Deciphering the paradigma of thrombosis in MPN

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AIRC

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Supported by an unrestricted education grant from Mary and Salomon Terner

April 16th 2011
Palazzo Vecchio, Florence

Jean Luc Villeval, Institut Gustave Roussy, Paris, France

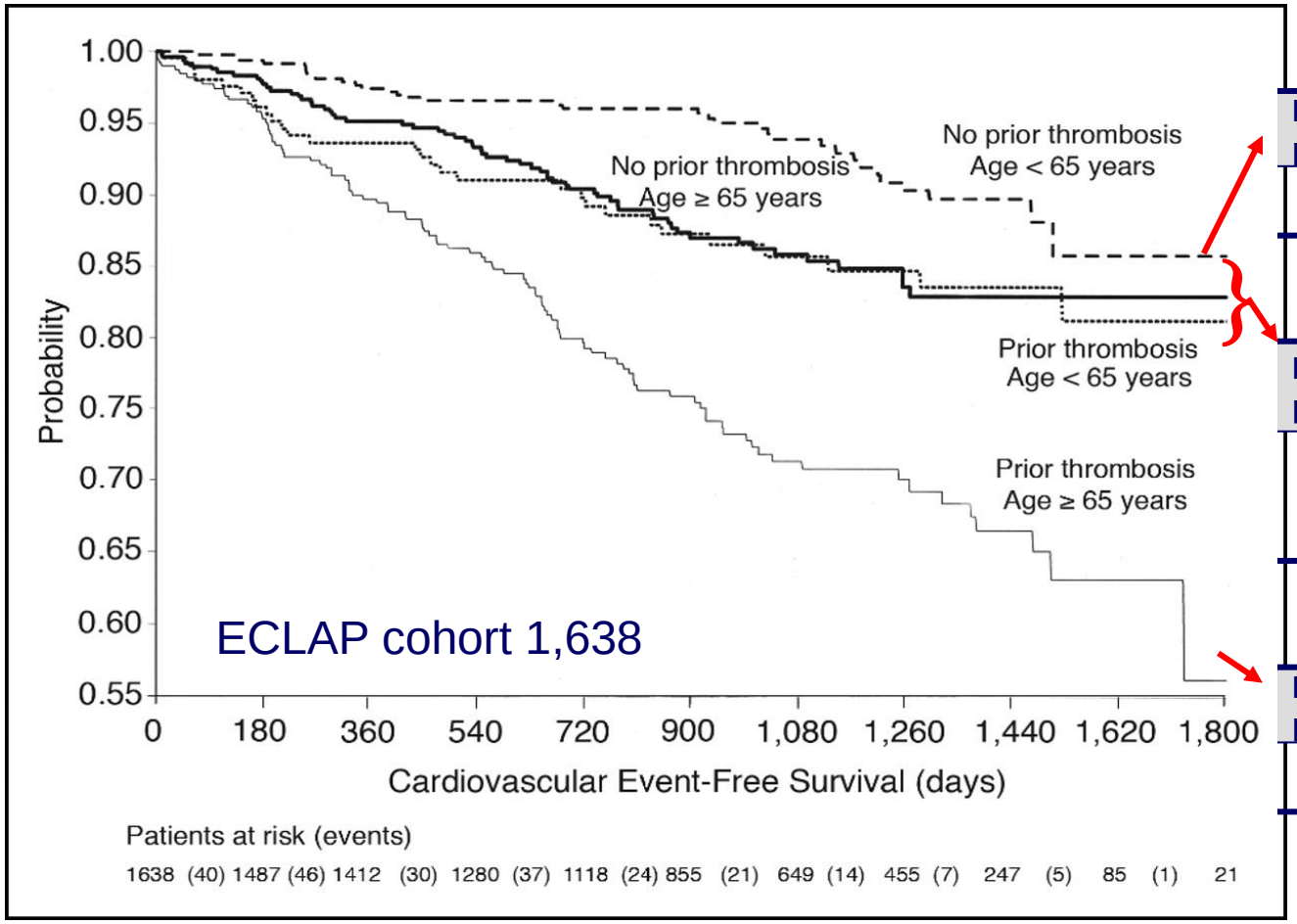
http://mpn-florence.com

Deciphering the paradigma of thrombosis in MPN

What is known

What should be done

PV: Major Vascular Events During Follow-up in ECLAP study



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 R et al., JCO 2005

Definition of “High-risk”:

risk of a serious vascular event

more than about 3% per annum

because of previous occlusive disease

or a predisposing condition

Antithrombotic Trialists’ Collaboration

Risk Factors for Thrombosis in ET: Age and History of Thrombosis

Events During Follow-up in BVF study

Low-risk *(n=517)*	***High risk*** *(n=546)*
(left untreated)	(100% treated)
Rate: 1.5 (%/patients/year)	2.0 (%/patients/year)

Carobbio A et al., Blood 2008

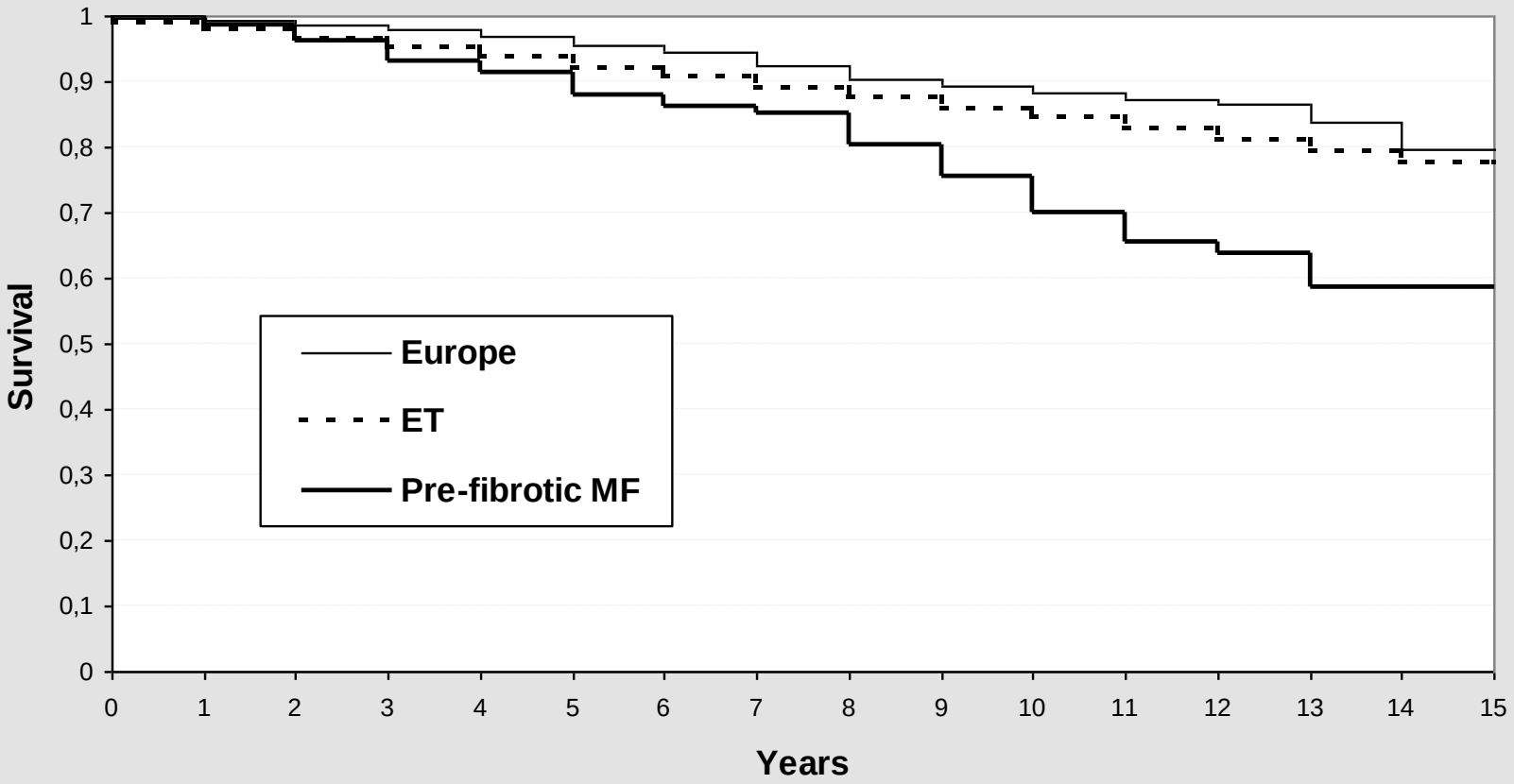
Main outcome events during follow-up in 891 strictly defined WHO-ET patients

	No	%	Rate, % patient-years (95% CI)
Patients with nonfatal thrombotic events	109	12	1.7 (1.4-2.1)
Arterial	79	9	1.2 (1.0-1.5)
AMI	17	2	0.26 (0.16-0.42)
Stroke-TIA	47	5	0.73 (0.54-0.97)
PAT	15	2	0.23 (0.14-0.38)
Venous (VTE)	37	4	0.6 (0.4-0.8)
Patients with fatal and nonfatal thrombotic events	**119**	13	**1.9 (1.6-2.3)**

Barbui et al, JCO 2011, Carobbio et al, Blood in press

ET and pre-fibrotic MF vs Europe*

Age- and sex-adjusted actuarial survival curves



*EUROSTAT 2008

(crude death rates, all causes of death, EU 27 countries)

