Thrombosis: a major complications in Ph Neg Myeloproliferative Neoplasms

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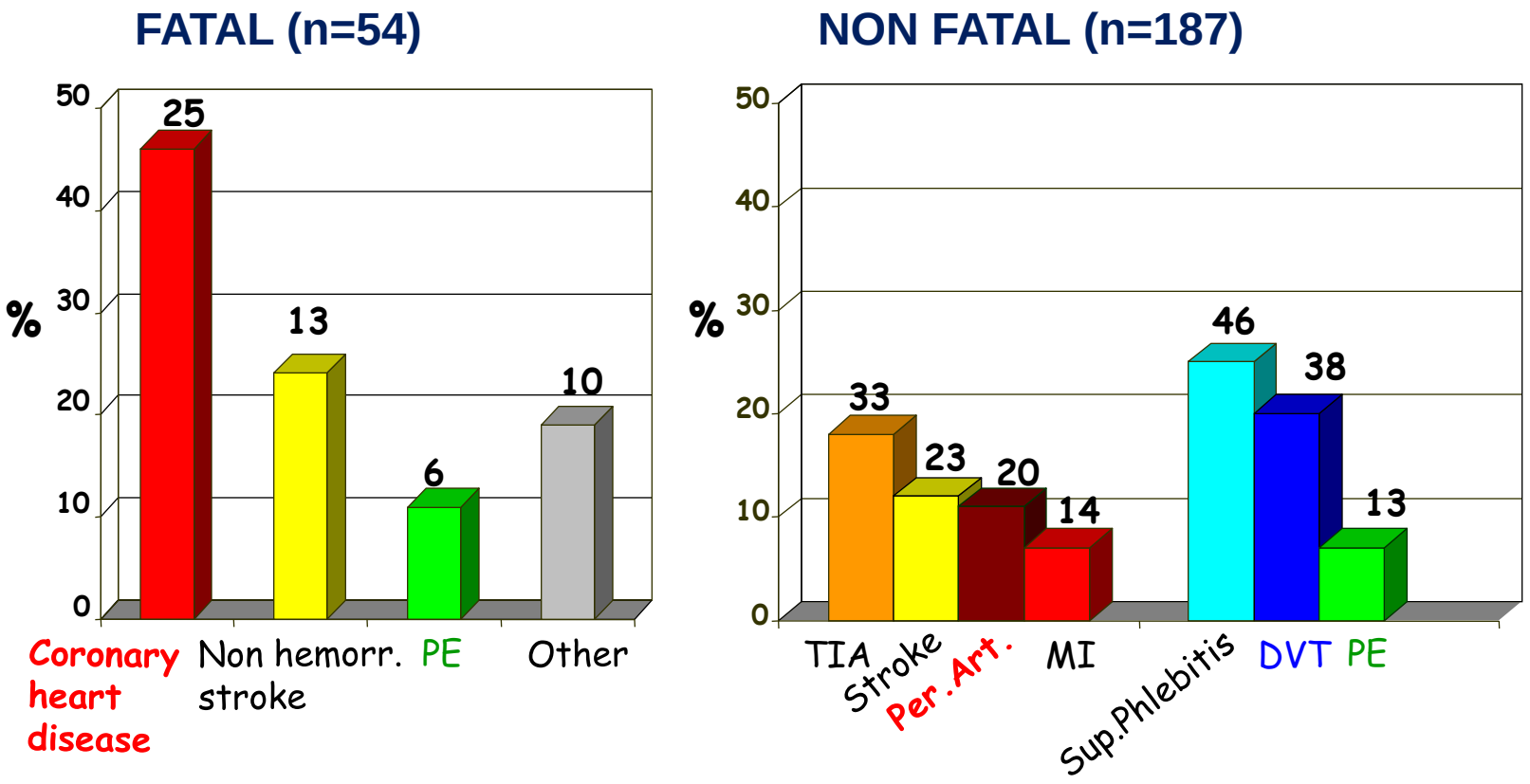
The most frequent sites of Thrombosis in MPNs

- **Arterial thrombosis** (acute myocardial infarction, cerebral and peripheral arterial occlusion)

- **Deep venous thrombosis** and pulmonary embolism. Splanchnic and cerebral vein thromboses

- **Microcirculatory disturbances** including erythromelagia and miscarriages

Type of thrombosis in ECLAP study (N=1638)



Marchioli et al, 23:2224-2232, 2005

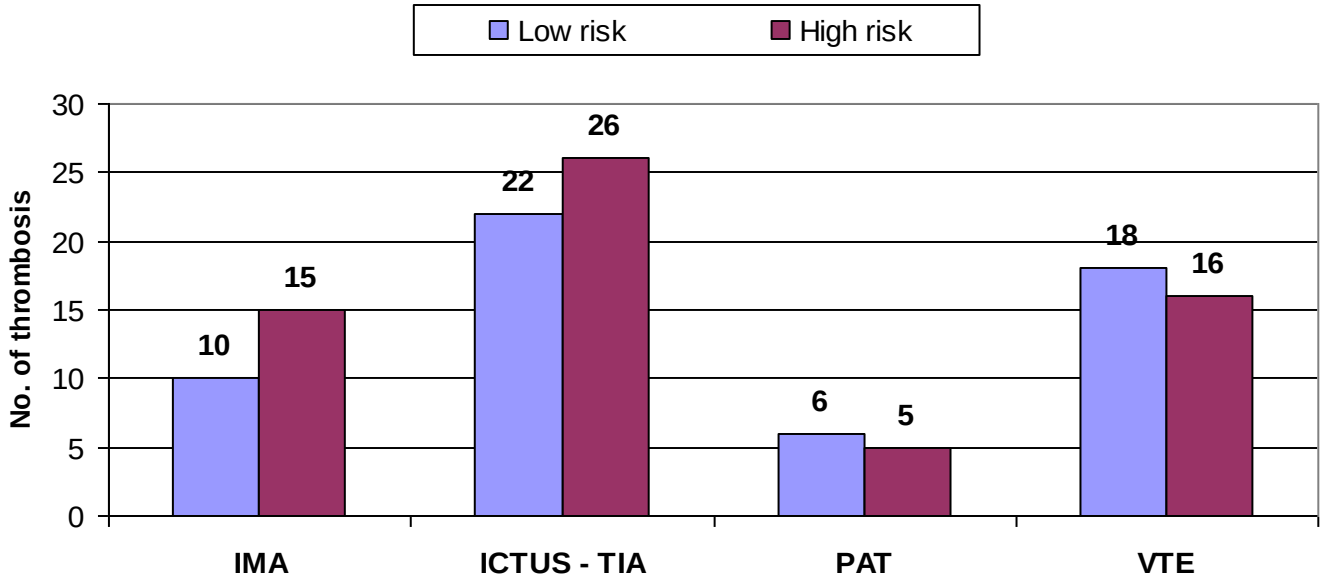
ET-BVF study :1063 pts

Events During Follow-up

Low-risk (n=517) *High risk (n=546)*

(left untreated) (100% treated)

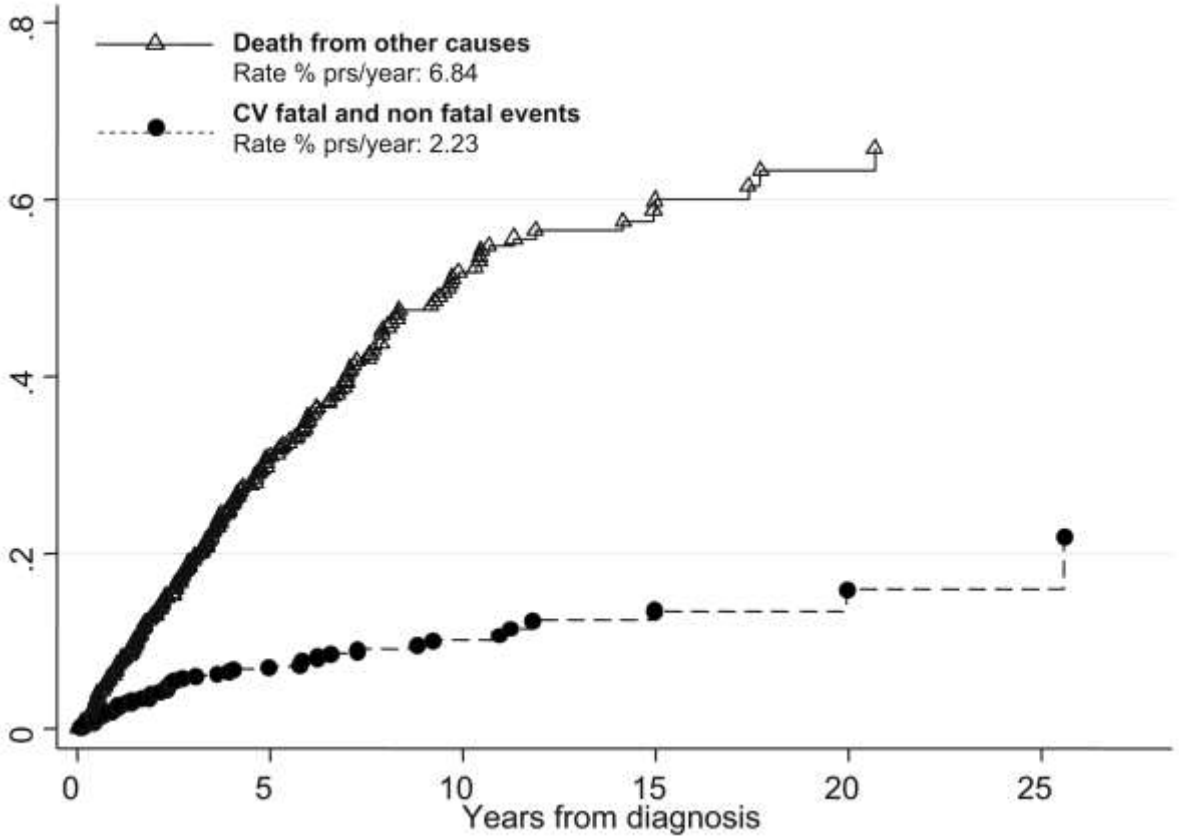
Rate: 1.5 (%/patients/year) 2.0 (%/patients/year)



Carobbio et al Blood 2008, Blood 2009; Barbui JCO2011)

