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12th Joyce Niblack Memorial Conference on Myeloproliferative Neoplasm

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# Managing ET in 2021


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# Agenda

- The impact of WHO-2016 diagnostic classification on outcomes in ET
- The IPSET-Thrombosis as a prognostic system to differentiate treatments
- News on therapy of low- and intermediate risks
- The current results on the incidence of thrombosis in WHO-ET

# WHO- 2016 Essential thrombocythemia (ET)

**Major criteria:**

1. Platelet count equal to or greater than 450 x $10^9$/uL
2. Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei.
   No significant increase or left-shift of neutrophil granulopoiesis or erythropoiesis and very rarely minor increase in reticulin fibers.

3. Not meeting WHO criteria for BCR-ABL1+ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms
4. Presence of *JAK2,* ***CALR*** or *MPL* mutation

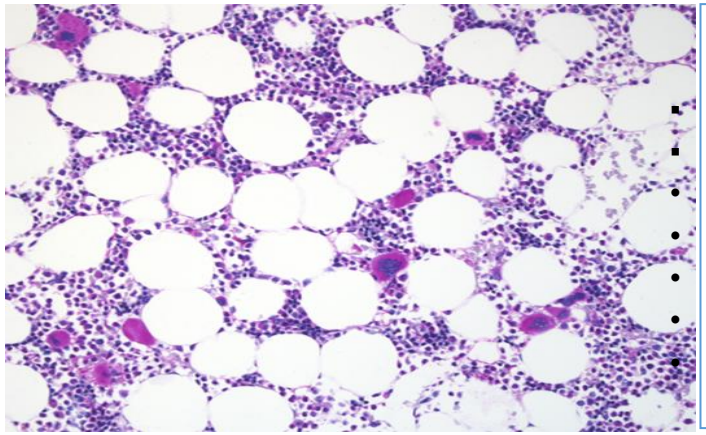
**Minor criteria:**

Presence of a clonal marker or absence of evidence for reactive thrombocytosis

**Diagnosis of ET requires meeting all four major criteria or the first three major criteria and one of the minor criteria**

# Recognizing ET from Prefibrotic-PMF

**ET**

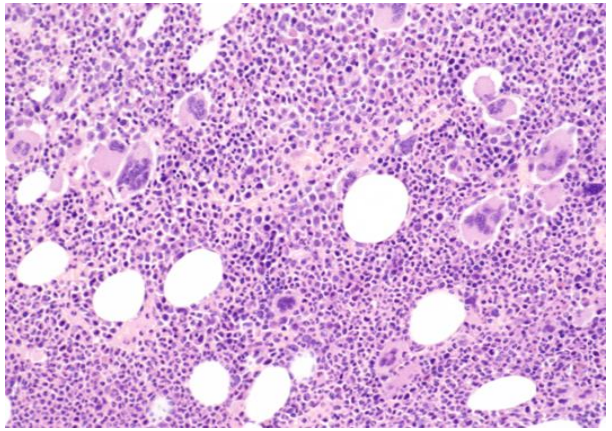


## Clinical implications:

- Clinical presentation is different (anemia, leukcytosis, LDH, splenomegaly)
- Thrombosis is similar to ET
- Time to disease progression is shorter in pre-PMF. 1
- Prefibrotic-PMF is associated with an almost double rate of hemorrhage compared to ET. Low vWF activity? Careful with aspirin

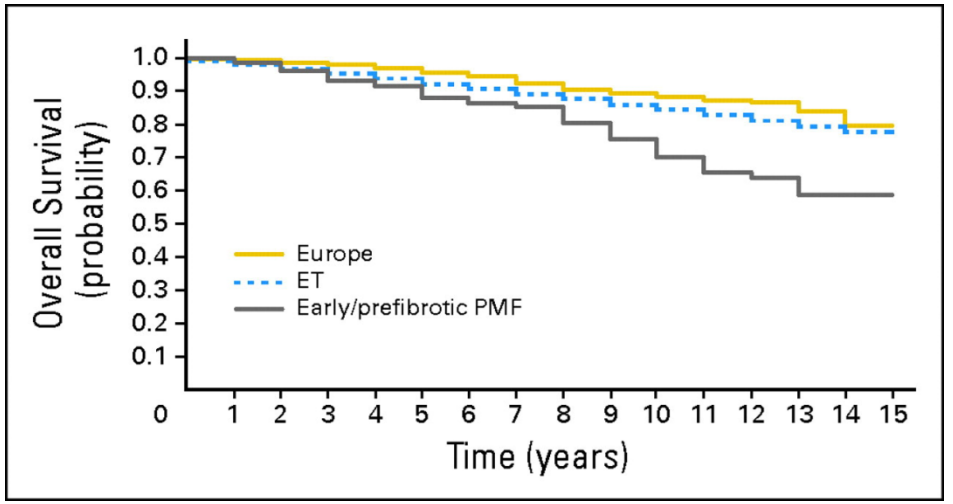
- ET and prefibrotic-PMF are distinct entities in the 2016 WHO classification.

