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Managing ET in 2019

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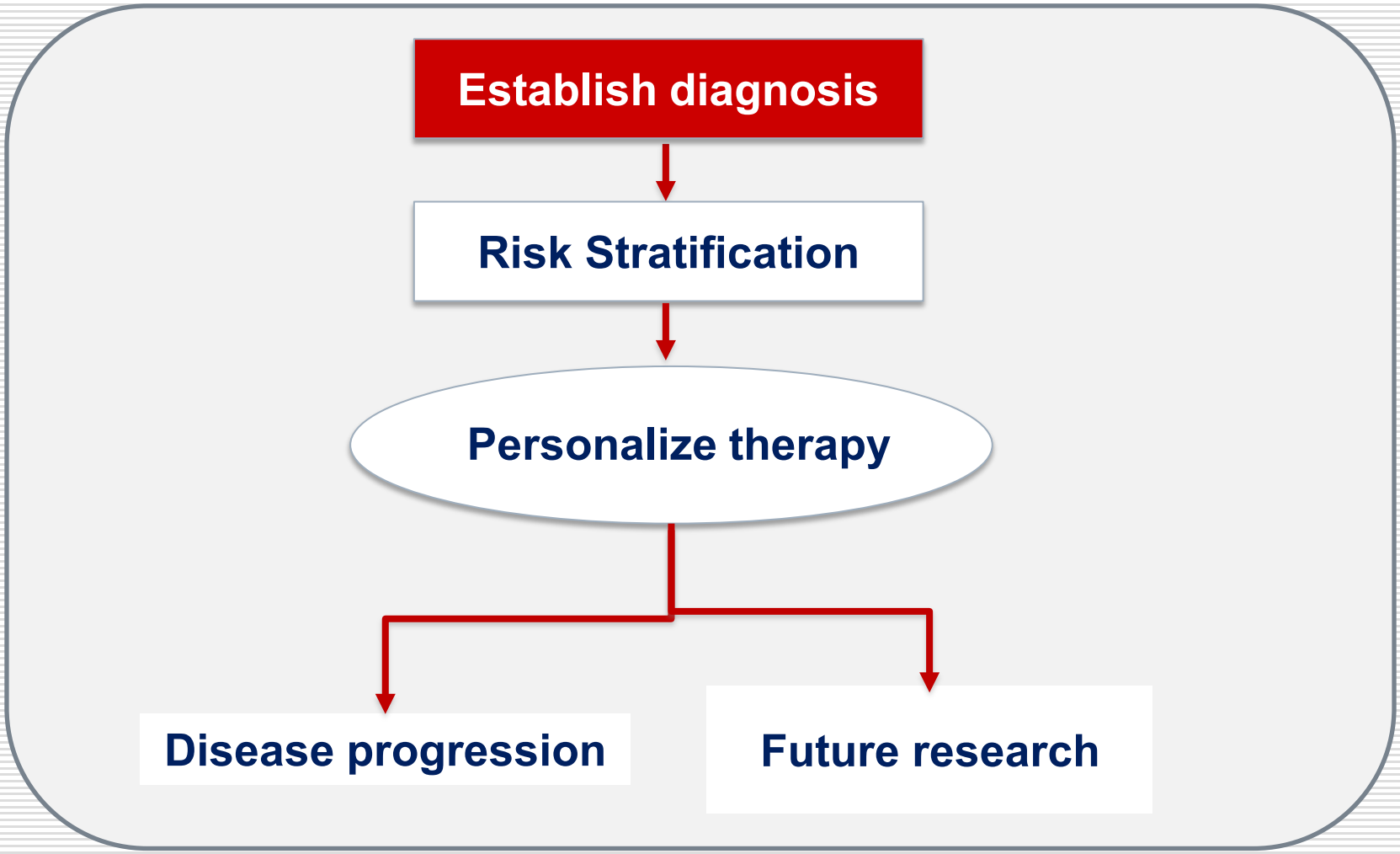
Managing ET in 2019



UPDATE - 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

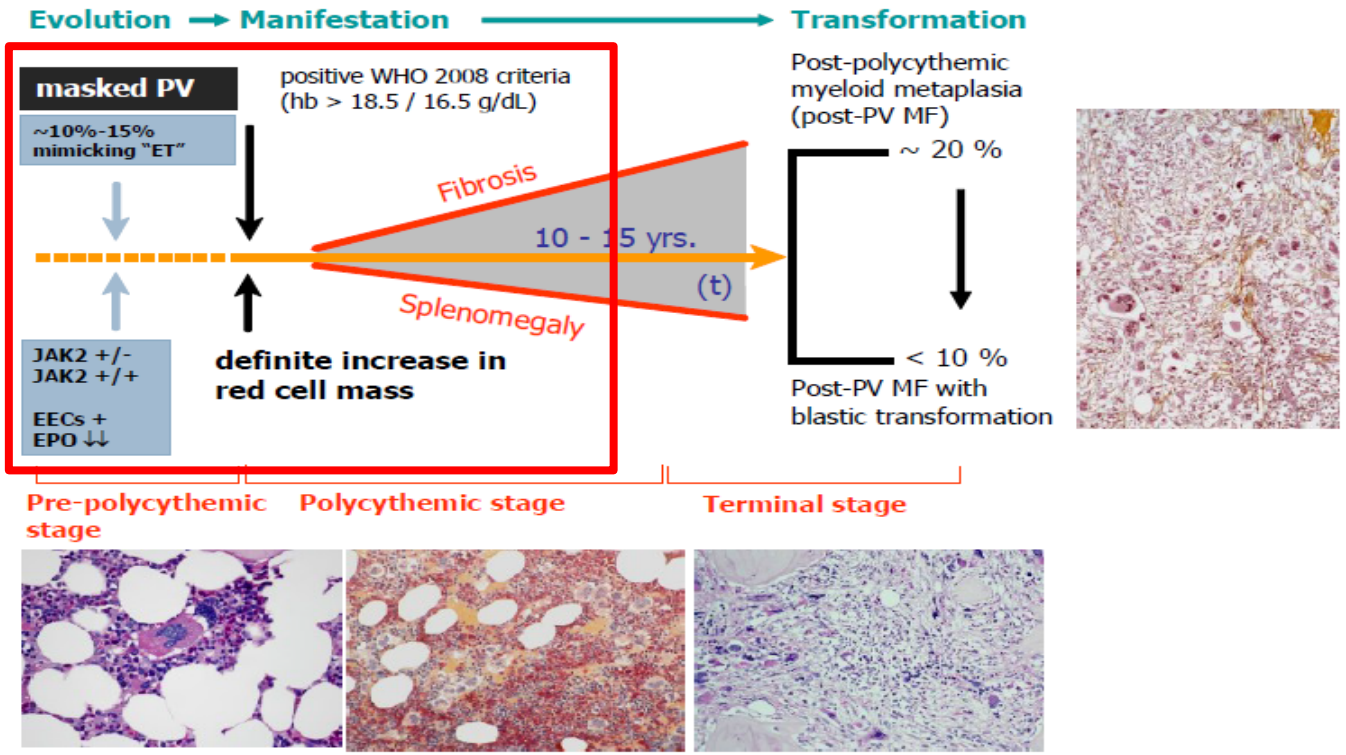
Diagnosis of ET requires meeting all four major criteria or the first three major criteria and one of the minor criteria

DIAGNOSIS

Recognizing ET from Early-Phase PV in JAK2 mutated patients

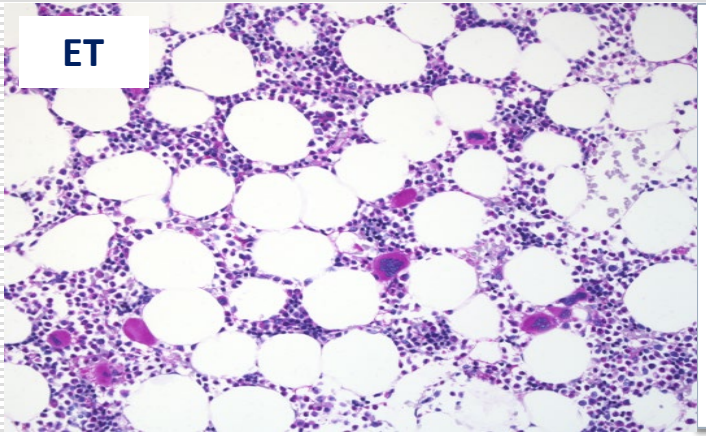
PV: WHO 2008 diagnostic criteria

Dynamics of the disease process in PV



DIAGNOSIS

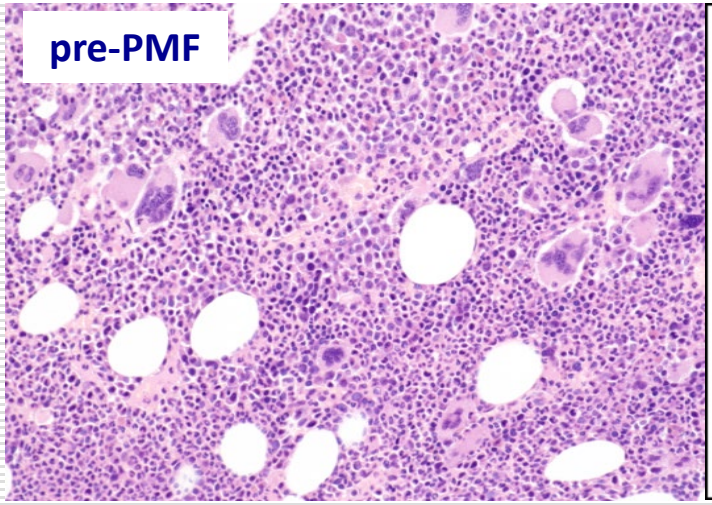
Recognizing ET from Prefibrotic-PMF



Clinical implications:

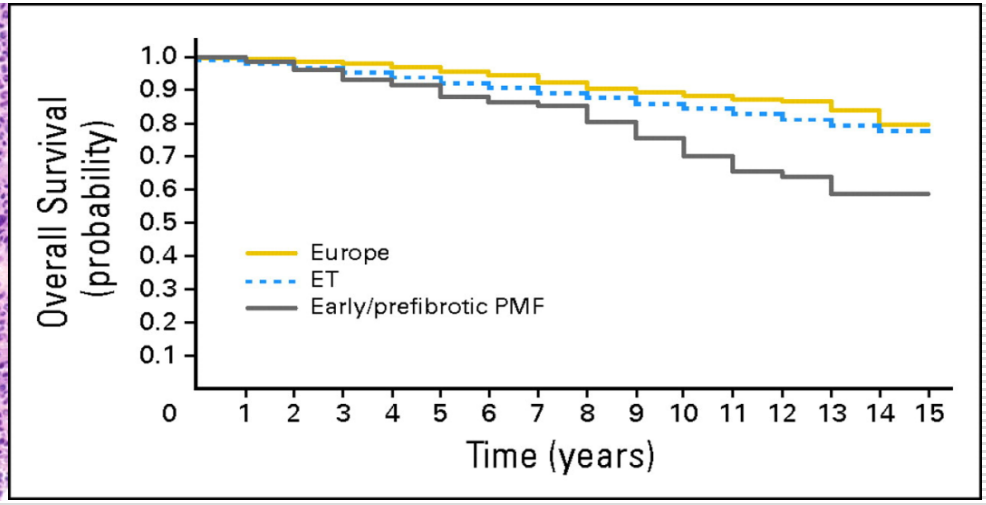
- Clinical presentation is different (anemia, leukcytosis, LDH, splenomegaly)
- Thrombosis is similar to ET
- Time to disease progression is shorter in pre-PMF[1]
- Prefibrotic-PMF is associated with an almost double rate of hemorrhage compared to ET
- Careful with aspirin