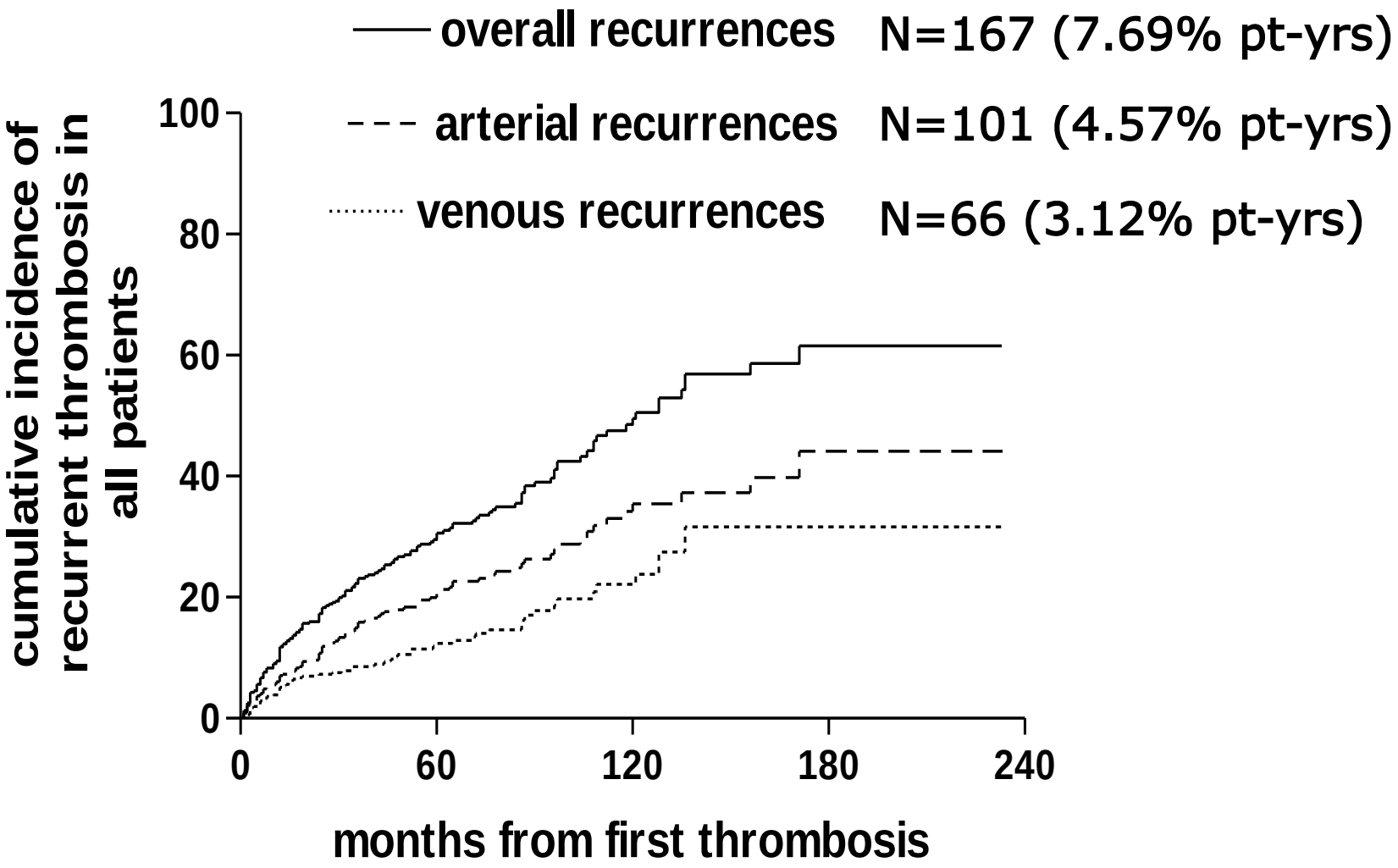
blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Figure 1 Cumulative incidence of fatal and nonfatal thrombotic events versus deaths from other causes (competing risk analysis) in 707 patients with primary myelofibrosis



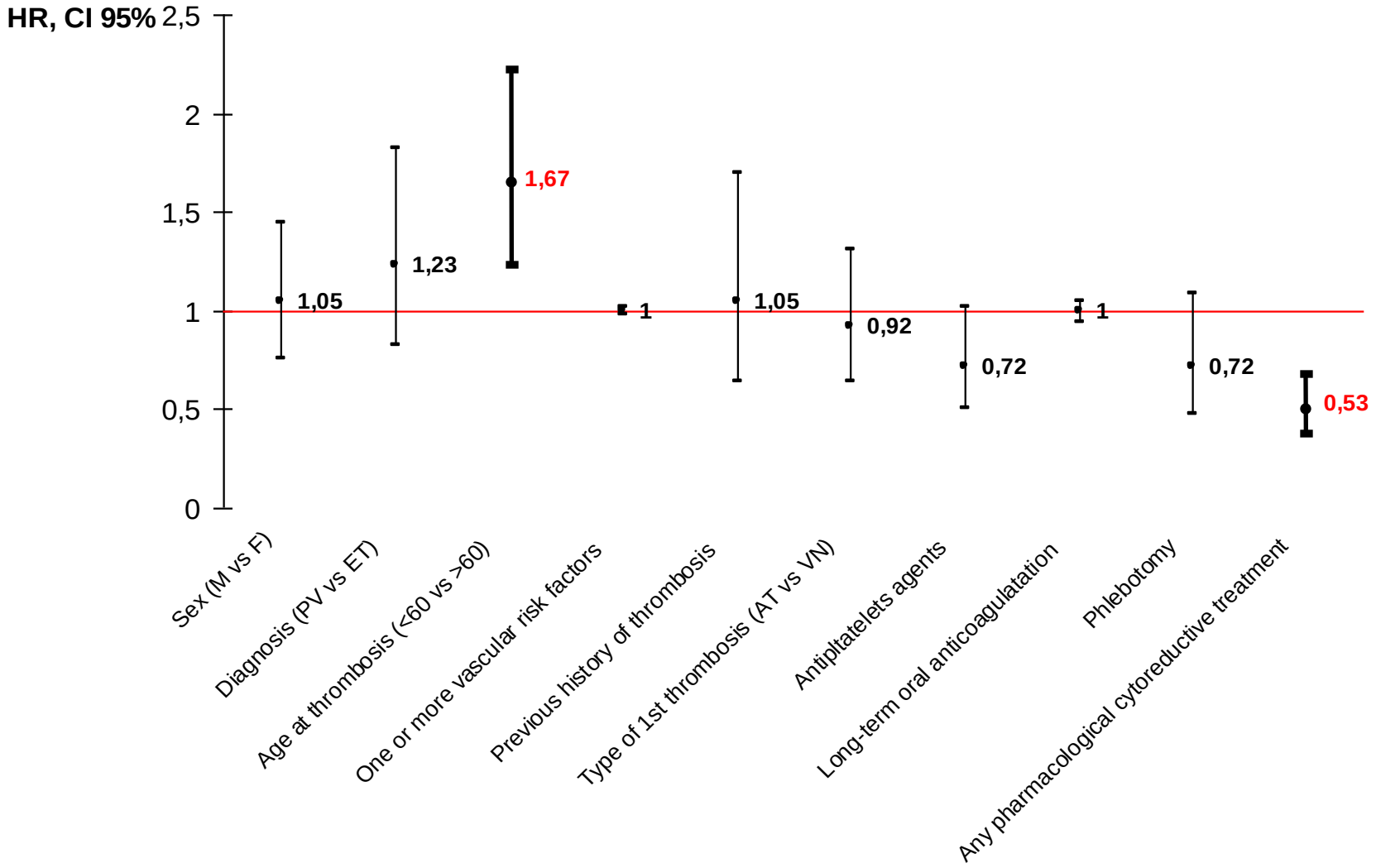
Barbui, T. et al. Blood 2010;115:778-782

RECURRENT THROMBOSIS IN POLYCYTHEMIA VERA AND ESSENTIAL THROMBOCYTHEMIA



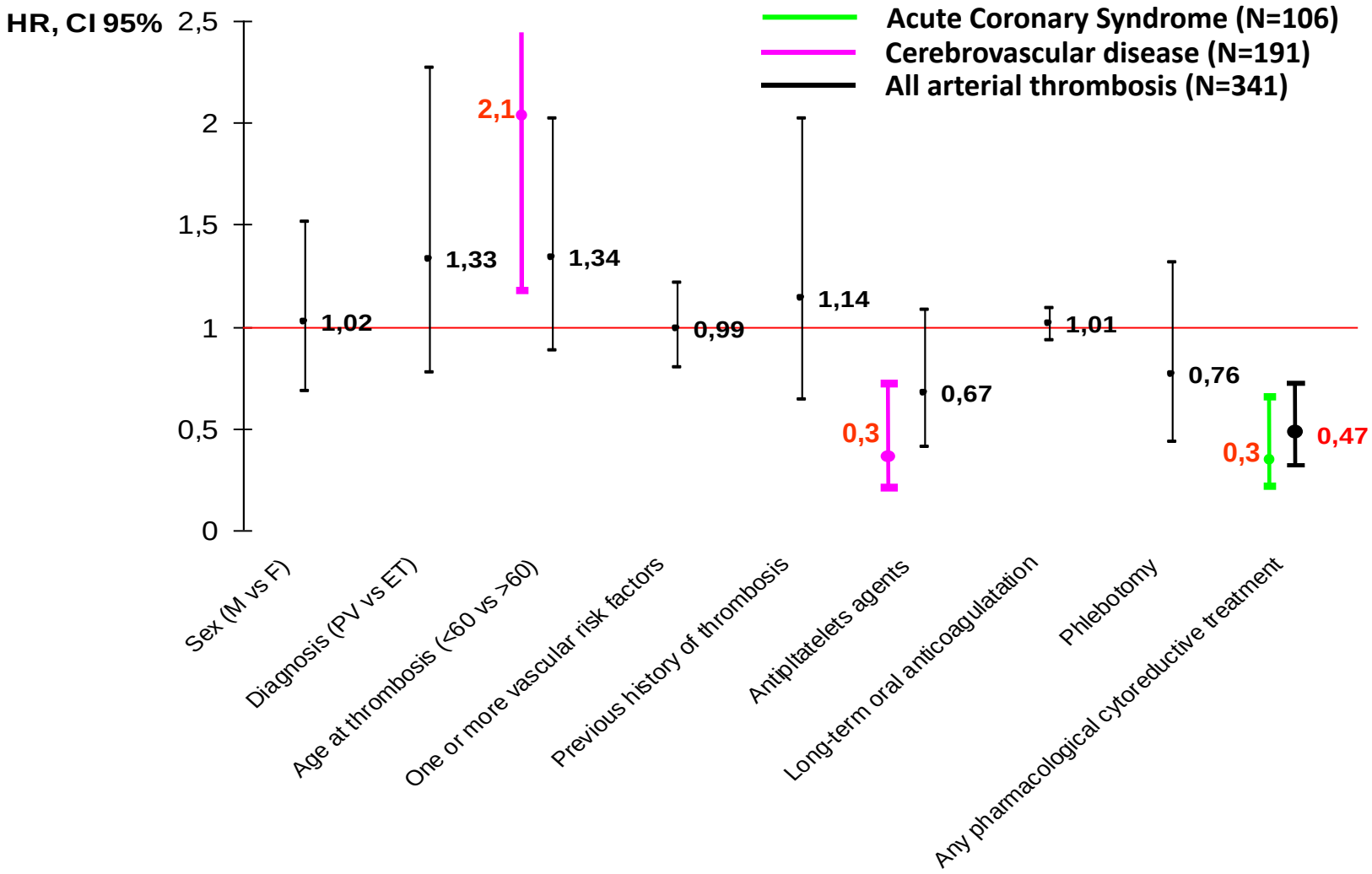
De Stefano V, Haematologica 2008

Risk factors for overall recurrent thrombosis according to the baseline characteristics (multivariable model)



