



Azienda
Ospedaliero
Universitaria
Careggi



**Settima
Giornata Fiorentina
dedicata ai pazienti con
malattie mieloproliferative
croniche**

Sabato 13 maggio 2017

CRIMM

Centro di Ricerca e Innovazione
per le Malattie Mieloproliferative
AOU Careggi



 **Policitemia vera**

Trombosi
(T. Barbui)

AULA ROSSA
Moderatori:
M. Ruggeri, A.M. Vannucchi

Trombosi nei pazienti con PV(n=1,545)

International IWG-MRT

Age < 60 years
and no previous
thrombosis
n=604 (40%)

Age ≥ 60 years
and/or previous
thrombosis
N=941 (60%)

Annual Rate 2.08 %

Stroke/TIA:	40 (32%)
IMA:	13 (10%)
PAT:	13 (10%)
DVT/PE:	28 (22%)
Splanchnic:	16 (13%)
Other/Unk:	16 (13%)

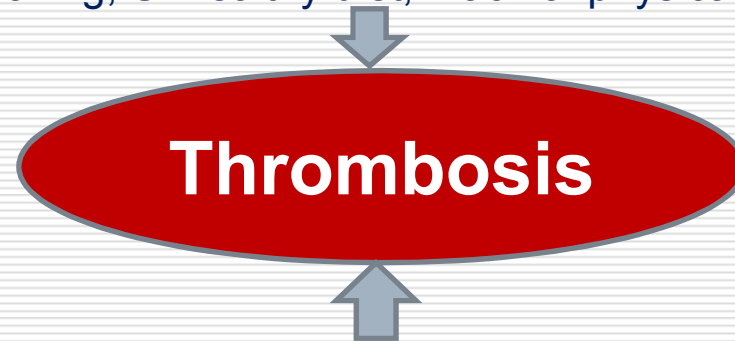
Annual Rate 3.14%

Stroke/TIA:	64 (33%)
IMA:	22 (11%)
PAT:	21 (11%)
DVT/PE:	60 (31%)
Splanchnic:	11 (6%)
Other/Unk:	17 (9%)

Come ridurre gli eventi vascolari nella PV

Fattori di rischio generali

Obesity Diabetes **Hypertension** Hyperlipidemia
Smoking, Unhealthy diet, Lack of physical activity