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



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

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



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

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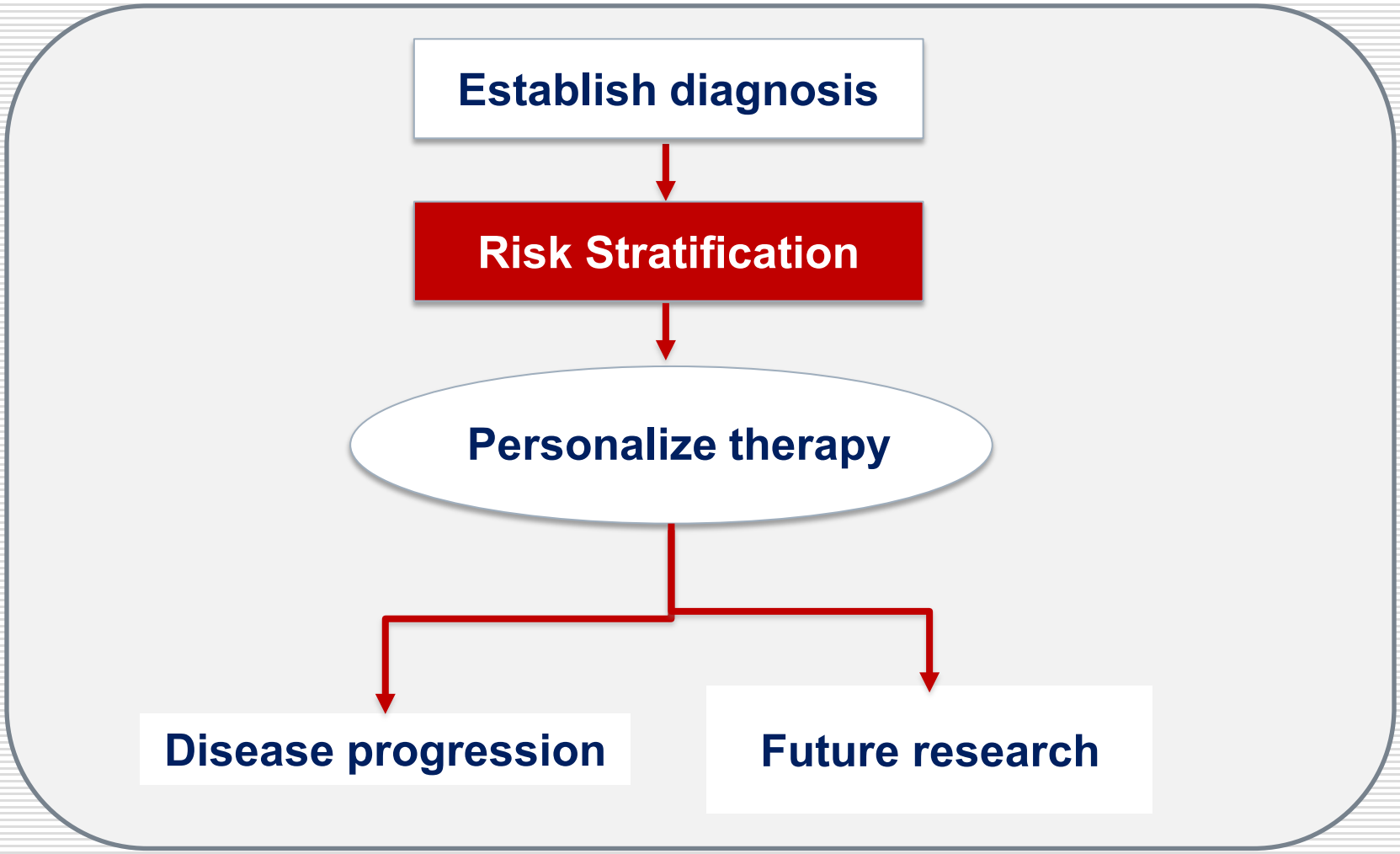
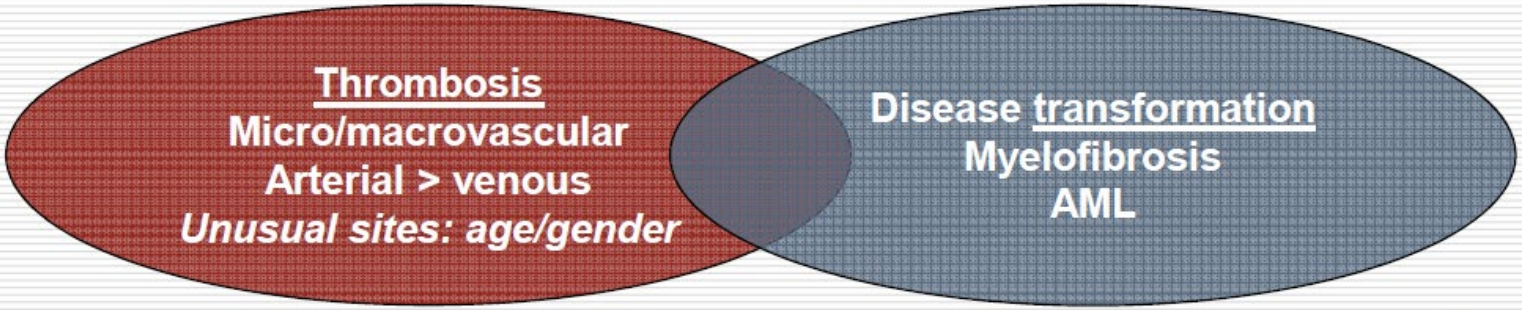


The ET disease burden



Newly diagnosed → Typically second decade

Symptoms

Cytokine: fatigue, pruritus, constitutional symptoms, bone pain

Vascular: headache, dizziness, numbness, decreased concentration, low mood, sexuality problems

Disease evolution: splenomegaly, constitutional symptoms

1. Mesa RA et al. Cancer. 2007; 109:68-76. 2.Scherber R et al. Blood. 2011;118:401-408.
3. Geyer HL et al. Blood. 2014; 123:3803-3810.

ELN recommendations for Risk stratification in ET/PV

*The **conventional prognostic systems** in ET/PV **are based upon age and previous history of thrombosis** that separate patients into low- (age <60 years and no history of thrombosis) or high-risk (age ≥ 60 years or prior thrombosis) categories.*

Jak2 mutation status is an independent factor for total thrombosis in ET (n= 891)*

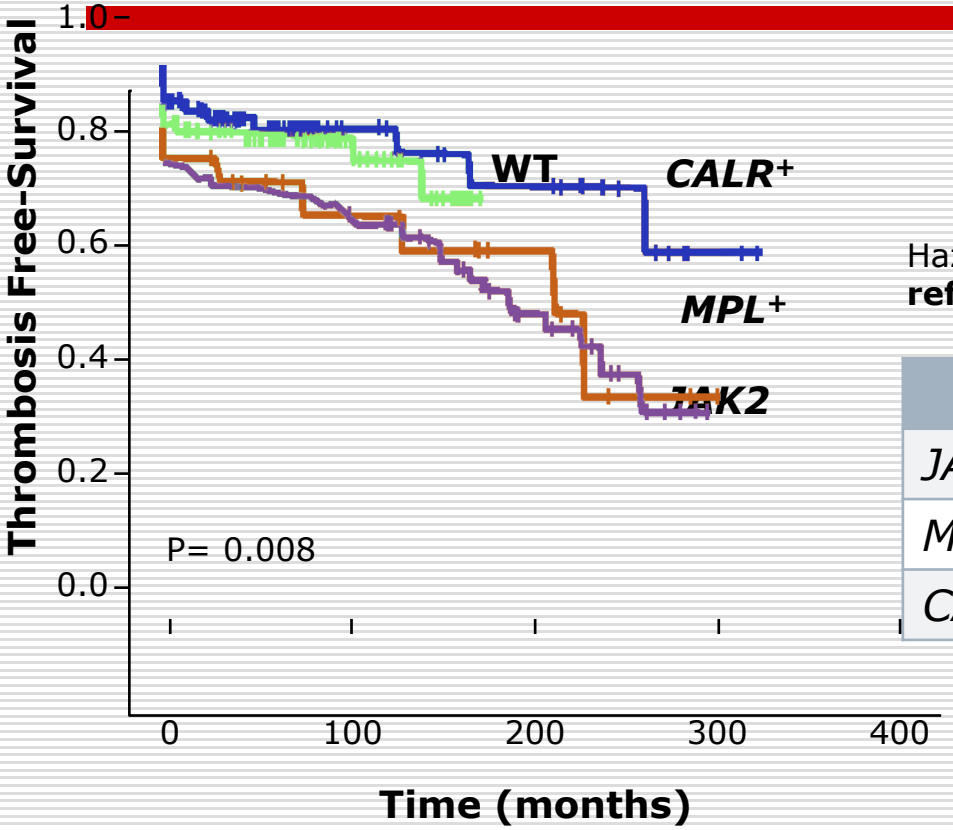
Risk factor	HR	95% CI
Age > 60	1.50	(1.00-2.25)
CV risk factors	1.56	(1.03-2.36)
Previous thrombosis	1.93	(1.27-2.91)
JAK2 V617F	2.04	(1.19-3.48)