**pre-PMF**



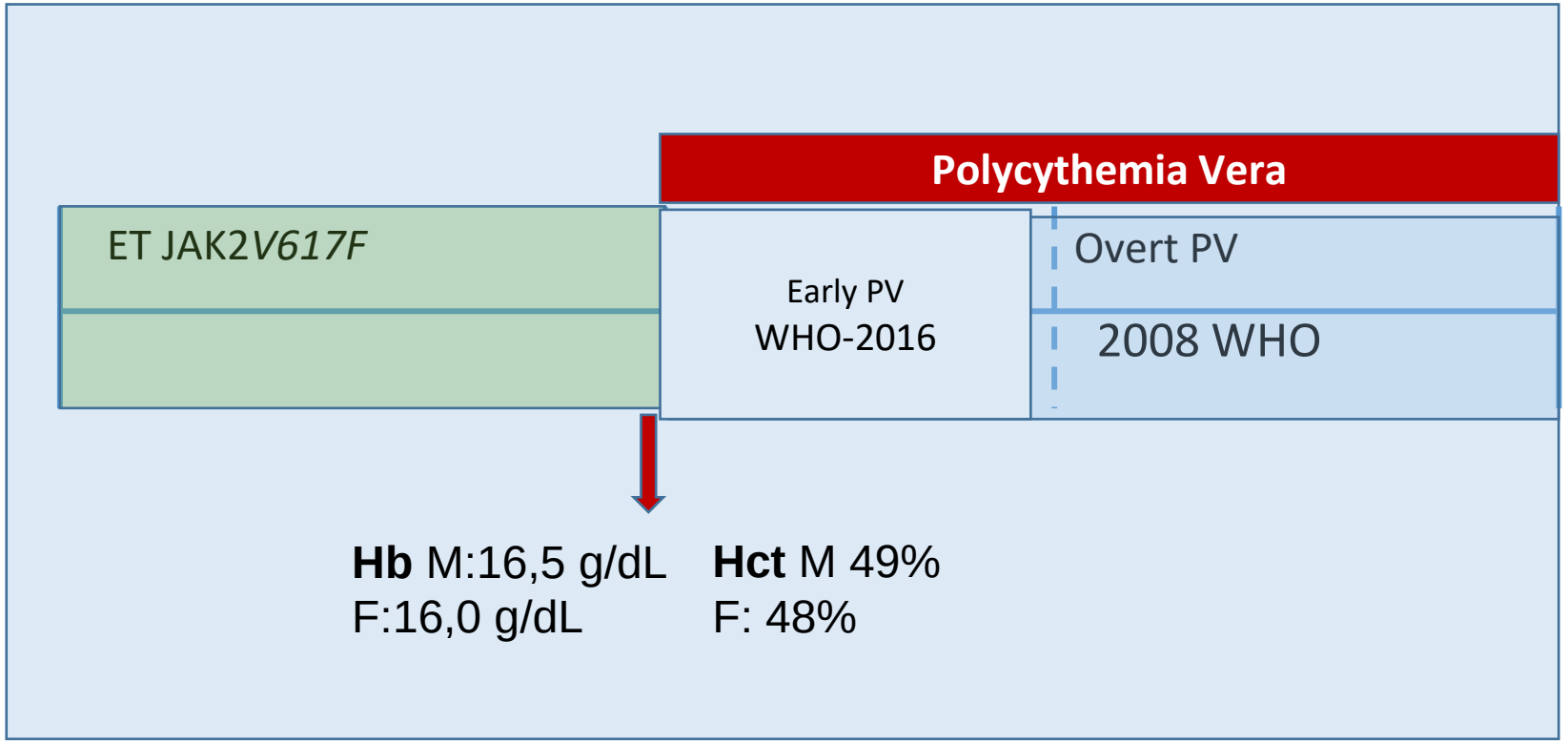
Arber D et al, Blood 2016; 127:2391.

**Survival estimates** for patients with essential thrombocythemia and early/prefibrotic primary myelofibrosis




1Barbui T, JCO 2011 2 Finazzi G, et al, Leukemia 2012; 26:716

# Recognizing ET from PV in JAK2*V617F* patients by Hb and Hct levels




Barbui et al, Leukemia 2014, Barbui et al. AJH 2013, 2014

# QUESTION

**Given that**

- diagnosis of WHO-ET included a fraction of pre-PMF and initial PV which can have different presentation and outcomes
- the bulk of our clinical information ( observational studies and RCTs) are based on pre-WHO diagnosis criteria

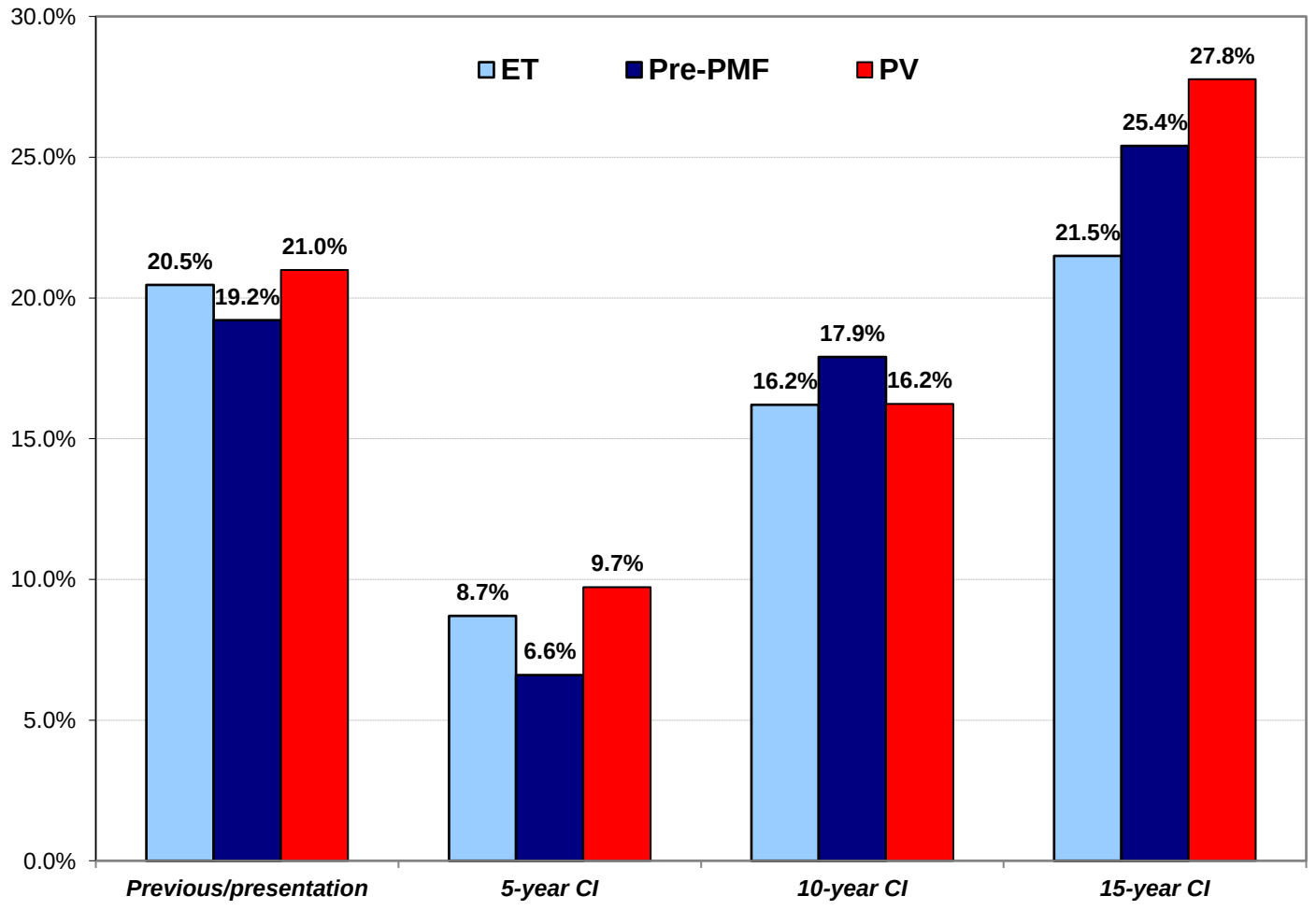
**WHAT IS THE CURRENT CLINICAL EPIDEMIOLOGY IN TERMS OF INCIDENCE OF THROMBOSIS, BLEEDING, EVOLUTION INTO MYELOFIBROSIS, ACUTE LEUKEMIA AND SURVIVAL IN**

