La Trombocitemia Essenziale: note introduttive

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Essential Thrombocythemia

This disorder is characterized by stem cell-derived clonal myeloproliferation with mutually exclusive JAK2, CALR and MPL (driver) mutations.

Table 1. WHO Diagnostic Criteria for Essential Thrombocythemia and Prefibrotic or Early-Stage Myelofibrosis.*

Essential Thrombocythemia	Prefibrotic or Early-Stage Myelofibrosis
Diagnosis requires all major criteria or the first three major criteria plus a minor criterion.	Diagnosis requires all major criteria and at least one minor criterion.
Major criteria	
Platelet count ≥450,000 per cubic millimeter	Megakaryocytic proliferation and atypia, without reticulin fibrosis >grade 1, accompanied by increased, age-adjusted bone marrow cellularity, granulocytic proliferation, and in many cases decreased erythropoiesis
Bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei; no substantial increase or left shift in neutrophil granulopoiesis or erythropoiesis; in rare instances, minor (grade 1) increase in reticulin fibers	Criteria for *BCR-ABL1*-positive chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, myelodysplastic syndrome, or other myeloid neoplasm not met
Criteria for *BCR-ABL1*–positive chronic myeloid leukemia, polycythemia vera, primary myelofibrosis, or other myeloid neoplasm not met	*JAK2* V617F, *CALR*, or *MPL* mutation or presence of another clonal marker or of minor reactive reticulin fibrosis in bone marrow†
JAK2 V617F, *CALR*, or *MPL* mutation	
Minor criteria	
Presence of clonal marker or of evidence of reactive thrombocytosis	Anemia not attributed to a coexisting condition
	Leukocytosis (≥11,000 cells per cubic millimeter)
	Palpable splenomegaly
	Lactate dehydrogenase level above upper limit of normal of institutional reference range

2016

* Data are from Arber et al.[7]

† In the absence of any of the three major clonal mutations, a search for other mutations associated with myeloid neoplasms (e.g., *ASXL1, EZH2, TET2, IDH1, IDH12, SRSF2,* and *SF3B1* mutations) may be helpful in determining the clonal nature of the disease. Minor (grade 1) reticulin fibrosis caused by infection is noteworthy, as are autoimmune disorders or other chronic inflammatory conditions, hairy-cell leukemia or other lymphoid neoplasms, metastatic cancer, or toxic (i.e., chronic) myelopathies.

The majority of patients with ET express the *JAK2* V617F mutation (~ 60%) , whereas the remainder harbor the mutations in *CALR* (~ 20%) or *MPL* (~ 3%) or none of the three driver mutations (10 to 20% are triple-negative)
(Tefferi A, Pardanani A., JAMA Oncol 2015)