* Multivariate model adjusted for: sex, Hb, WBC and plt counts, HU and aspirin

*Leukocytosis associated with arterial and not venous thrombosis

Carobbio A et al. Blood 2011;117:5857-9; Barbui T et al. Blood 2012

CALR Mutated patients have lower rate of thrombosis in Essential thrombocythemia

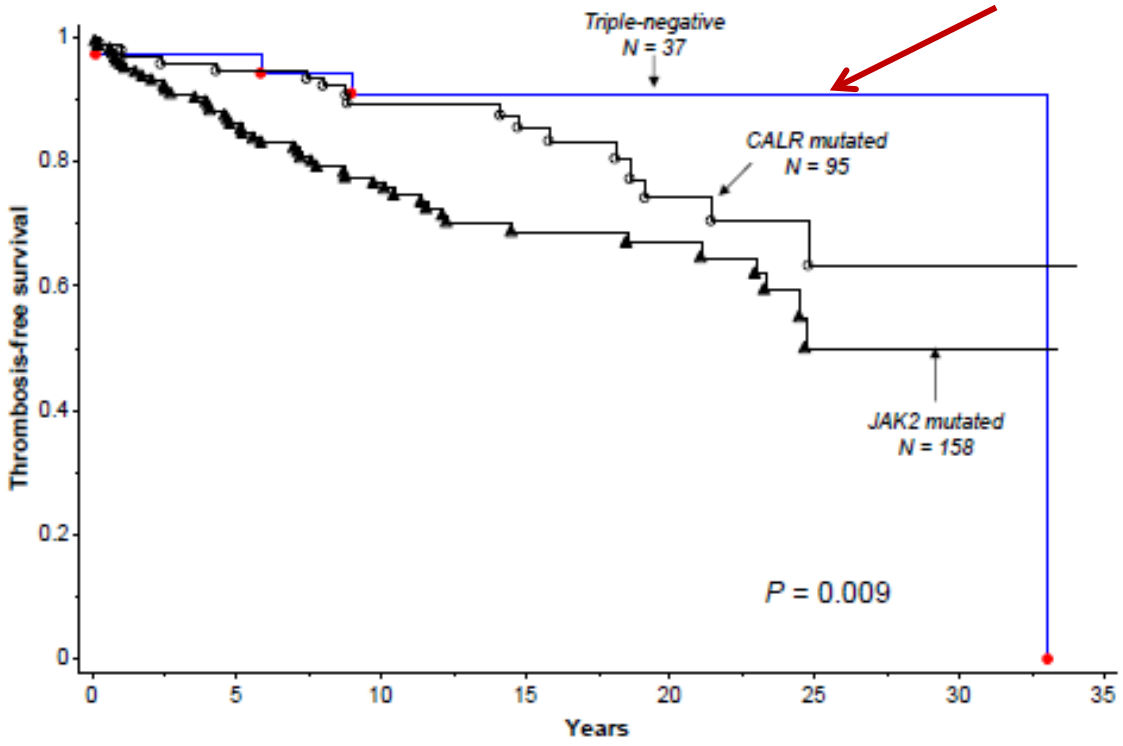


Hazard Ratio: **Wild type patients were taken as a reference population**

	HR	95% CI
JAK2 mut	1.78	1.06-3.18
MPL mut	1.65	1.70-3.92
CALR mut	0.74	0.33-1.00

Rotunno G, et al. Blood. 2014; 123:1552-5

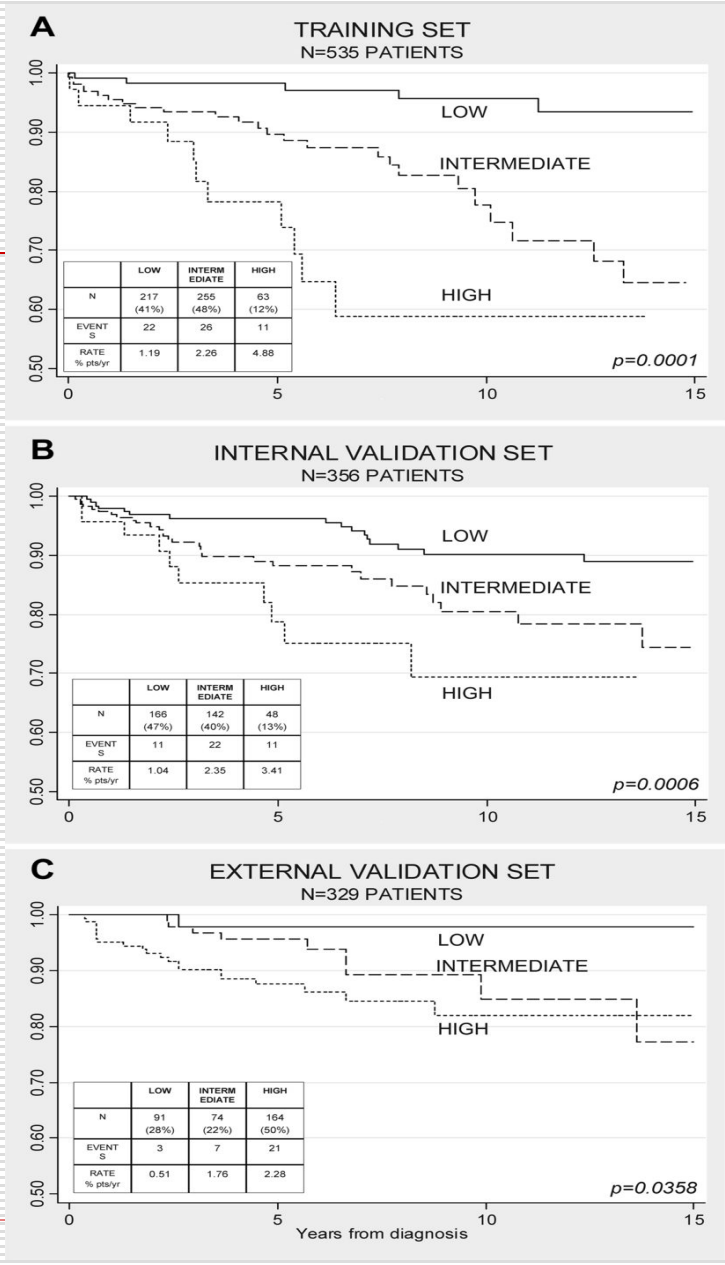
Thrombosis –free survival in patients with ET who were triple-negative or harbored JAK2 or CALR mutations (n=290)



Gangat et al, European J Hematology, 2014

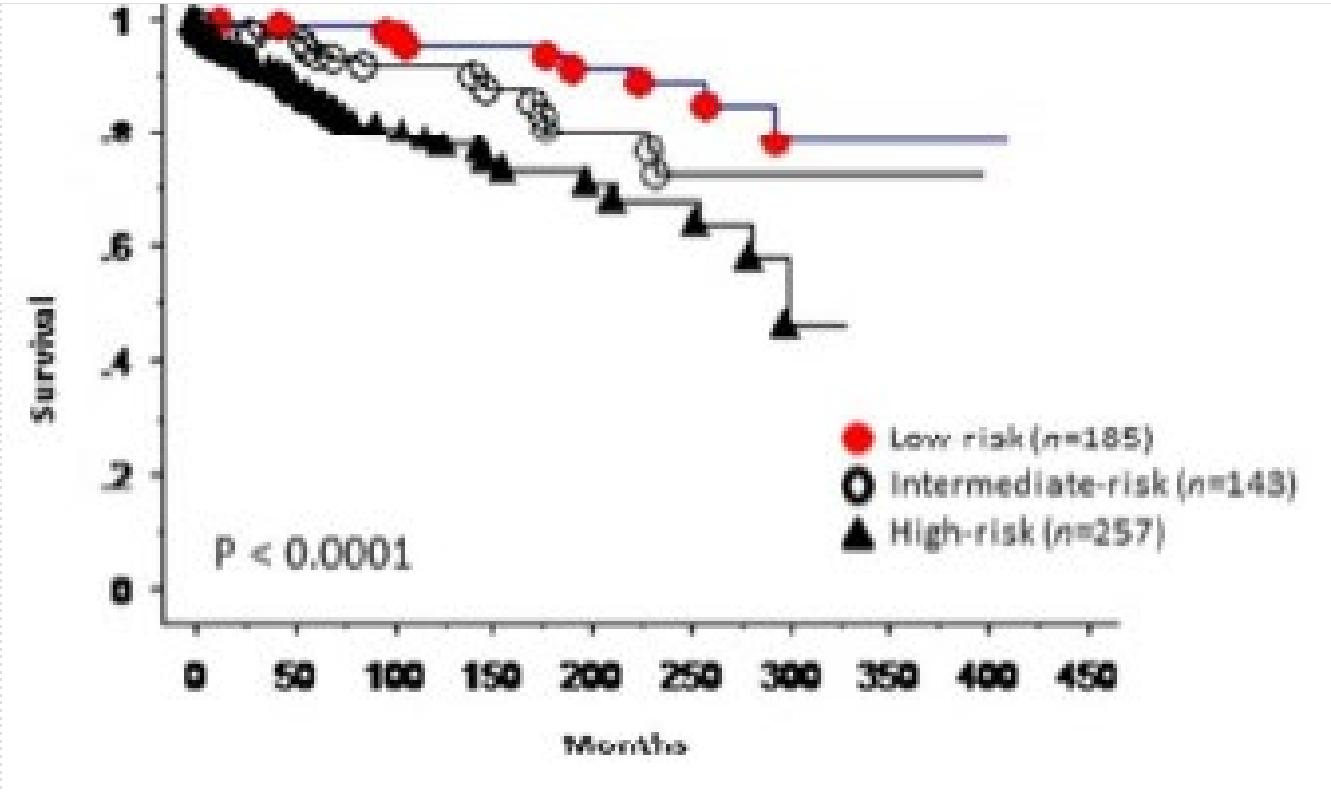
IPSET-Thrombosis Model

- **Model in WHO-defined ET**
  - ***Factors***: age > 60 years (1 point), thrombosis history (2 points), cardiovascular risk factors (1 point), and *JAK2* V617F (2 points).
  - ***Model***: LR if < 2 points;
    IR if 2 points;
    HR if > 2 points
  - ***Risk of thrombosis***:
    1.03% p/y (LR),
    2.35% p/y (IR)
    3.56% p/y (HR
  - This model better predicts thrombosis than conventional one and is not affected by CALR-mutation (Finazzi et al, Blood 2015)



