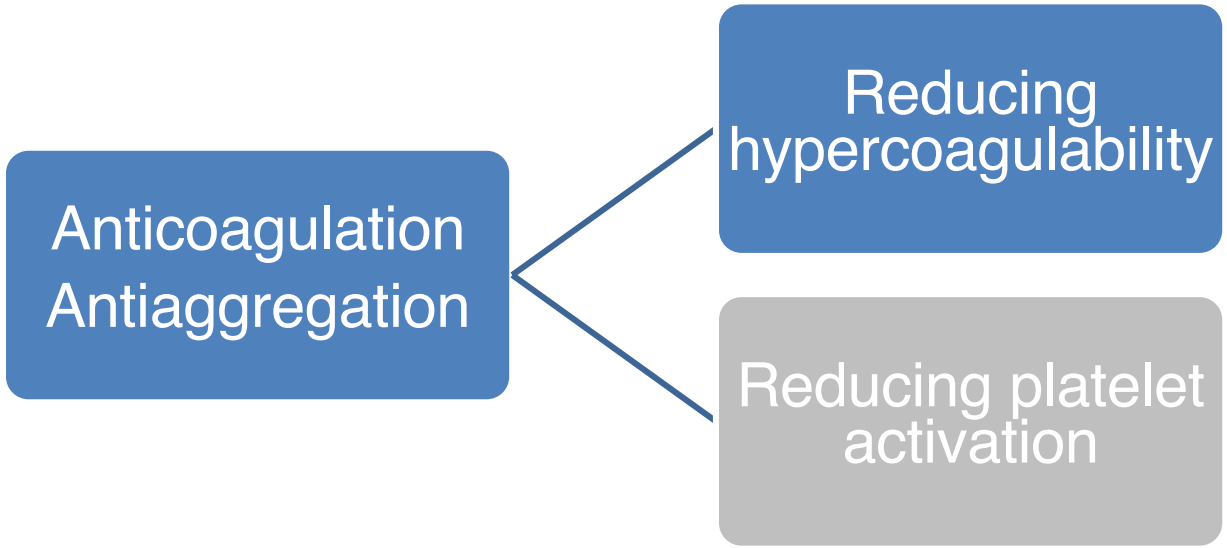
Probability of Survival Free of a Thrombotic Event



Landolfi, R. et al. N Engl J Med 2004;350:114-124

The NEW ENGLAND JOURNAL of MEDICINE

Targets of antithrombotic treatment

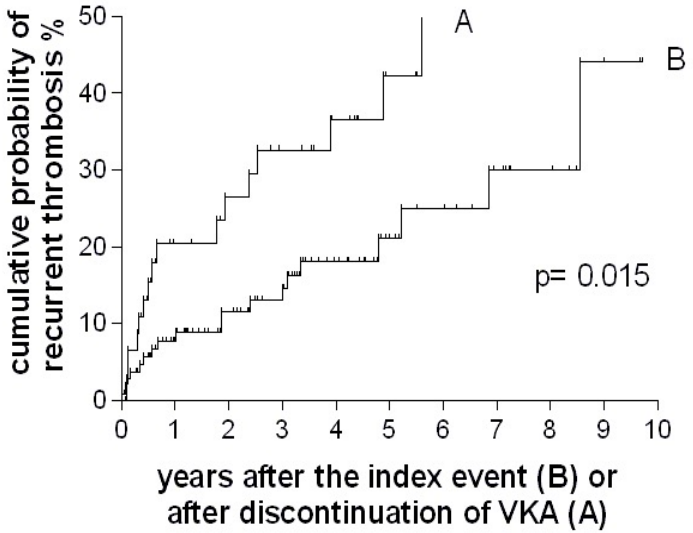


ELN-WP9 project
Thrombosis recurrences in MPN.
Analysis of 1032 index events

Index event	No. Centers	Design	No. Pts
Cerebral vein thrombosis *Martinelli et al, Am J Hematol 2014*	11	**Case-control study** • Cases: MPN with CVT • Controls: MPN and DVT	135 48 87
Deep vein thrombosis *De Stefano et al, Leukemia 2016*			
Splanchnic vein thrombosis *De Stefano et al, Blood Cancer J 2016*	23	**Retrospective cohort study** **Retrospective cohort study**	206 181
Cerebral arterial thrombosis *De Stefano et al, Blood Cancer J 2018*	22	**Retrospective cohort study** • TIA or • Ischemic Stroke	597 270 327

Recurrences after leg venous thrombosis and pulmonary embolism (n=206)

Cumulative probability of recurrent thrombosis in patients who discontinued VKA after index thrombosis (curve A) or did not (curve B).