**“TRUE ESSENTIAL THROMBOCYTHEMIA”**

Barbui T, et al, BCJ 2020

# WHO-2016: **Previous and incident thrombotic complications**

in ET (n=891), Pre-PMF (n=180) and PV (n=397)

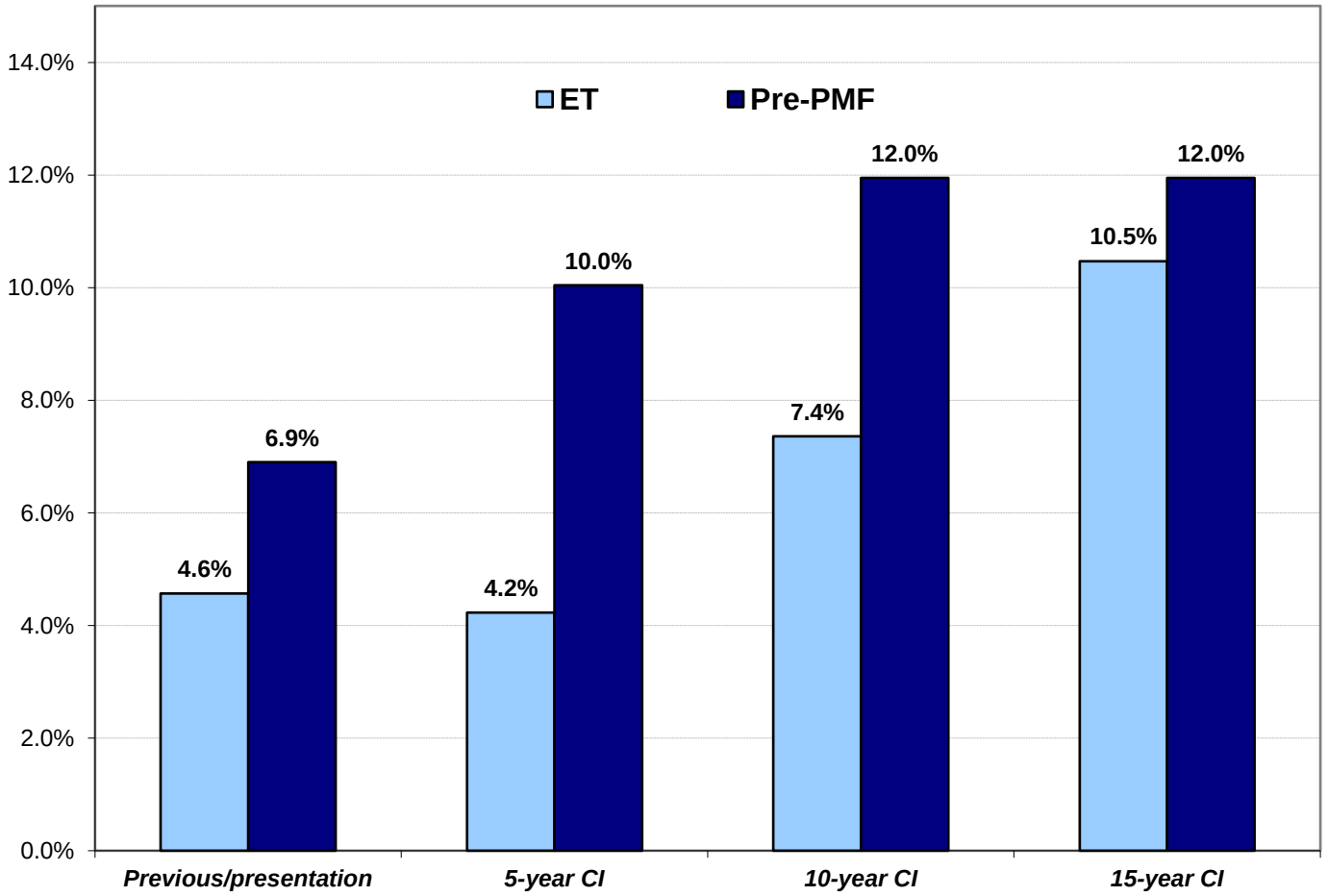



Barbui et al. Blood Cancer Journal (2018) 8:15

# WHO-2016: Summary of clinical correlation

## **Previous and incident bleeding complications**

in ET (n=891) and Pre-PMF (n=180)