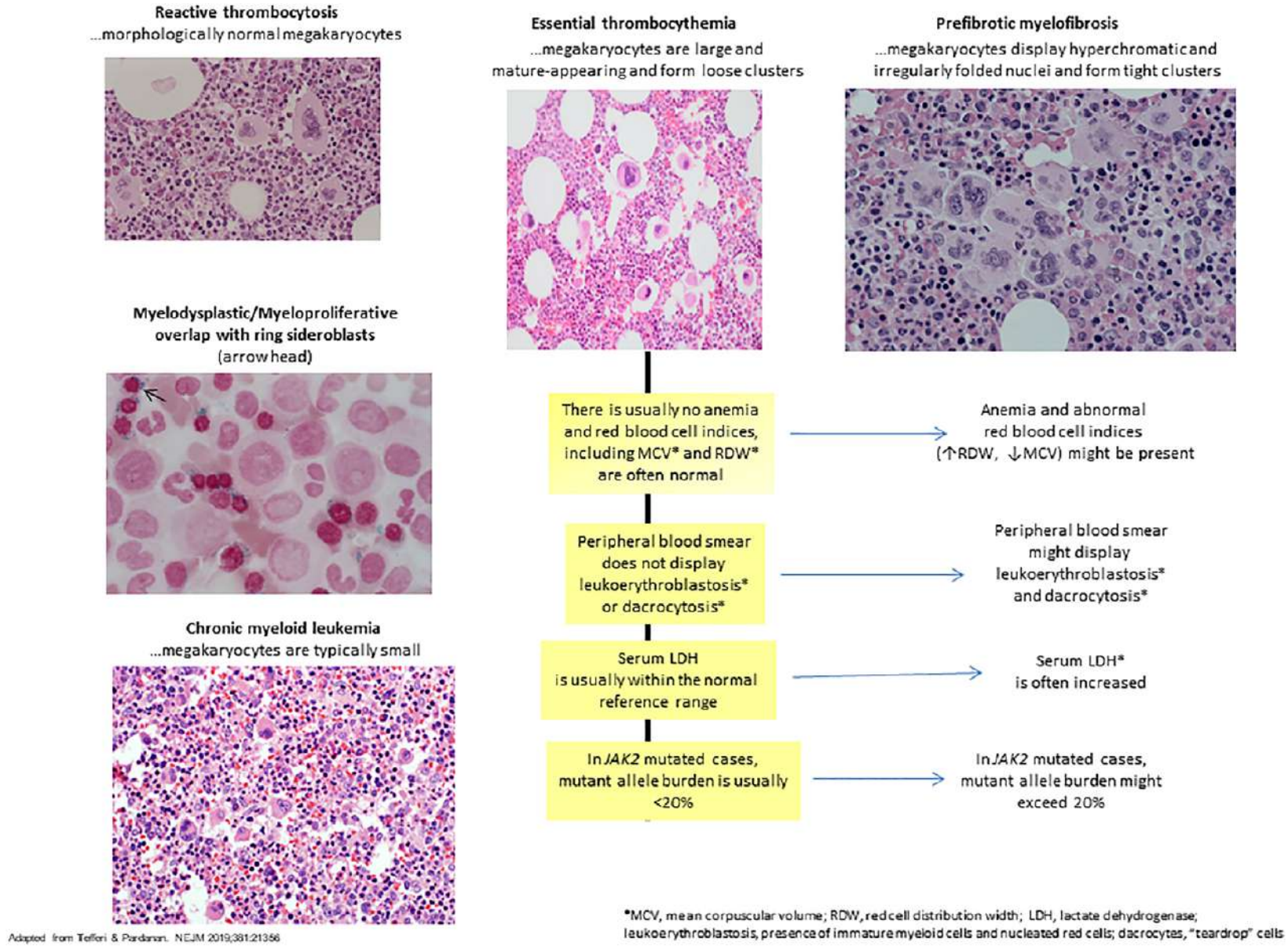
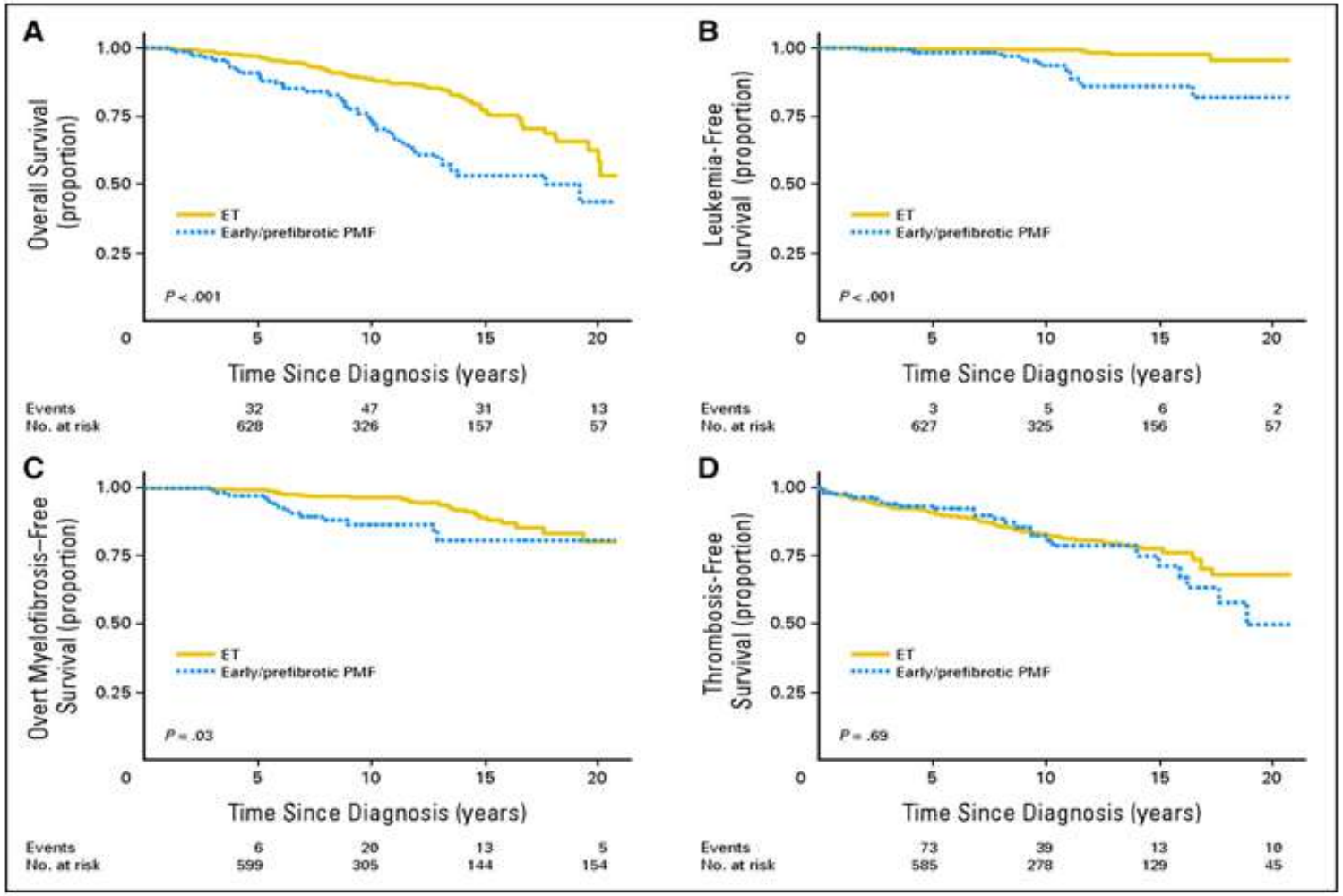


FIGURE 3 Distinguishing features between essential thrombocythemia and other causes of thrombocytosis. Bone marrow morphology in ET was courtesy Dr Anna Ruskova (Haematologist) Auckland City Hospital, New Zealand

Survival and Events in ET vs. “Pre-fibrotic” PMF



(A) Overall, (B) leukemia-free, (C) overt myelofibrosis–free, and (D) thrombosis-free survivals of patients with true ET (n = 891) vs early/prefibrotic PMF (n = 180)

Barbui T *et al.*, J Clin Oncol 2011; 29:3179-84

Essential Thrombocythemia: principal clinical-laboratoristic details

In a retrospective study involving 1076 ET pts (Szuber N. et al., Mayo Clin Proc 2019):

- The incidence of Essential Thrombocythemia was estimated at:

1.2 to 3.0 per 100,000 population per year.

- Median age at diagnosis was 58 years (range, 18 to 96), 67% were women;

- Palpable splenomegaly was present in 17%, and the median platelet count was 876.000/mmc

(range, 451.000 to 3.460.000/mmc);

- Leukocytosis was documented in 26% of patients, and an abnormal karyotype was detected in 9%;

- A history of thrombosis at or before diagnosis was present in 21% (arterial 13%, venous 8%)

ET: clinical outcome 1

Thrombosis

In the the Mayo Clinic experience:

- During a median follow-up of 9.9 years, 15% of the patients had arterial thrombosis and 8% had venous thrombosis.

These findings were similar to those described in 891 patients with

ET as defined by the WHO criteria **(Barbui T et al. Blood 2012)**.

Haemorrages

- Major bleeding (most commonly gastrointestinal) was observed in 4% at or before diagnosis and in 6% during followup;
- **Predictors of bleeding included previous hemorrhage and aspirin use.**
- Bleeding in patients with ET is in some cases associated with acquired von Willebrand's disease, which results from a selective loss of large von Willebrand's factor multimers.