Median follow-up 3.0 y

Recurrence rate

PV rate 5.3% y
ET rate 6.8%y
MF rate 13.3%y

Rate on VKA …… 4.9% y
-bleeding……. 2.4% y
Rate off VKA…..... 8.7% y
- bleeding…….. 0.7% y

De Stefano V et al, Leukemia 30, 2032-2038, 2016

Rate of recurrent thrombosis after proximal DVT and/or PE In MPN vs non-MPN population

	Time after discontinuation of VKA		Time after VTE during therapy with VKA	
Rate of recurrent thrombosis after proximal DVT and/or PE	*1 year*	*5 years*	*1 year*	*5 years*
VTE provoked by a nonsurgical reversible risk factor	5%	15%	0.6%	1.8%
Unprovoked VTE	10%	30%	1.2%	3.6%
MPN-related DVT of legs and/or PE	**20%**	**42.3%**	**7.8%**	**21.1%**

Kearon C et al, Chest 141(2 Suppl): e419S-e496S, 2012.
De Stefano V et al, Leukemia 30, 2032-2038, 2016

Rate of major bleeding during VKA treatment in MPN vs non-MPN population

	Duration of VKA treatment	
Rate of major bleeding	**1 year**	**5 years**
Low-risk patients	3%	1.5%
Moderate risk patients	6%	3%
High risk patients	25%	12.5%
MPN patients	**2.8%**	**8.9%**

In non-MPN patients the duration of VKA treatment is associated with a decrease in the bleeding risk; in MPN patients long-term VKA treatment upgrades the risk of bleeding

Kearon C et al, Chest 141(2 Suppl): e419S-e496S, 2012.
De Stefano V et al, Leukemia 30, 2032-2038, 2016

Barbui T, De Stefano V, Carobbio A et al

Direct Oral Anticoagulants for Myeloproliferative Neoplasms (MPN-DOACs): results from an international study on 442 patients

Leukemia 2021

442 MPN receiving DOACs * :

PV 178 ET 172 PMF 92

Rivaroxaban 187 Apixaban 157 Dabigatran 50 Edoxaban 48

***AF on primary / secondary prophylaxis 203**

Previous VTE 239

Incidence rate of thrombosis per 100 pt-years				
	VKA		DOACs	
	Non-MPN	MPN	Non-MPN	MPN
AF (primary prophylaxis)	1.2 – 1.8	2.7 (PV)	1.0 - 1.4	1.5
AF (secondary prophylaxis)	2.7 – 3.2		2.0 – 2.8	4.6
VTE (recurrent thromboses)		5.3		4.5
VTE (recurrent VTE) [treatment less/more than 3 months]	3.3 / 3.7	4.2	3.7 / 1.5	3.4

Incidence rate of major bleeding per 100 pt-years				
	VKA		DOACs	
	Non-MPN	MPN	Non-MPN	MPN
AF (overall)	2.4 – 3.4	2.7 (PV)	1.6 – 3.1	3.0
VTE (secondary prophylaxis) [treatment less/more than 3 months]	3.1 / 1.6	1.7	1.8 / 0.6	2.3

Atrial Fibrillation:

Connolly SJ et al, Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139.

Granger CB et al, Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981.

Hankey GJ et al, Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. Lancet Neurol. 2012 Apr;11(4):315-22.

Giugliano RP et al, Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369(22):2093.

Lip GYH et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. Chest. 2018 Nov;154(5):1121-1201.

de Freitas AS, Alvarez-Larrán A. Risk of thrombosis and hemorrhage in patients with polycythemia vera and atrial fibrillation treated with prophylactic oral anticoagulants. Ann Hematol. 2016;95(11):1903-4.

Venous Thromboembolism:

Wu C et al. Case fatality of bleeding and recurrent venous thromboembolism during, initial therapy with direct oral anticoagulants: a systematic review. Thromb Res. 2014;134(3):627-32.

Wu C et al. Case-fatality of recurrent venous thromboembolism and major bleeding associated with aspirin, warfarin, and direct oral anticoagulants for secondary prevention. Thromb Res. 2015;135(2):243-8.

De Stefano V et al. High rate of recurrent venous thromboembolism in patients with myeloproliferative neoplasms and effect of prophylaxis with vitamin K antagonists. Leukemia. 2016;30(10):2032-2038.

Conclusions and Future directions

- Thrombosis still remains a major complications in MPN
- Primary prevention trials of thrombosis-related endpoints in MPNs are difficult to conduct, requiring large accrual with long follow-up periods. Surrogate biomarkers for thrombosis should be explored and validated.
- However, more aggressive approaches are suggested for low-risk PV patients
- The role of hydroxyurea in preventing arterial but not venous thromboses should be better definied in the clinical practice
- Peg-Interferons and JAK2 inhibitors are promising drugs for the hematologic control, but their efficacy in the reduction of major thrombosis is suspected but not yet proven.
- DOACs are effective and safe as VKA in prevention of recurrent venous thromboembolism; yet, this point remains an unmet clinical need