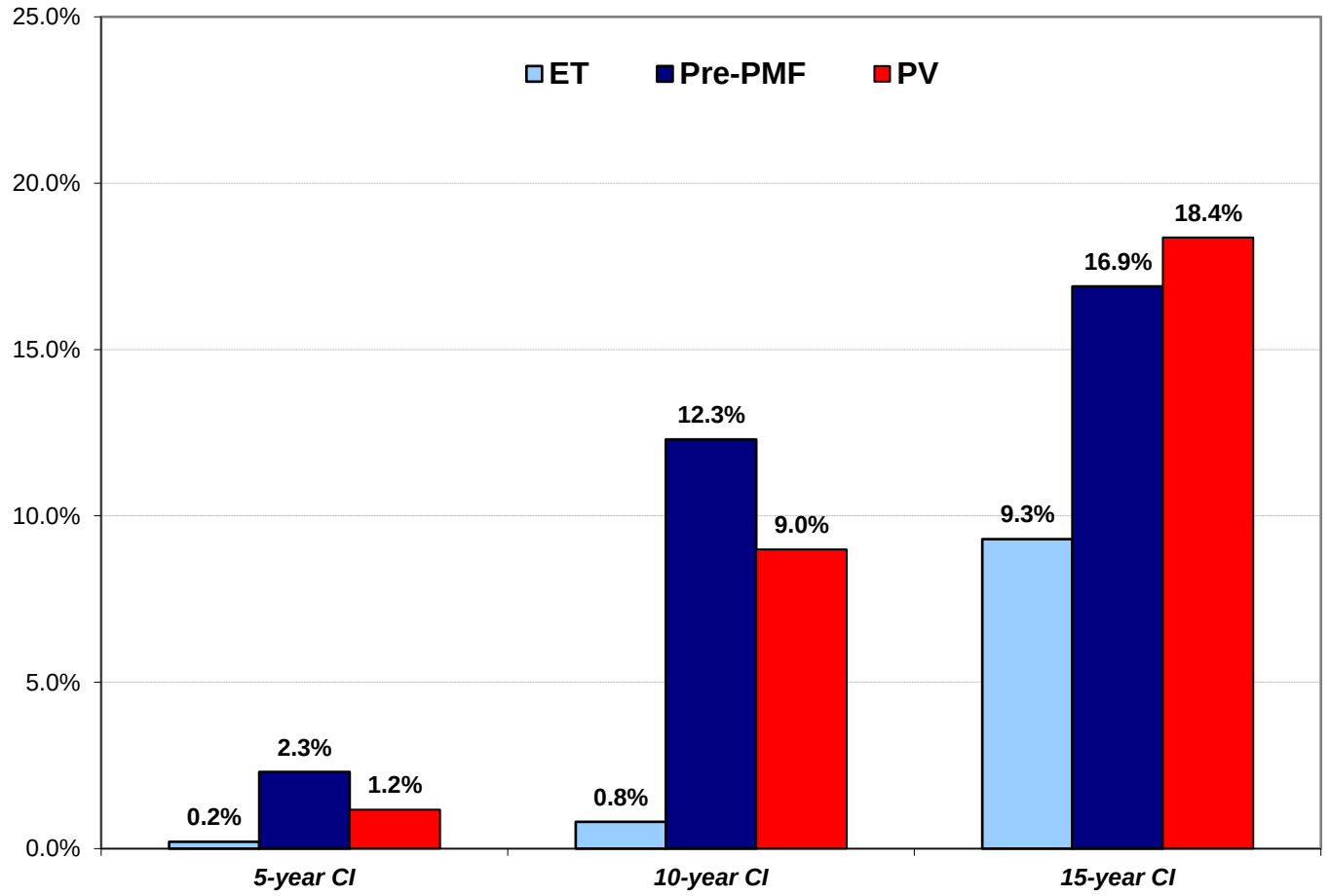



Barbui et al. Blood Cancer Journal (2018) 8:15

# WHO-2016: Summary of clinical correlation

## **Incidence of Myelofibrosis**

in ET (n=891), Pre-PMF (n=180) and PV (n=397)

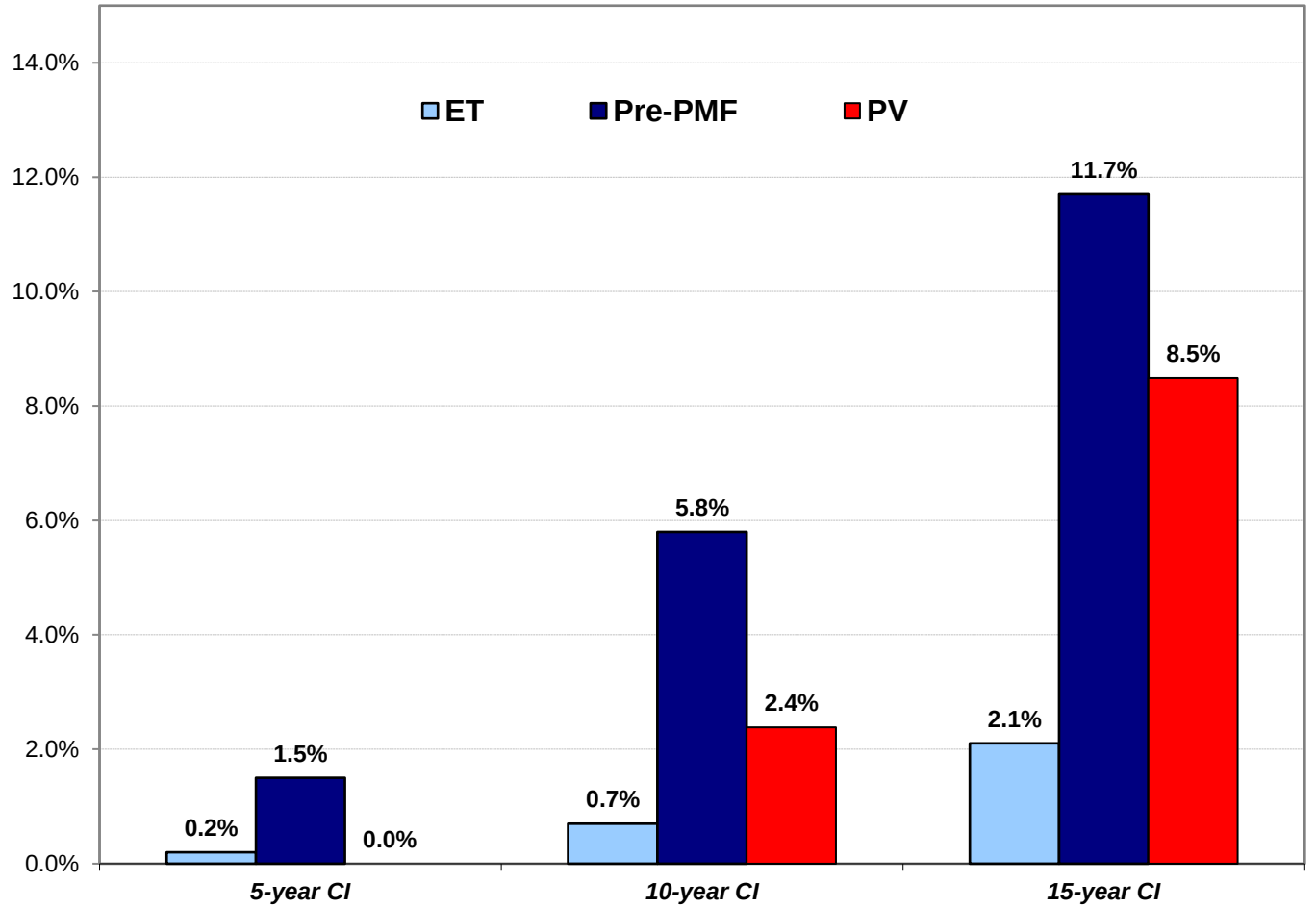



Barbui et al. Blood Cancer Journal (2018) 8:15

# WHO-2016: Summary of clinical correlation

## **Incidence of Blastic Phase**

in ET (n=891), Pre-PMF (n=180) and PV (n=397)




Barbui et al. Blood Cancer Journal (2018) 8:15

# IPSET-thrombosis revised: 2016
**(WHO-ET)**

| Risk factor | HR | Multi-variate P value |
|---|---|---|
| Age > 60 | 1.44 | P=0.150 |
| CV risk factors (Tobacco, HTN, DM) | 1.55 | P=0.082 |
| Prior thrombosis | 2.08 | P=0.008 |
| *JAK2* V617F | 1.78 | P=0.025 |