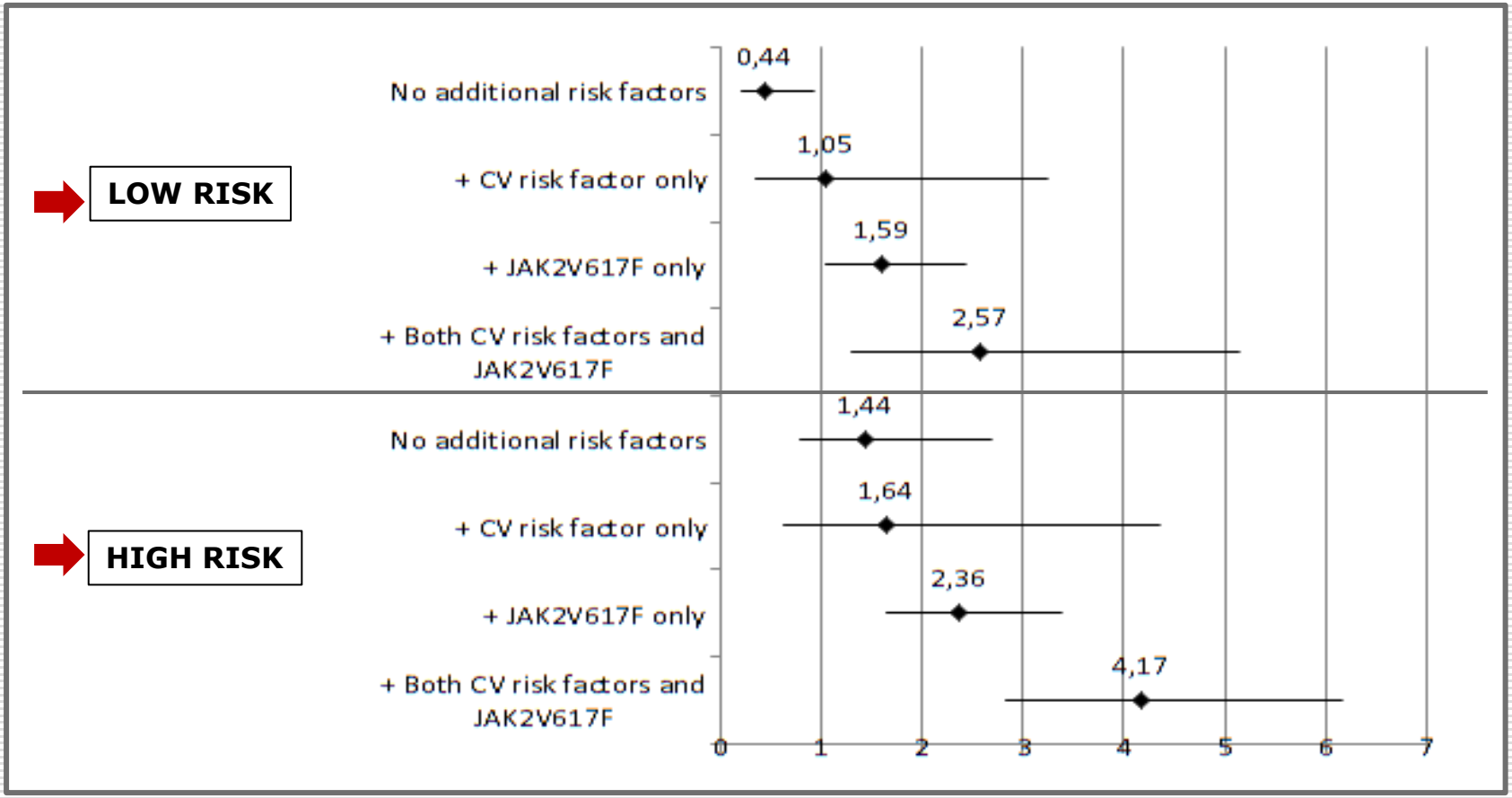
Barbui et al. Blood 2012 Dec 20;120(26):5128-33

Validation of IPSET-thrombosis model in 585 patients with ET (Mayo Clinic)



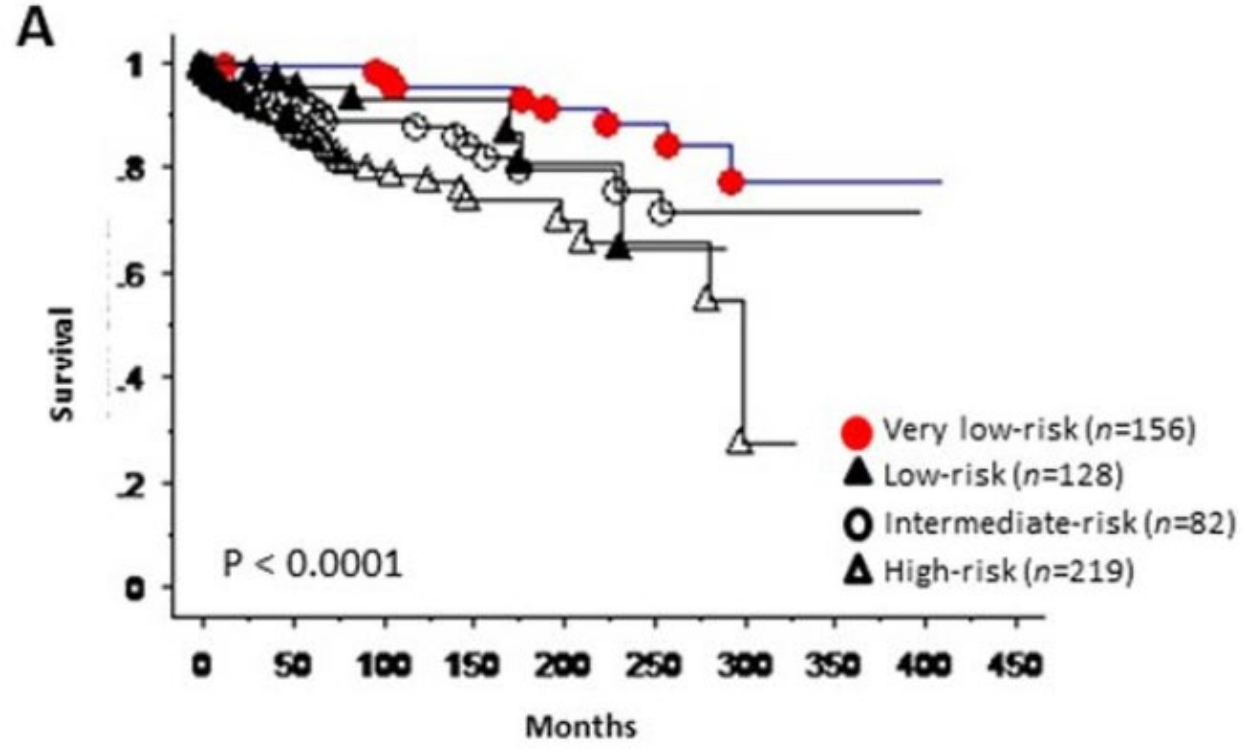
RISK STRATIFICATION

Revised IPSET-Thrombosis. Influence of risk factors on the rate of vascular events in a cohort of 1019 conventionally defined low and high risk patients with ET



Barbui T et al. Blood Cancer J. 2015; Barbui T. AJH 2016

Validation of the revised International Prognostic Score of Thrombosis for Essential Thrombocythemia (IPSET-thrombosis) in 585 Mayo Clinic patients



Am J Hematol 2016

ELN and NCCN recommendations for Risk stratification in ET

*In ET, **the IPSET system** that includes age, previous thrombosis, cardiovascular risk factors, and JAK2V617F mutation, is the recommended prognostic system and it should be scored in all patients at diagnosis*

Barbui T et al, JCO 2011; Leukemia 2018 Mesa et al, National Comprehensive Cancer Network® (NCCN®)

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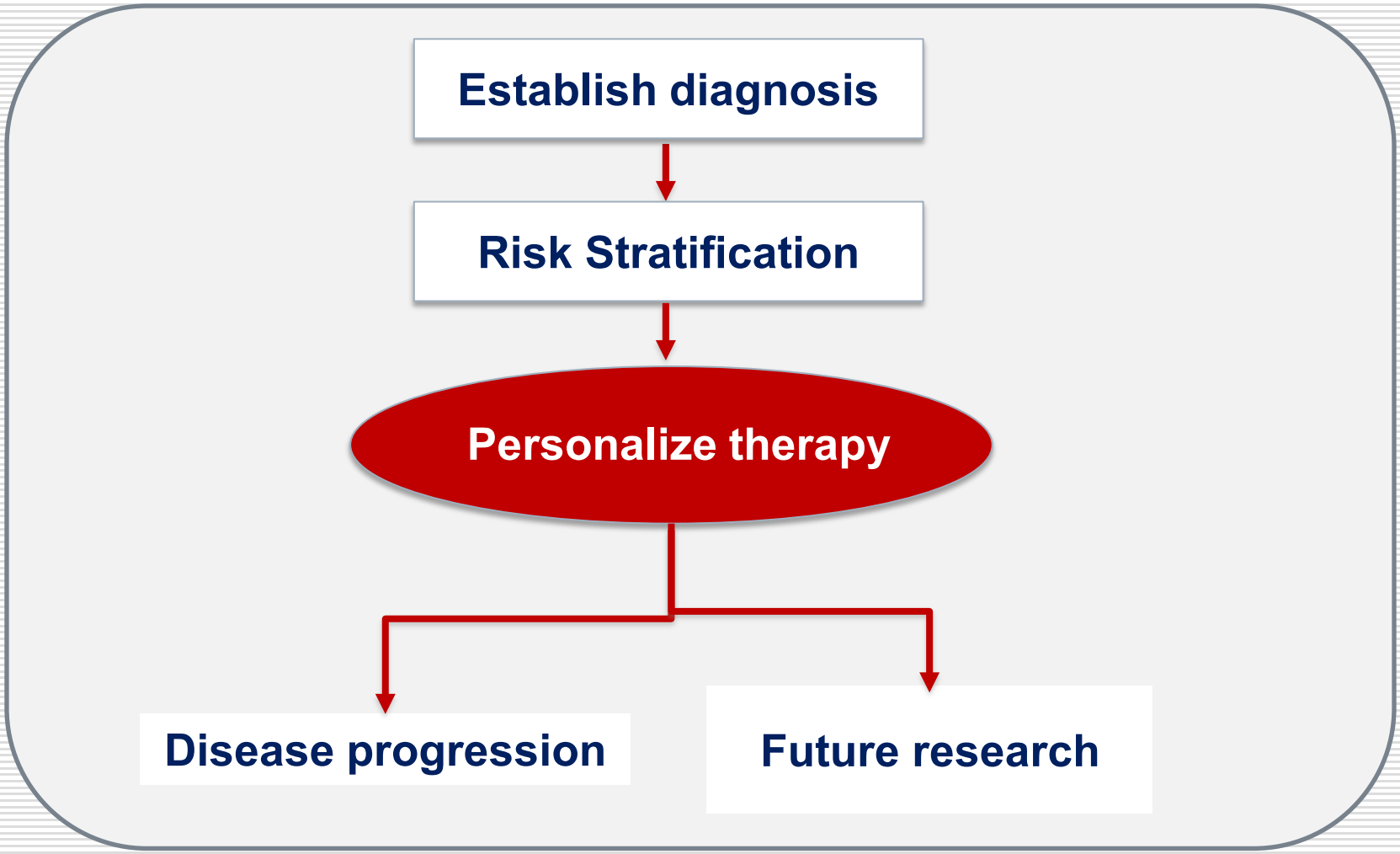