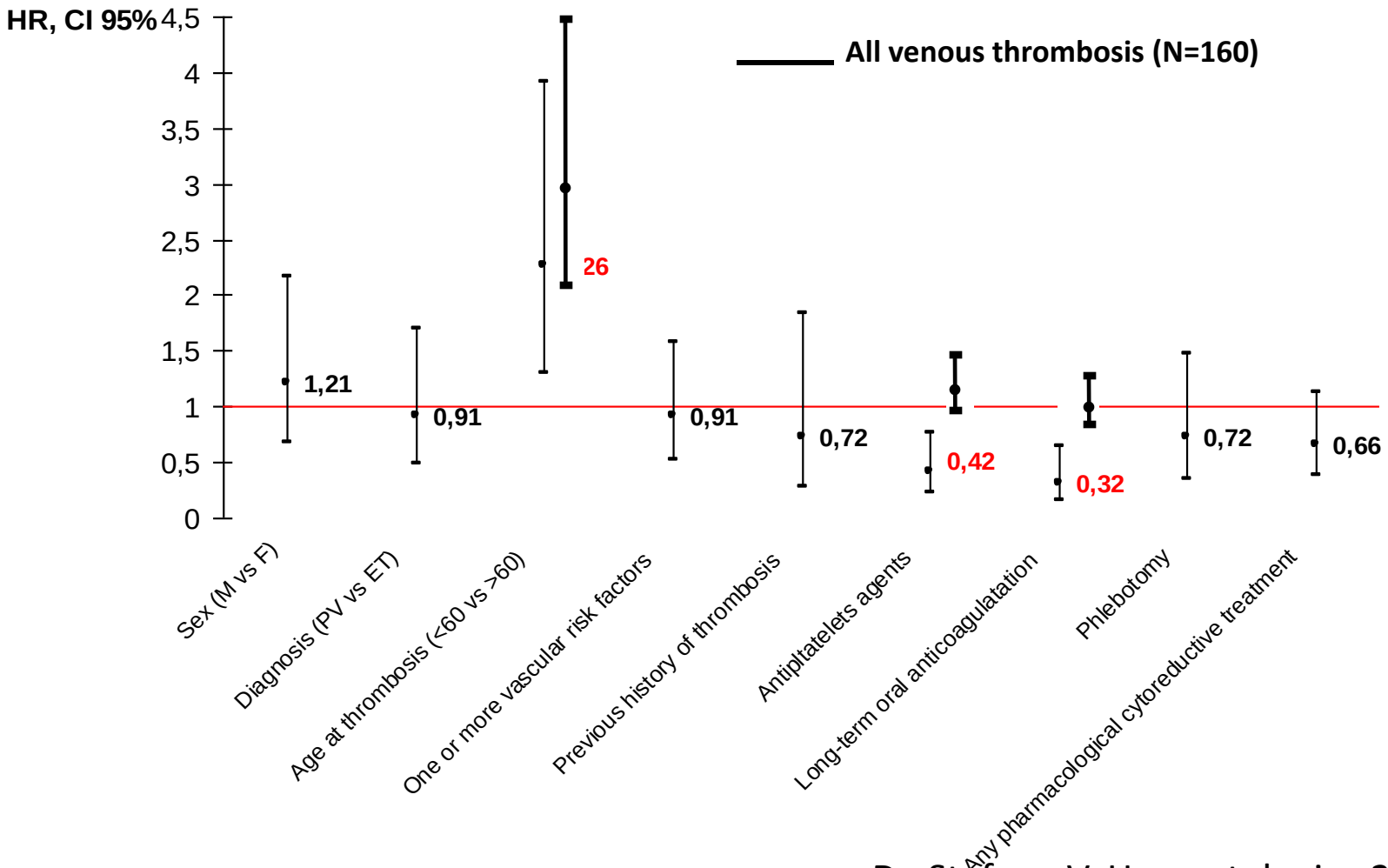
De Stefano V, Haematologica 2008

Risk factors for recurrent thrombosis of patients with first arterial thrombosis according to the baseline characteristics (multivariable model)



De Stefano V, Haematologica 2008

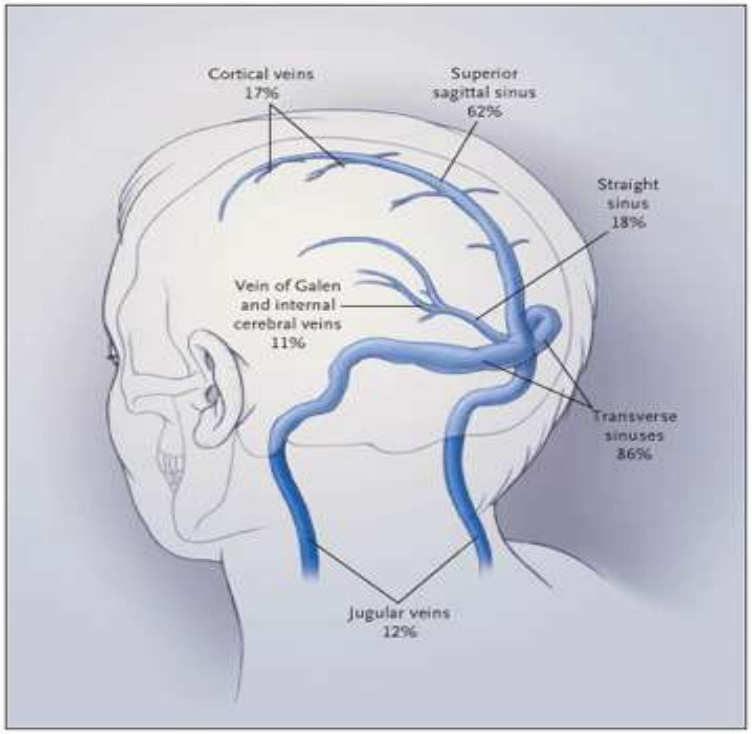
Risk factors for recurrent thrombosis of patients with **first venous thrombosis** according to the baseline characteristics (multivariable model)



De Stefano V, Haematologica 2008

Rare Venous Thrombosis in MPN

Cerebral vein thrombosis



Responsible for less than 1% of all strokes, most often affects **young adults and children**, annual incidence rates include 4 permillion of the population, 7 per million children and about 12 per million deliveris

Obstruction of cerebral veins causes cerebral oedema and venous infarction, while occlusion of venous sinuses causes intracranial hypertension. **Symptoms** are recent unusual headache, stroke-like symptoms .
The most sensitive **diagnostic test** is MRI ,or high resolution computed tomography (CT) as an initial examination is useful but it can be normal initially.

TIMING OF CVT OCCURRENCE

	CVT cases
	N= 48
Before diagnosis of MPN	***8 (17)***
At diagnosis	***22 (46)***
After diagnosis of MPN	***18 (38)***

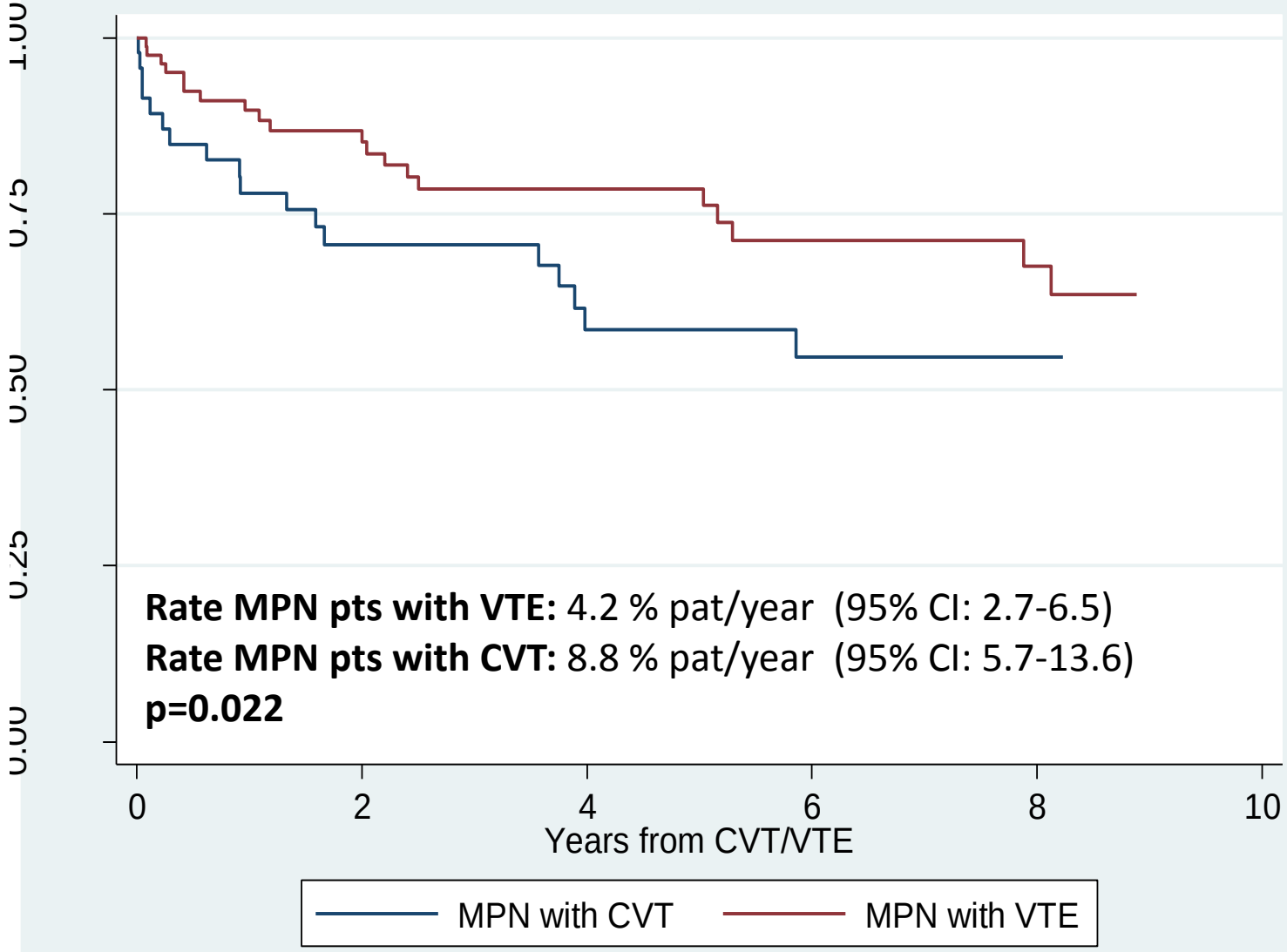
Martinelli et al, submitted

EVENTS DURING FOLLOW-UP

Data during follow-up	CVT cases	MPN VTE	p
Median follow-up, years (range)	6.09 (0-34)	10.3 (0-31)	**0.019**
Cytoreductive treatment, n (%)	36 (75)	63 (72)	0.745
Long-term antithrombotic treatment, n (%)	45 (94)	73 (84)	0.099
Recurrent thrombosis, n (%)	20 (42)	22 (25)	**0.049**
Venous thrombosis	***9 (19)***	***11 (13)***	
Splanchnic vein thrombosis	***6 (13)***	***6 (7)***	
Arterial thrombosis	***4 (8)***	***5 (6)***	
Cerebral vein thrombosis	***1 (2)***	***-***	
Hematological evolutions, n (%)	3 (6)	8 (9)	0.404
PPV-MF	*-*	*1 (1)*	
PET-MF	*3 (6)*	*7 (8)*	
Acute Leukemia	*-*	*-*	
Deaths, n (%)	4 (8)	17 (20)	0.135