**Very Low Risk:**
Age ≤ 60, no thrombosis
*JAK2* negative

**Low Risk:**
Age ≤ 60, no thrombosis
*JAK2* positive

**Intermediate**
Age > 60
No thrombosis,
*JAK2* negative

**High risk**
Thrombosis or Age > 60 and *JAK2* mutated

Thrombosis Risk

Barbui et al, Blood 2012, BCJ 2015; Haider et al, Am J Hematol 2016

# Essential Thrombocythemia*

The guidelines from the National Comprehensive Cancer Network (NCCN) and European LeukemiaNet (ELN) are based on the International Prognostic Score for Essential Thrombocythemia (IPSET)**

**Table 2. NCCN and ELN Guidelines for Risk Stratification and Treatment in Patients with Essential Thrombocythemia.***

| Guideline | Very Low Risk† | Low Risk† | Intermediate Risk†‡ | High Risk |
|---|---|---|---|---|
| **NCCN**[33] | | | | |
| Patient characteristics | Age ≤60 yr, no prior thrombosis, *JAK2* V617F mutation absent | Age ≤60 yr, no prior thrombosis, *JAK2* V617F mutation present | Age >60 yr, no prior thrombosis, *JAK2* V617F mutation absent | Age >60 yr, no prior thrombosis, *JAK2* V617F mutation present |
| Rate of thrombosis | 0.44%/yr, with no cardiovascular risk factors; 1.05%/yr with risk factors | 1.59%/yr with no cardiovascular risk factors; 2.57%/yr with risk factors | 1.44%/yr with no cardiovascular risk factors; 1.64%/yr with risk factors | 2.36%/yr with no cardiovascular risk factors; 4.17%/yr with risk factors |
| Management of cardiovascular risk factors | Aspirin, 81–100 mg/day for vascular symptoms§ | Aspirin, 81–100 mg/day for vascular symptoms§ | Aspirin, 81–100 mg/day for vascular symptoms§ | Aspirin, 81–100 mg/day for vascular symptoms§ |
| Treatment | Cytoreductive therapy not recommended as initial treatment¶ | Cytoreductive therapy not recommended as initial treatment¶ | Cytoreductive therapy not recommended as initial treatment¶ | First-line therapy with hydroxyurea or interferon alfa-2a or anagrelide, second-line therapy with hydroxyurea, interferon alfa-2a,‖ or anagrelide, or referral to clinical trial |

* Tefferi A and Pardanani A, NEJM . Nov 2019 ** Barbui T et al, Blood 2012

# Aspirin Treatment in ET

- **No randomized clinical trials**

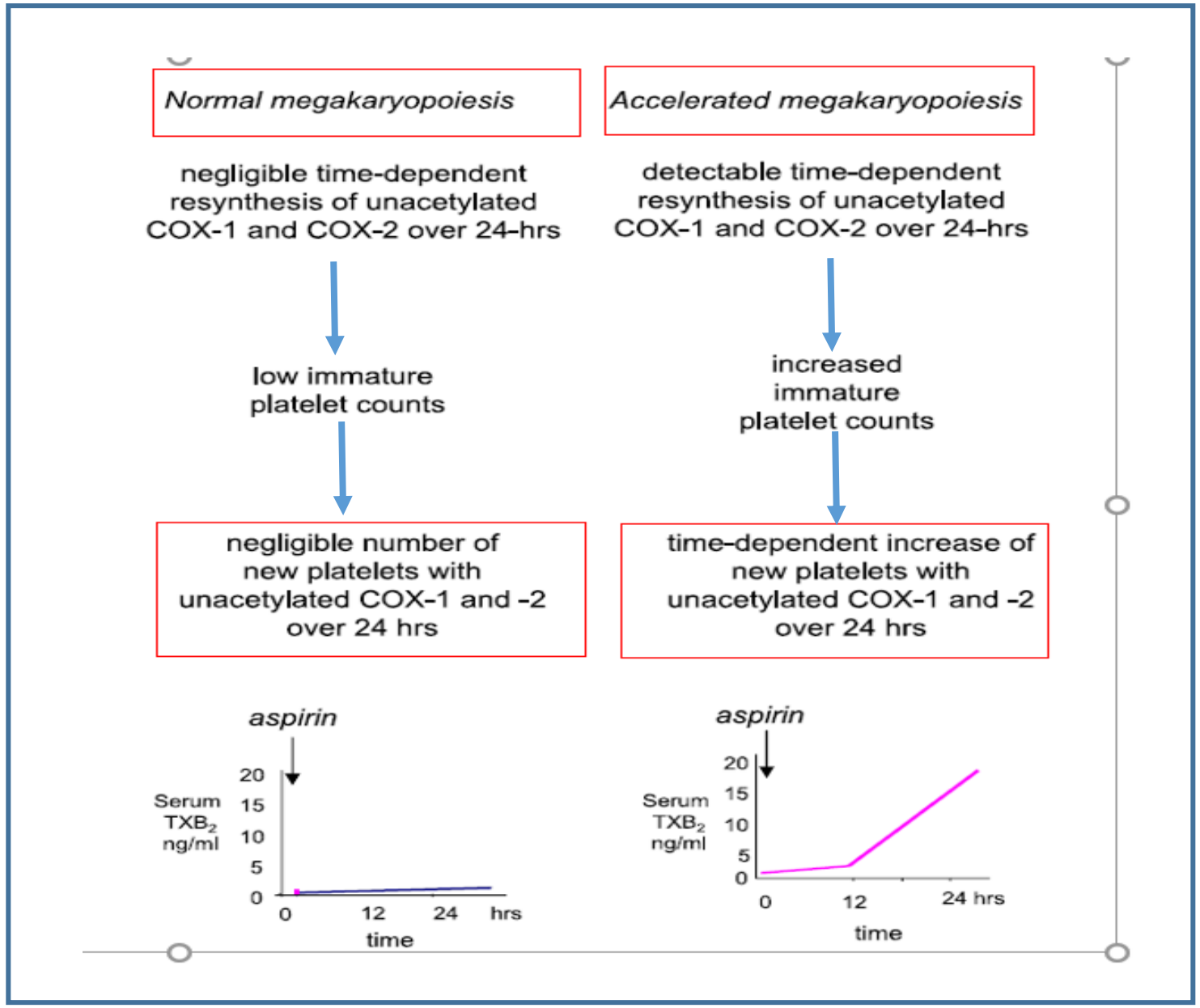
- **In *CALR*-mutated patients**, antiplatelet therapy did not affect the risk of thrombosis but is associated with a higher incidence of bleeding (12.9 vs. 1.8 x1000 pt-yrs, p=0.03).

- **In *JAK2*V617F-mutated patients**, low-dose aspirin is associated with a reduced incidence of thrombosis with no effect on the risk of bleeding.

- **In pre-PMF** aspirin is associated with increase risk

Alvarez-Larran A, Haematologica; 2016;. Barbui T et al, JCO 2011.