  (median follow-up from the time of diagnosis was 6.2 years (range, 0 to 27.0)

Szuber N. et al., Mayo Clin Proc 2019; Barbui T. et al., Blood 2012; Finazzi G. et Al, Leukemia 2012

Essential Thrombocythemia: clinical outcome 2

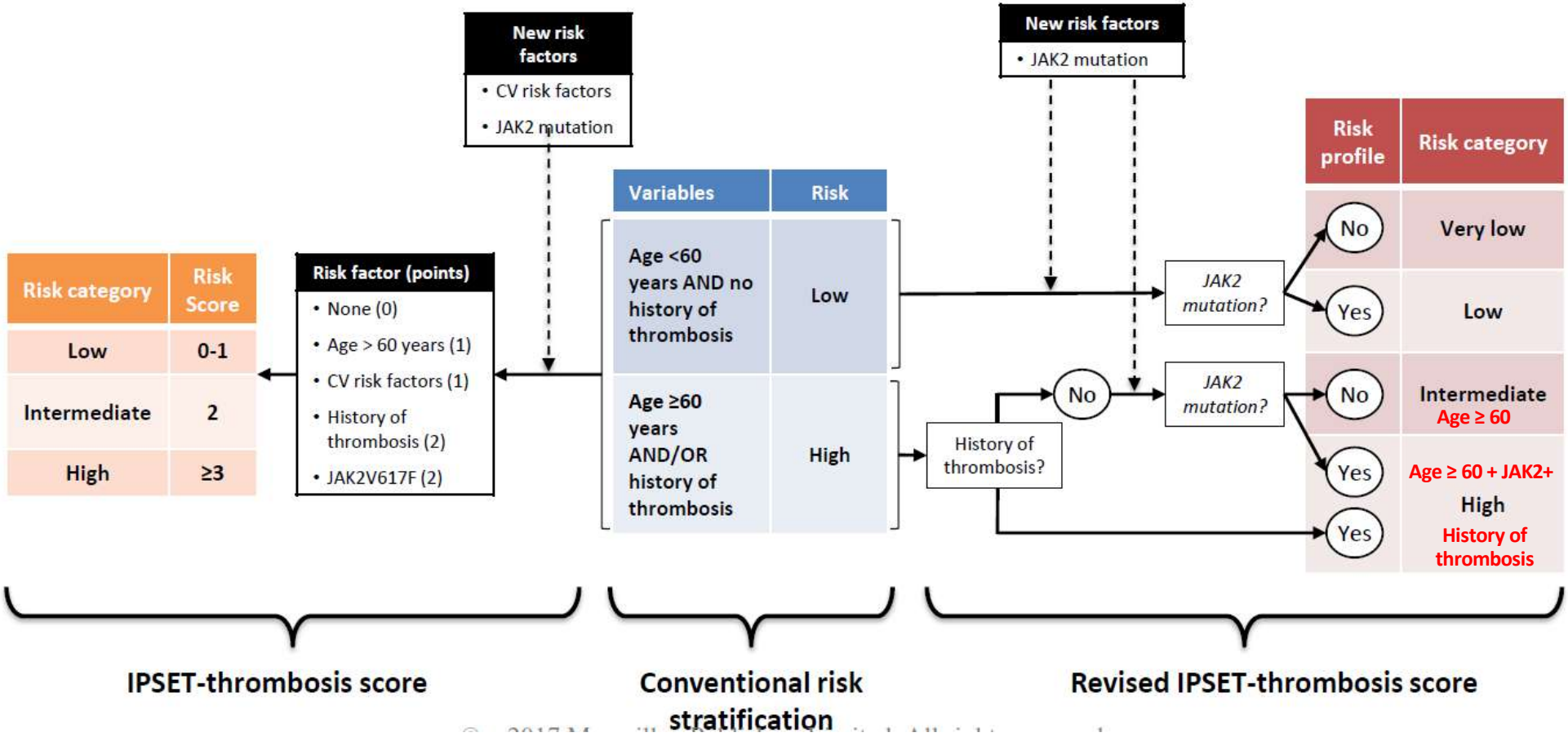
After a median follow-up of 10 years (with some patients followed for up to 47 years):

- Death had occurred in 43%,
- Leukemic transformations in 4%,
- Myelofibrosis in 13%,
- **New thrombosis in 21%,**
- The median overall survival was 18 years (26.7 years among patients with a low risk of thrombosis),
- A significantly shorter survival rate than that of age- and sex-matched controls from the general population.

(Szuber N. et al., Mayo Clin Proc 2019)

TE is burdened by a **rate of thrombotic events ranging from 0.44 to 2.36 %/pts-yr** (ranging from very Low to High risk categories).

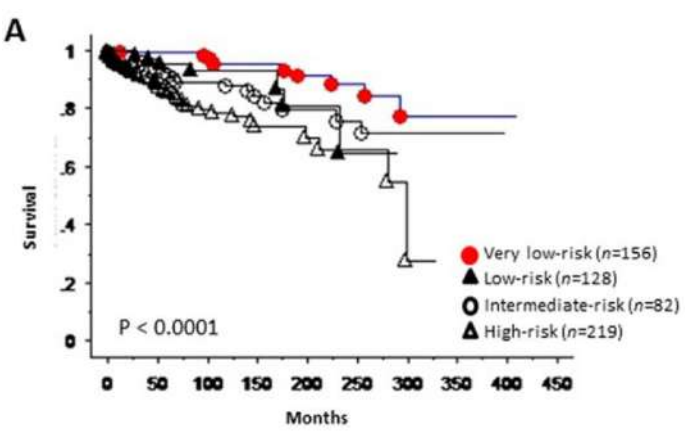
Patients with **TE** can be **stratified according to IPSET or revised IPSET –thrombosis classification, into 3 or 4 risk categories respectively**:



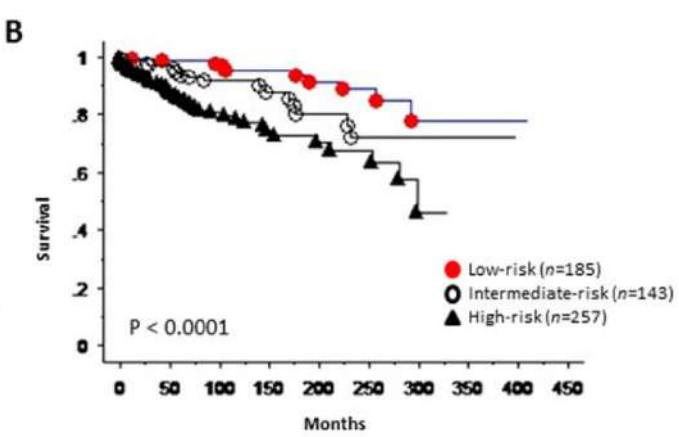
Validation of the revised international prognostic score of thrombosis for essential thrombocythemia (IPSET-thrombosis) in 585 Mayo clinic patients