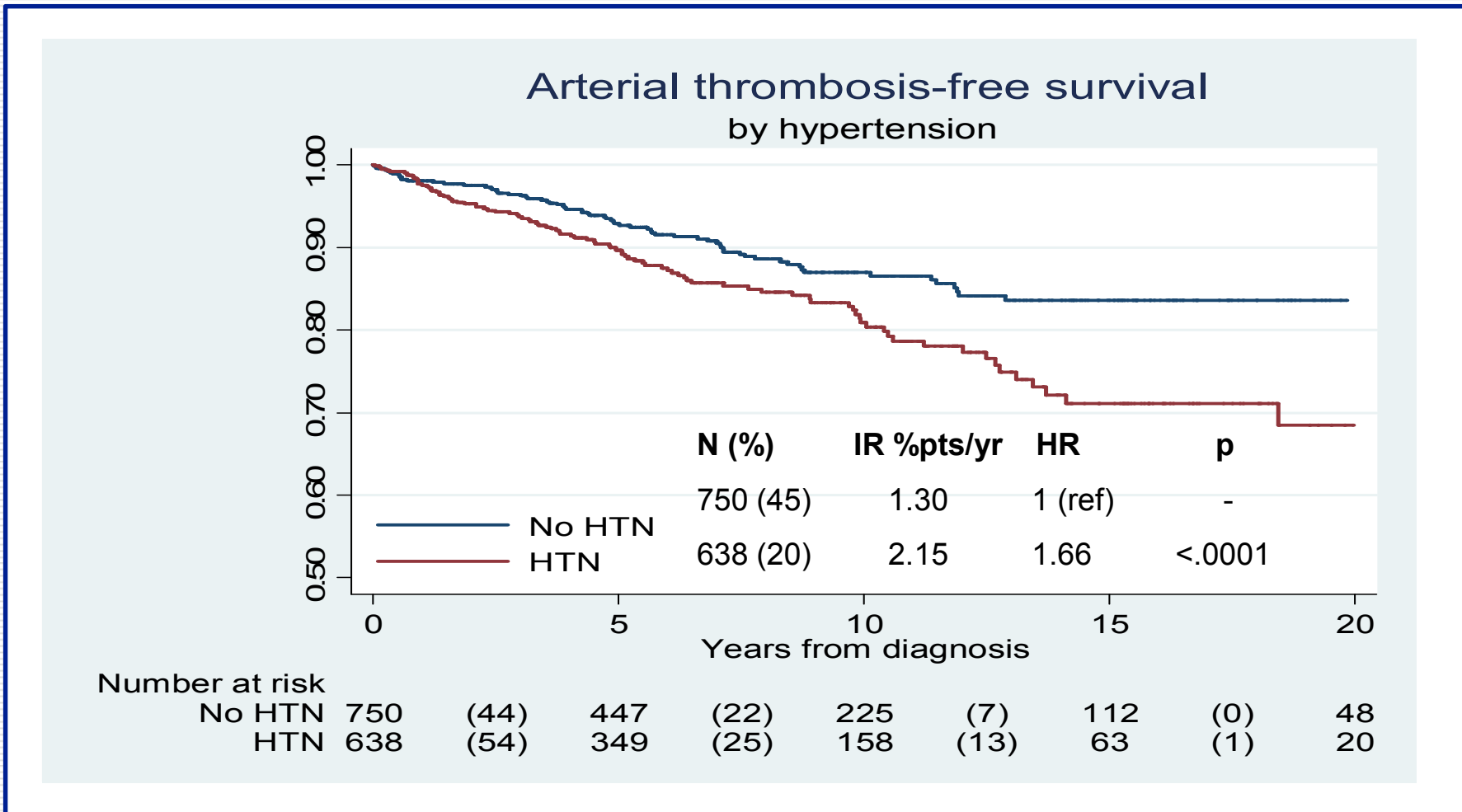
Fattori di rischio legati alla malattia

Hyperviscosity, Leukocyte and platelet abnormalities
Inflammation, Mutational status

Quali sono le condizioni di maggior rischio di trombosi nella PV (n=1545)

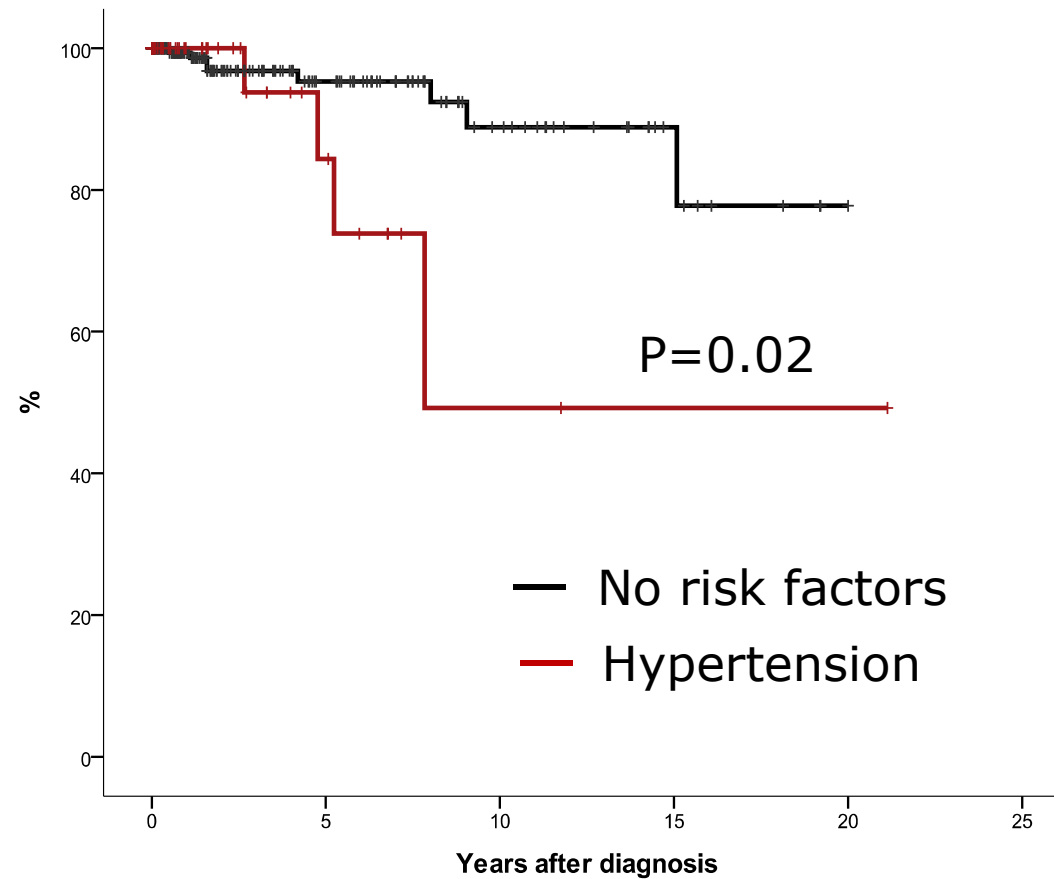
	Additional risk factors	N (%)	# Event	Inc. Rate % pts/yr (95% CI)	P-value
Low risk		604 (40)			
	None	274 (45)	43	1.69 (1.25-2.28)	ref
	+age 50-60	67 (11)	14	2.23 (1.32-3.76)	0.178
	+Hypertension	113 (19)	23	2.36 (1.57-3.55)	0.046
	+Both	150 (25)	31	2.60 (1.83-3.69)	0.002
Highrisk		941 (60)			
	None	443 (47)	68	2.40 (1.89-3.05)	ref
	+Hypertension	434 (46)	91	3.65 (2.97-4.48)	0.013
	+WBC > 20 x10 ⁹ /L	40 (4)	13	5.35 (3.11-9.21)	0.009
	+Both	24 (3)	6	5.70 (2.56-12.7)	0.005