# Effect of different aspirin regimens on serum TXB2

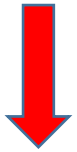



Pascale S. et al. Blood 2012;119:3595

# Are platelet levels up to 1500×$10^9$/l risk factors for thrombosis?

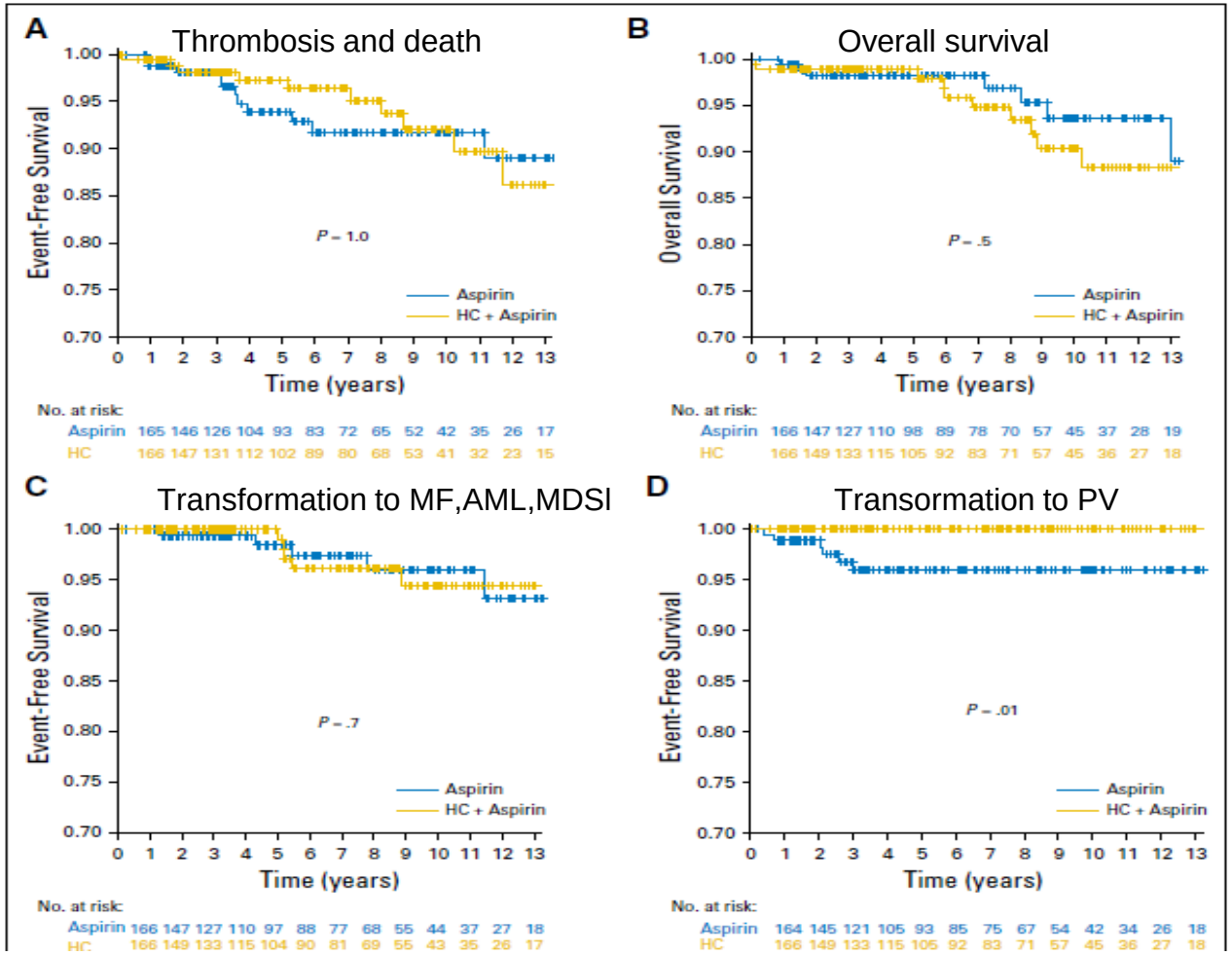
***No treatment for low-risk thrombocythaemia: results from a prospective controlled study*** *(Ruggeri M, …..Barbui T (BJH 1998*)

**We conclude that** the thrombotic risk in young ET patients, with no thrombotic history and a platelet count up to 1500×$10^9$/l, is not increased compared to the normal population and that a conservative therapeutic approach should therefore be considered in these patients.



**Comments by UK Investigators ( Letter, BJH 1998)**This clearly has relevance to the study design of the current Medical Research Council Primary Thrombocythaemia (MRC PT1) study (TC Pearson et al, 1998)

# Hydroxycarbamide Plus Aspirin Versus Aspirin Alone inPatients With Essential Thrombocythemia Age 40 to 59 Years Without High-Risk Features