Haider M et al. AJH 2016

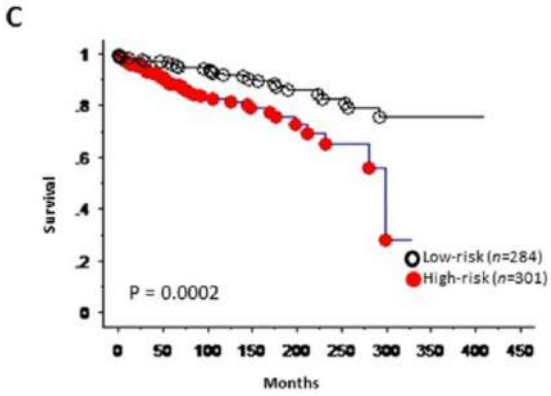
- "The major limitation of the current and previous relevant studies is the fact that they are all retrospective and that patients were not treated in a uniform fashion. This confounds accurate assessment of risk factors".
- "In addition, because of sample size for informative cases, we lumped together both arterial and venous thrombosis, which might not be scientifically sound".
- "Future studies would benefit from a prospective study design that considers arterial and venous thrombosis separately."
- The revised IPSET-thrombosis needs confirmation in prospective studies, especially after risk-adapted therapy will be uniformed



Revised IPSET score



IPSET score



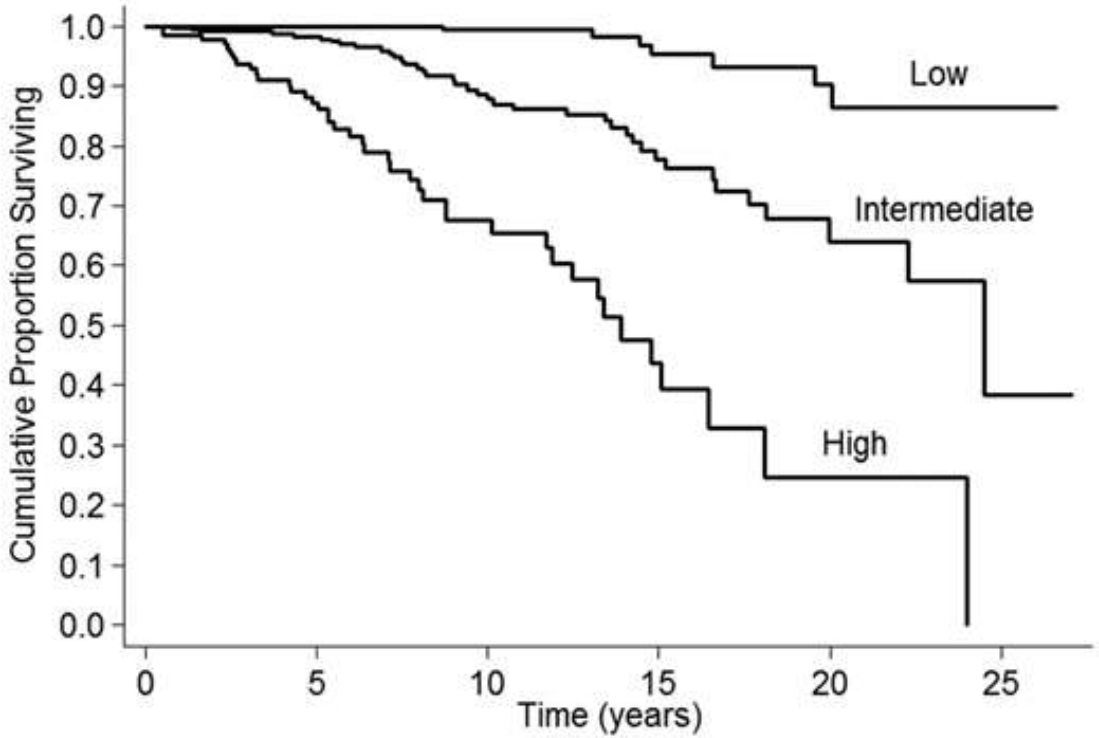
Conventional scoring

Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments

De Stefano V. et al.
Haematologica 2008

- **259**/1988 (13%) ET pts, with a history of thrombosis (68% arterial) showed recurrent thrombosis
- **Overall incidence of recurrences was 5.9% pt-yrs in <60yrs and 8.9% pt-yrs in >60yrs**
- Age >60yrs as main risk factor for recurrence, in particular in pts with cerebrovascular disease and venous thromboembolism.
- Leukocytosis significantly impacted (3.5 fold increasing) on thrombotic risk of younger pts
- Thrombophilia was found to be associated with higher risk of recurrence
- **Cytoreductive** treatment halves the incidence of re-thrombosis in patients with PV or ET, notably in those with first **arterial thrombosis**, **particularly** in patients with **acute coronary syndrome**.
- The **protection** offered by **cytoreduction** and long-term treatment with **oral anticoagulants are effective** in patients with **first venous thromboembolism**.
- **Antiplatelet** treatment **reduces the risk of recurrence in patients with cerebrovascular disease but also in those with venous thromboembolism.**
- The substantial **equivalence in efficacy and safety of secondary antithrombotic prophylaxis with either antiplatelet agents or oral anticoagulants in patients with venous thromboembolism** calls for prospective randomized trials specifically designed to investigate the optimal treatment in this setting.