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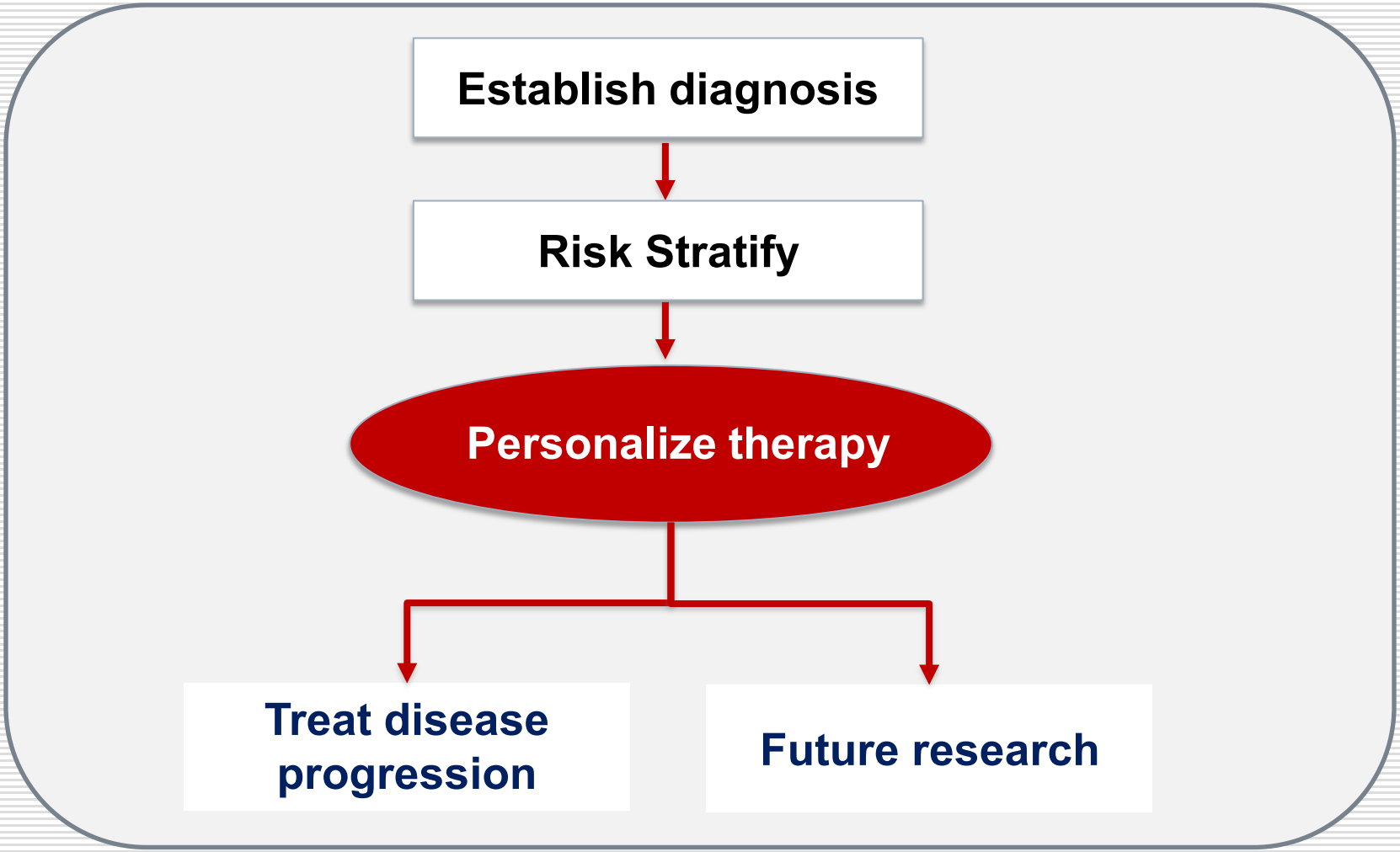


THERAPY

Low dose aspirin by risk of thrombosis in patients with ET

Very low thrombotic risk: No aspirin

- No history of thrombosis
- Age <60 years
- JAK2V617F-unmutated
- No cardiovascular risk factors (CVR)

Low thrombotic risk : Yes aspirin

- No history of thrombosis
- Age <60 years
- JAK2V617F-mutated and/or CVR present

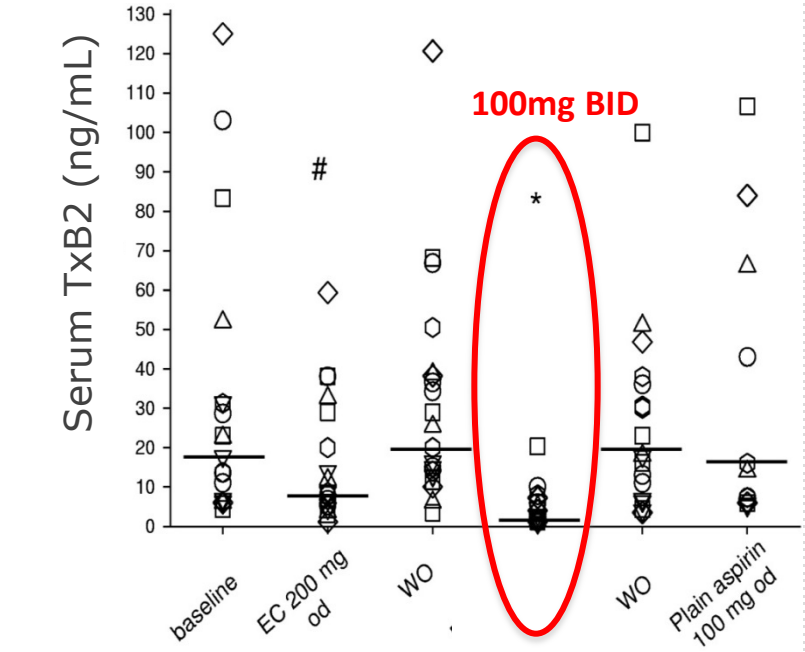
High thrombotic risk: Aspirin twice?

- History of thrombosis and/or Age ≥ 60 year
- JAK2V617F-mutated and/or CVR present

"Personalized" Aspirin Treatment: 0, 1, 2 daily?

- **In *CALR*-mutated patients**, antiplatelet therapy did not affect the risk of thrombosis but was 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 was associated with a reduced incidence of thrombosis with no effect on the risk of bleeding.
- **In pre-PMF** aspirin is associated with increase risk

Effect of different aspirin regimens on serum TXB2



A randomized trial (ARES) is ongoing.

Alvarez-Larran A, Haematologica 2016; 8:926.Pascale S et al. Blood 2012;119:3595. Barbui T et al, JCO 2011

Cytoreductive therapy for LOW-RISK with levels of platelets up to 1500×10^9/l ?

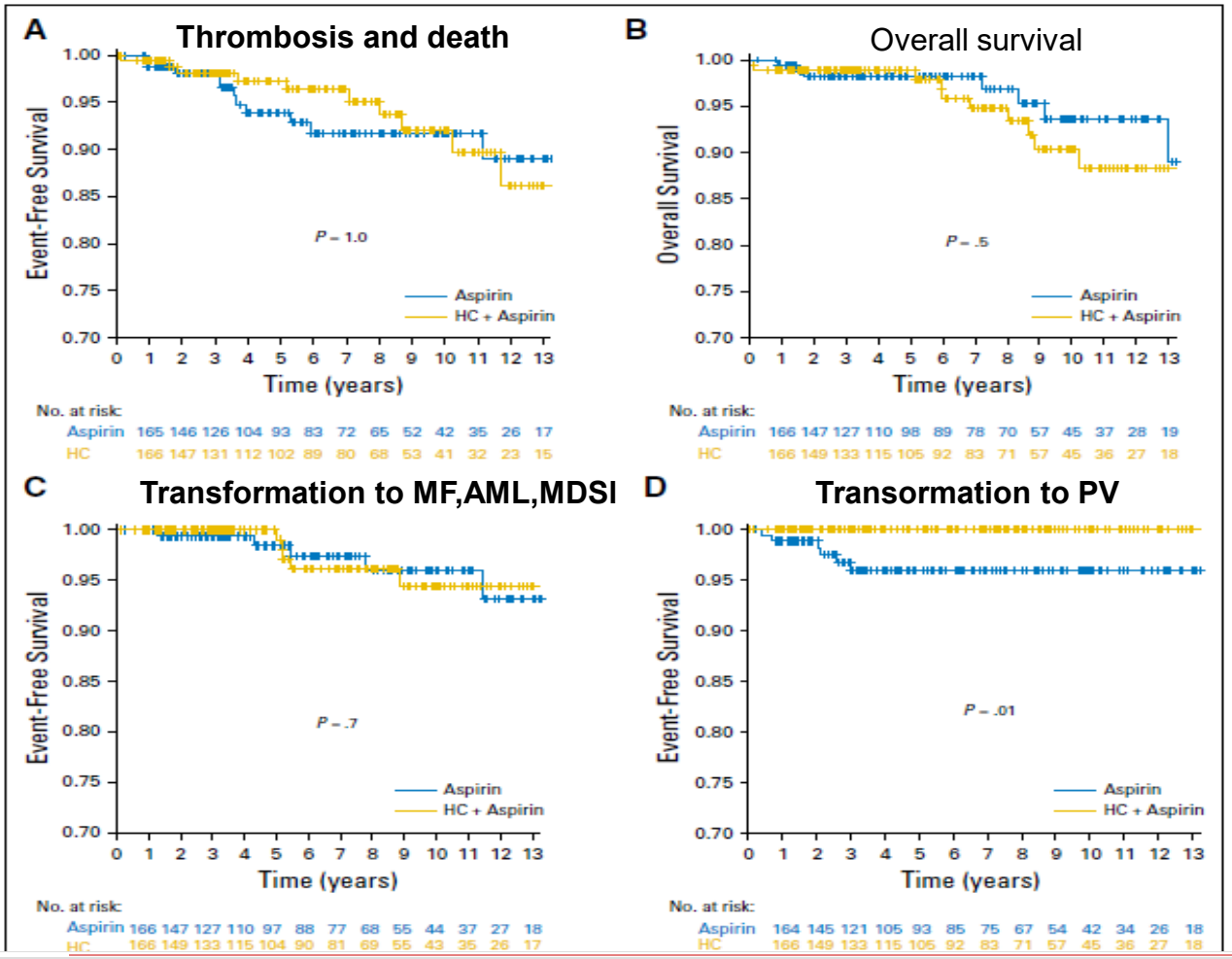
No treatment for low-risk thrombocythaemia: results from a prospective study (Ruggeri M.…Barbui T . BJH 1998)

We conclude that the thrombotic risk in young ET patients, with no thrombotic history and a platelet count $<1500\times10^9$/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)

CYTOREDUCTION THERAPY IN LOW-RISK ?