Martinelli et al, submitted

THROMBOSIS-FREE SURVIVAL



Martinelli et al, submitted

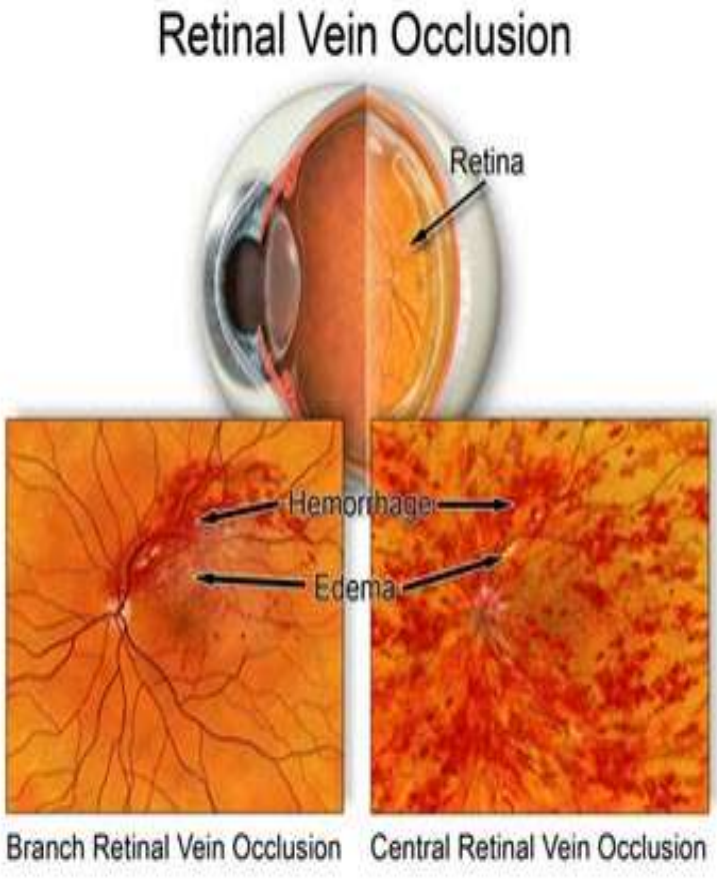
RECURRENT THROMBOSIS FREE SURVIVAL

Multivariate analysis after stepwise backward selection procedure:

	HR (95% CI)	p-value
CVT vs VTE cases	1.79 (1.01-3.33)	0.044
Unprovoked event	2.04 (1.07-3.89)	0.031

Martinelli et al, submitted

Rare Thrombosis in MPN



Over the age of 40 years the annual incidence is 16/1000 of which 75% are branch retinal vein occlusion and 25% central retinal vein occlusion . **Over 64 years** 5/1000/year.
Prevalence of JAK2 V617F 1.1%

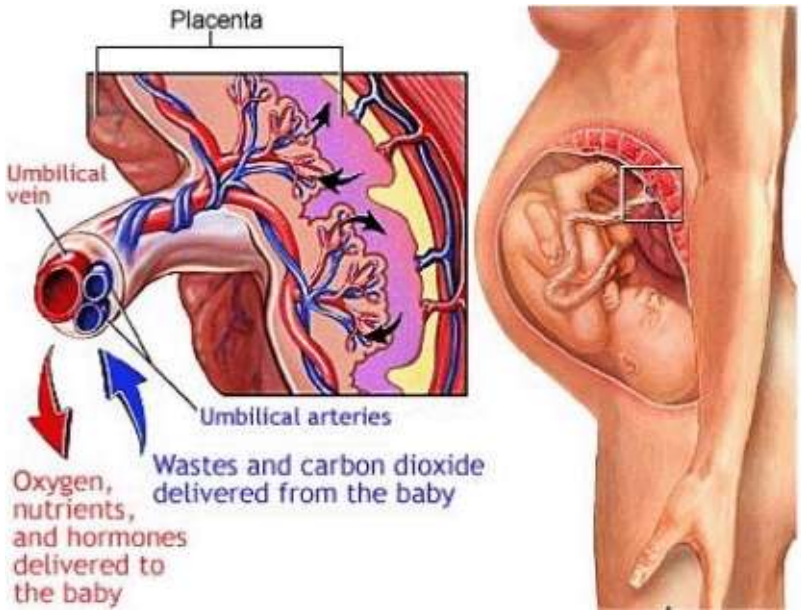
Typical presentation is with acute, painless visual loss in one eye.
The diagnosis can usually be made by clinical examination alone.

Risk factors are hypertension, diabetis, no thrombophilia, rare MPN

Treatment with LMWH for 1–6 months (2B).
Routine therapy with warfarin or anti-platelet agents is not recommended (2C).

Rare Thrombosis in MPN:

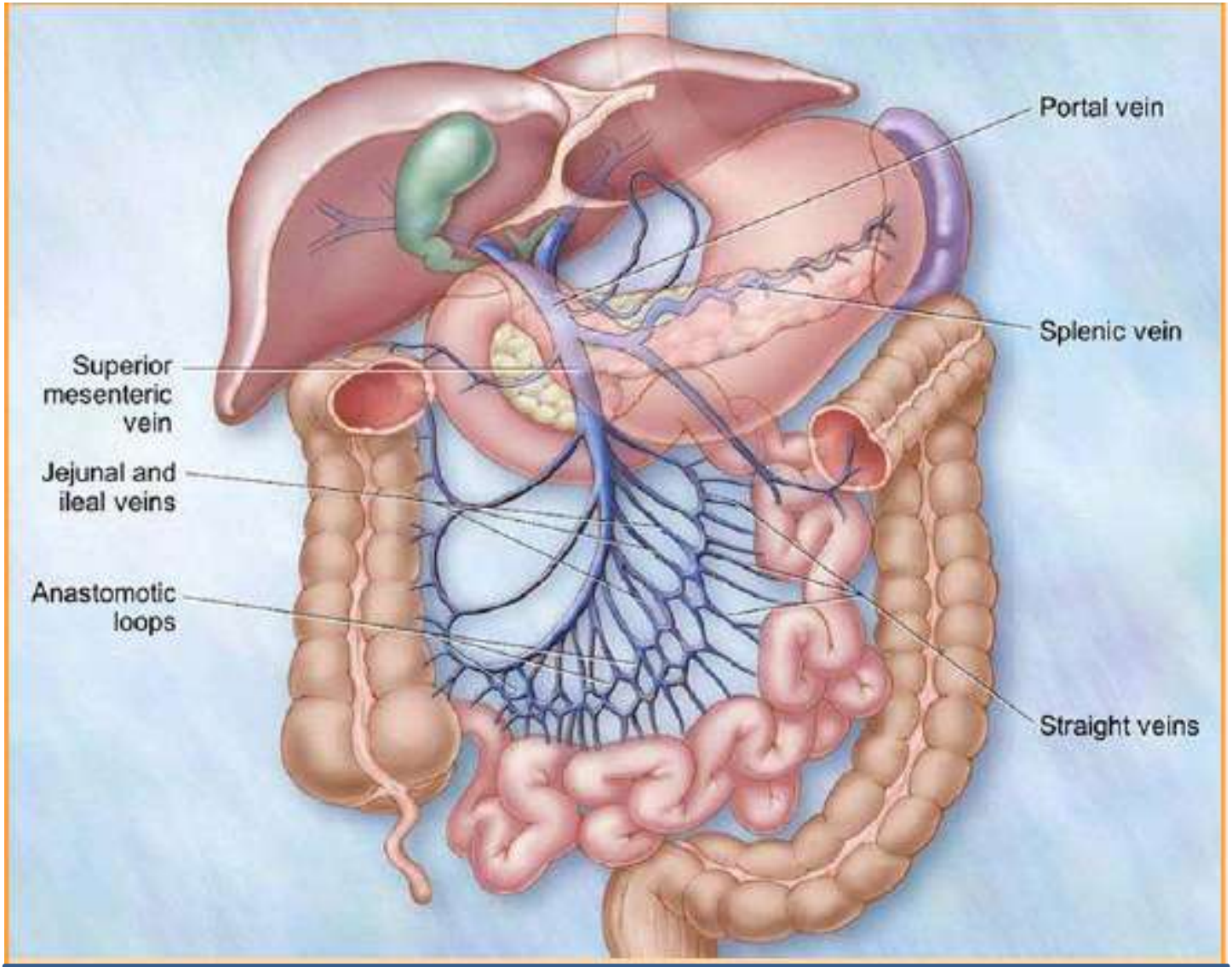
Thrombotic occlusion of the placental circulation



In MPN pregnancies **the prothrombotic state may affect the remodeling of maternal spiral arteries** essential for adequate blood volume delivery to the placenta.

If remodeling of the maternal spiral arteries is impaired by **microthrombi leading to impaired blood delivery, the resultant placental hypoperfusion** may form the basis of the abnormal fetal-maternal interaction and increase the risk of preeclampsia and growth restriction in MPN pregnancies.

Rare Thrombosis in MPN: Splanchnic vein thrombosis



SVT-DIFFICULTIES TO MEET WHO CRITERIA FOR MPN

- ✓ hemodilution
- ✓ occult bleeding
- ✓ hypersplenism related to portal hypertension
- ✓ possible elevation of Epo in BCS (liver ischemia)

NEW DRUGS?

“Resolution of esophageal varices in myelofibrosis during Ruxolitinib therapy : a case report”

Koschmieder , N Engl J Med. 2012

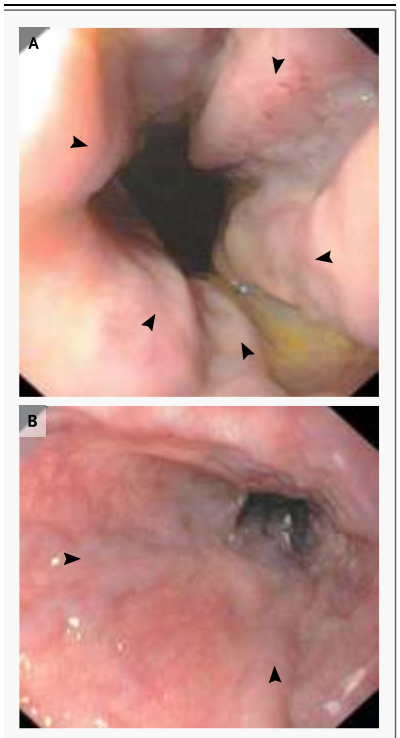


Figure 1. Esophageal Varices.
Endoscopy showed large (>5 mm) esophageal varices (arrowheads) before the initiation of ruxolitinib therapy (Panel A) and smaller (<3 mm) varices (arrowheads) 1 year after the initiation of ruxolitinib therapy (Panel B).