Barbui T, Thiele J et al, JCO 2011

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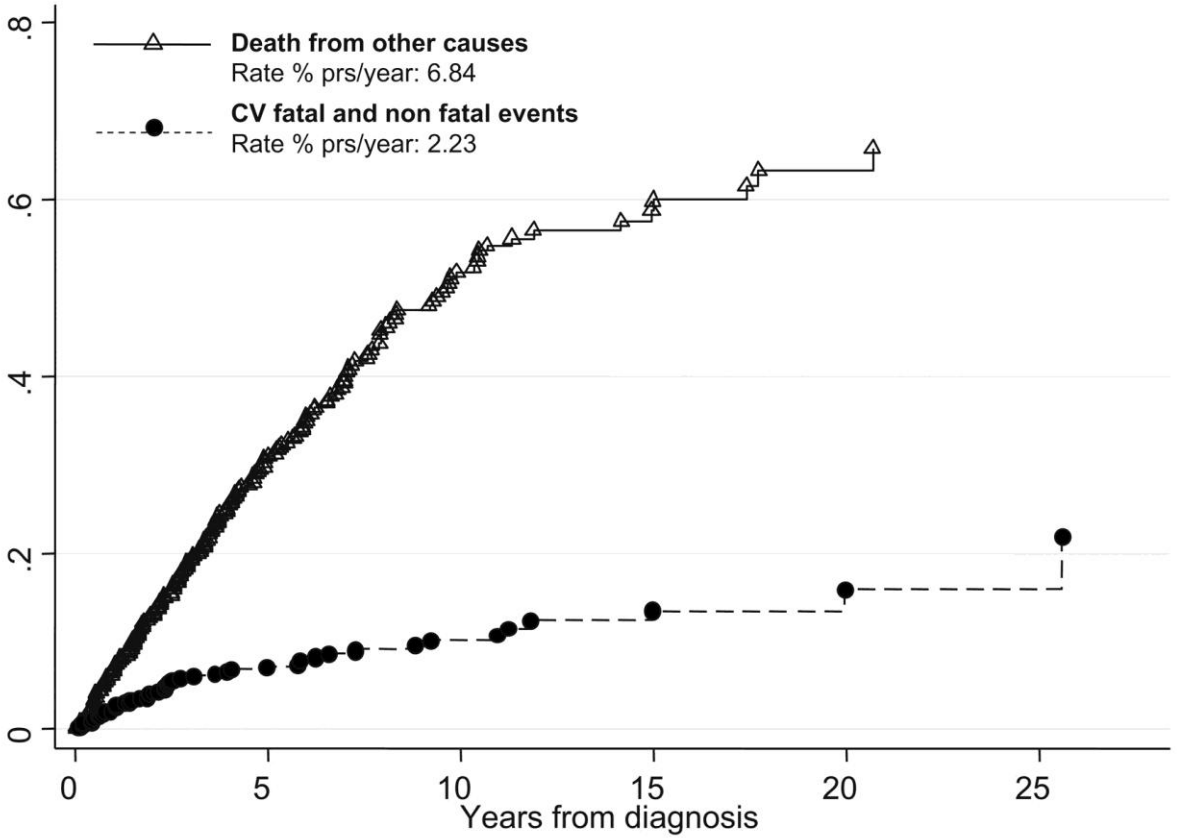
Figure 1 Cumulative incidence of fatal and nonfatal thrombotic events versus deaths from other causes (competing risk analysis) in 707 patients with primary myelofibrosis



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

Rate of incident thrombosis in MPN

PV…… 6% pts per year

ET…… 2 % pts per year

PMF…… 2 % pts per year

ELN European LeukemiaNet

Philadelphia–Negative Classical Myeloproliferative Neoplasms: Critical Concepts and Management Recommendations from European LeukemiaNet

Authors: *Tiziano Barbui, Giovanni Barosi, Gunnar Birgegard, Francisco Cervantes, Guido Finazzi, Martin Griesshammer, Claire Harrison, Hans Carl Hasselbalch, Rudiger Hehlmann,* ***Ronald Hoffman****, Jean-Jacques Kiladjian, Nicolaus Kröger,* ***Ruben Mesa****, Mary F. Mc Mullin,* ***Animesh Pardanani****, Francesco Passamonti, Alessandro M. Vannucchi, Andreas Reiter,* ***Richard T. Silver, Srdan Verstovsek, Ayalew Tefferi.***

Barbui et al, JCO 2011

Deciphering the paradigma of thrombosis in MPN

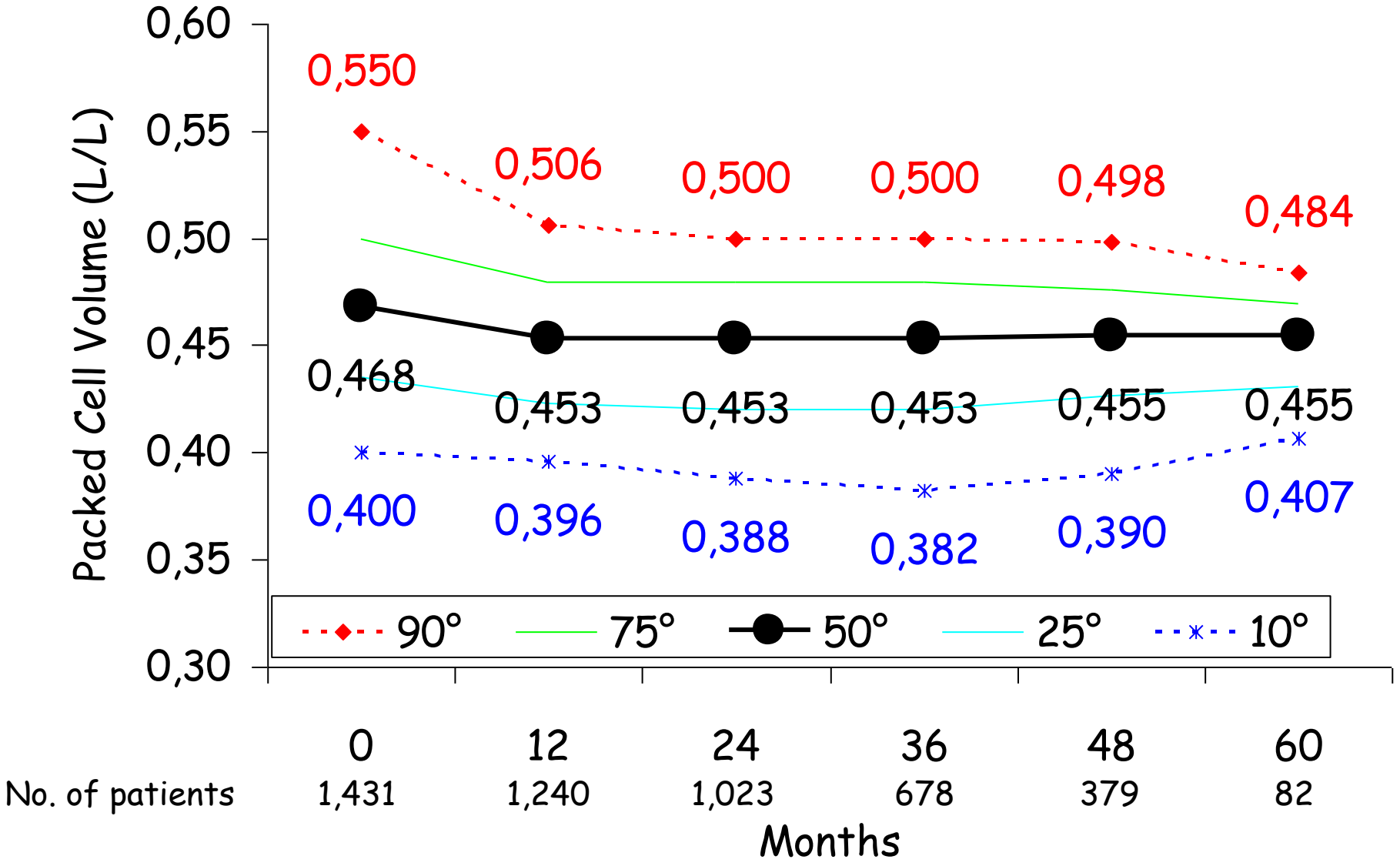
What is known

What should be done

HEMATOCRIT

< 45% ?

Hematocrit

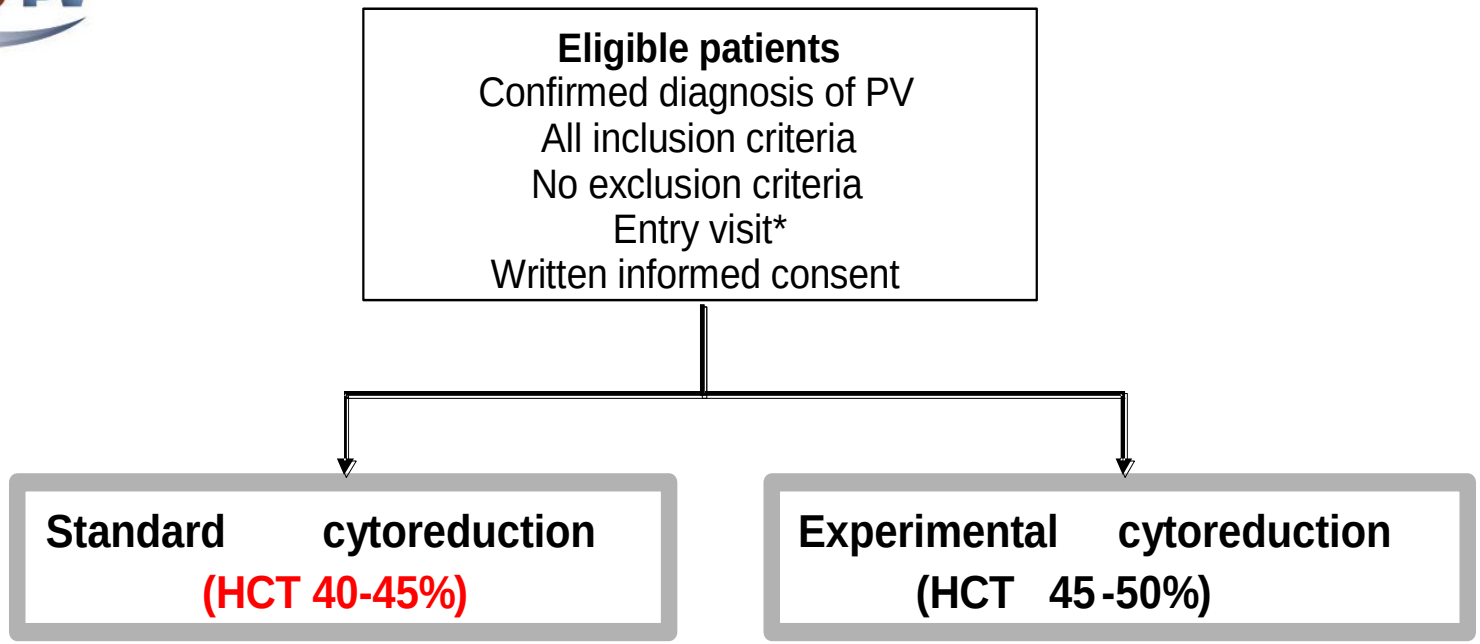

Packed Cell Volume (L/L)
0,60
0,55
0,50
0,45
0,40
0,35
0,30
0,550
0,506
0,500
0,500
0,498
0,484
0,468
0,453
0,453
0,453
0,455
0,455
0,400
0,396
0,388
0,382
0,390
0,407
90°
75°
50°
25°
10°
0
12
24
36
48
60
No. of patients
1,431
1,240
1,023
678
379
82
Months

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
Hematocrit (%)	≤ 45 (N=556)	1 (Reference)
	46-50 (N=530)	0.89 (0.6-1.3), 0.6
	> 50 (N=345)	1.04 (0.6-1.8), 0.9