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



CONCLUSION

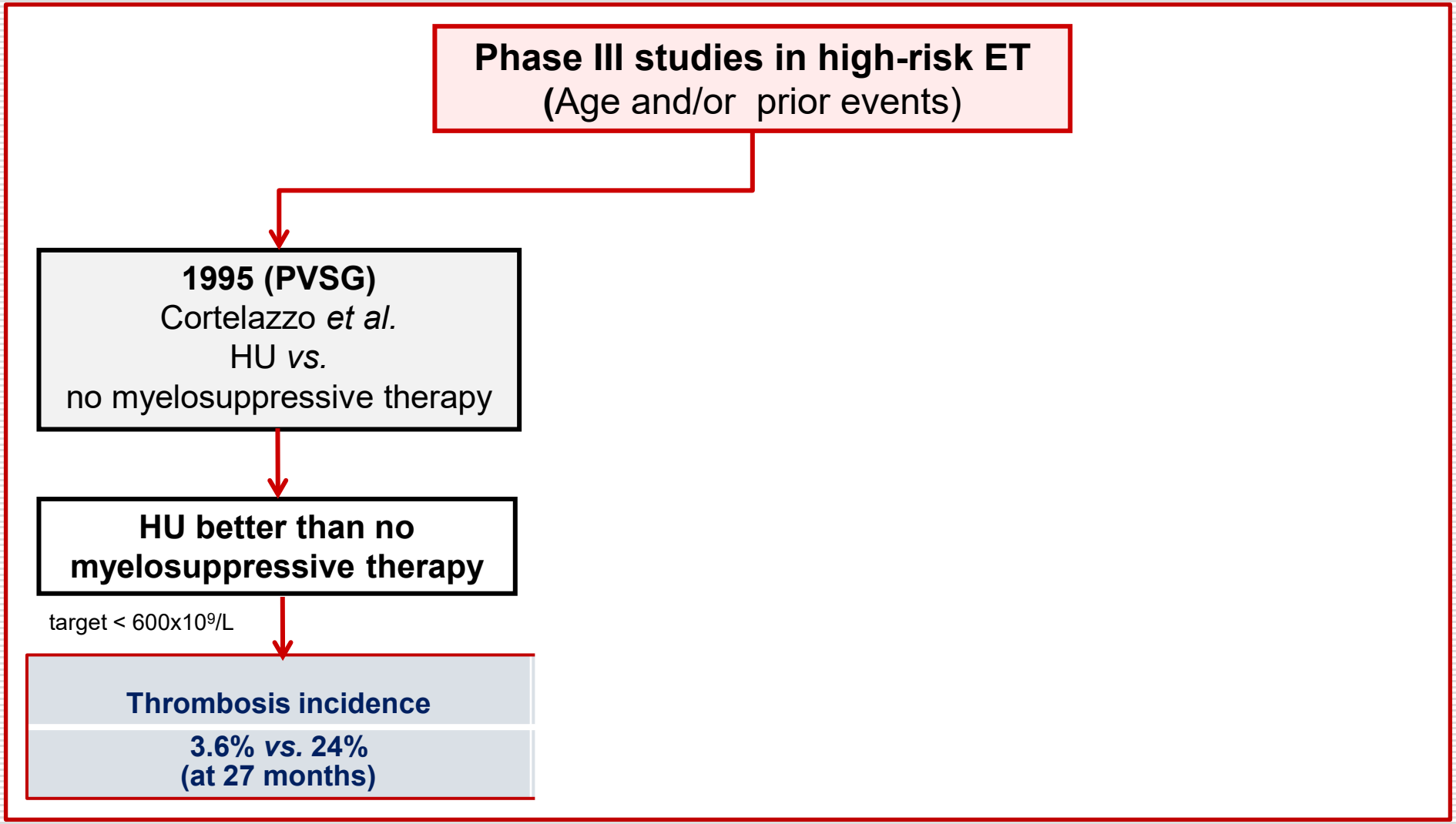
In patients with ET age 40 to 59 years and lacking high-risk factors for thrombosis or extreme thrombocytosis, preemptive addition of hydroxycarbamide to aspirin did not reduce vascular events,myelofibrotic transformation, or leukemic transformation.

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

CYTOREDUCTION THERAPY IN HIGH-RISK

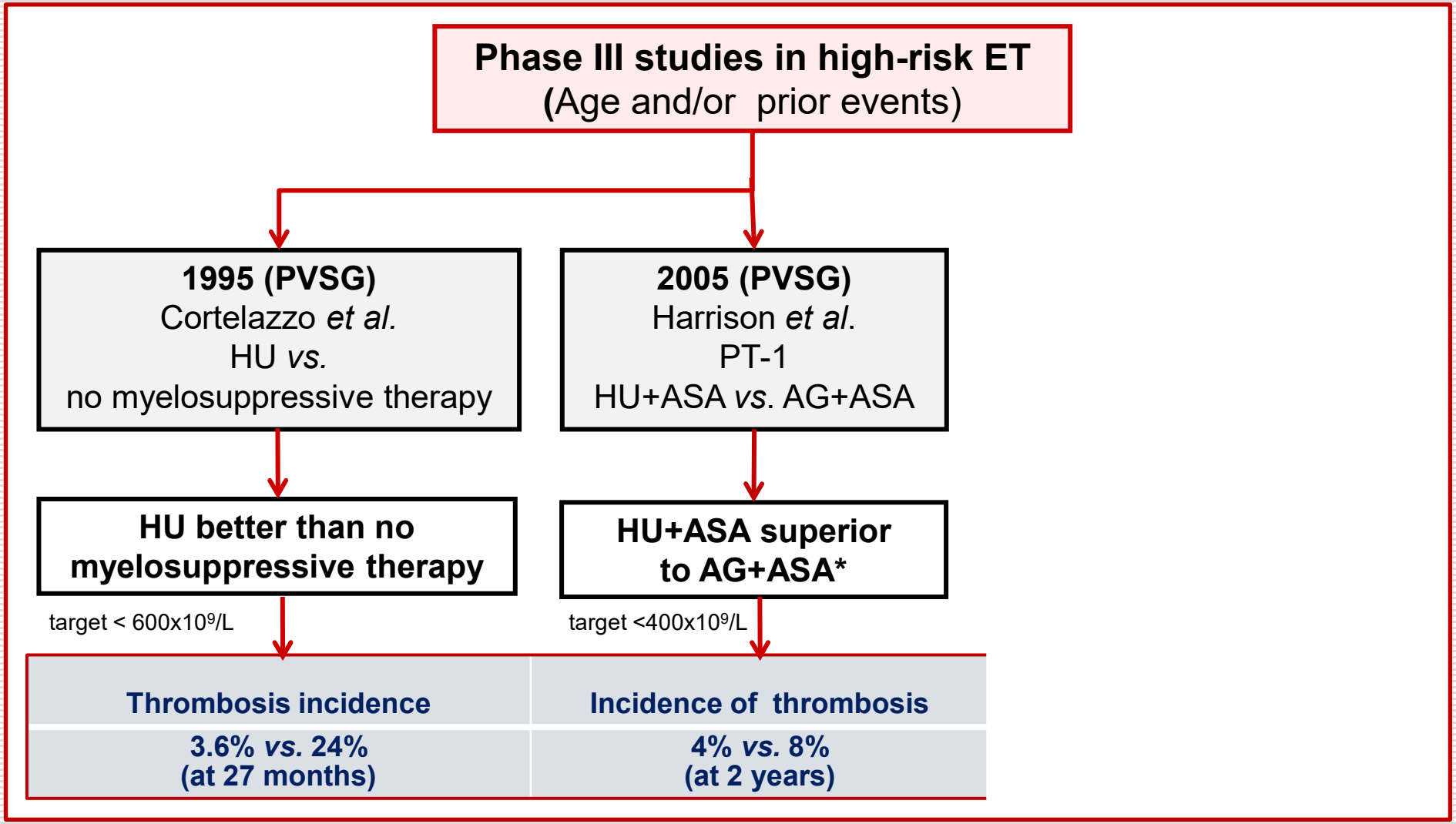
Randomized Clinical Trials in ET



Cortelazzo *et al.* N Engl J Med 1995;332:1132; Harrison *et al.* N Engl J Med 2005;353:33; Barbui T New Engl J Med , 2005; Gisslinger *et al.* Blood 2013;121:172

CYTOREDUCTION THERAPY IN HIGH-RISK

Randomized Clinical Trials in ET



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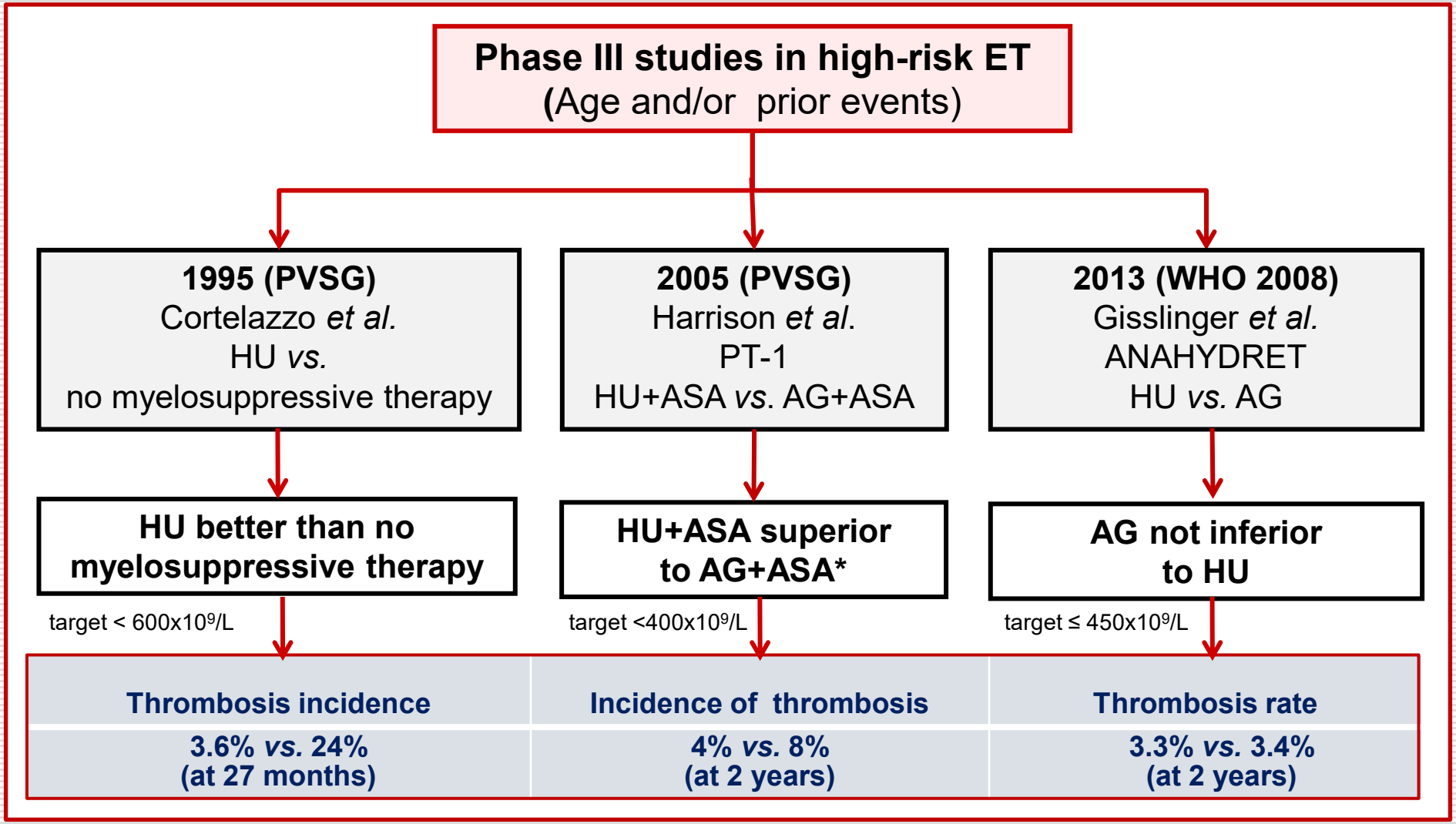
CYTOREDUCTION THERAPY IN HIGH-RISK