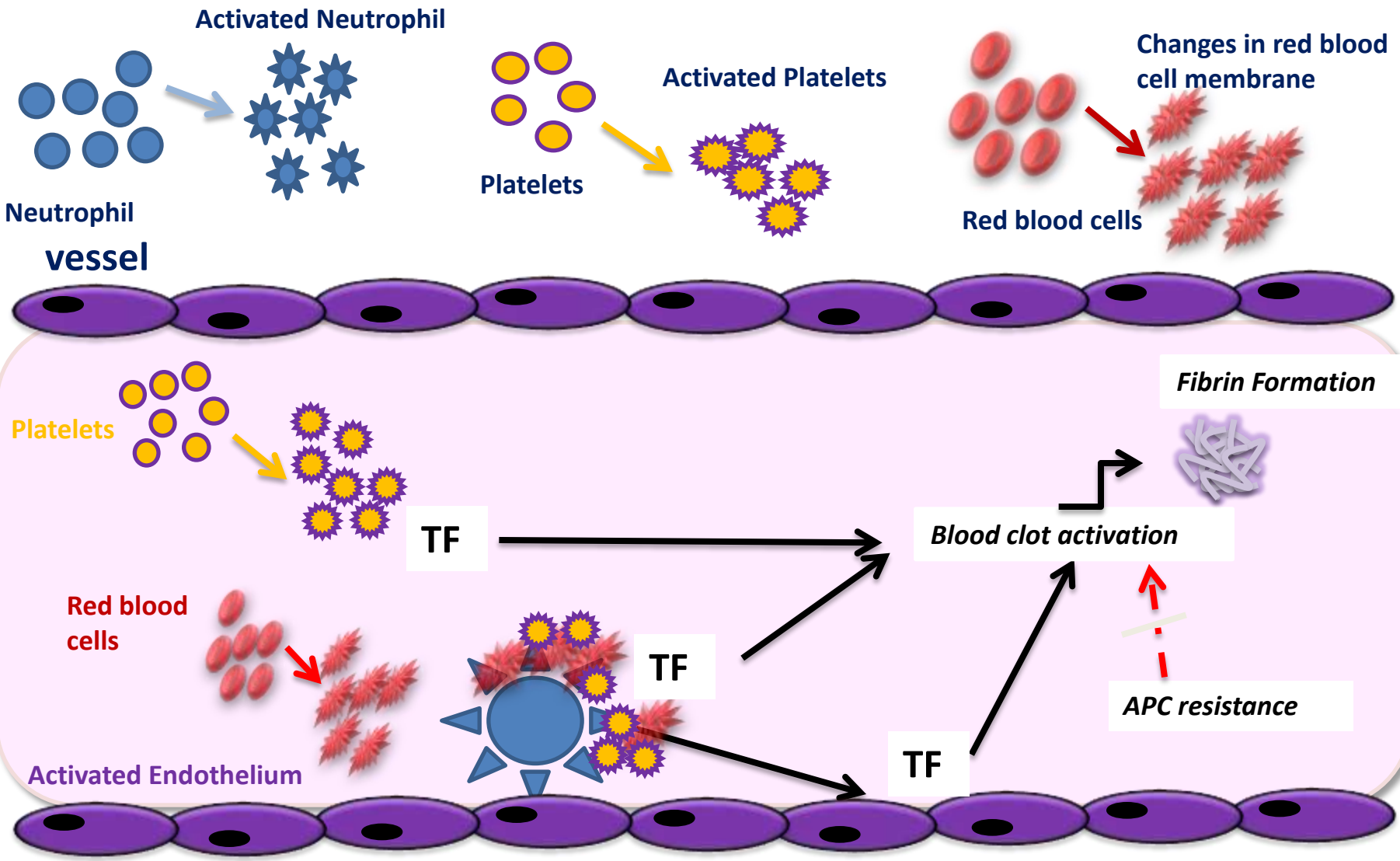
- Gastrointestinal bleeding 13 days after starting of Ruxolitinib due to esophageal varices, with one reoccurrence after 28 days.
- Treated with cyanoacrylate injections and ligations.
- Spleen reduction if 42%.
- No other episodes of bleeding or needs of banding in the subsequent two years of therapy with Ruxolitinib

Pathogenesis of Thrombosis in MPN

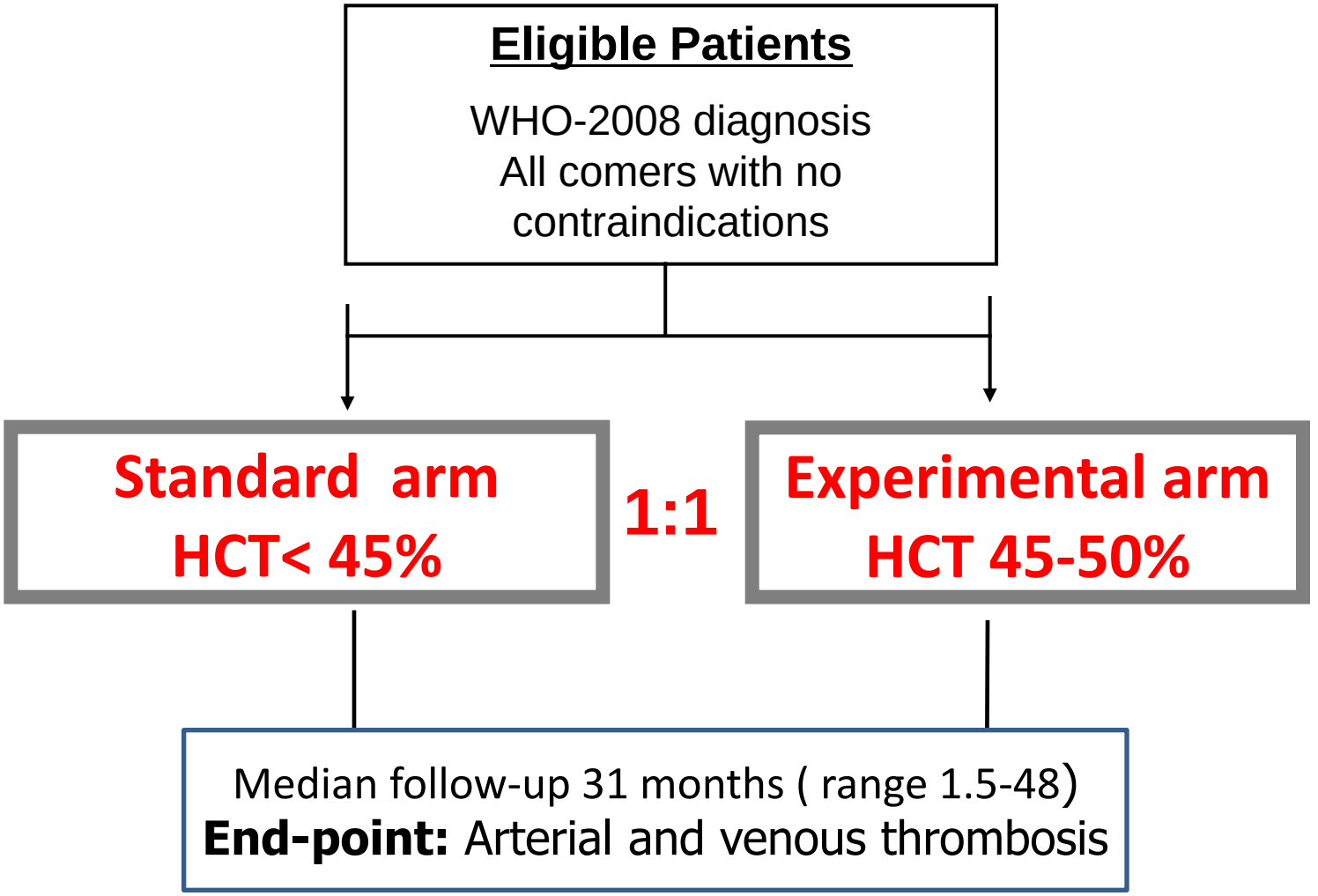
- Activation of the vascular endothelium
- Procoagulant changes in plasma proteins
- Quantitative and qualitative abnormalities of blood cells

Barbui, Finazzi, Falanga. Blood 2013; 122:2176

Pathogenesis of Thrombophilia in MPN



Barbui, Finazzi, Falanga. Blood 2013; 122:2176


Eligible Patients
WHO-2008 diagnosis
All comers with no contraindications
Standard arm
HCT< 45%
1:1
Experimental arm
HCT 45-50%
Median follow-up 31 months (range 1.5-48)
End-point: Arterial and venous thrombosis

NEJM 2013

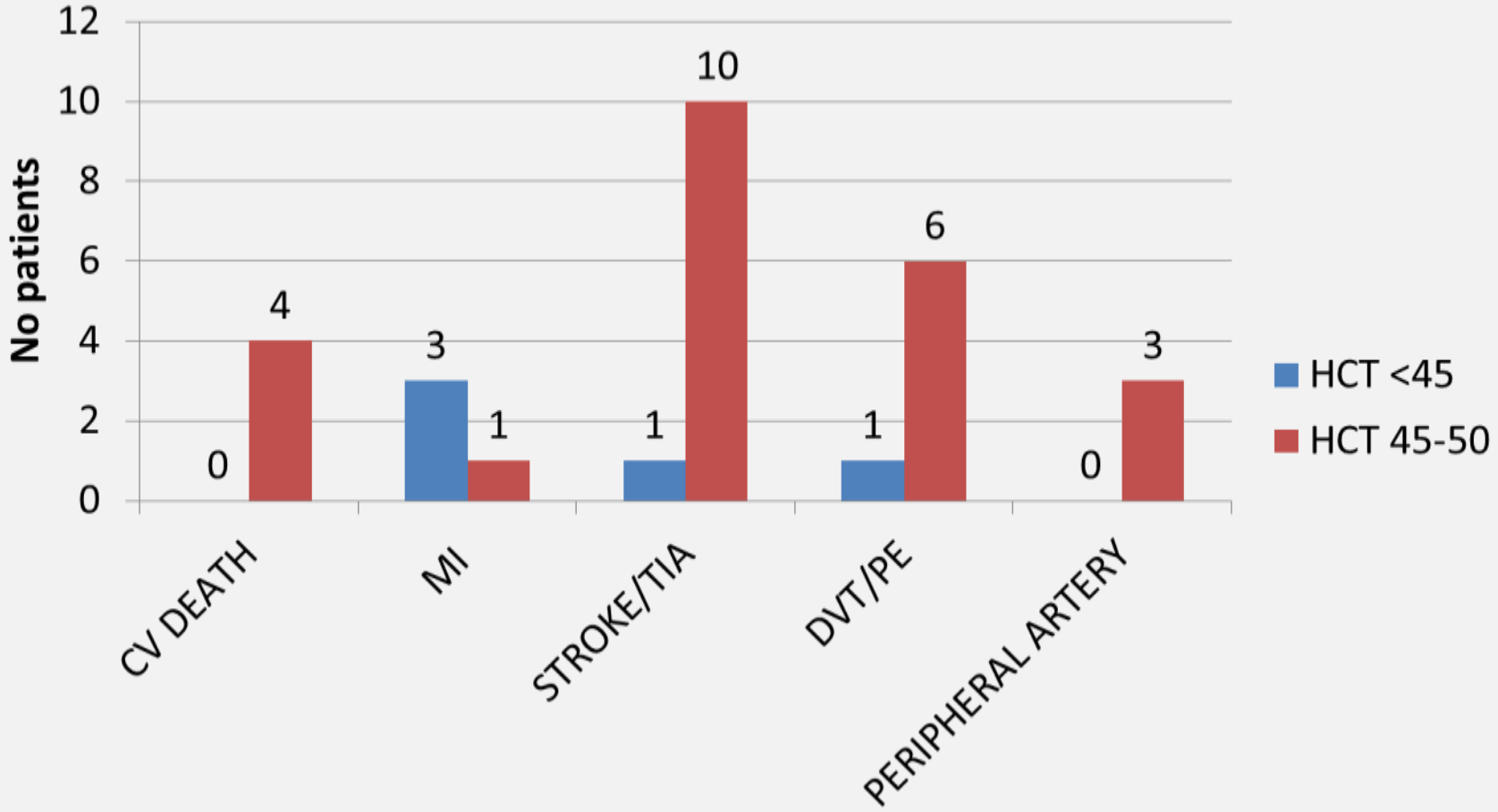
Primary EndPoint

	HCT <45% N=182 (49.9)	HCT 45-50% N=183 (50.1)	Total N=365	HR (95%CI)	P
Primary Endpoint (n, %) (CV death, MI, stroke, PAT, DVT, PE, TIA and abdominal thrombosis)	**5* (2.8)**	**18* (9.8)**	**23 (6.3)**	**3.91 (1.45-10.53)**	**0.005**
IR %person/year	**1.1**	**4.4**	**2.7**		
Total CV events (n, %) (Primary plus superficial vein thrombosis)	**8 (4.4)**	**20 (10.9)**	**28 (7.7)**	**2.69 (1.19-6.12)**	**0.012**
IR %person/year	**1.9**	**5.0**	**3.4**		