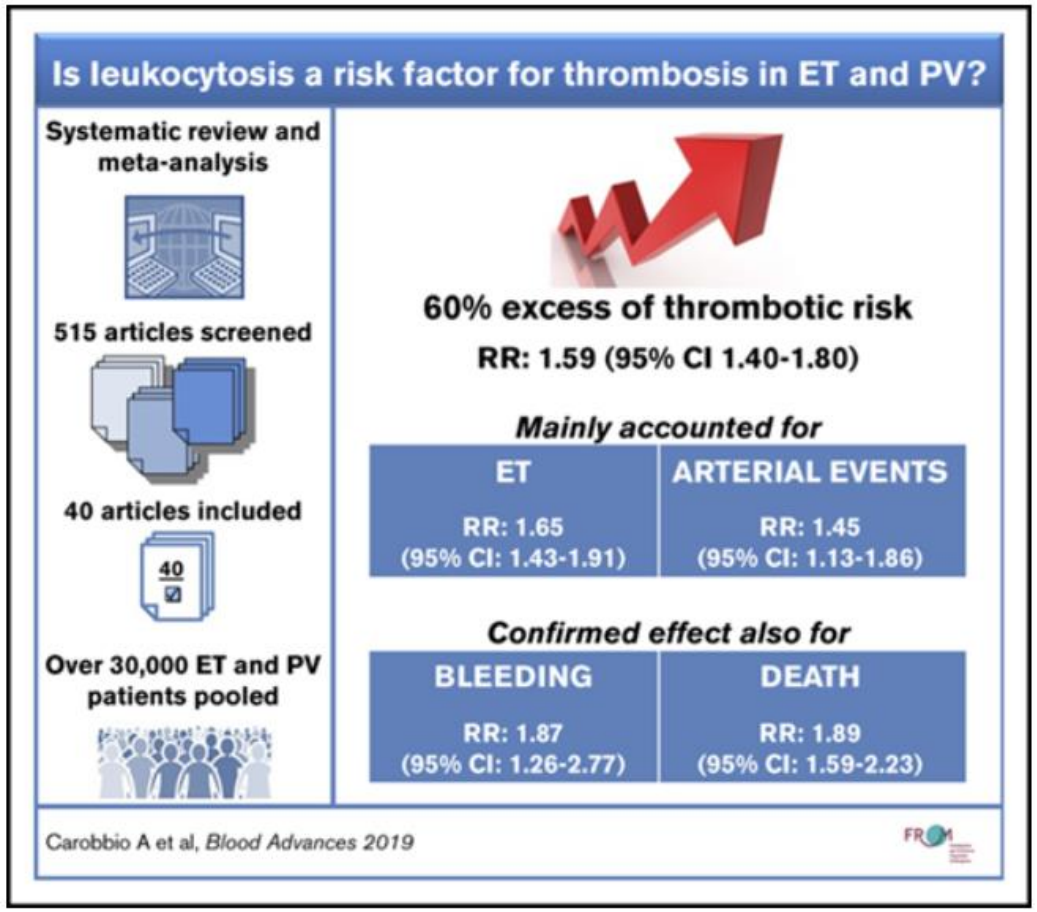

**CONCLUSION**

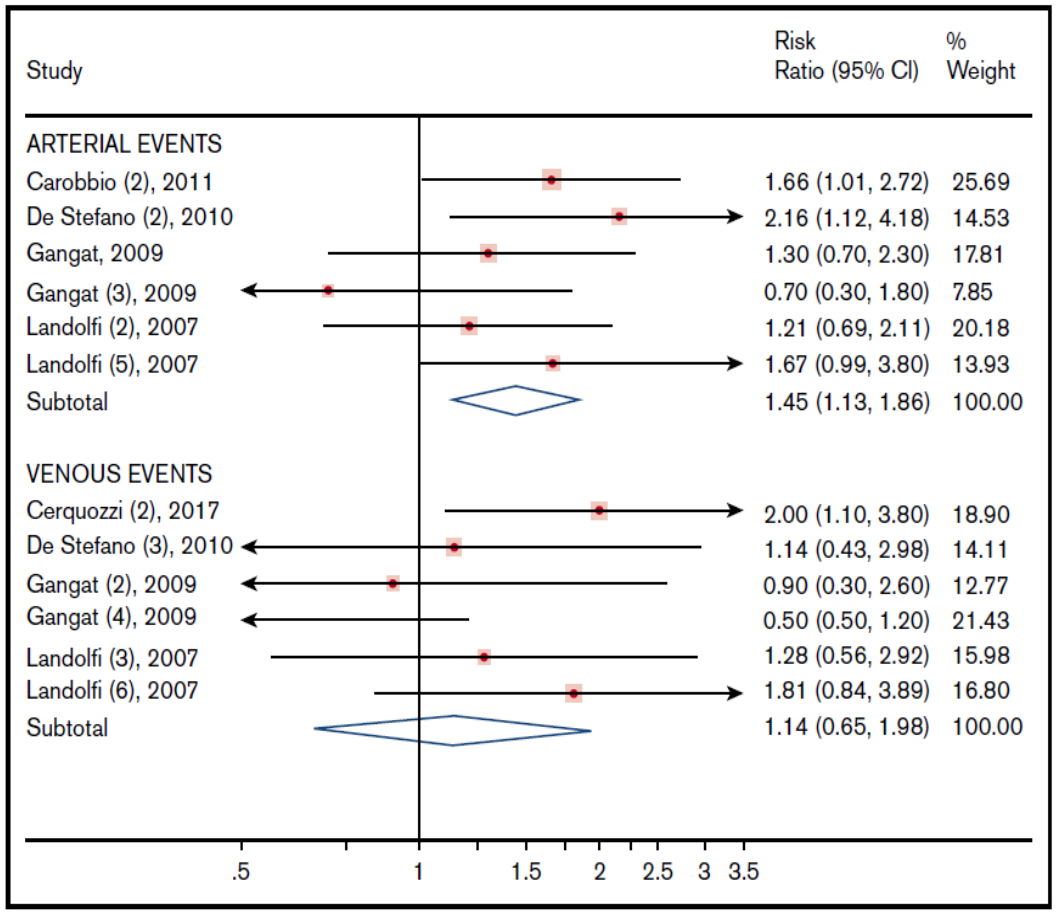
In patients with ET age 40 to 59 years and lacking high-risk factors for thrombosis or extreme thrombocytosis, **preemptive addition of HU to aspirin did not reduce vascular events, myelofibrotic transformation, or leukemic transformation.**

Patients age 40 to 59 years without other clinical indications for treatment (such as previous thrombosis or hemorrhage) who have **a plateletcount,1,500x 10L should not receive cytoreductive therapy.**

*J Clin Oncol 36:3361-3369. © 2018 I*

# Leukocytosis and thrombosis in essential thrombocythemia and polycythemia vera: a systematic review and meta-analysis




Carobbio A, et al, Blood advances 2020

National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2020
# Essential Thrombocythemia