Randomized Clinical Trials in ET



Cortelazzo *et al.* N Engl J Med 1995;332:1132; Harrison *et al.* N Engl J Med 2005;353:33; Barbui T New Engl J Med , 2005; Gisslinger *et al.* Blood 2013;121:172

ELN recommendations for cytoreductive therapy in high-risk ET

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

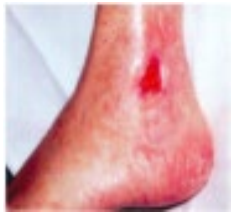
However, even though the majority of the experts indicated ***anagrelide*** *as an appropriate choice for first-line therapy in ET,* ***the panel did not reach a consensus on recommending the agent in this setting,*** *arguing that the evidence of non-inferiority with hydroxyurea was of insufficient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

THERAPY

HU resistant and intolerant patients

Non hematologic toxicities

- Leg ulcers or
- other unacceptable HU-related non-hematological toxicities, gastrointestinal symptoms, pneumonitis or fever at any dose of hydroxycarbamide



Hematologic toxicities

- Neutrophil count <1,000/mL
- platelet count <100,000/mL
- Hb <10 g/dL

Treatment options for hydroxyurea intolerant or refractory patients

- Pegylated interferon-α (IFN-α)
- Anagrelide
- Busulfan
- Ruxolitinib

THERAPY

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.

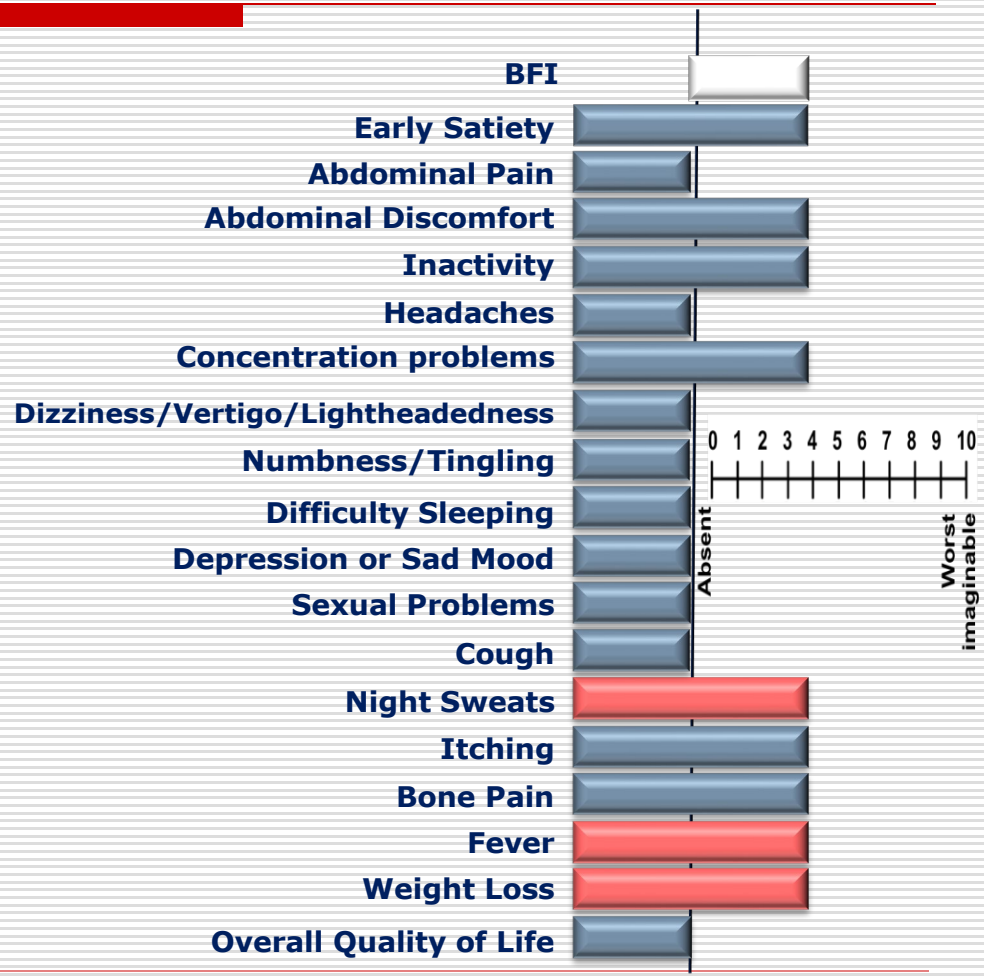
Editorial (Finazzi , Blood 2017)
At variance to patients with PV, ruxolitinib does not represent the first choice for most ET patients resistant or intolerant to HC, with the possible exception of those **severely symptomatic, particularly for pruritus.**

THERAPY

Addressing Symptoms

- Assessment of symptoms (in provider's office) at baseline and during FU is recommended in all patients.
- MPN-SAF or MPN-SAF TSS is assessed by the patients themselves.
- Changes in symptom status can be a sign of disease progression.
- Symptom response to treatment can justify continued use of drugs.

NCCN Guidelines v2.2018



Geyer H et al. JCO 2016; 34:151. Scherber R et al, Blood 2011; 118:401. Emanuel RM et al, JCO 212; 30:4098

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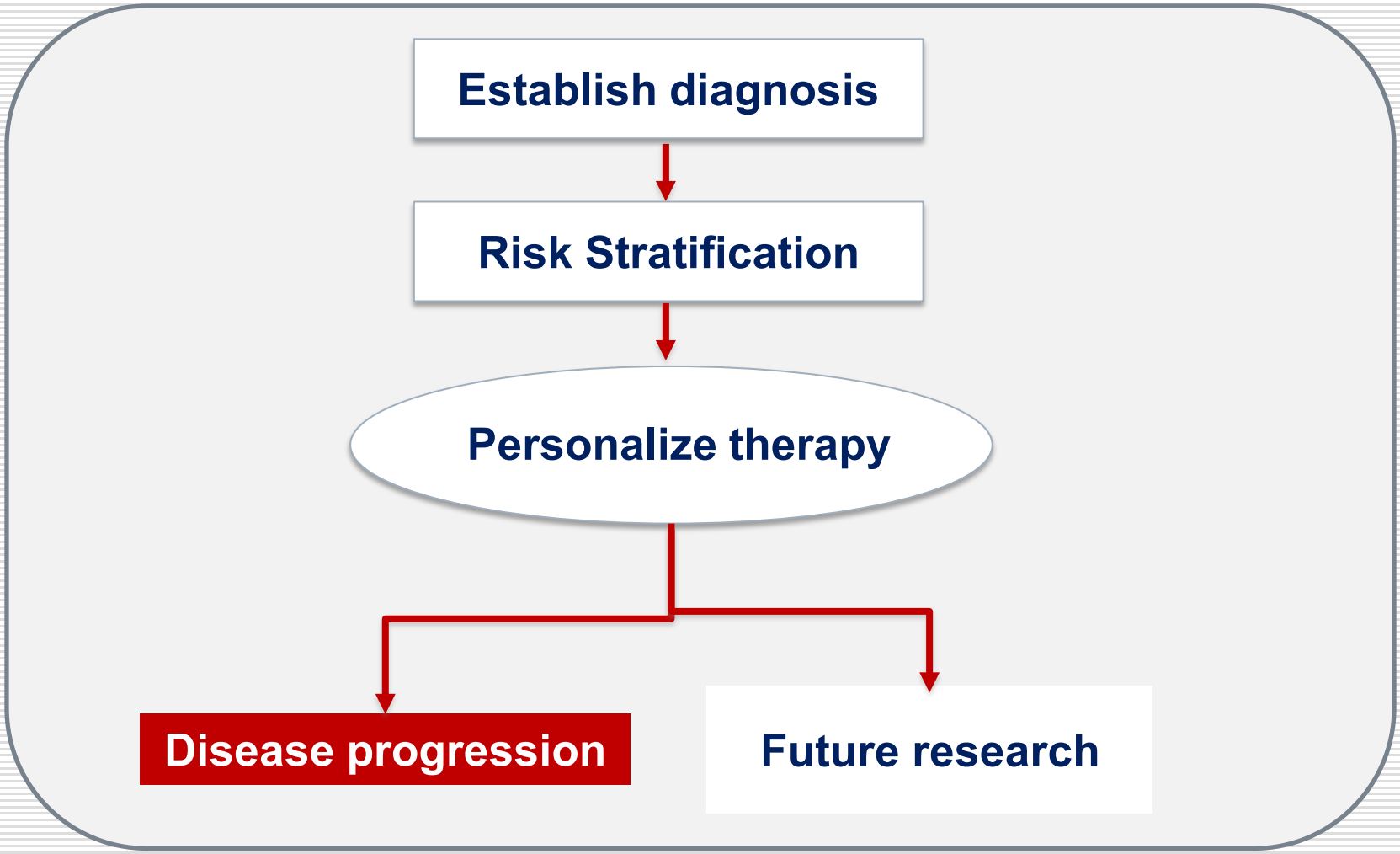


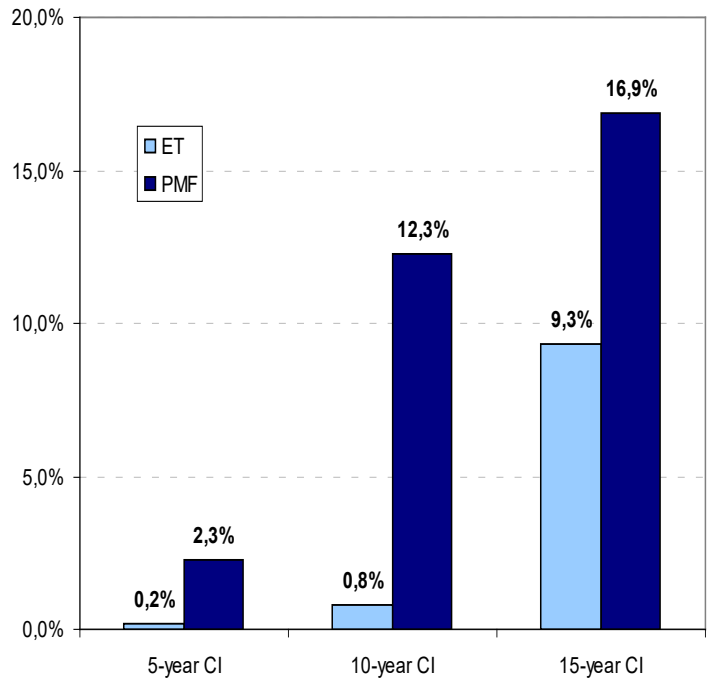
Diagnosis and Cumulative Incidence of Myelofibrosis in “true ET” vs prefibrotic MF