* 0 deaths in HCT<45%; 4 deaths in HCT 45-50%

NEJM 2013

CV Death and Major Thrombosis



NEJM 2013

CYTO-PV Vs ECLAP: Event during FUP

(censored events at Cyto-PV maximum time Fup)

	CYTO-PV		ECLAP: Censored Events at 3.5 Years	
	N (%)	**IR (100 person/yrs)**	**N (%)**	**IR (100 person/yrs)**
Primary Endpoint (CV death, MI, stroke, PAT, DVT, PE, TIA and abdominal thrombosis)	14 (3.8)	**2.4**	165 (10.1)	**4.2**
Total CV events (Primary Endpoint plus superficial thrombosis)	19 (5.2)	**3.2**	215 (13.1)	**5.6**

Barbui et al, ASH 2013

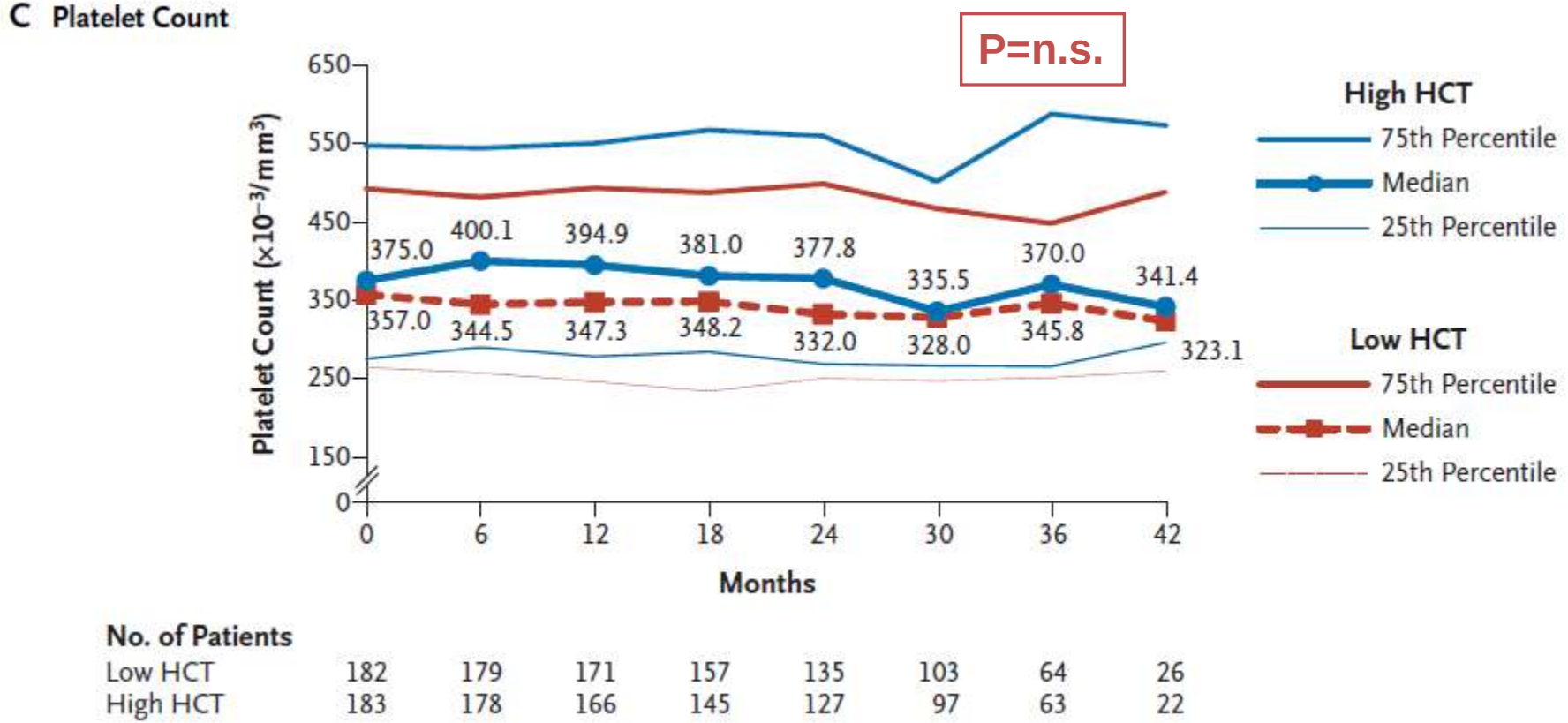
CYTO-PV Vs ECLAP: distribution of patient at inclusion by RISK (age and previous thrombosis)

Total CV events in follow-up by risk group

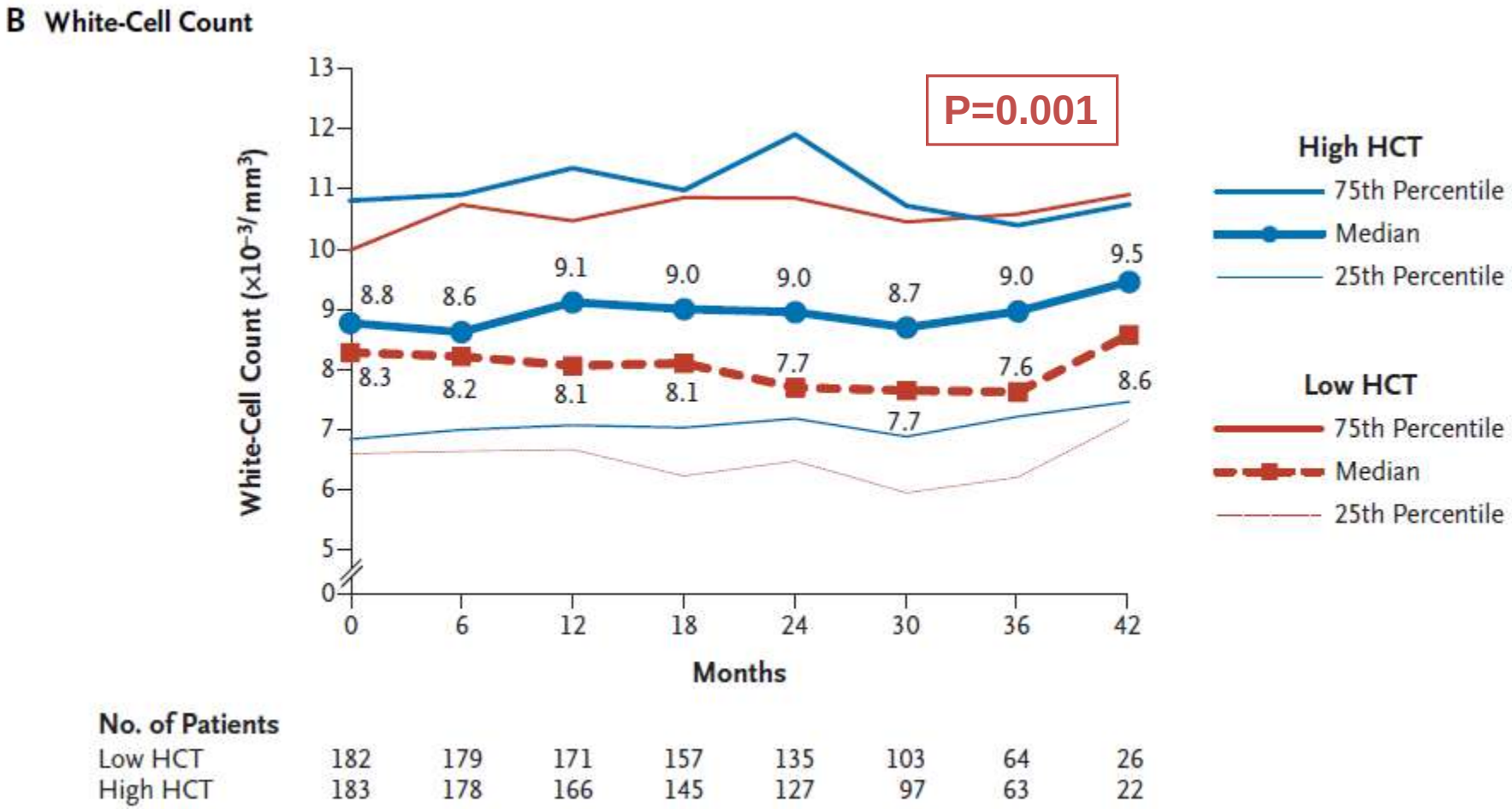
(CV death, MI, stroke, PAT, DVT, PE, TIA, abdominal and superficial thrombosis)

	No Previous Thrombosis		Previous Thrombosis		Overall
	Age <65	Age ≥65	Age <65	Age ≥65	
CYTO-PV IR per 100 person/yrs	**2.0**	**4.4**	3.8	**2.9**	**3.2**
ECLAP IR per 100 person/yrs	**2.5**	**4.9**	5.0	**10.9**	**5.5**

PLATELET COUNT DURING THE STUDY



WHITE-CELL COUNT DURING THE STUDY



Time-dependent multivariable analysis on the risk of major thrombosis in CYTO-PV study (N = 365)

WBC (109/L)	Events/Pts (%)	HR (95% CI)	P-Value
< 6.0	2/54 (3.7)	1	(reference)
6.0-12	15/237 (6.3)	2.39 (0.5-10.8)	0.26
>12	**11/74 (14.9)**	**4.89 (1.1-22.7)**	**0.04**

Barbui et al, ASH 2013

Time-dependent multivariate analysis on the relative risk of major thrombosis among men and women with Polycythemia Vera (N = 1,638)*

		Hazard ratio (95% CI), P-value
White blood cell count ($x10^9$/l)	≤ 10 (N=990)	1 (Reference)
	10.1-15 (N=365)	1.06 (0.7-1.6), 0.8
	> 15 (N=241)	**1.71 (1.1-2.6), 0.02**

*Model adjusted for: age, gender, time from PV diagnosis to recruitment, thrombotic or hemorrhagic events prior to recruitment, smoking, history of diabetes, hypertension, claudicatio intermittens, erythromelalgia, splenomegaly, circulating immature cells, leukocyte count, total blood cholesterol, phlebotomy use, interferon use, hydroxyurea use, antiplatelets use, anticoagulants use, ^{32}P use, busulfan use, chlorambucil use, and pipobroman use