Uno dei fattori di rischio per trombosi nella PV è l'ipertensione arteriosa



*Validation in a Spanish cohort**

Time to thrombosis in 285 low risk patients managed with phlebotomies and aspirin



Come ridurre gli eventi vascolari nella PV

Fattori di rischio generali

Obesity Diabetes Hypertension Hyperlipidemia
Smoking, Unhealthy diet, Lack of physical activity



Thrombosis



Fattori di rischio legati alla malattia

Hyperviscosity, Leukocyte and platelet abnormalities
Inflammation, Mutational status

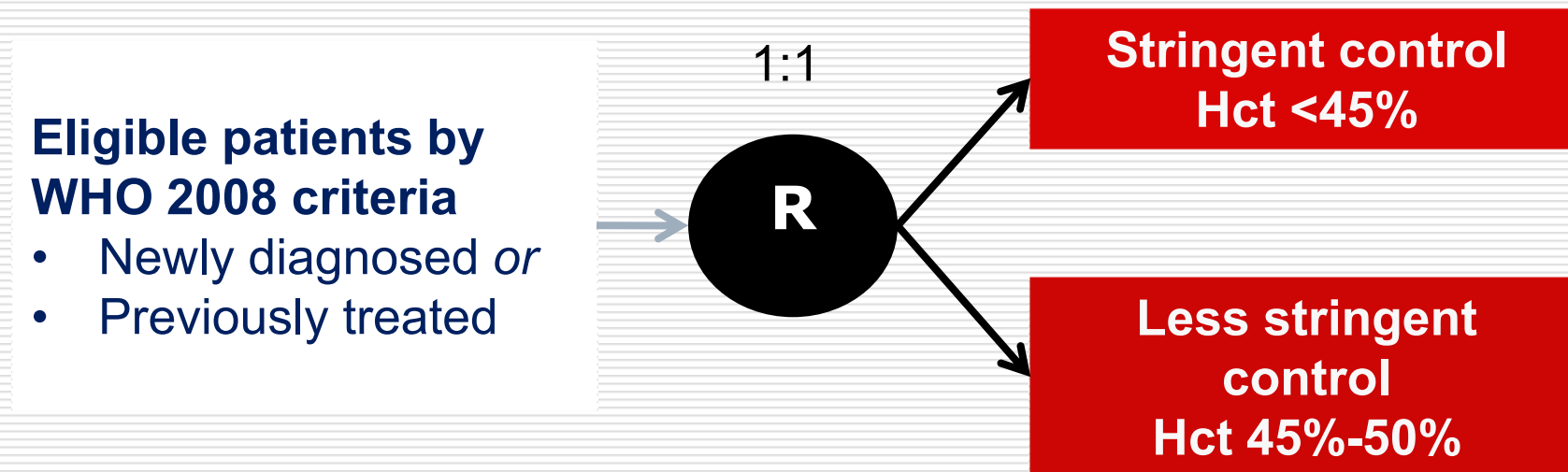
Ematocrito nella PV

ET



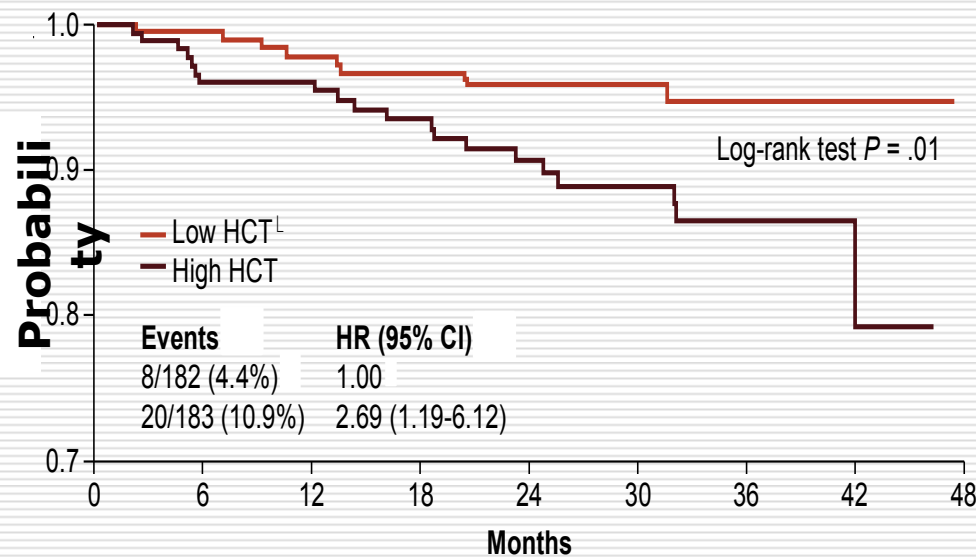
Cardiovascular Events and Intensity of Treatment in PV¹

CYTO-PV Collaborative Group Trial



Primary endpoint: time until death from CV causes or thrombotic events
Median follow-up: 31 months (range 1.5-48)

L'incidenza di trombosi venose e arteriose è diminuita se si mantiene un ematocrito inferiore a 45%



In patients with **hematocrit levels $\geq 45\%$** , the risk of CV-related **death or major thrombosis** was increased approximately **4 times** ($P = 0.007$) versus patients with hematocrit $< 45\%$ ¹

Low HCT	182	(1)	176	(3)	165	(2)	151	(1)	127	(0)	94	(1)	60	(0)	18	(0)	0
High HCT	183	(7)	167	(0)	159	(4)	141	(4)	108	(2)	91	(2)	53	(1)	11	(0)	0

Attenzione anche al numero di globuli bianchi e non solo all'ematocrito

Time-Dependent Multivariable Analysis on Risk of Major Thrombosis in CYTO-PV

- Subanalysis of CYTO-PV study (N = 365)
- WBC categorized into approximate quartiles and recorded in last clinical visit before the thrombotic event

^a Adjusted for age, gender, CV risk factors, previous thrombosis, and hematocrit levels.

WBC Class (x 10 ⁹ /L)	Events/ Patients (%)	HR (95% CI) <i>P</i>
<7.0	4/100 (4.0)	1.00