*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

Di Nisio, Barbui T. et al., Brit J Haemat, 2006

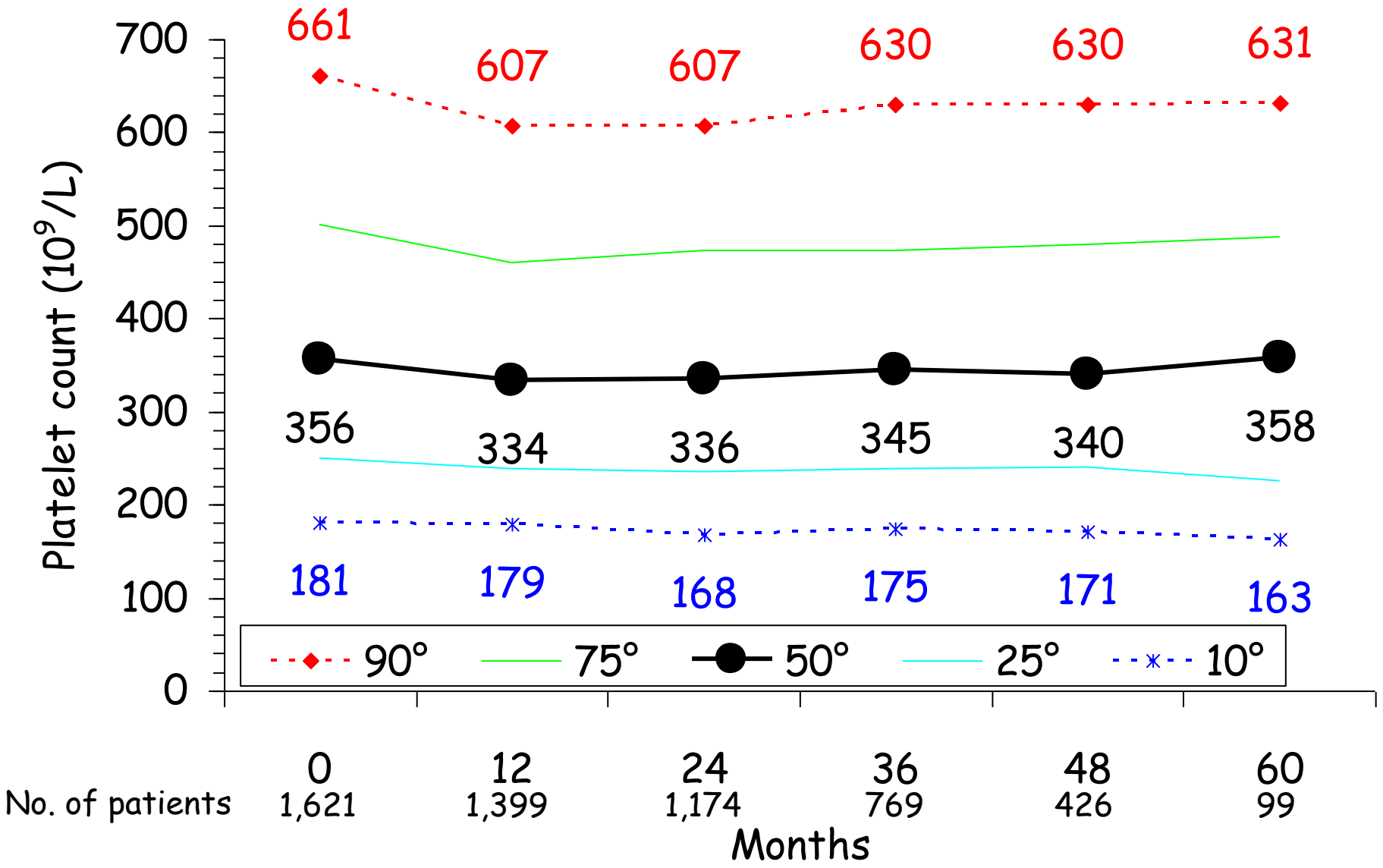


A patient can be randomized in the trial, provided she/he meets all recruitment criteria.
Clinical visits at 3*, 6*, 12*, 18, 24*, 30, 36*, 42, 48*, 54, 60* months.
* the following laboratory tests must be performed: hematocrit, hemoglobin, red and white cell count, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, uricoemia, glucose levels, total CK, ALT, AST, creatinine, potassium, sodium, fibrinogen, spleen and liver ultrasonography (specific tests for PV to added).

Figure 1 – Study design

Platelet count < 400,000
Leukocytes < 10,000

Platelets


Platelet count (10^9/L)
700
600
500
400
300
200
100
0
661
607
607
630
630
631
356
334
336
345
340
358
181
179
168
175
171
163
90°
75°
50°
25°
10°
0
12
24
36
48
60
No. of patients
1,621
1,399
1,174
769
426
99
Months

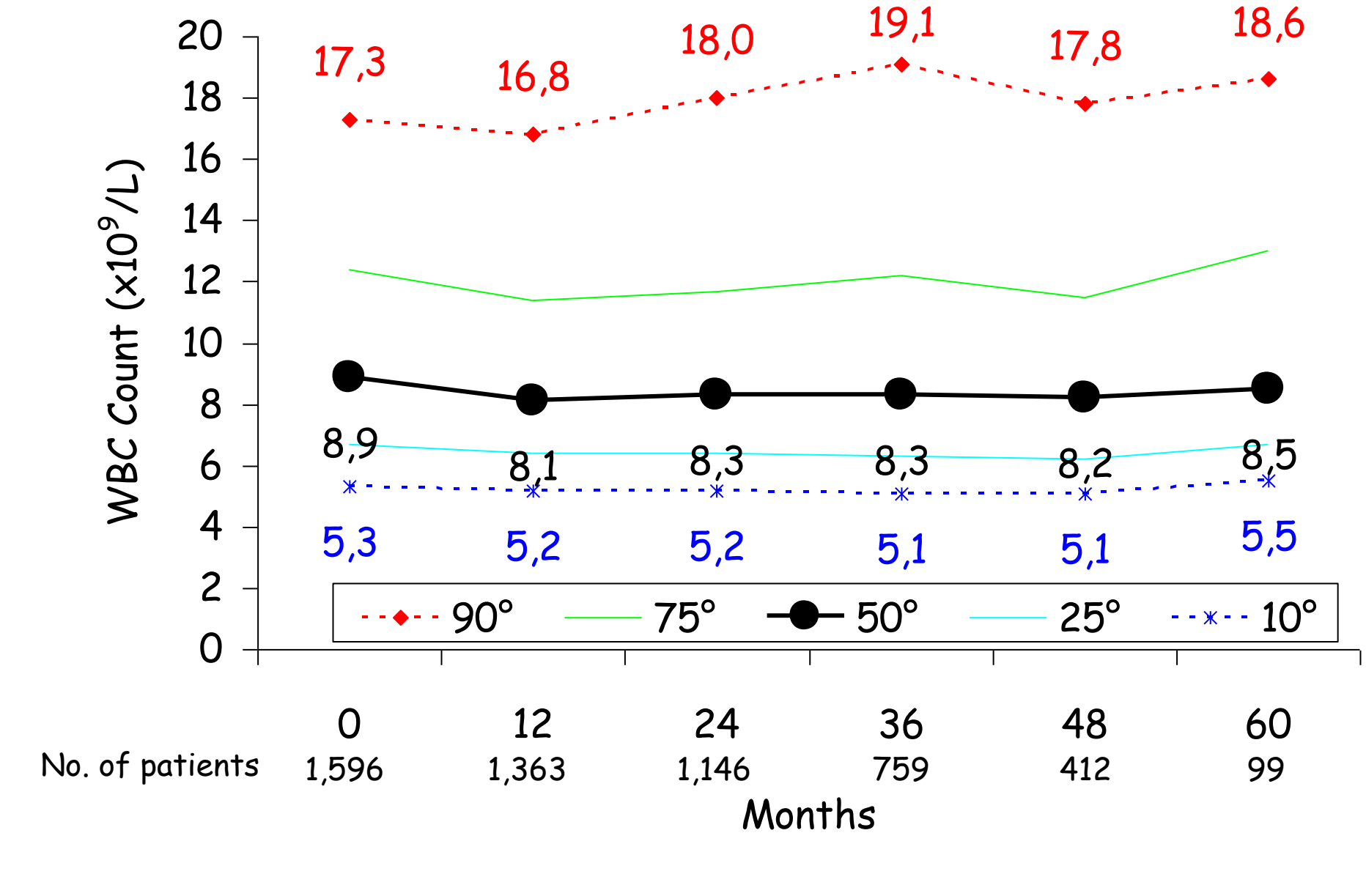
Time-dependent multivariate analysis on the relative risk of major thrombosis among men and women with Polycythemia Vera (N = 1,638)*

		Hazard ratio (95% CI), P-value
Platelet number (x10^9/l)	≤ 300 (N=592)	1 (Reference)
	301-500 (N=622)	0.78 (0.5-1.2), 0.2
	> 500 (N=407)	0.67 (0.4-1.1), 0.1

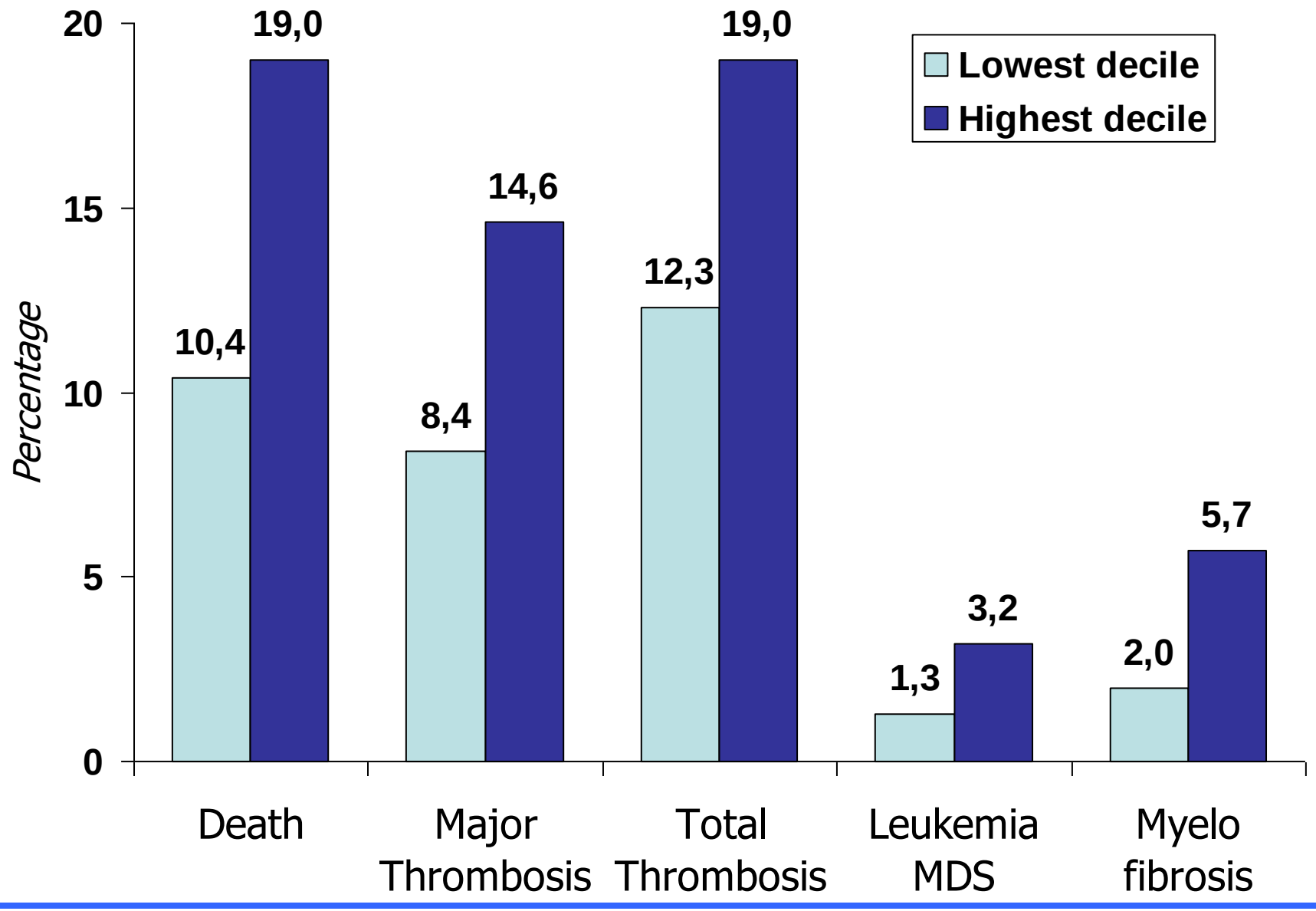
*Model adjusted for: age, gender, time from PV diagnosis to recruitment, thrombotic or hemorrhagic events prior to recruitment, smoking, history of diabetes, hypertension, claudicatio intermittens, erythromelalgia, splenomegaly, circulating immature cells, leukocyte count, total blood cholesterol, phlebotomy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