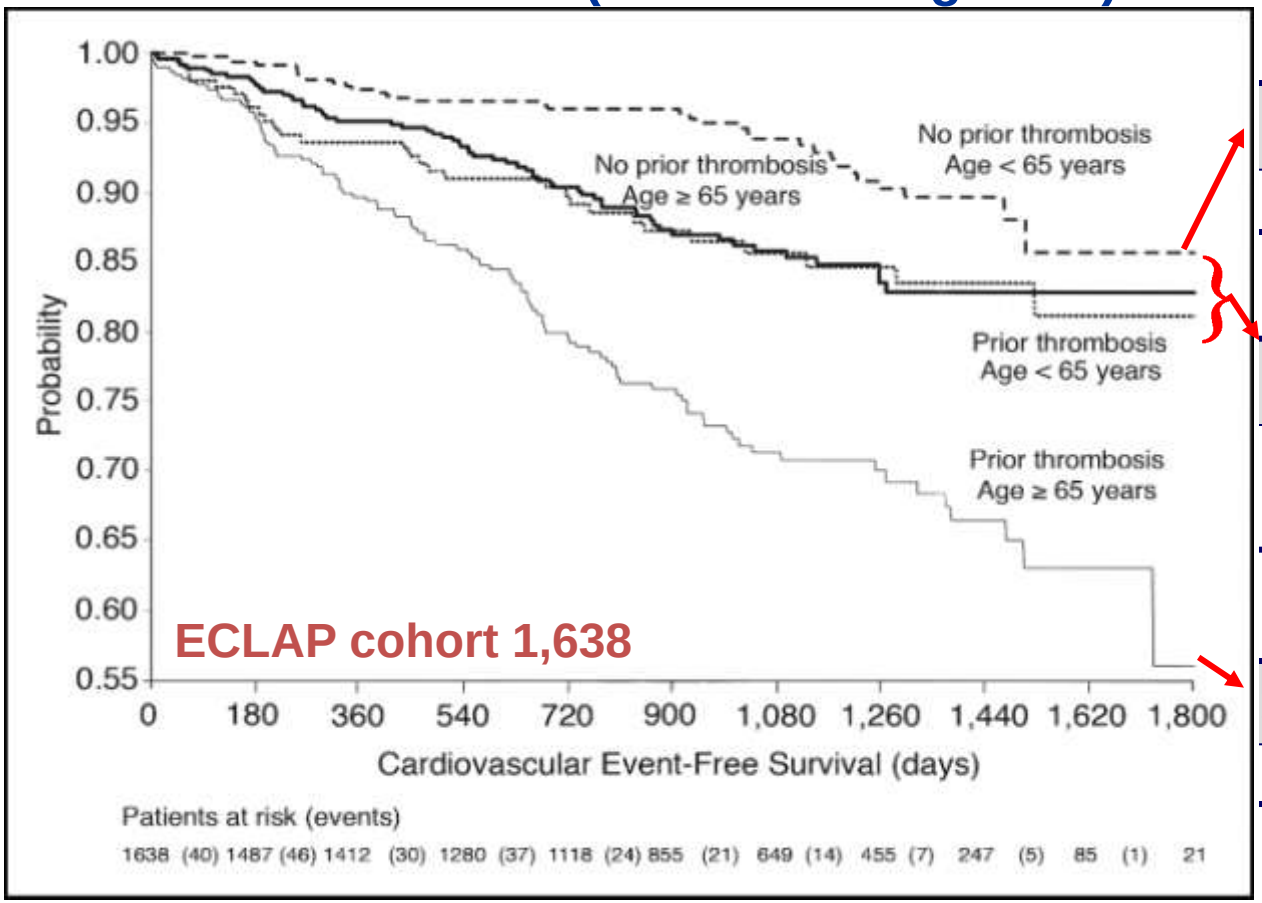
Landolfi et al., Blood 2006

Prognostic studies may change over time

- **diagnosis** (PVSG,WHO-2008,WHO 2014)
- **biomarkers**

Risk Factors for Thrombosis in ECLAP-study

(PVSG-PV diagnosis)



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 et al, 23:2224-2232, 2005

Leukemia (2014), 1–7

www.nature.com/leu

REVIEW

An overview on *CALR* and *CSF3R* mutations and a proposal for revision of WHO diagnostic criteria for myeloproliferative neoplasms

A Tefferi[1], J Thiele[2], AM Vannucchi[3] and T Barbui[4]

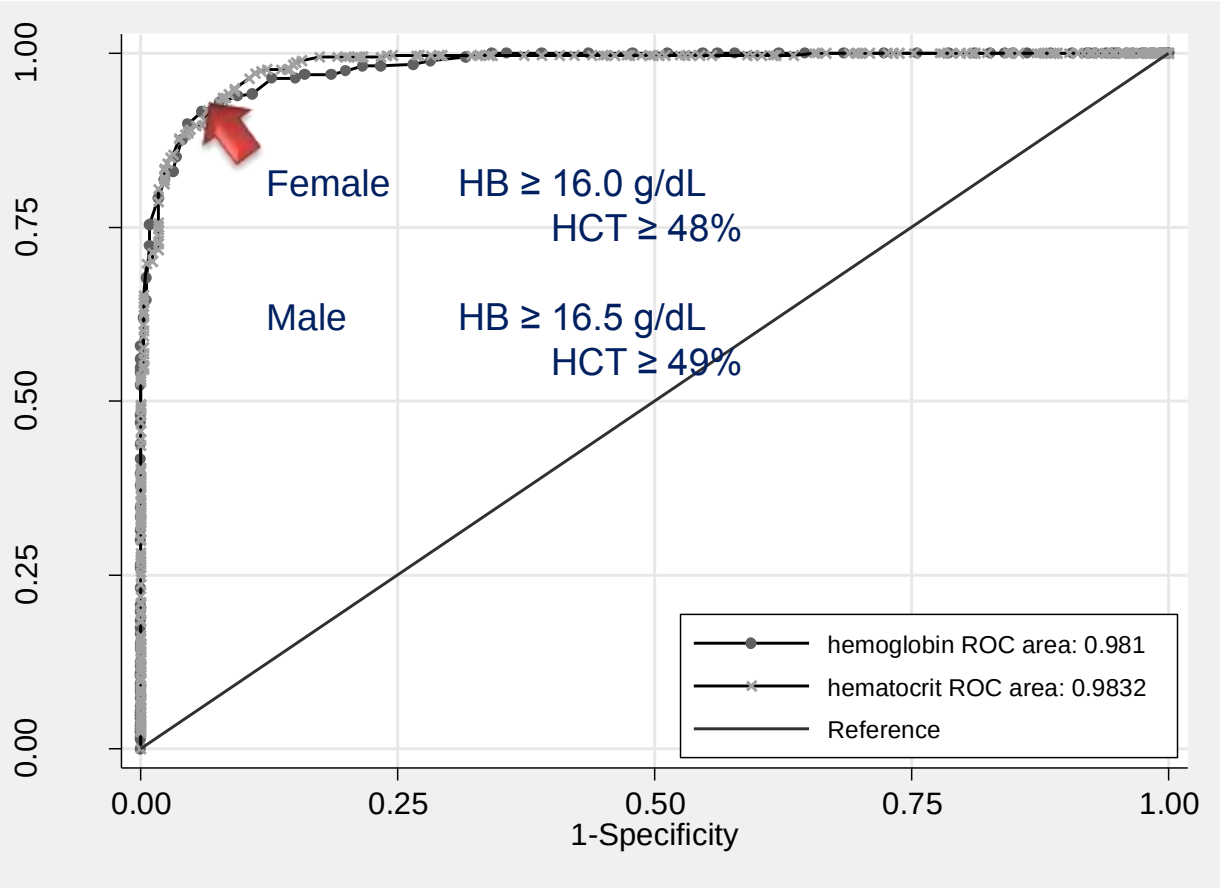
Proposal: Hb/Hct values should be lowered in JAK2 mutated patients for the diagnosis of PV

Among 397 patients JAK2 mutated and with bone marrow morphology consistent with WHO-PV

- **257 (65%)** met the full WHO-2008 criteria.

- **140 (35%)** were classified and treated as PV, although they did not meet the hemoglobin level threshold that is required for the diagnosis of WHO-defined PV. **These patients were operationally defined as «masked PV».**

Discriminating between ET and PV in JAK2V617F patients ROC curves of hemoglobin and hematocrit

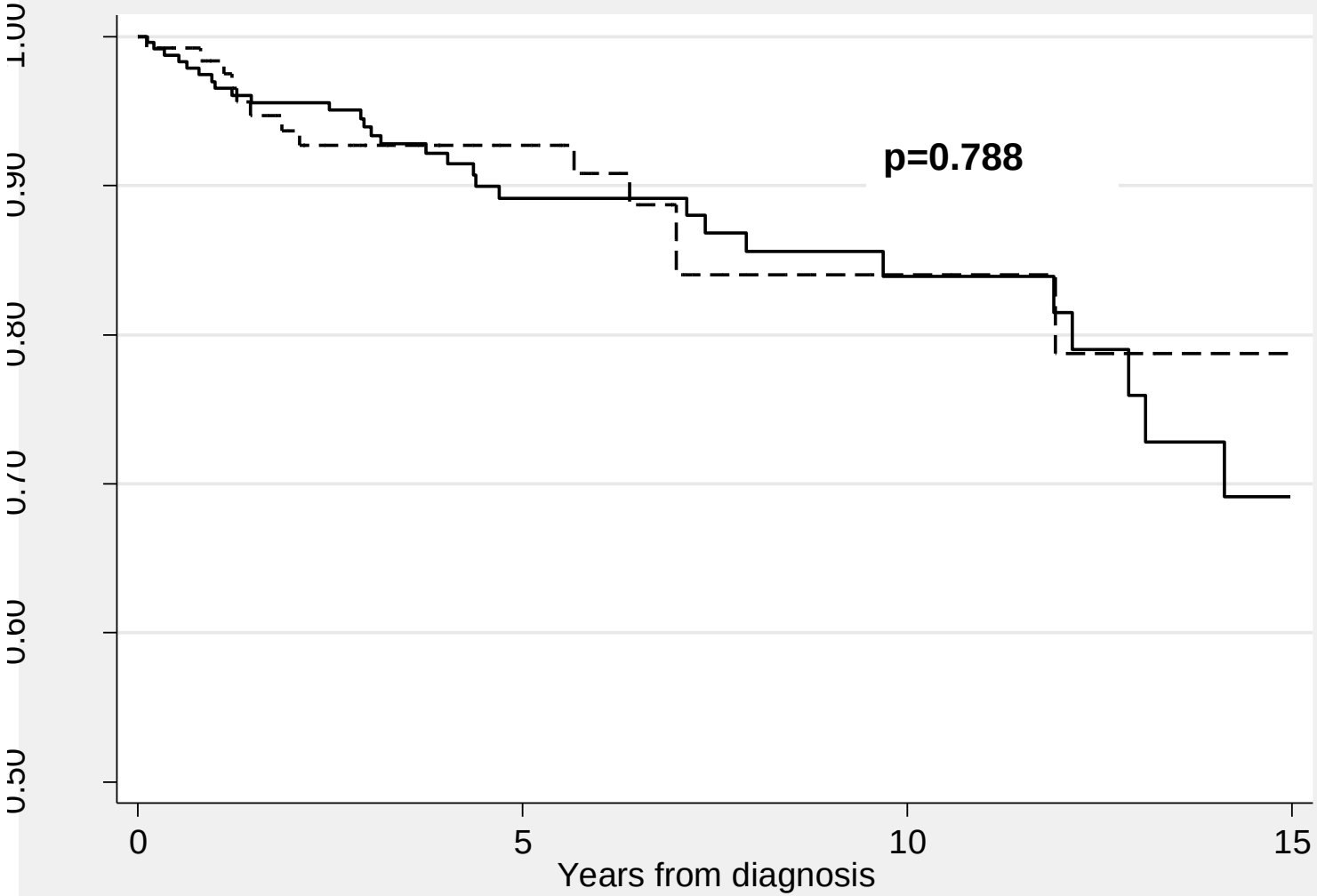


	Obs	ROC Area	Std. Err.	Asymptotic Normal [95% Conf.	Interval]
hemoglobin	745	0.9810	0.0036	0.97384	0.98807
hematocrit	745	0.9832	0.0036	0.97622	0.99019

Ho: area(hemoglobin) = area(hematocrit)
chi2(1) = 0.57 Prob>chi2 = 0.4499

*Barbui T et al, AJH 2014

Thrombosis-free survival in masked and overt PV



Barbui et al, AJH 89:52-54,2013

Multivariate analysis on the relative risk of major thrombosis among patients with masked (n=66) and overt (n=97) PV

Cox model testing mPV versus overt PV	HR (95% CI)	P-value
(0) Unadjusted	2.69 (1.15-3.14)	0.009
Sequentially adjusted		
(1) + Age, sex	2.03 (1.05-3.91)	0.035
(2) + Previous thrombosis	2.16 (1.12-4.15)	0.021
(3) + Cardiovascular risk factors	2.02 (1.03-3.94)	0.040
(4) + Treatments*	1.71 (0.88-3.64)	0.203

Model 0: Unadjusted model. Reference category: overt PV.
Model 1: age (2 categories), sex.
Model 2: model 1 plus thrombotic events at/or prior to diagnosis (yes/no).
Model 3: model 2 plus cardiovascular risk factors (yes/no).
Model 4: model 3 plus phlebotomy use (yes/no), cytoreductive therapy (yes/no), aspirin (yes/no).