7.0-8.4	4/84 (4.8)	1.58 (0.39-6.43) .52
8.5-11.0	8/88 (9.1)	2.69 (0.80-9.05) .11
≥11.0	12/93 (12.9)	3.90 (1.24-12.3) .02

**Se anche i globuli bianchi sono importanti
per il rischio vascolare perché fare solo salassi
in combinazione con aspirina nei giovani asintomatici
con PV**

Annual rate of thrombosis in MPN and general population (% patients)

General population without risk factors*	0.6%
General population with multiple CV risk factors**	0.90 %
PV patients (n=1,545) §§	
Low-risk.....	2.08%
Highrisk.....	3.14%

* *Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant 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*

Low-PV

LOW-PV

Randomized Clinical Trial

RCT testing the benefit/risk profile of pegylated-proline-Interferon-alpha-2b (AOP2014) added to phlebotomy + low-dose aspirin in low-risk patients with WHO-Polycythemia Vera (PV)

ClinicalTrials.gov NCT03003325

Sponsor: Fondazione per la Ricerca Ospedale Maggiore (Bergamo, Italy)

Collaborator: AOP Orphan Pharmaceuticals

Centri Italiani :

**Bergamo, Milano, Verona, Vicenza, Cuneo, Novara,
Torino, Bologna, Firenze, Bari, Catania, Roma-Gemelli,**

Quali farmaci utilizzare negli alti rischi per ridurre l'incidenza di trombosi

PRIMA LINEA

- Idrossiurea
- Interferone
- Busulfano

SECONDA LINEA

- Ruxolitinib?
 - Studi nuovi Farmaci
 - Busulfano
-

CONCLUSIONE

La terapia viene somministrata per ridurre il rischio vascolare avendo cura di non aumentare altri rischi (leucemie, altri tumori)

Assess and address all vascular risk factors

Low Risk



- Phlebotomy
- LD-Asa (all)

High Risk



- Phlebotomy
- LD-Asa
- Cytoreduction
 - HU
 - IFN- α
- Anticoagulants (if prior venous event)
- Second line (IFN- α , HU or busulphan)
- Consider Ruxolitinib for resistant/refractory to conventional agents