Di Nisio , Barbui T. et al., Brit J Haematol. 2006

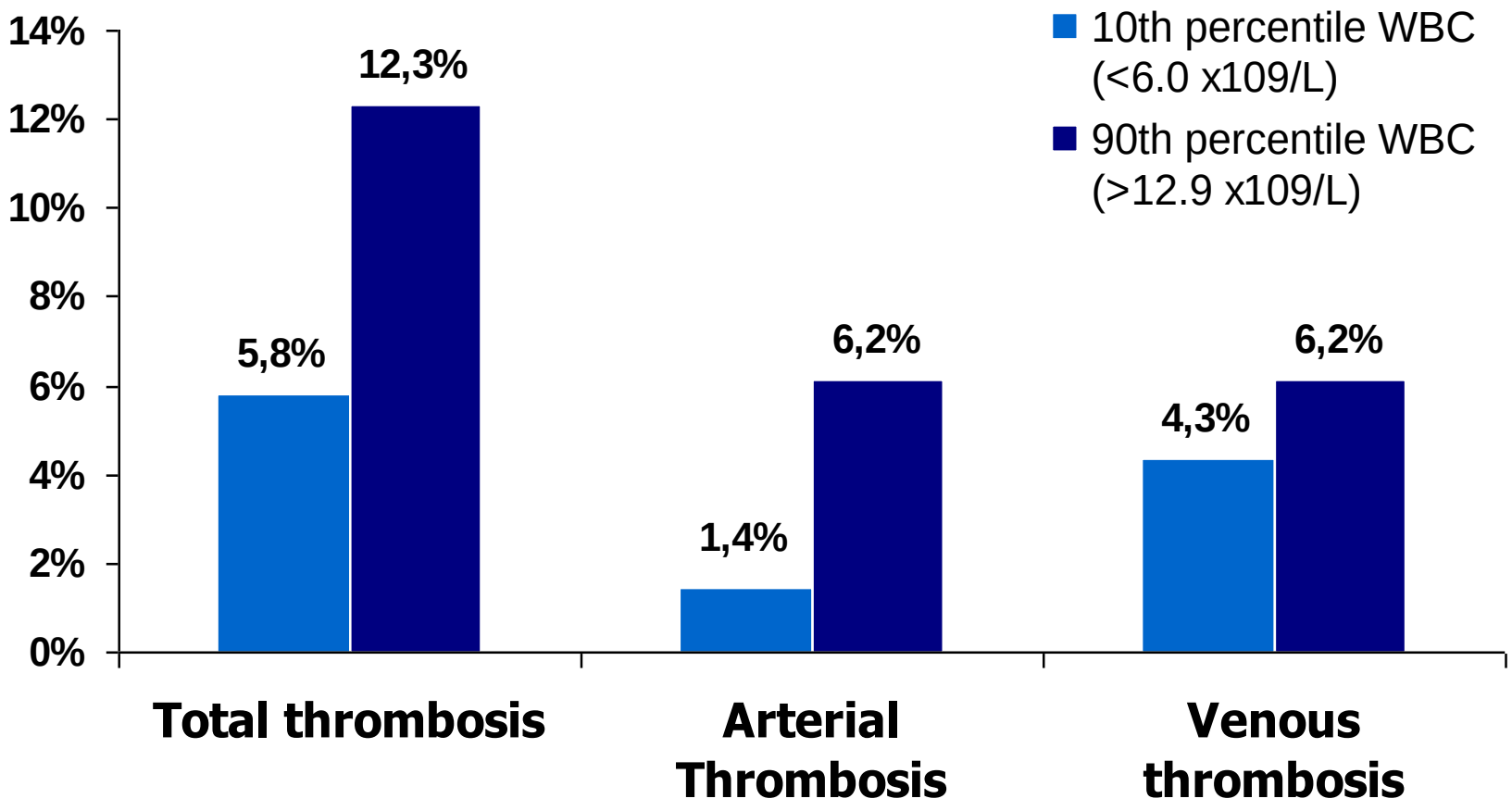
White Blood Cells



Outcome events – ECLAP study



Outcome events - ET



Time-dependent multivariable analysis on the relative risk of major thrombosis in ECLAP study (N = 1,638)*

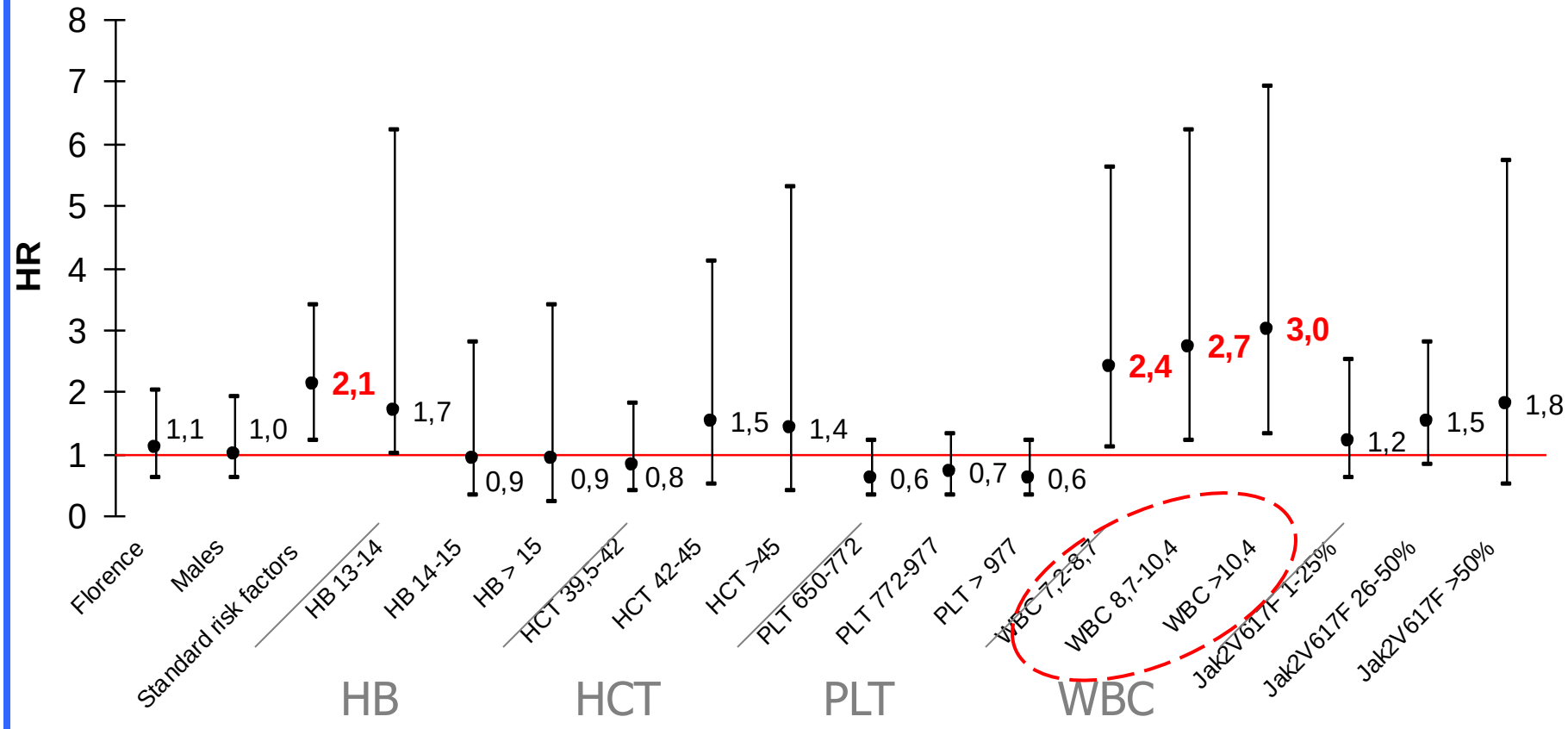
		Hazard ratio (95% CI), P-value
White blood cell count ($x10^9$/l)	≤ 10 (N=990)	1 (Reference)
	10.1-15 (N=365)	1.06 (0.7-1.6), 0.8
	> 15 (N=241)	**1.71 (1.1-2.6), 0.02**

***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 2007*

Risk factors for thrombosis

Cox Multivariable Analysis



**** Reference categories:***

Bergamo centre; Females; Low risk factors; HB < 13 g/dL; HCT < 39.5 %; PLT < 650 (x10^9/L); WBC <7.2 (x10^9/L); Absence of $JAK2^{V617F}$

Carobbio A et al., Blood 2007; JCO 2008 Barbui T et al,Blood 20010

PT-1 randomized clinical trial in high risk ET patients

(*Hydroxyurea+asa vs Anagrelide+asa)*

WBC & major hemorrhage	p=0.01
WBC & **thrombosis**	**p=0.05**
Plts & major hemorrhage	p =0.0005
Plts & thrombosis	**NS**

Campbell submitted 2010

Mechanisms of thrombogenesis in MPN
Role of inflammation

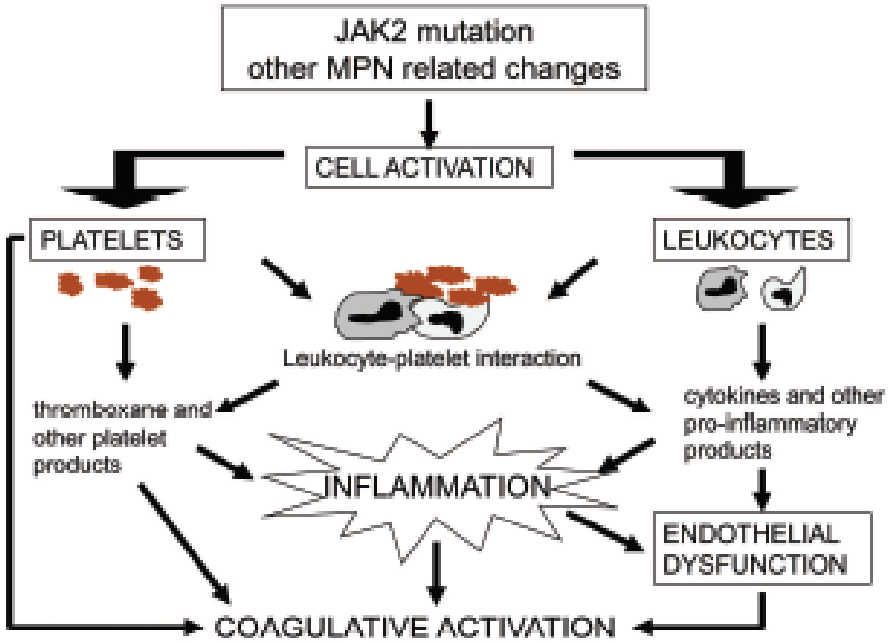


Figure 1. Mechanisms which, in myeloproliferative neoplasms (MPN), can increase the thrombotic risk through cell activation and inflammation.