2014 proposed revision for World Health Organization (WHO) Diagnostic Criteria for Polycythemia Vera

		Polycythemia Vera (PV)*
Major Criteria	1	Hemoglobin >16.5 g/dL (men) >16 g/dL (women **or** Hematocrit >49% (men) >48% (women)
	2	BM findings consistent with WHO criteria
	3	Presence of *JAK2* mutation
Minor criteria	1	Subnormal serum erythropoietin level

*PV diagnosis requires meeting either all three major criteria or the first two major criteria and one minor criterion.

Prognostic studies may change over time

- **diagnosis** (PVSG,WHO-2008,WHO 2014)
- **biomarkers** (JAK-2 allele burden and CALR in ET)

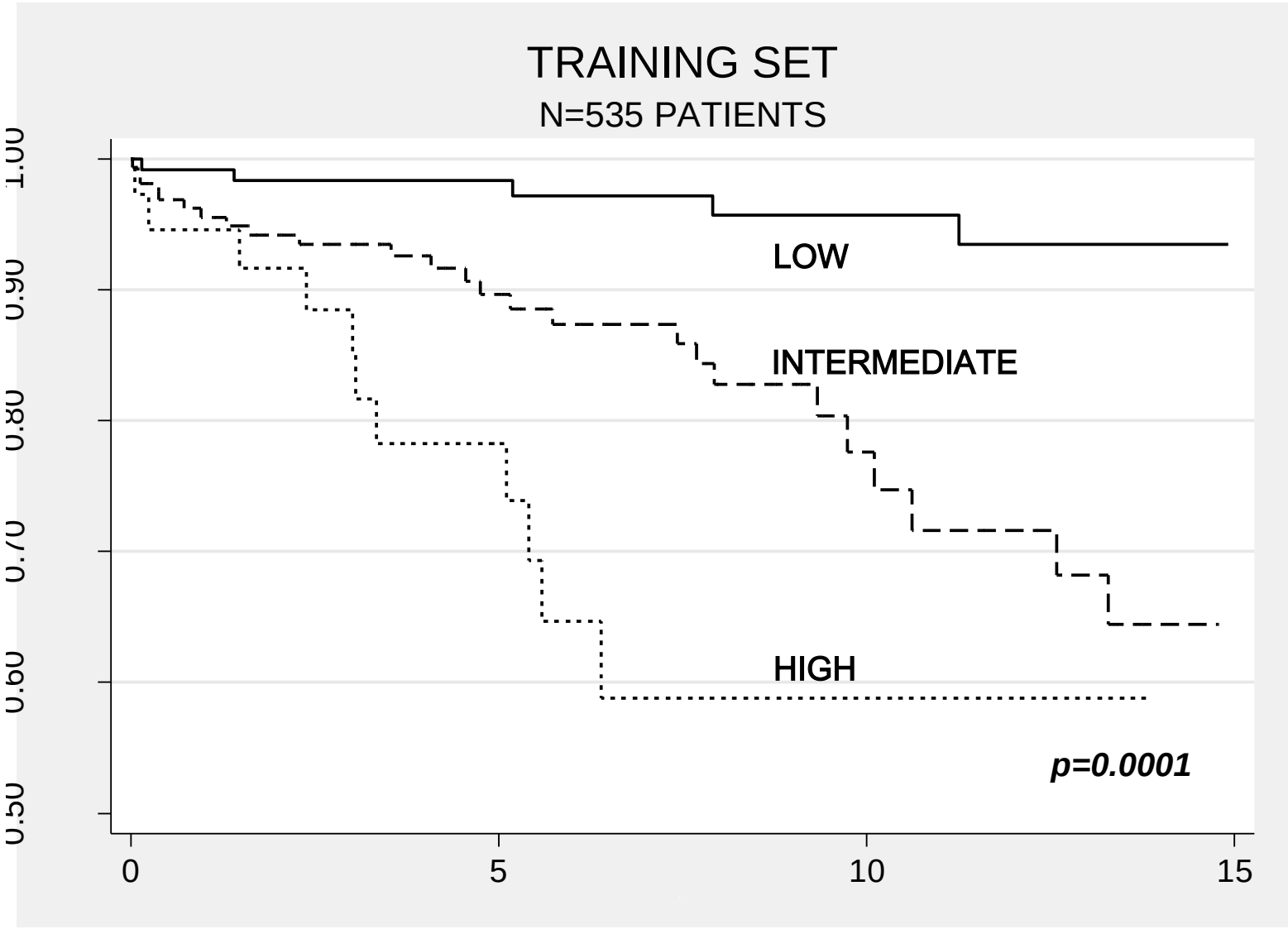
THROMBOSIS in WHO-ET (*inception cohort)*
(n= 891)

Risk factor	HR	scores
Age > 60	1.50	1
CV risk factors	1.56	1
Previous thrombosis	1.93	2
JAK2 V617F	2.04	2

* Multivariate model adjusted for: sex, hemoglobin ,leukocyte and platelet counts, Hydroxyurea and aspirin use.

Score: 0 low-risk
Score: 1-2 intermediate risk
Score => 3 high risk

Barbui et al, J Clin Oncol. 2011 Aug 10;29(23):3179-84; Barbui et al,Blood 2012.
Carobbio et al, Blood. 2011 Jun 2;117(22):5857-9. Epub 2011 Apr 13.



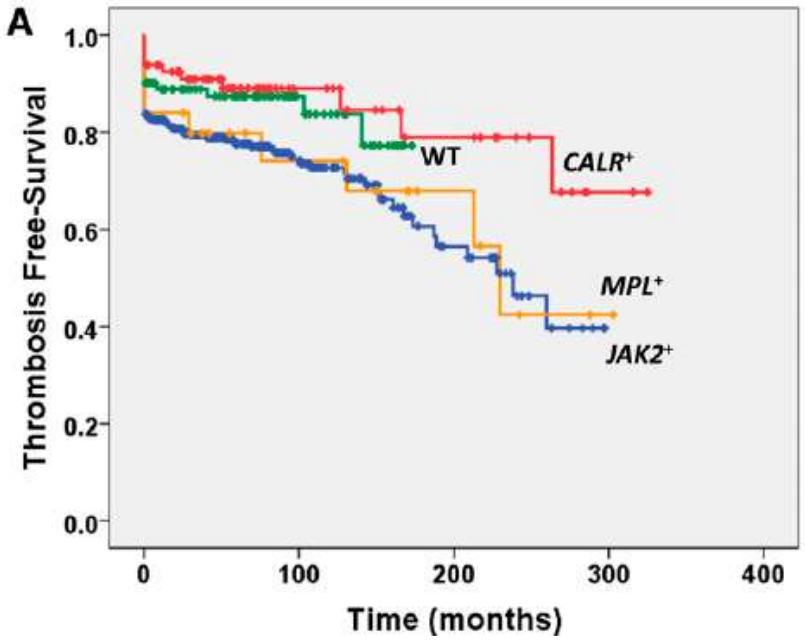
Barbui et al, Blood 2012

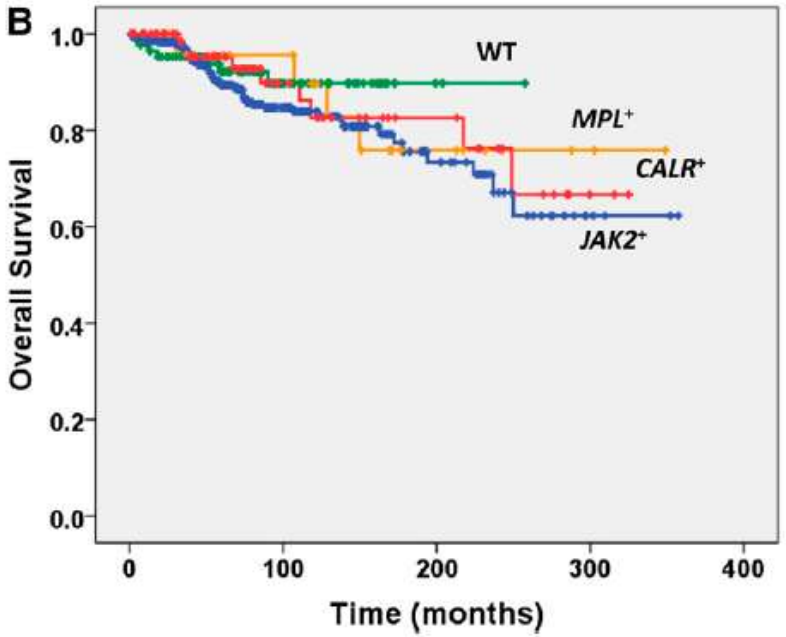
Distribution of thrombotic rates (n= 1220 patients) according to standard risk factors and the new IPSET-thrombosis model

IPSET-thrombosis / Standard Risk factors	LOW	INTERMEDIATE	HIGH	TOTAL
LOW	281 48% 0.59 %pts-yr	277 47% 1.55 %pts-yr	32 5% 1.77 %pts-yr	590 100% 0.95 %pts-yr
HIGH	193 31% 1.27 %pts-yr	194 31% 2.67 %pts-yr	243 39% 3.71 %pts-yr	630 100% 2.86 %pts-yr
TOTAL	474 39% 1.03 %pts-yr	471 39% 2.35 %pts-yr	275 23% 3.56 %pts-yr	1220 100% 1.77 %pts-yr

Age > 60 point 1 ; CV risk factors point 1; Previous thrombosis:point 2; JAK2 V617F point 2

Barbui et al, Blood 2012





blood
2014 123: 1552-1555
doi:10.1182/blood-2013-11-538983 originally published online December 26, 2013

Impact of calreticulin mutations on clinical and hematological phenotype and outcome in essential thrombocythemia

Giada Rotunno, Carmela Mannarelli, Paola Guglielmelli, Annalisa Pacilli, Alessandro Pancrazzi, Lisa Pieri, Tiziana Fanelli, Alberto Bosi and Alessandro M. Vannucchi

Overall, these data indicate that CALR patients are less prone to thrombotic events compared with JAK21 and MPL1; of note, their risk was similar to patients lacking any mutations.

ESH EUROPEAN SCHOOL OF HAEMATOLOGY

6th INTERNATIONAL CONFERENCE ON MYELOPROLIFERATIVE NEOPLASMS

Estoril, Portugal

October 23-25, 2014

Chairs: T. Barbui, A.R. Green, R. Levine, H.L. Pahl, R. Skoda, W. Vainchenker, A. Vannucchi

Topics:
- The genomics and genetics of MPNs
- Molecular and cellular pathogenesis of MPNs
- Diagnosis, classification and molecular monitoring
- Jak2 Inhibitors and novel therapies in MPN

To register and for further information: www.esh.org