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

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

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

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Barbui T, JCO 2011

Recognizing ET from PV in JAK2V617F patients by Hb and Hct levels

ET JAK2V617F

<table>
<thead>
<tr>
<th>Polycythemia Vera</th>
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<tbody>
<tr>
<td>Early PV WHO-2016</td>
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<tr>
<td>Overt PV</td>
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<tr>
<td>2008 WHO</td>
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</table>

Hb M: 16.5 g/dL, F: 16.0 g/dL
Hct M: 49%, F: 48%

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)

WHO-2016: Summary of clinical correlation
Previous and incident bleeding complications
in ET (n=891) and Pre-PMF (n=180)

WHO-2016: Summary of clinical correlation

Incidence of Myelofibrosis

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

WHO-2016: Summary of clinical correlation

Incidences of Blastic Phase in ET (n=891), Pre-PMF (n=180) and PV (n=397)

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

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>HR</th>
<th>Multi-variate P value</th>
</tr>
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<tbody>
<tr>
<td>Age &gt; 60</td>
<td>1.44</td>
<td>P=0.150</td>
</tr>
<tr>
<td>CV risk factors (Tobacco, HTN, DM)</td>
<td>1.55</td>
<td>P=0.082</td>
</tr>
<tr>
<td>Prior thrombosis</td>
<td>2.08</td>
<td>P=0.008</td>
</tr>
<tr>
<td>JAK2 V617F</td>
<td>1.78</td>
<td>P=0.025</td>
</tr>
</tbody>
</table>

**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**

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>
<thead>
<tr>
<th>Table 2. NCCN and ELN Guidelines for Risk Stratification and Treatment in Patients with Essential Thrombocythemia.*</th>
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<tbody>
<tr>
<td><strong>Guideline</strong></td>
</tr>
<tr>
<td>Patient characteristics</td>
</tr>
<tr>
<td>Rate of thrombosis</td>
</tr>
<tr>
<td>Management of cardiovascular risk factors</td>
</tr>
<tr>
<td>Treatment</td>
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</table>

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 **JAK2V617F-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

Effect of different aspirin regimens on serum TXB2

**Normal megakaryopoiesis**

- Negligible time-dependent resynthesis of unacetylated COX-1 and COX-2 over 24-hrs
- Low immature platelet counts
- Negligible number of new platelets with unacetylated COX-1 and -2 over 24 hrs

**Accelerated megakaryopoiesis**

- Detectable time-dependent resynthesis of unacetylated COX-1 and COX-2 over 24-hrs
- Increased immature platelet counts
- Time-dependent increase of new platelets with unacetylated COX-1 and -2 over 24 hrs

Are platelet levels up to 1500×10⁹/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 1500×10⁹/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 in Patients 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 platelet count, 1,500 x 10^9/L should not receive cytoreductive therapy.
Leukocytosis and thrombosis in essential thrombocythemia and polycythemia vera: a systematic review and meta-analysis

![Graph showing increased risk of thrombotic events in ET and PV](image)

### Table: Risk Ratios

<table>
<thead>
<tr>
<th>Study</th>
<th>Arterial Events</th>
<th>Venous Events</th>
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<tbody>
<tr>
<td><strong>ET</strong></td>
<td><strong>RR: 1.65 (95% CI 1.43-1.91)</strong></td>
<td><strong>RR: 1.87 (95% CI 1.26-2.77)</strong></td>
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<tr>
<td><strong>Arterial Events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carobbio (2), 2011</td>
<td>1.66 (1.01, 2.72)</td>
<td>2.00 (1.10, 3.80)</td>
</tr>
<tr>
<td>De Stefano (2), 2010</td>
<td>2.16 (1.12, 4.18)</td>
<td>1.14 (0.43, 2.98)</td>
</tr>
<tr>
<td>Gangat, 2009</td>
<td>1.30 (0.70, 2.30)</td>
<td>1.14 (0.43, 2.98)</td>
</tr>
<tr>
<td>Gangat (3), 2009</td>
<td>0.70 (0.30, 1.80)</td>
<td>0.90 (0.30, 2.60)</td>
</tr>
<tr>
<td>Landolfi (2), 2007</td>
<td>1.21 (0.69, 2.11)</td>
<td>0.50 (0.20, 1.80)</td>
</tr>
<tr>
<td>Landolfi (5), 2007</td>
<td>1.67 (0.99, 3.00)</td>
<td>1.28 (0.56, 2.92)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>1.45 (1.13, 1.86)</td>
<td>1.14 (0.65, 1.98)</td>
</tr>
<tr>
<td><strong>Risk Ratio (95% CI)</strong></td>
<td>1.00-2.00</td>
<td>1.00-2.00</td>
</tr>
</tbody>
</table>

Carobbio A, et al, Blood advances 2020
TREATMENT FOR HIGH-RISK ESSENTIAL THROMBOCYTHEMIA

- Monitor for new thrombosis, acquired VWD, and/or disease-related major bleeding
- Manage cardiovascular risk factors (see MPN-H)
  - Aspirin (81–100 mg/day) C
  - Preferred regimens: Hydroxyurea
  - Other recommended regimens: Peginterferon alfa-2a (based on other patient-specific variables) or Anagrelide

Adequate response → Continue treatment

Monitor response and signs/symptoms of disease progression (MPN-10; MPN-E 2 of 2)
  - every 3–6 months or more frequently as clinically indicated d,e,i,k

- Inadequate response or Loss of response → See ET-4

Disease progression to MF/AML g,h → Post-ET MF, see MPN-2; Advanced phase MF/AML, see MF-4
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.

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).

CR was defined as correction of hematocrit (<45% without phlebotomy for PV), platelet count (<400×10⁹/L), white blood cell count (<10×10⁹/L), and resolution of splenomegaly and disease-related symptoms.

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)

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
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<tbody>
<tr>
<td><strong>Dx before 2005</strong></td>
<td>IR: 1.28 % pts/yr; 95% CI: 0.41-2.05</td>
<td>IR: 1.58 % pts/yr; 95% CI: 0.51-4.89</td>
<td>IR: 3.58 % pts/yr; 95% CI: 2.08-6.17</td>
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<tr>
<td>IR per 100 person/yr</td>
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</table>

| **Dx after 2005**  | 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 |
| IR per 100 person/yr |                          |                          |                           |

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.