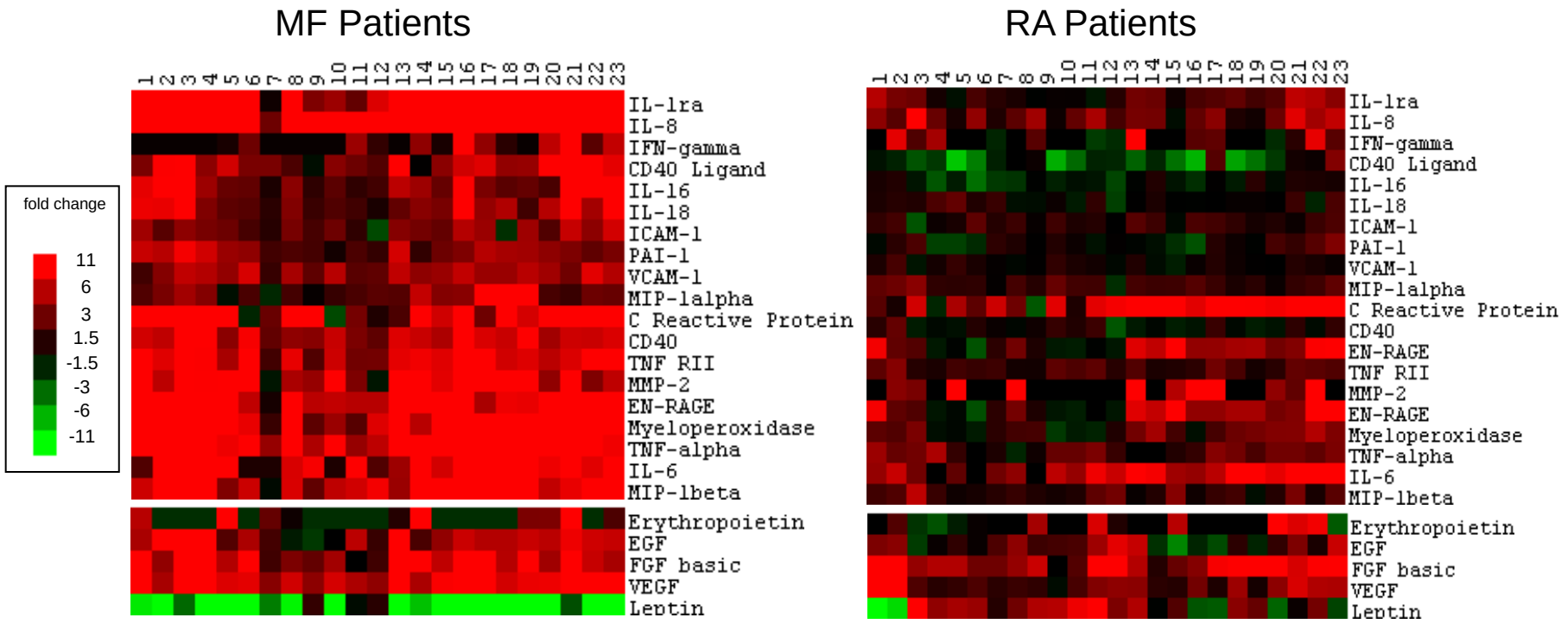
Landolfi , Haematologica 2011

OTHER BIOMARKERS

Linking inflammation to thrombosis

Cytokine and Growth Factor Levels in Patients with MF and Active Rheumatoid Arthritis

- The elevated levels of pro-inflammatory cytokines and growth factors in MF exceed that observed in RA in terms of both breadth and degree of elevation



Tefferi et al., Blood. 112:2804

VOLUME 29 · NUMBER 10 · APRIL 1 2011

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ORIGINAL REPORT

Circulating Interleukin (IL)-8, IL-2R, IL-12, and IL-15 Levels Are Independently Prognostic in Primary Myelofibrosis: A Comprehensive Cytokine Profiling Study

Ayalew Tefferi, Rakhee Vaidya, Domenica Caramazza, Christy Finke, Terra Lasho, and Animesh Pardanani

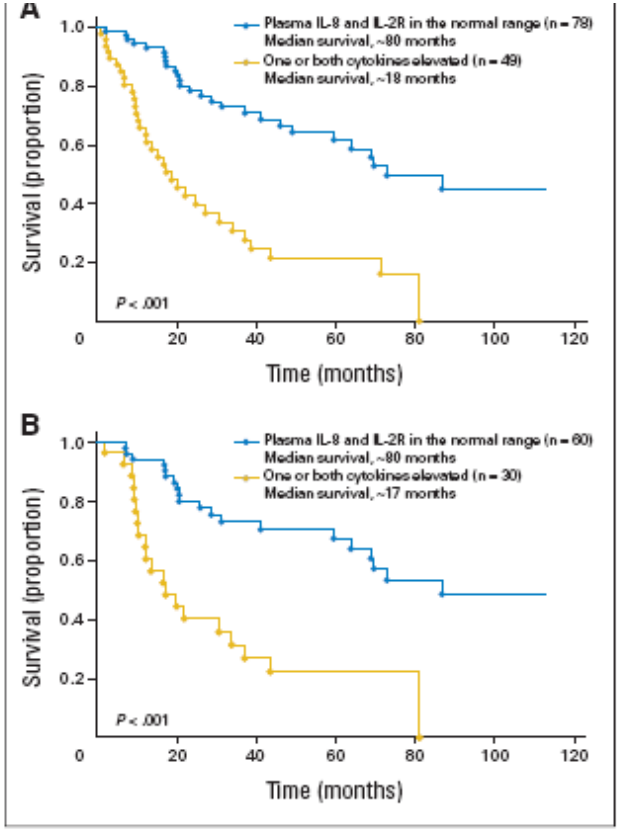


Fig 1. Survival data of (A) all 127 patients and (B) 90 treatment-naive patients with primary myelofibrosis stratified by the presence or absence of interleukin 8 (IL-8) and IL-2R levels that exceed three standard deviations above the normal mean.

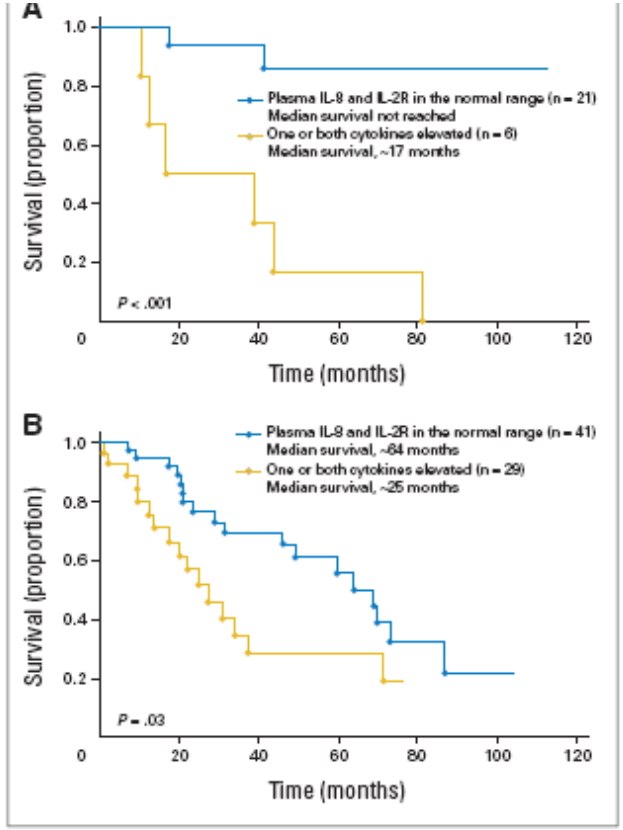
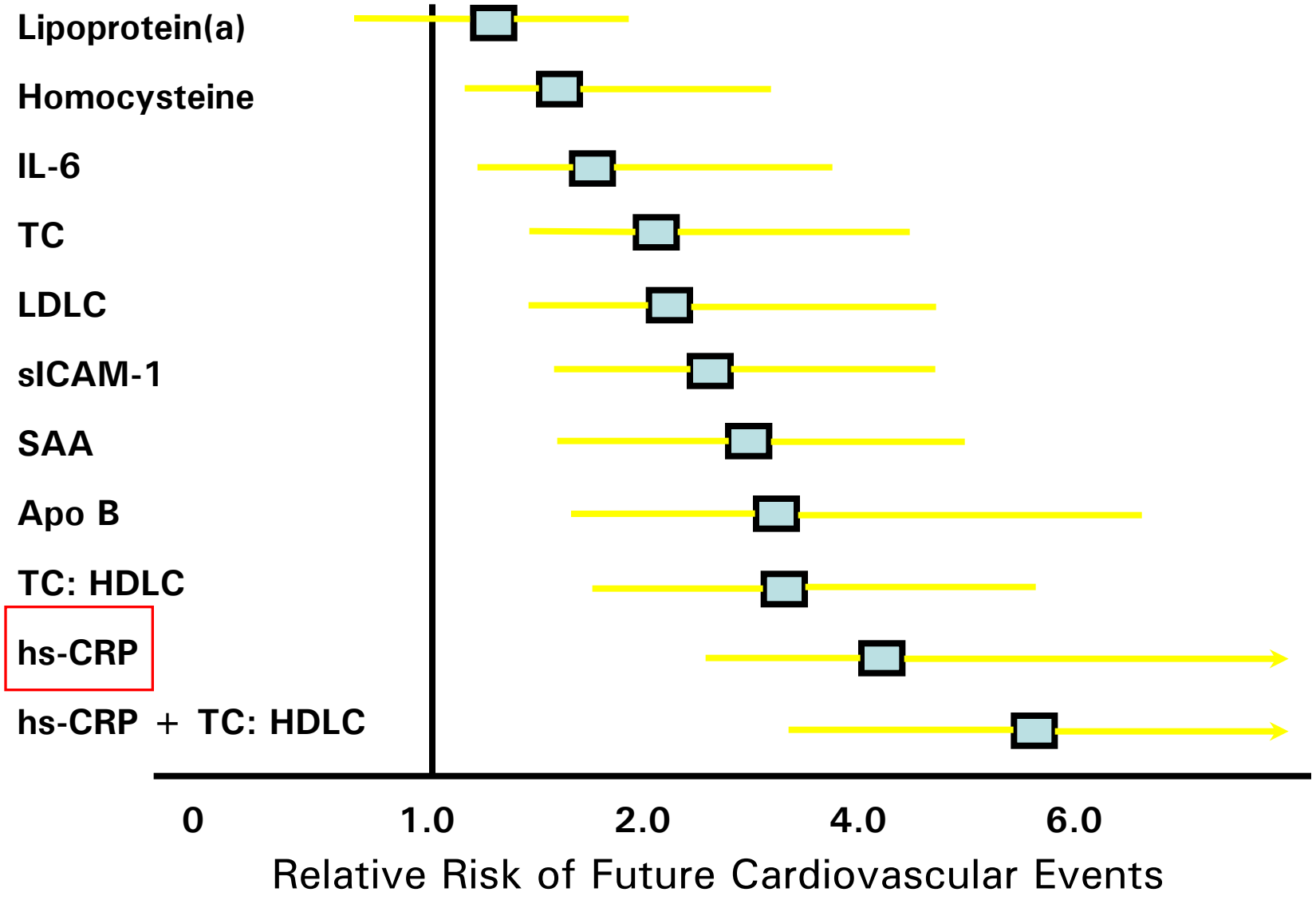