ET: Survival According to Prognostic Score



Prognostic factors and score

Age ≥ 60 years:	2
History of thrombosis:	1
WBC ≥ 11 x 10^9/L:	1

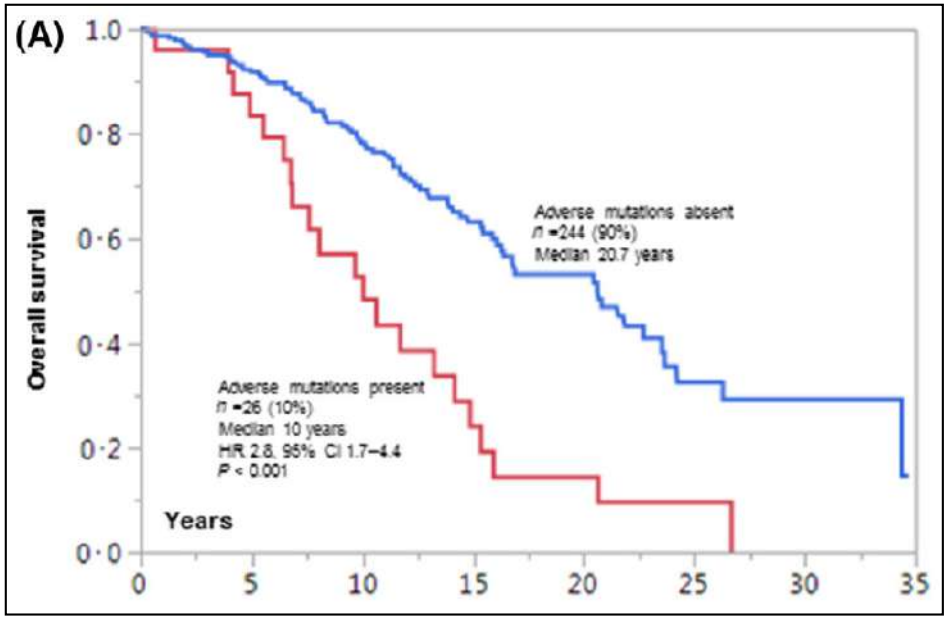
Prognostic groups

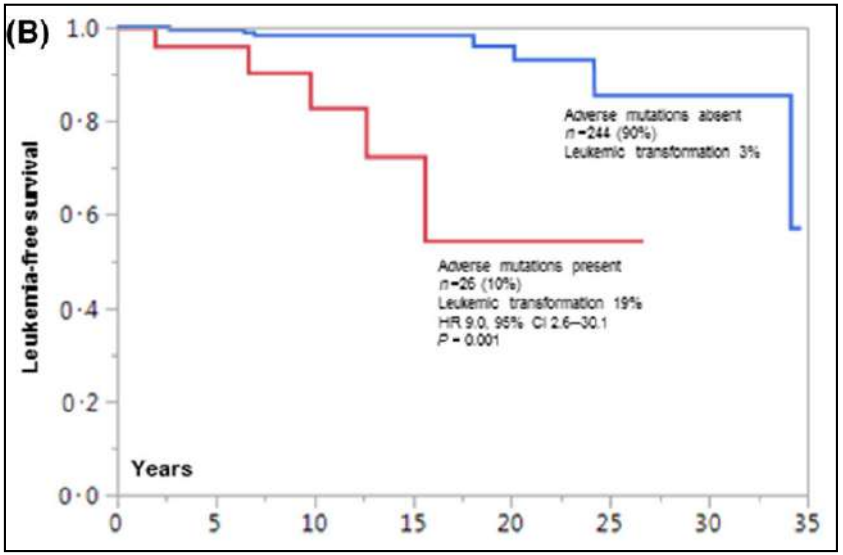
• Low	0
• Intermediate	1-2
• High	3-4

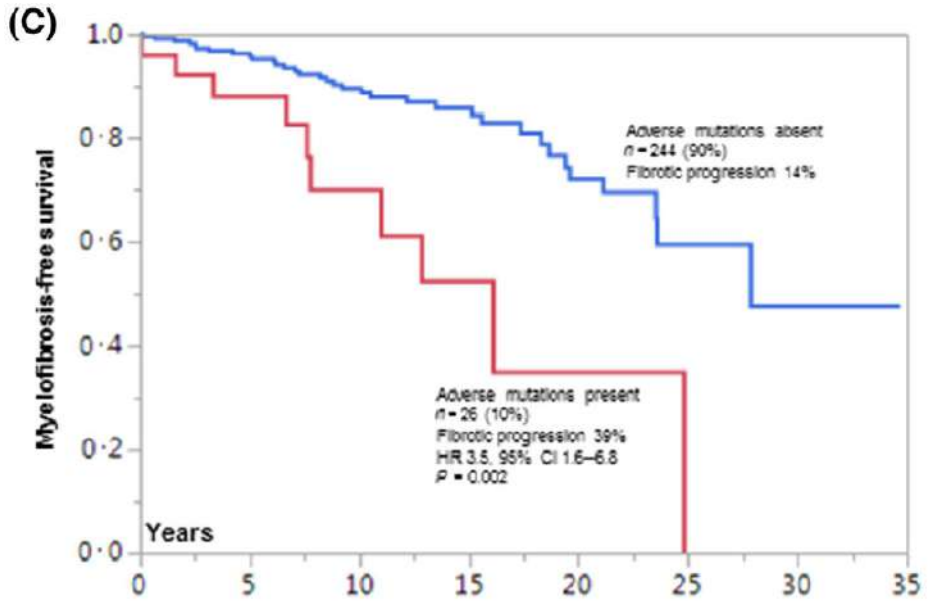
Passamonti F *et al.*, Blood 2012; 120:1197-01

Mutation-enhanced international prognostic systems for essential thrombocythaemia and polycythaemia vera