REQUIRED CRITERIA

1. Prior WHO Diagnosis of PV or ET
2. Bone marrow fibrosis 2-3/ 3 scale (3-4 on 4 scale)

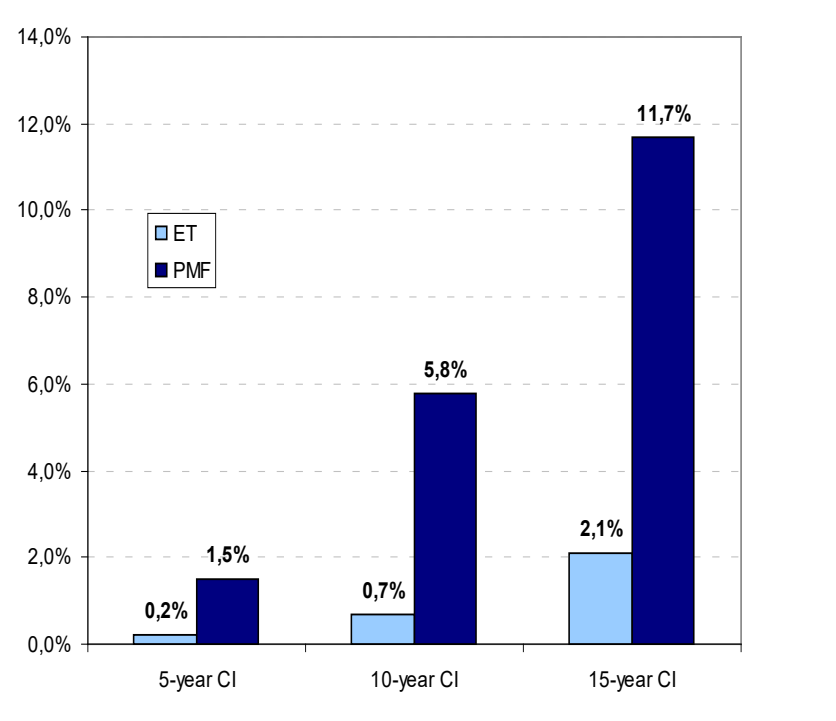
ADDITIONAL CRITERIA (2 Required)

1. Anemia, decreased cytoreduction
2. Leukoerythroblastic peripheral blood picture
3. Increasing splenomegaly
   - Increase >5cm (palpable)
   - New palpable splenomegaly
4. Development of constitutional symptoms
   - >10% weight loss
   - Night Sweats
   - Unexplained Fever >37.5^{0}C



Barbui et al, JCO 2011

Cumulative Incidence of Leukemia and role of cytoreductive drugs in “True ET vs pre-PMF”



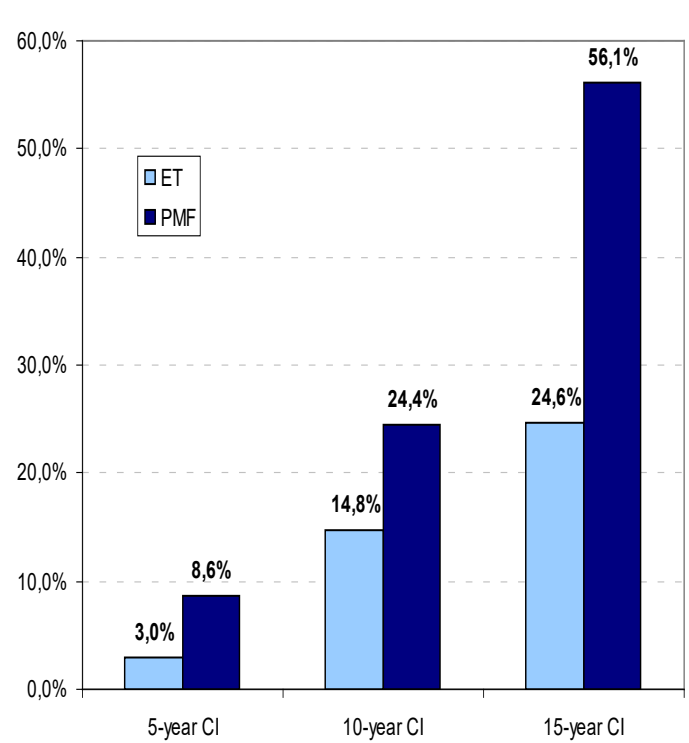
The Leukemia controversy in MPNs:

Is AML a natural progression of myeloproliferative disorders, a secondary sequela of therapy or a combination of both?

- Leukemic transformation may occur in untreated ET and PV patients (25%)
- HU alone does not seem to increase the natural risk of AML/MDS
- A significant association with AML/MDS is observed when HU is used in patients previously or sequentially treated with alkylating agents

Barbui et al, JCO 2011

Cumulative Incidence of Death and risk factors in “True ET and Pre-PMF”



Parameters at diagnosis	HR (95%CI)	P value
BM histology (PMF vs ET)	**1.60 (1.05-2.44)**	**0.03**
Age > 60 years	**6.70 (4.34-10.3)**	**<0.0001**
Male Gender	1.30 (0.91-1.86)	0.15
WBC > 11 $x10^9$/L	**2.01 (1.39-2.90)**	**<0.0002**
HB < 12 g/dL	**2.95 (1.73-5.04)**	**<0.0001**
PLT > 1000 $x10^9$/L	1.30 (0.90-1.90)	0.16
$JAK2^{V617F}$	1.48 (0.80-2.76)	0.21
Reticulin fibrosis grade 1	1.06 (0.57-1.98)	0.85
Previous thrombosis	**2.81 (1.95-4.06)**	**<0.0001**

Barbui et al, JCO 2011

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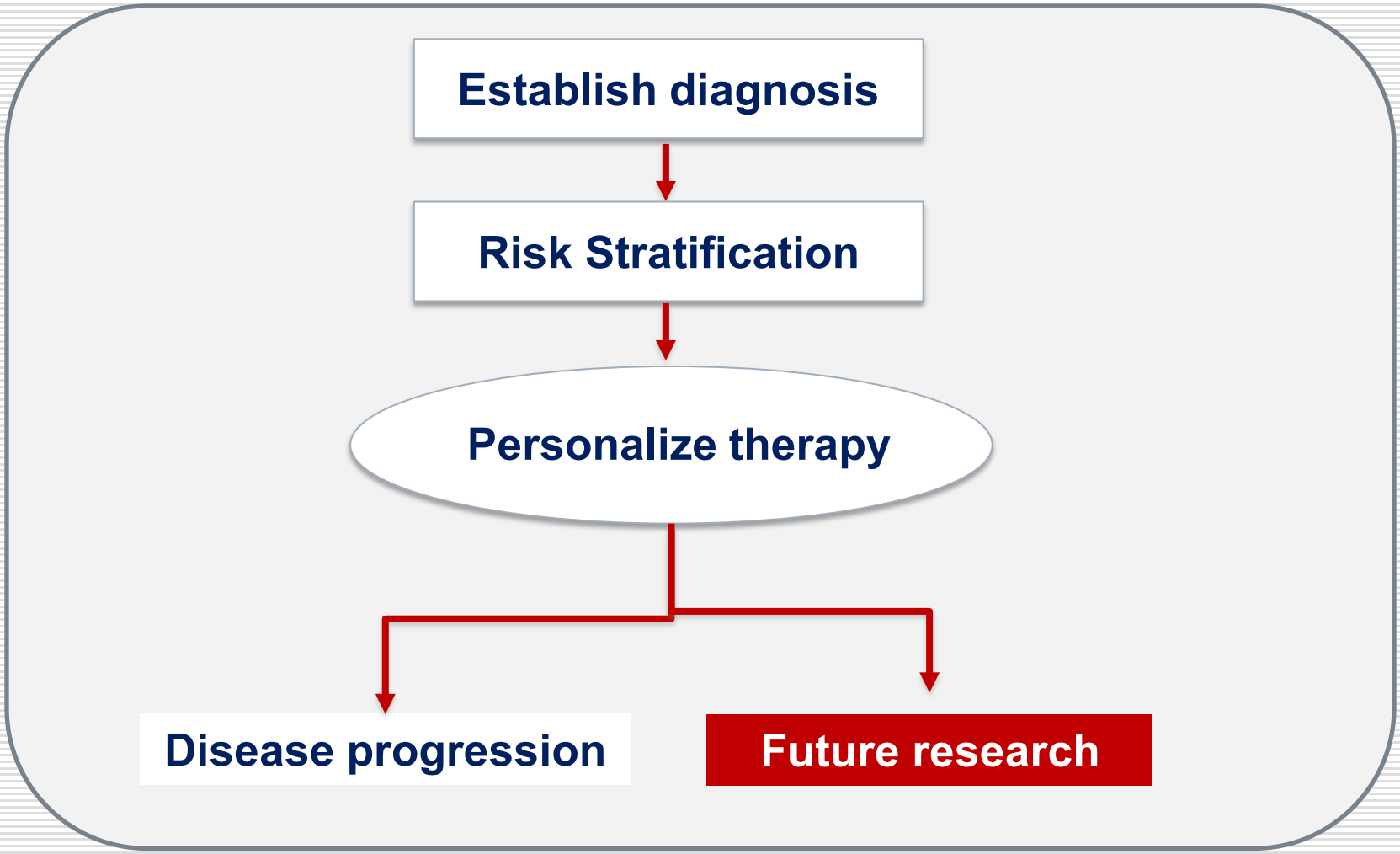

Annual rate of first incident vascular event (per 100 persons per year) in general population* and in MPN

General population without risk factors* 0.5%

General population with multiple CV risk factors** 0.9%

ET (n=1,019)§ …… 1.1-2.4 %
PV (n=1,545) §§ …… 2.0-3.1 %
PMF (n=707) §§§ ……. 2.2 %

Arterial thrombosis (60-70%) (cerebral, acute myocardial infarction and peripheral arterial occlusion); Deep venous thrombosis and pulmonary embolism; Splanchnic and cerebral vein thrombosis

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

Summary (1)

- ET diagnosis should be differentiated from early PV and pre-PMF
- Standard risk classification is IPSET thrombosis
- Patients at low-risk with thrombocytosis up to 1.5×10^9 should not be treated with cytoreductive drugs
- Low-dose aspirin is not for every patient

Summary (2)

- Hydroxyurea is the standard cytoreductive therapy in high risk patients
- IFN in younger patients should be preferred
- Angrelide is recommended for patients refractory or intolerant to HU.
- Ruxolitinib does not seem to reduce the vascular events. It could benefit patients with severe symptoms.
- Investments from the companies in developing clinical trials with new molecules and hard endpoints.