Fig 2. Survival data of (A) 27 intermediate-1–risk patients and (B) 70 intermediate-2–risk patients with primary myelofibrosis stratified by the presence or absence of interleukin 8 (IL-8) and IL-2R levels that exceed three standard deviations above the normal mean. Risk categorization is according to the Dynamic International Prognostic Scoring System plus model.[5]

C-Reactive Protein

- **CRP is an acute-phase protein** produced by the liver in response to cytokine production (IL-6, IL-1, tumor necrosis factor) during tissue injury, inflammation, or infection.
- **Standard CRP tests** determine levels which are increased up to 1,000-fold in response to infection or tissue destruction.
- **High sensitivity CRP assays** detect levels of CRP within the normal range. These levels were proven to predict future cardiovascular events.

Risk Factors for Future Cardiovascular Events: WHS



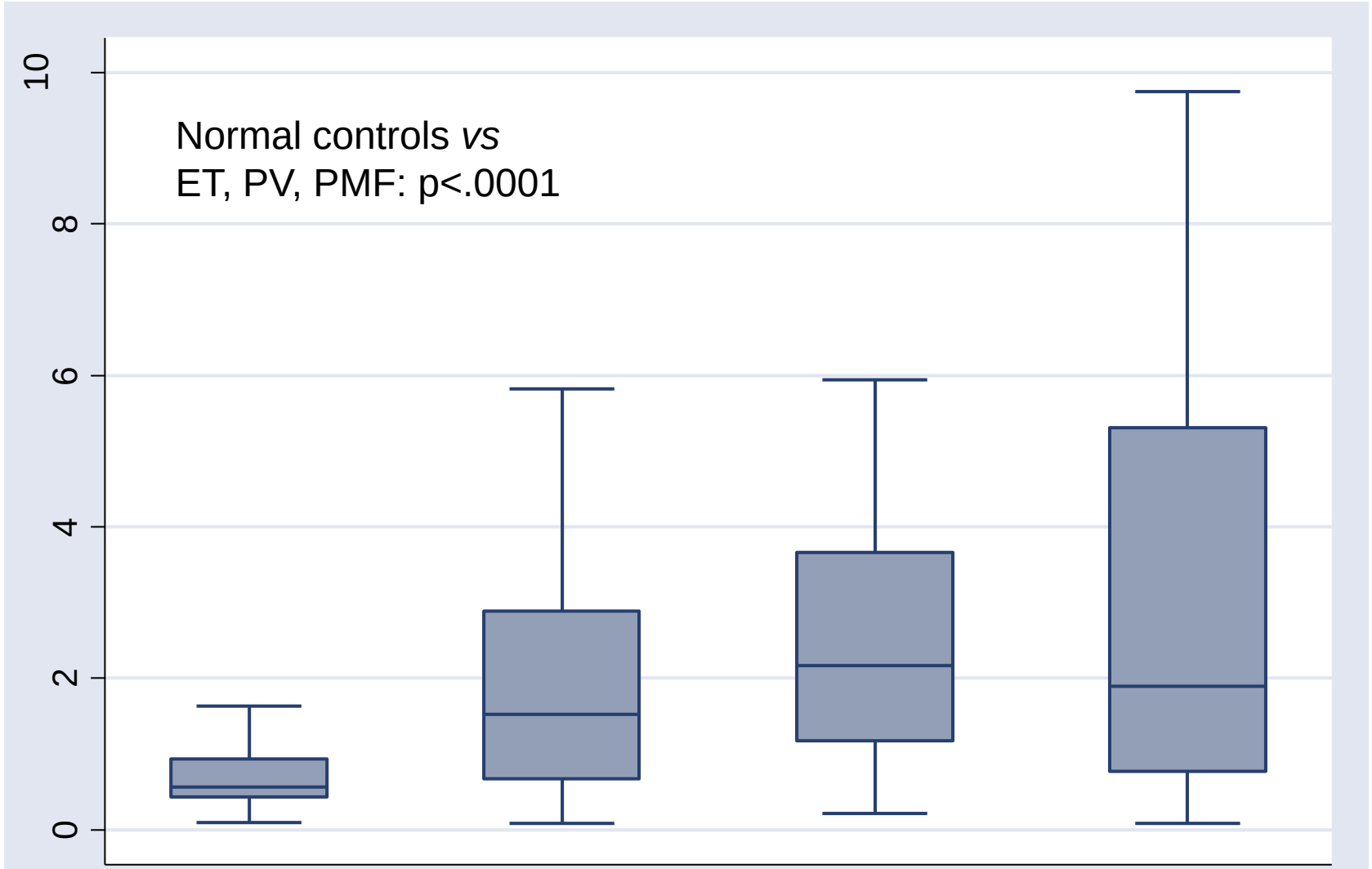
Ridker et al, *N Engl J Med.* 2000;342:836-43

Hs-CRP in MPNs

- We tested the hypothesis that blood levels of hs-CRP could be correlated with

  thrombotic complications in patients with ET and PV and explored the relationship with JAK2V617F mutation.

High sensitivity C-reactive protein (hs-CRP)



Barbui T et al, Haematologica 2011

hs-CRP tertiles and risk of thrombosis

	1.0 to 3.0 mg/L hs-CRP			More than 3.0 mg/L hs-CRP		
	OR*	**95% CI**	***P***	**OR***	**95% CI**	***p***
Unadjusted	1.89	0.89-3.99	0.10	**2.59**	**1.21-5.51**	**0.014**
Adjusted for						
+ Age	1.82	0.86-3.86	0.12	**2.27**	**1.04-4.95**	**0.039**
+ Sex	1.83	0.86-3.91	0.12	**2.36**	**1.08-5.18**	**0.032**
+ Disease	1.80	0.84-3.85	0.13	**2.25**	**1.02-4.96**	**0.045**
+ JAK2V617F burden	1.60	0.73-3.47	0.23	2.11	0.93-4.80	0.074

***Reference categories: hs-CRP < 1.0 mg/L**

Barbui T et al, Haematologica 2011

QUESTION

Does the strength of association between these biomarkers and thrombosis justify their use as surrogate of primary end-points in clinical trials?

Surrogate endpoint: definition

- A surrogate endpoint of a clinical trial is a **laboratory measurement or a physical sign** used as a substitute for a clinically meaningful endpoint

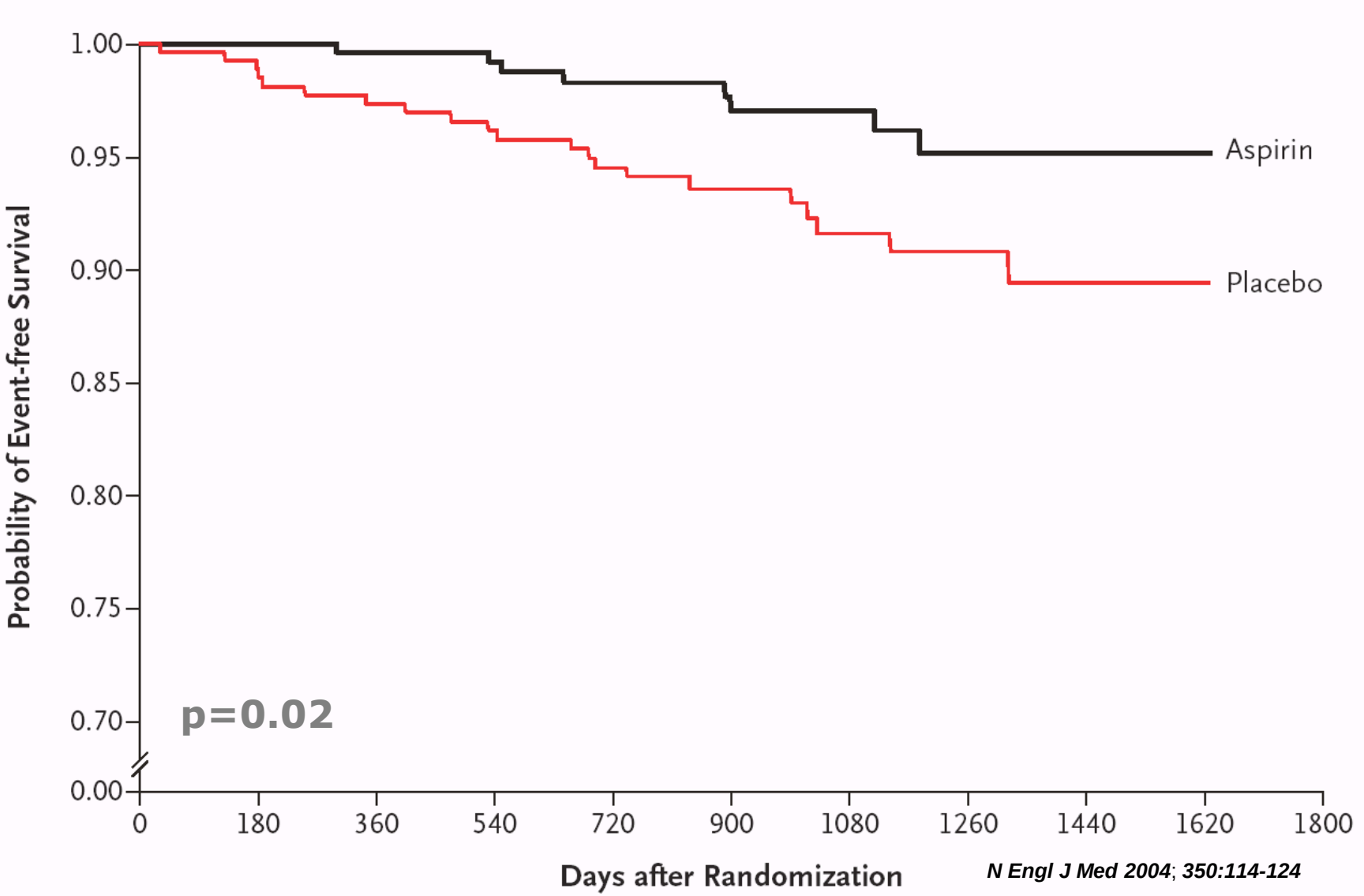
- **Changes** induced by a therapy on a surrogate endpoint **are expected to reflect changes in a clinically meaningful endpoint.**

- **Surrogate end points can be useful in phase 2 screening trials** for identifying whether a new intervention is promising enough to justify a large definitive trial with clinically meaningful outcomes.