NCCN Guidelines Index
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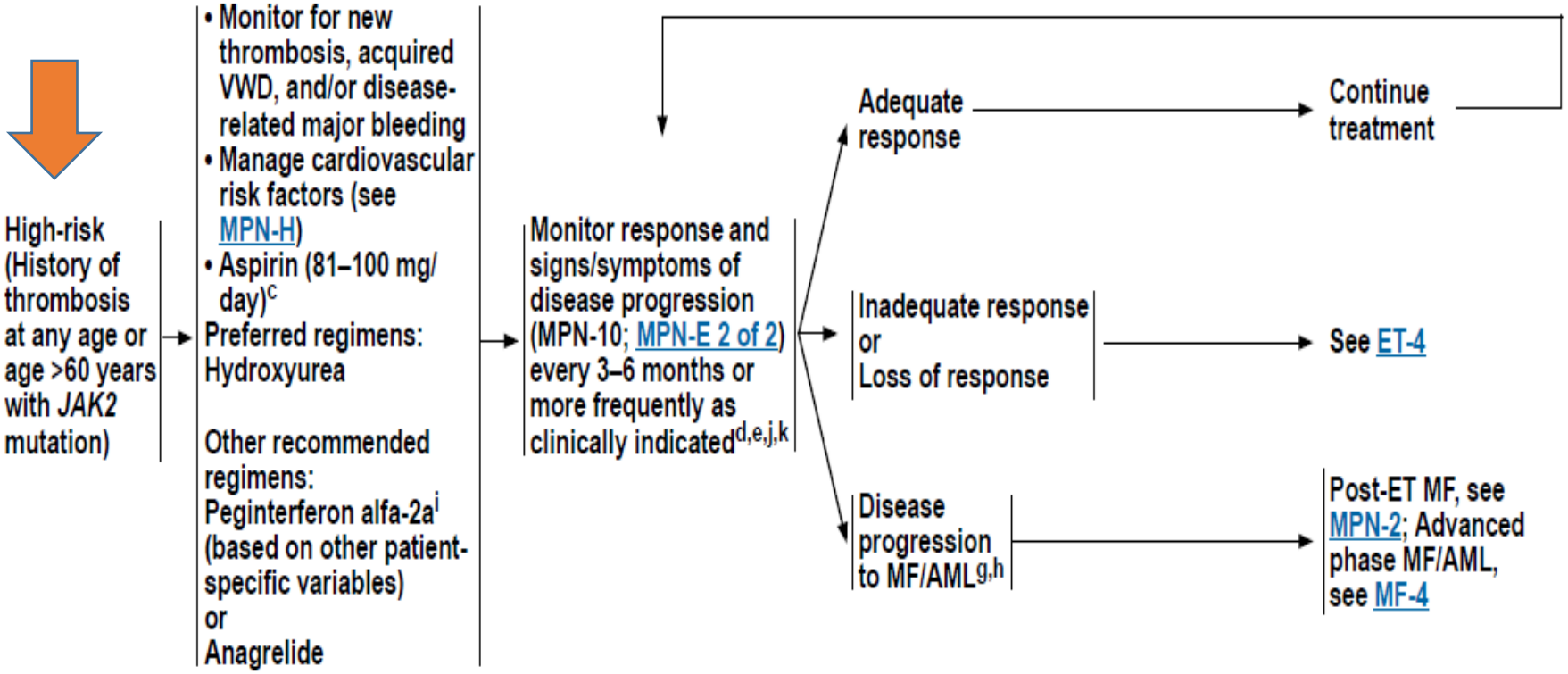
Discussion

## TREATMENT FOR HIGH-RISK ESSENTIAL THROMBOCYTHEMIA[a]



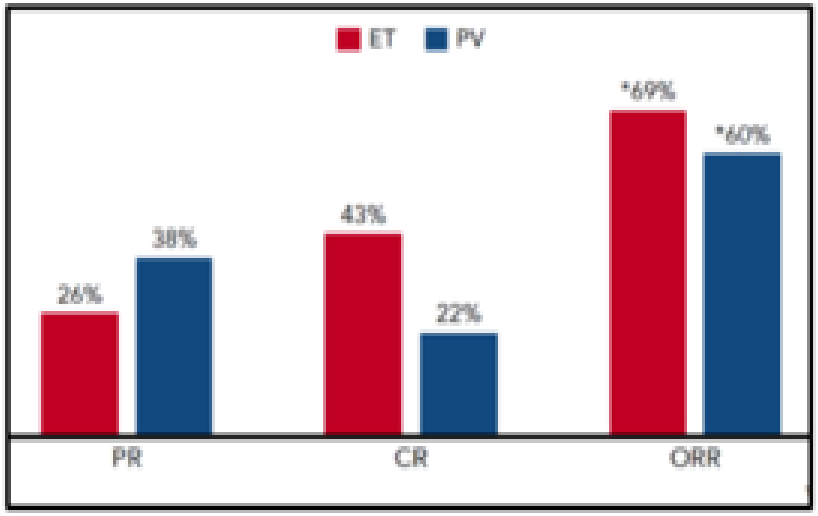

[a]See Special Considerations in the Treatment of PV and ET (MPN-H)

# ELN recommendations for cytoreductive therapy in high-risk ET

*The Panel agreed on recommending* ***hydroxyurea and INFα as first-line therapy*** *agents.*

*However, even though the majority of the experts indicated* ***anagrelide*** *as an appropriate choice for first-line therapy in ET,* ***the panel did not reach a consensus on recommending the agent in this setting,*** *arguing that the evidence of non-inferiority with hydroxyurea was of insufficient quality, and the risk-benefit ratio unfavourable.*

# Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea.




**CR was defined** as correction of hematocrit (<45% without phlebotomy for PV), platelet count (<400×$10^9$/L), white blood cell count (<10×$10^9$/L), and resolution of splenomegaly and disease-related symptoms.

**This prospective, open-label, phase II clinical** trial was conducted across sites in North America and Europe.

A total of 115 patients were enrolled**: 65 patients with ET** and 50 patients with PV. All participants had disease that was either resistant (32.5%) or intolerant (67.5%) to hydroxyurea.

The investigators observed that the presence of **a *CALR* mutation** was associated with superior clinical, but not molecular, response (56.5% vs. 28.0%, respectively; odds ratio = 3.34; 95% CI 1.28-8.67; p=0.01).

Yacoub A et al, Blood 2019

# Ruxolitinib for essential thrombocythemia refractory or intolerant of hydroxyurea

**Phase II study** (Vertovsek et al Blood 2014)

Hydroxyurea resistant ET patients can **achieve clinically meaningful and durable reductions in platelet and WBC counts** and **improvements in ET-related symptoms** with ruxolitinib treatment.

**RCT Ruxo vs BAT** (Harrison et al Blood 2017)

Ruxolitinib **significantly improved some disease-related symptoms,** but rates of thrombosis, hemorrhage, or transformation were not different.

.

# Rate of major thrombosis by IPSET risk groups and calendar period of diagnosis in ET (n=891)

(AMI, stroke, PAT, DVT, PE, TIA, abdominal)

| | Low | Intermediate | High |
|---|---|---|---|
| **Dx before 2005** IR per 100 person/yrs | IR: **1.28** % pts/yr; 95% CI: 0.41-2.05 | IR: **1.58** % pts/yr; 95% CI: 0.51-4.89 | IR: **3.58** % pts/yr; 95% CI: 2.08-6.17 |
| **Dx after 2005** IR per 100 person/yrs | IR: **1.04** % pts/yr; 95% CI: 0.43-2.49 | IR: **1.85** % pts/yr; 95% CI: 0.93-3.71 | IR: **3.21** % pts/yr; 95% CI: 2.07-4.98 |

Barbui T et al, unpublished

# CONCLUSION

- Special **attention to bone marrow morphology** is required in order to distinguish ET from pre-PMF and *JAK2*-mutated ET from PV.
- Such details are prognostically relevant as **bleeding, survival, myelofibrosis and AML has been shown to be significantly worse** in pre-PMF than in “true ET”..
- **Life-shortening morbidities in ET are largely due to vascular events**—both arterial and venous clotting as well as hemorrhage.
- The **revised IPSET-thrombosis should guide the choice of therapy** in clinical practice and should be considered in clinical trials.
- **Thrombosis and bleeding remain an unmet need** and rigorous RCT in well diagnosed ET WHO-patients, are needed.