Tefferi A. et al. BJH 2019



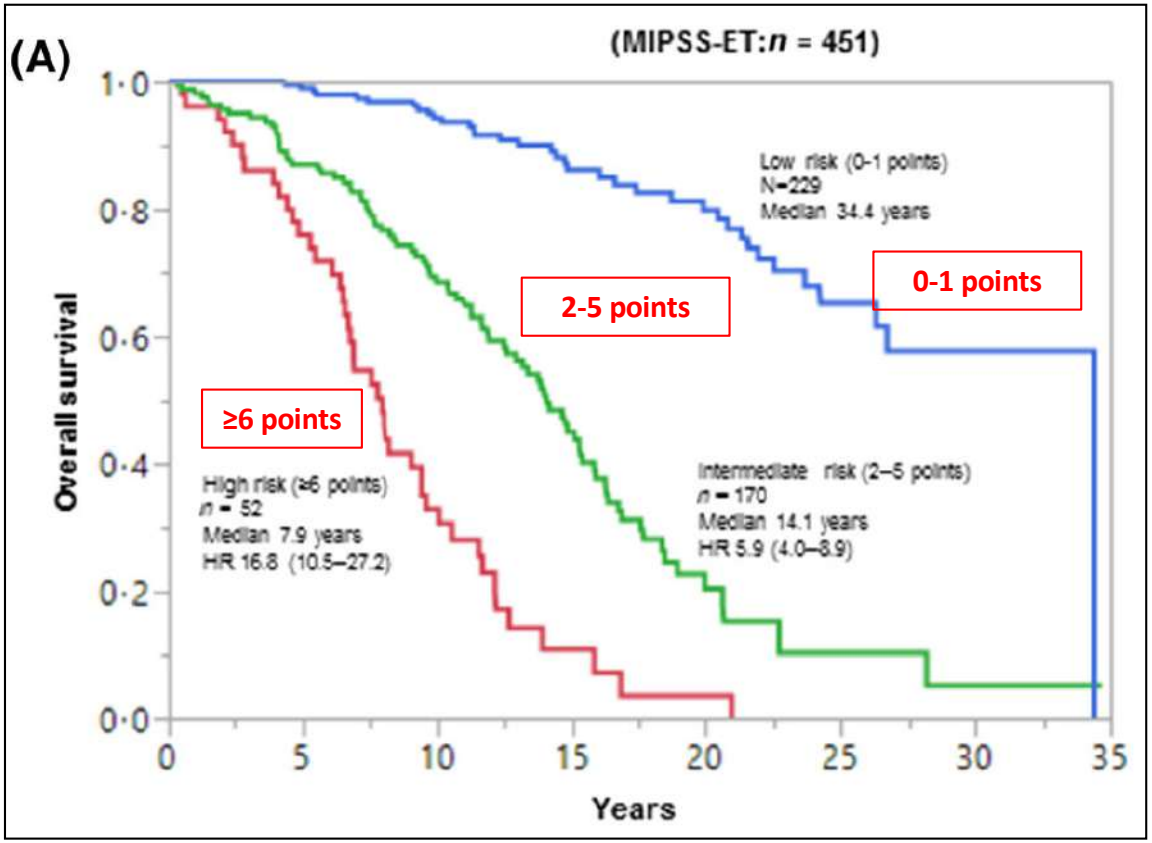




Overall **(A)**, leukaemia-free **(B)** and myelofibrosis-free **(C)** survival among 270 molecularly-annotated Mayo Clinic patients with ET, stratified by the presence or absence of **"adverse" mutations (SRSF2, SF3B1, U2AF1 and TP53)**.

Mutation-enhanced international prognostic systems for essential thrombocythaemia and polycythaemia vera

Tefferi A. et al. BJH 2019



MIPSS-ET derived from Mayo Clinic and Florence University cohorts, was based on **four risk factors**: **presence of adverse mutations** (**SRSF2, SF3B1, U2AF1 and TP53**) **(two points)**; **age >60 years (four points)**; **male sex (one point)** and **Leukocyte count ≥11x10^9/L (one point).**

ET treatment…..what drugs…..how to use them?

- **The main objective is to prevent the thrombo-haemorrhagic complications**

Aspirin

1) Increased thromboxane A2 (TXA2) biosynthesis has been reported in patients with ET
2) In ET the accelerated formation and release of platelets with unacetylated COX-1 and/or COX-2 could impair inhibition and hasten the recovery of TXA2-dependent platelet function during the 24-hour aspirin-dosing interval.
3) Incomplete inhibition of platelet TXA2 bio-synthesis by a standard aspirin regimen in ≥80% of patients with ET.

Patrono C et al. Blood 2013; Dragani A et al. Blood 2010; Giaretta A. et al. Clin Pharmaol Ther 2017; Dillinger JG et al. Thromb Res 2012; Pascale S et al. Blood 2012; Rocca B et al. Blood 2020.

Hydroxyurea

Anagrelide

Peg-IFN alfa-2a

Ruxolitinib

Imetelstat

Bomedemstat (Imago)