- **Definitive phase 3 trials are required,** except for rare circumstances in which the validity of the surrogate end point has already been rigorously established.

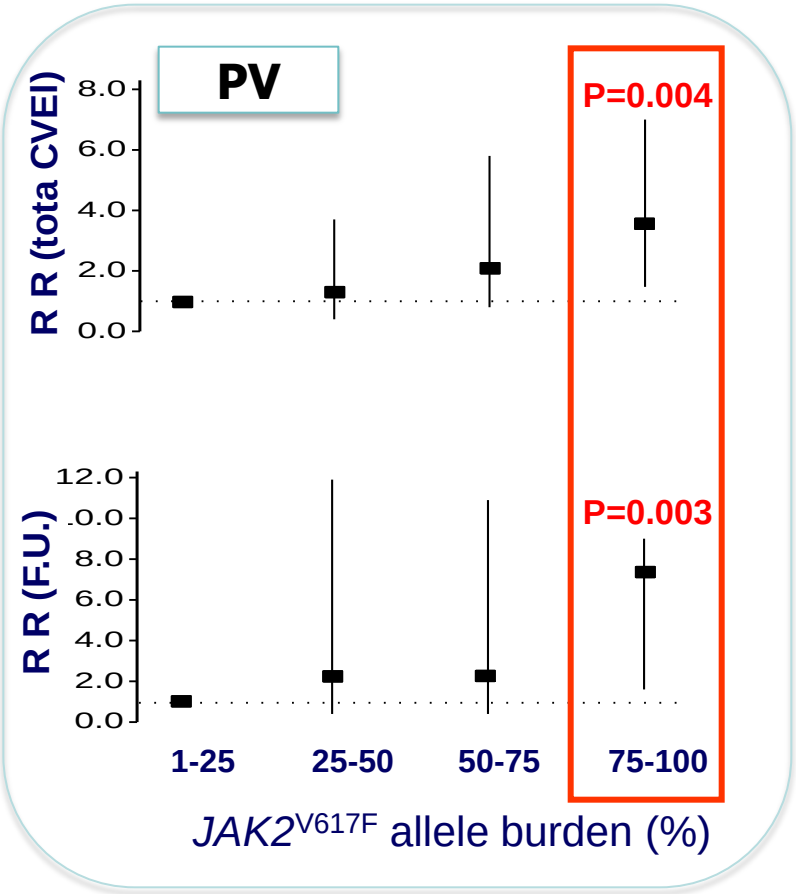
PROBABILITY OF SURVIVAL FREE

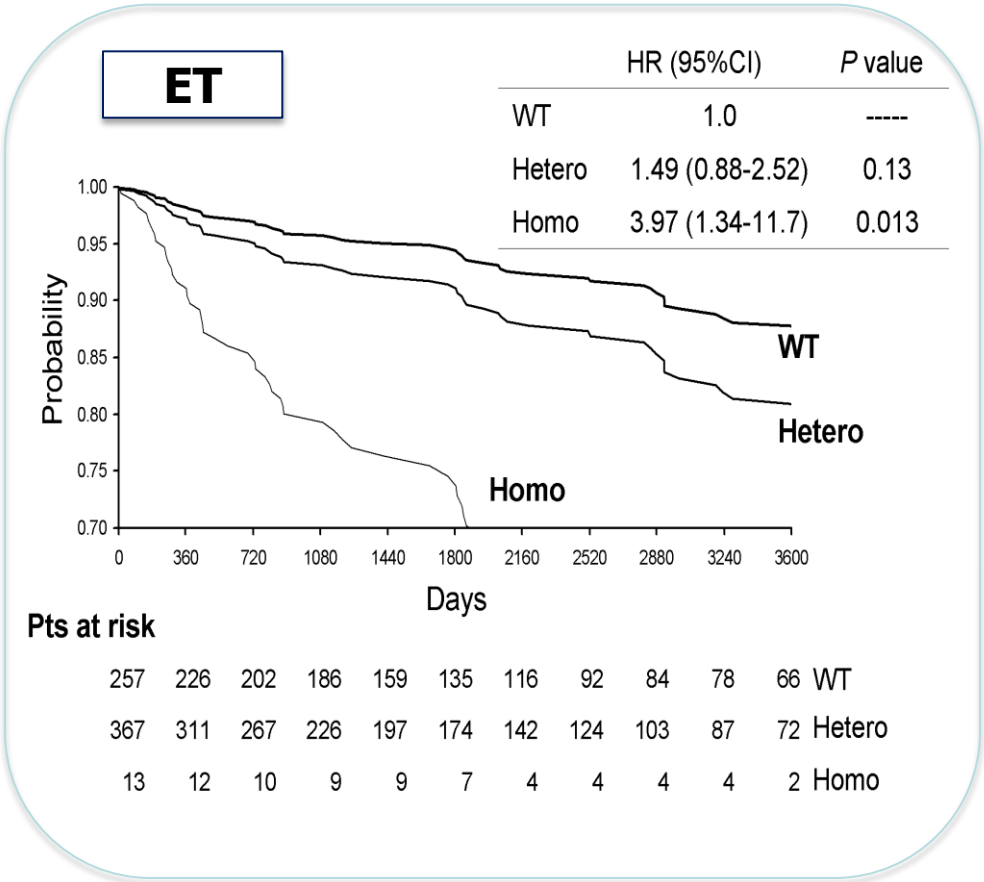
OF MYOCARDIAL INFARCTION, STROKE, AND DEATH FROM CARDIOVASCULAR CAUSES, PULMONARY EMBOLISM AND DEEP VEIN THROMBOSIS



N Engl J Med 2004; *350:114-124*

JAK2 V617F and Thrombosis in PV or ET





Vannucchi et al, Blood 2007; Vannucchi et al, Leukemia 2007

blood
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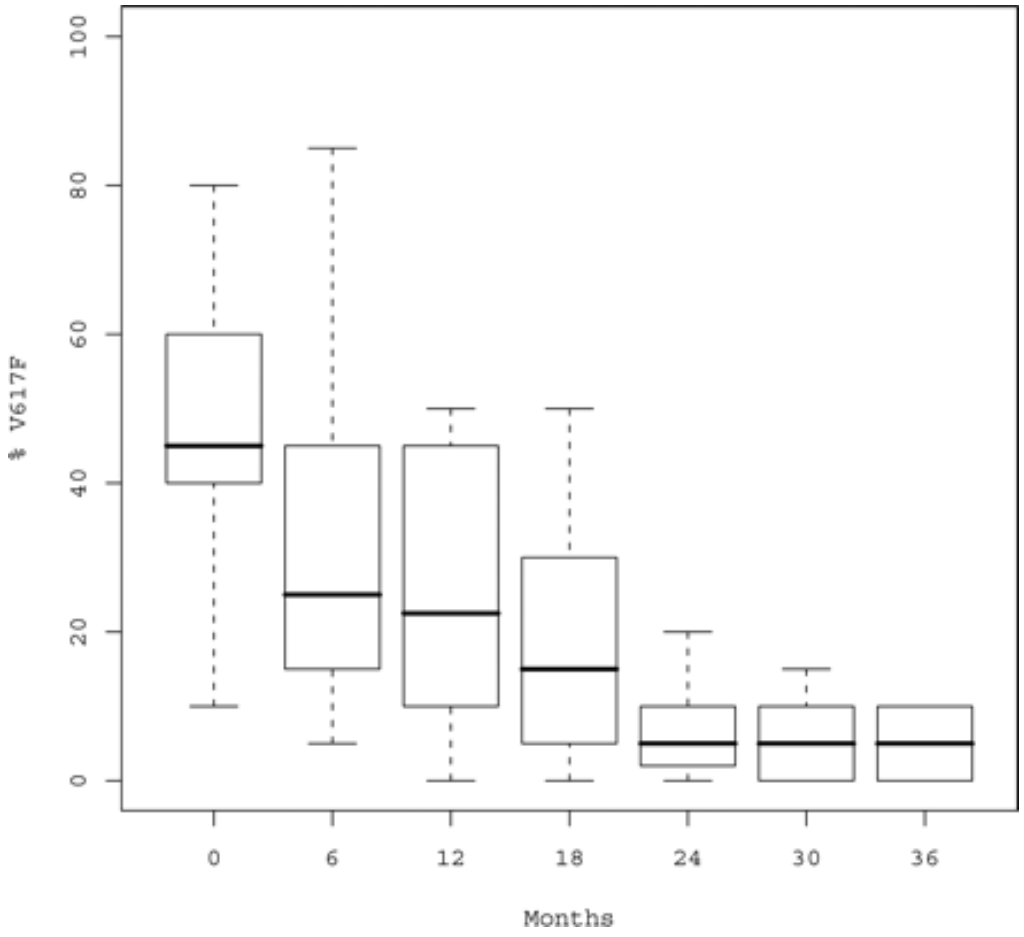
Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in PV

Evolution of %V617F during treatment with peg-IFN-2a



Kiladjian, J.-J. et al. Blood 2008;112:3065-3072

Randomised Trial of Pegylated Interferon Alfa -2a versus Hydroxyurea for the treatment of high risk polycythemia vera and high risk essential thrombocythemia(MPD-RC trial)

Primary end points

To evaluate the ability of therapy (Pegylated Interferon α 2a vs. Hydroxyurea) to achieve ***Complete Response*** *(By LeukemiaNet Criteria) in patients with either high risk polycythemia vera or high risk essential thrombocythemia (stratified by disease group)* ***after 24 months of therapy.***

Secondary end points

*Partial response,JAK2 V617F allele burden, toxicity and tolerability****,major cardiovascular events, evolution to AML or MF,overall survival***

Study population -

CYTO-PV is a multicenter, randomized, controlled trial with diagnosis of PV (WHO 2008)

designed to be conducted, without need of special facilities. It is an independent, investigator-generated, pragmatic trial with broad selection criteria

to mimic clinical practice in order to strengthen the transferability of its results to the population of PV patients.

Sample size calculation

Time to death and major thrombotic events
are the primary endpoints(PEP) of the sudy

Assumption for PEP

In the ECLAP study (median follow-up 2.8 years)
the cumulative incidence of PEP was

- 5.5% per year in the overall population of PV pts
- 6.95% per year in high-risk PV group

Number of patients to be recruited

The minimum follow-up is set at 5 years.
The expected cumulative rate of PEP is 5%
(25% in 5 years).The minimum clinically relevant beneficial effect is set at 30% reduction of PEP.

Number of patients to be recruited is 1000.

Definition of clinico-hematologic response in ET

Response grade	Definition
Complete response	1. Platelet count =< 400 x109/L AND 2. No disease related symptoms AND 3. Normal spleen size on imaging AND 4. WBC count < 10 x 109/L
Partial response	In patients who do not fulfill the criteria for complete response: Platelet count below 600 x 109/L or decrease > 50% of baseline
No response	Any response that does not satisfy partial response

Barosi et al, Blood, 14 May 2009, Vol. 113, No. 20, pp. 4829-4833

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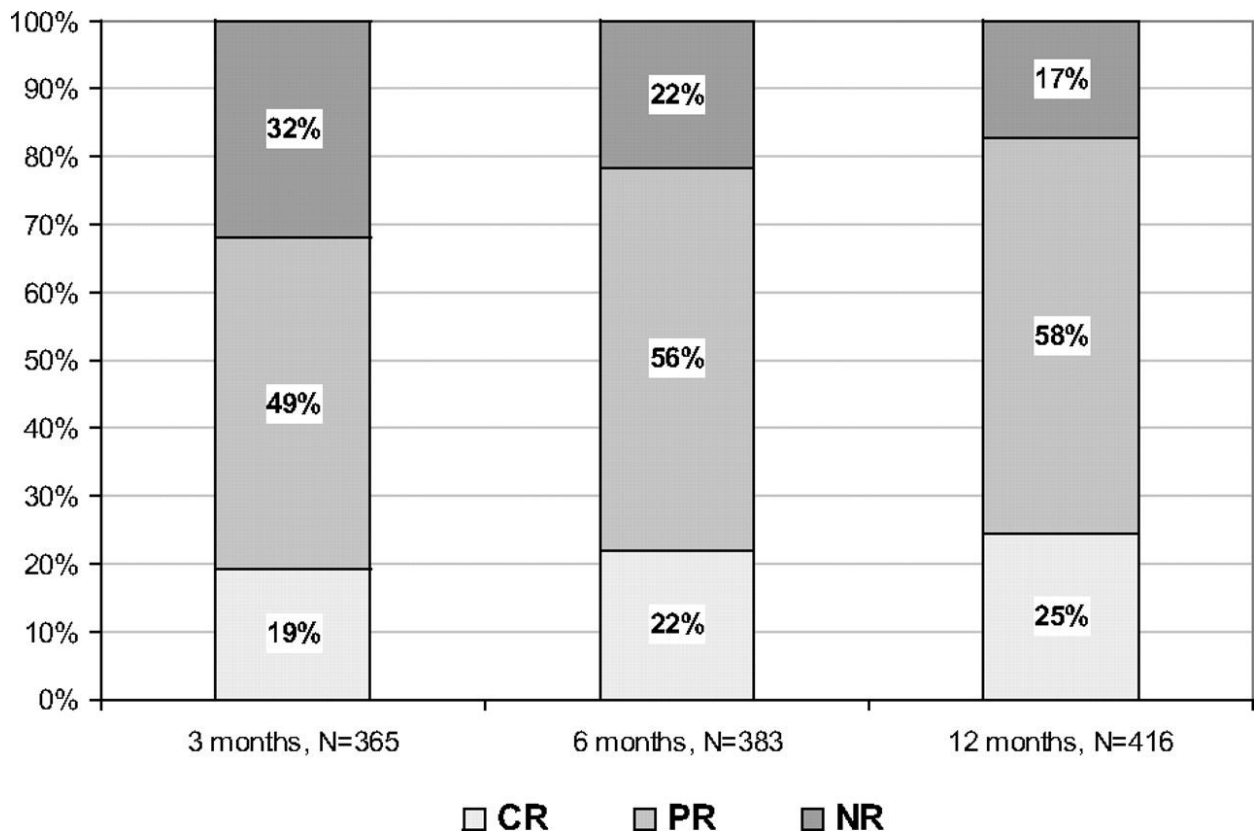
Hydroxyurea in essential thrombocythemia:

Figure 1 Rate of responses according to ELN criteria



Carobbio, A. et al. Blood 2010;116:1051-1055

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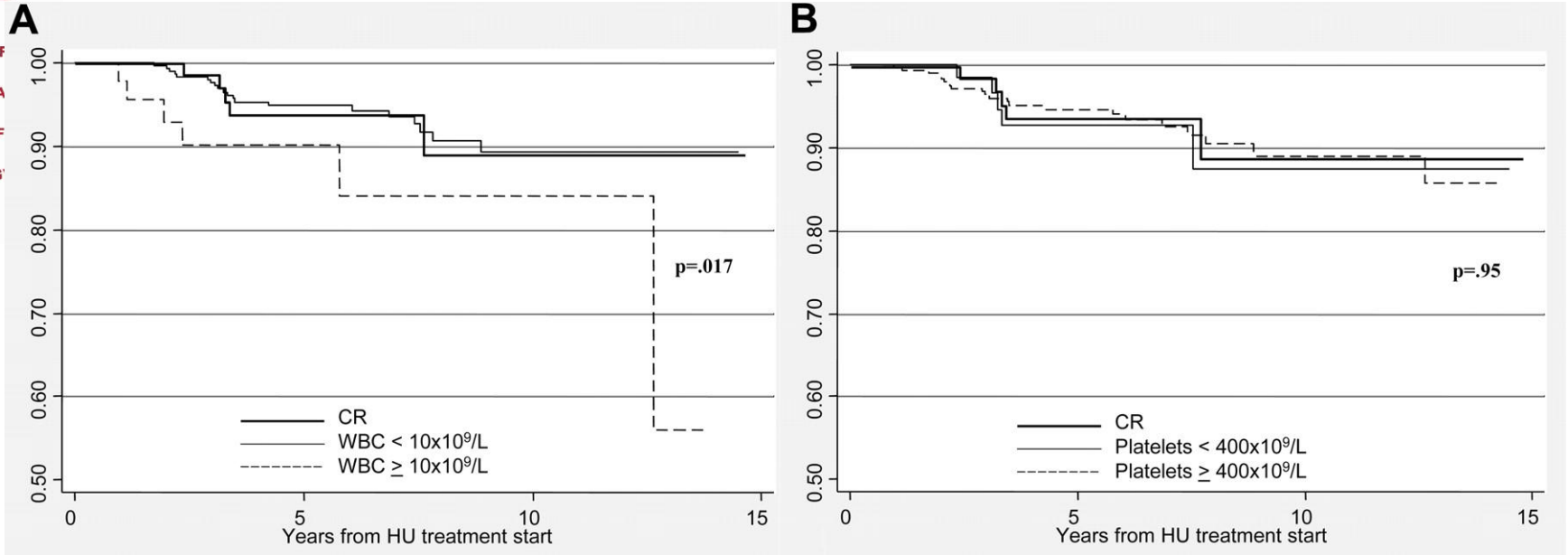
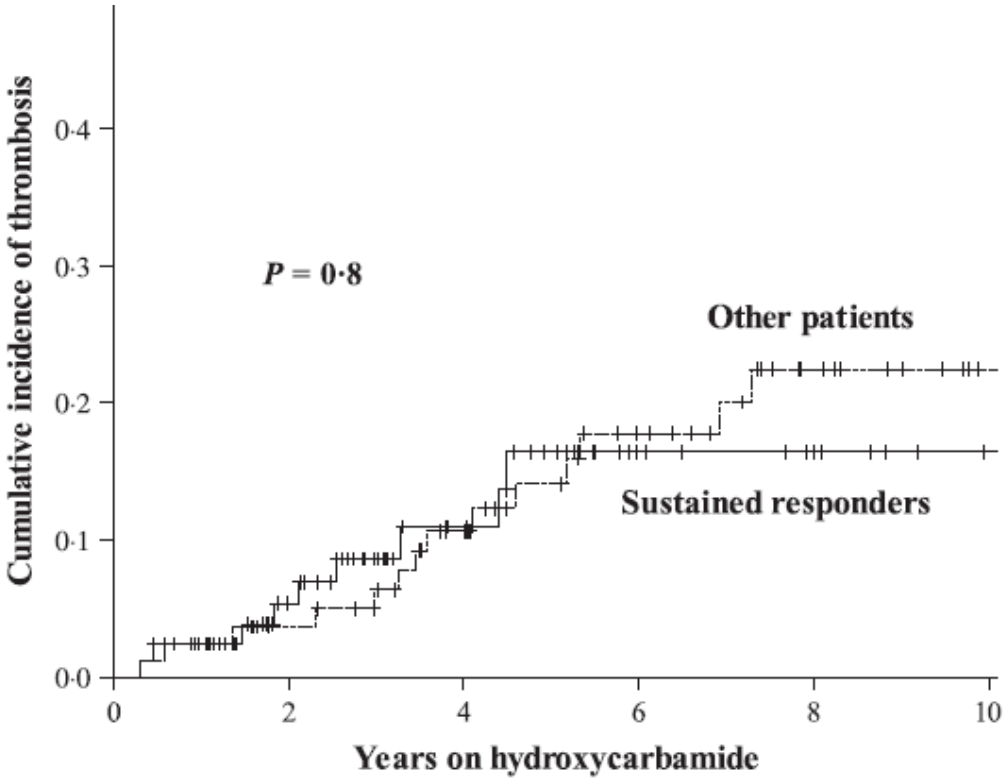
Figure 2 Thrombosis-free survival



Carobbio, A. et al. Blood 2010;116:1051-1055

Clinical evaluation of the European LeukaemiaNet criteria for clinicohaematological response and resistance/intolerance to hydroxycarbamide in essential thrombocythaemia



 British Journal of Haematology, **152**, 81–88

European LeukemiaNet

Definition of clinically relevant end points in Ph-neg Myeloproliferative Neoplasms

ELN-WP9 2011 project

*To provide guidance in the **definition of clinically relevant end-points and appropriate surrogates** that can expedite new drug approvals for MPNs*

ACKNOWLEDGEMENT

Bergamo	S. Cortelazzo,G Finazzi, A Falanga, A Carobbio, A Rambaldi and our patients.
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GIMEMA	MPN Working Party

ELN	and particularly JJ Kiladjian
Cologne	J Thiele

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MPD-Consortium	R Hoffman and S Fruchtman