Pelabresib

Vorinostat

Navitoclax

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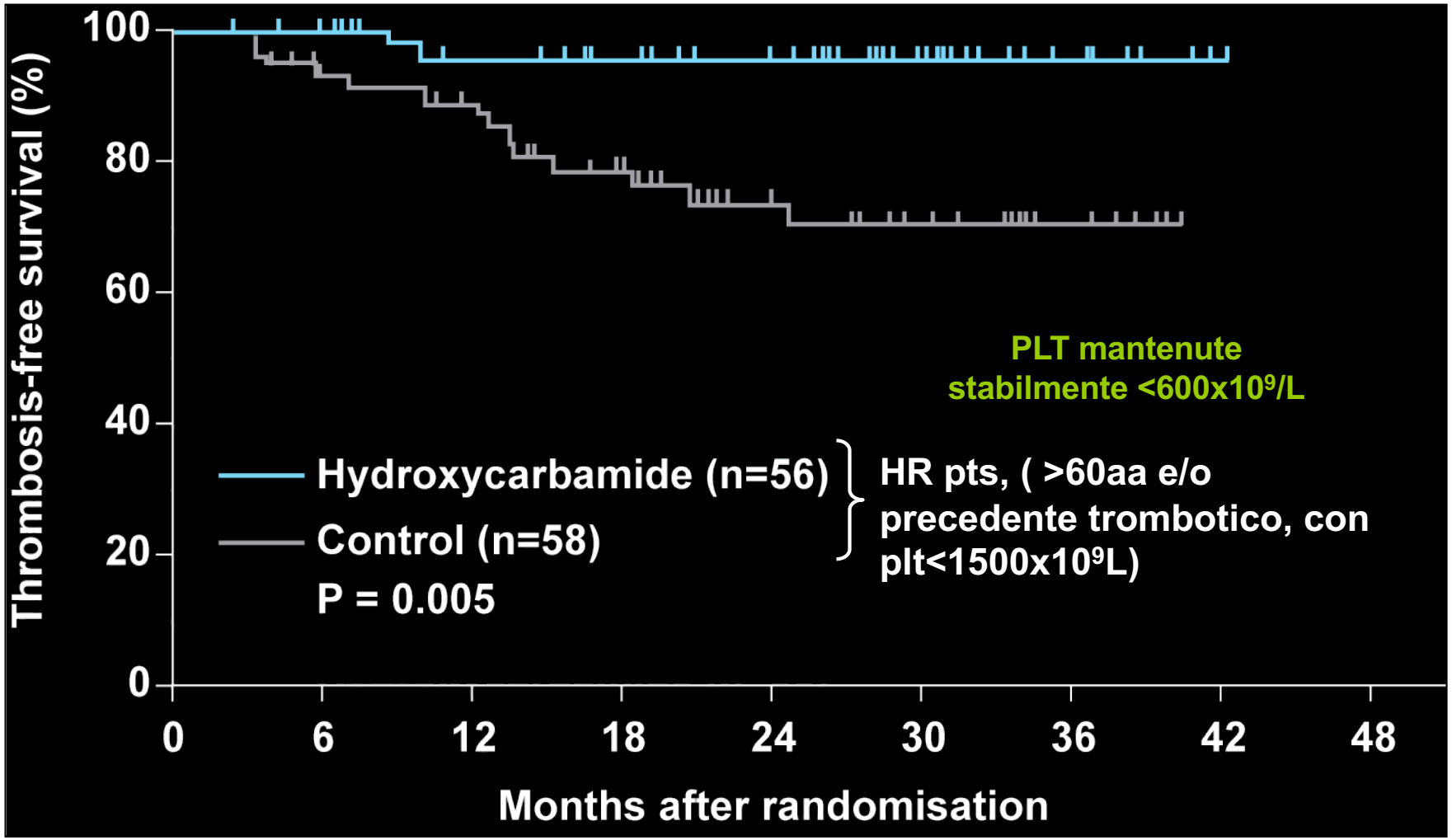
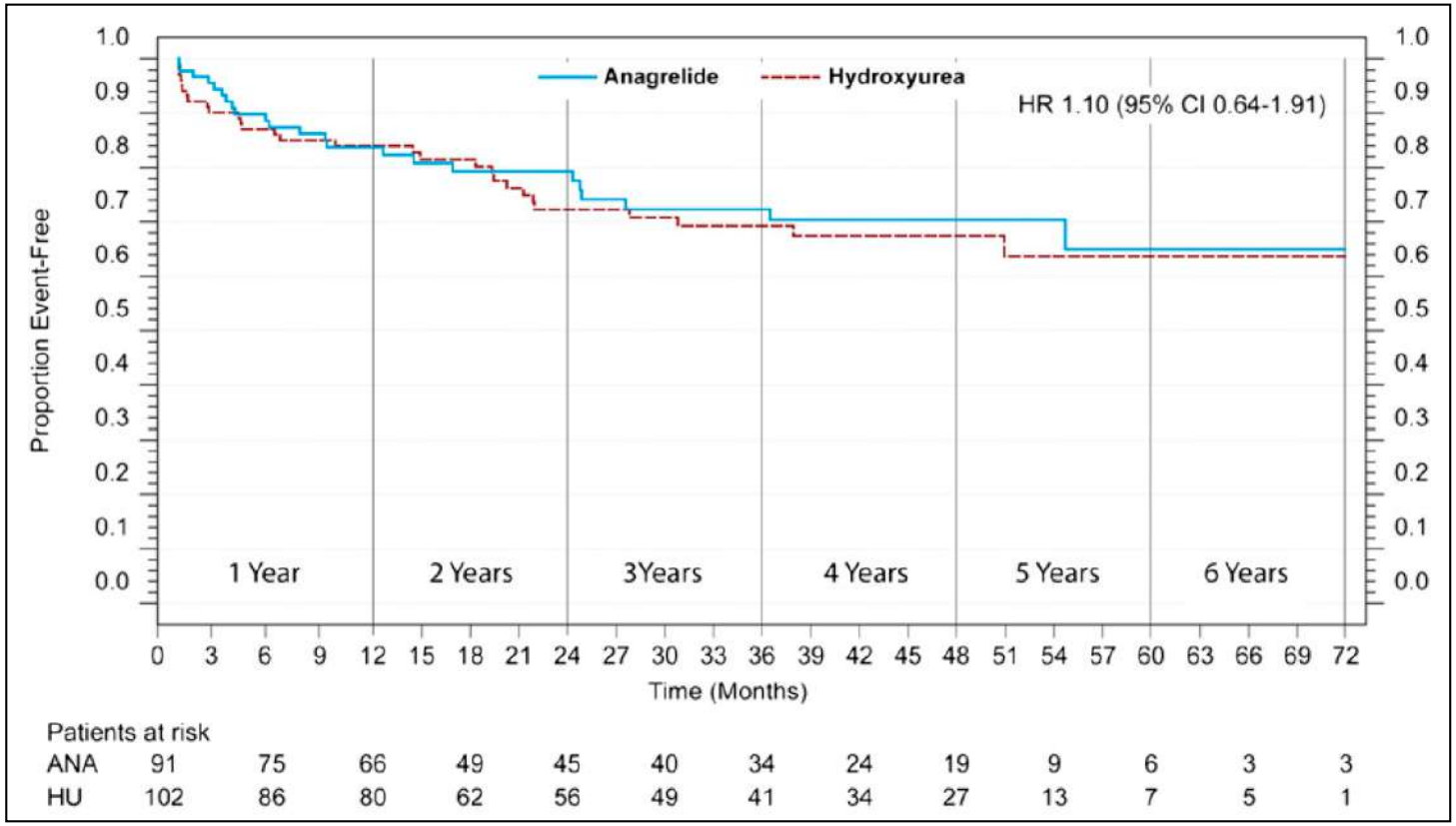
Piastrinosi, trattamento citoriduttivo e impatto clinico nella TE



Cortelazzo S, Finazzi G, Ruggeri M, et al. *N Eng J Med* 1995;332:1132-1136

Anagrelide compared with hydroxyurea in WHO-classified essential thrombocythemia: the ANAHYDRET Study, a randomized controlled trial

Gisslinger H. et al. Blood 2013



Noninferiority of anagrelide in comparison with hydroxyurea in WHO-ET, a phase 3 trial

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
ELN[18]				
Patient characteristics**				
Rate of thrombosis**	—	Score of 0–1, 1.03%/yr	Score of 2, 2.35%/yr	Score ≥3, 3.56%/yr
Management of cardiovascular risk factors	—	Low-dose aspirin for microvascular symptoms§	Low-dose aspirin for microvascular symptoms§	Low-dose aspirin for microvascular symptoms§
Treatment				
First line	—	Cytoreductive therapy not recommended for initial treatment¶	Cytoreductive therapy not recommended for initial treatment¶	First-line therapy, hydroxyurea or interferon alfa-2a
Second line	—	—	—	Cytoreductive therapy with interferon alfa-2a or anagrelide

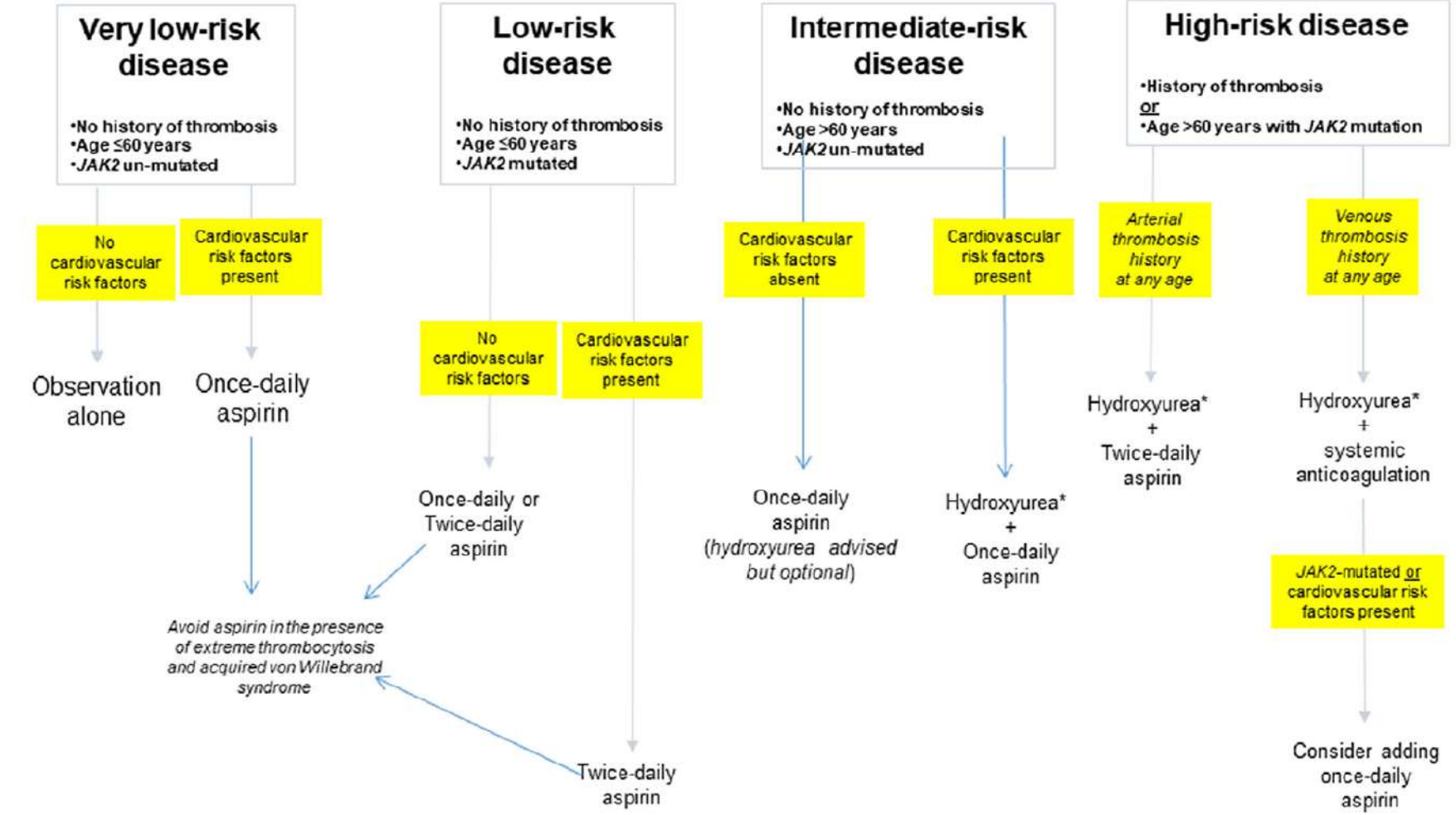
Revised-IPSET score 2015

IPSET score 2012

Tefferi A.&Pardanani a., NEJM 2019

Current Treatment Recommendations in Essential Thrombocythemia

Tefferi &Barbui, AJH 2020



*Second-line treatment in hydroxyurea intolerant or refractory patients is pegylated IFN-alpha or busulfan

FIGURE 6 Treatment algorithm for essential thrombocythemia

Recurrent Venous Thrombosis in Patients with Polycythemia Vera and Essential Thrombocythemia

De Stefano et al. Clinical Leukemia 2007

Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments

De Stefano et al. Haematologica 2008

Influence of the JAK2 V617F mutation and inherited thrombophilia on the thrombotic risk among patients with essential thrombocythemia

Valerio De Stefano, Tommaso Za, Elena Rossi, Alessia Fiorini, Angela Ciminello, Claudia Luzzi, Patrizia Chiusolo, Simona Sica, and Giuseppe Leone

Haematologica 2009

Leukocytosis is a risk factor for recurrent arterial thrombosis in young patients with polycythemia vera and essential thrombocythemia

De Stefano et al. AJH 2010

Increased risk of recurrent thrombosis in patients with essential thrombocythemia carrying the homozygous JAK2 V617F mutation

De Stefano et al. Annal Hematol 2010

Platelet activation and inhibition in polycythemia vera and essential thrombocythemia

Carlo Patrono,[1] Bianca Rocca,[1] and Valerio De Stefano[2]

Blood 2013

A randomized double-blind trial of 3 aspirin regimens to optimize antiplatelet therapy in essential thrombocythemia

Rocca B….. De Stefano V et al. Blood 2020