Is the recommended hematocrit target in polycythemia vera evidence-based? “YES”

Alessandro M Vannucchi
University of Florence, Italy
Hematocrit is central to polycythemia vera.....
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...... for diagnosis (as a [debated] surrogate of increased red cell mass expressed as hemoglobin level)
Hematocrit is central to polycythemia vera.....

...... **for diagnosis** (as a [debated] surrogate of increased red cell mass expressed as hemoglobin level)

...... **for therapy** (as a [debated] surrogate of thrombosis risk)
Thrombosis-free Survival in PV and ET

Cause of death | %
---|---
Fatal thrombosis | 41
Hemorrhages | 4
AML/MF | 13
Other cancers | 20
Other cause | 22

PV
n=397
CE=59 (14.9%)

ET
n=637
CE=73 (11.5%)

Wasserman LR, J Mt Sinai Hsp 1959; Vannucchi AM, Blood 2007; Marchioli R, JCO 2005
Risk Factors for Thrombosis in PV: Certain & (still largely) Uncertain

Certain

“Individual-associated”
Not modifiable

Marchioli, R. et al. JCO 2005; 23:2224-2232
Risk Factors for Thrombosis in PV:
Certain & (still largely) Uncertain

**Certain**

- Thrombocytosis
- Leukocytosis
- Erythrocytosis

“Individual-associated”
Not modifiable

**Uncertain**

- “Disease-associated”
Potentially modifiable

Marchioli, R. et al. JCO 2005; 23:2224-2232

from J. Spivak, mod
## Current Therapeutic Recommendations for PV

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk Variables</th>
<th>PV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low</strong></td>
<td>Age &lt;60, no thrombosis</td>
<td>• Phlebotomies to target Hct</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td>+ CV risk factors</td>
<td>• LD Aspirin</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td>Age &gt;60 OR Previous thrombosis</td>
<td>• Myelosuppression ± Phlebotomies to target Hct  • LD Aspirin</td>
</tr>
</tbody>
</table>

**Target Hct:**  
- Males: <45%  
- Females: <42%
Hematocrit and blood viscosity

- The viscosity of blood depends on the viscosity of the plasma in combination with the Hct.
- The relation between hematocrit and viscosity is complex and may be expressed by the formula of Einstein:
  \[ \eta = \eta_{\text{plasma}} (1+2.5 \text{ Hct}) \]
- Therefore, higher hematocrit level implies higher blood viscosity.
Negative effects of elevated red cell mass are more pronounced in larger vessels

- Red cell aggregation increases at high Hct level, favouring vascular stasis
- The resulting enhanced interplay between platelet, leukocytes and vessel wall might facilitate thrombosis

Hematocrit, Blood Viscosity and Cerebral Blood Flow

- Cerebral Blood Flow (CBF) was decreased of 44% in transgenic mice with EPO-driven erythrocytosis (Hct=0.85) vs controls, and normalized after hemodilution.

- Significant inverse relationships between CBF and Hct and between CBF and blood viscosity in humans.

Hematocrit, Blood Viscosity and Cerebral Blood Flow in Polycythemia Vera

- In 16 PV patients, the mean CBF was 37.9 ml/100g/min vs 69.1 ml/100g/min in controls (P<0.001).
- Lowering the Hct from 0.54 to 0.45 was associated with a 73% increase of CBF and 30% reduction in blood viscosity.
- Since “a low CBF was found at Hct levels of 0.46 to 0.52, Hct levels that are currently considered acceptable in the management of PV may therefore be too high” (Thomas DFJ, Lancet 1977; 310:161-3)
One possible mistake.....

..........is to use information from studies in patients with reactive forms of erythrocytosis (*where no substantial increase of thrombosis rate has been ever convincingly demonstrated*) to derive information applicable to polycythemia vera.......
Pathogenesis of thrombosis in Polycythemia Vera is a complex affair.
• Retrospective study covering 332 patient years, with 56 cardiovascular events in 38 individuals
• Each patient-year was allocated to the appropriate PCV range and the mean age of patients during the years in which their PCV values were in each range was calculated.
Vascular occlusive episodes and haematocrit in primary proliferative polycythemia

![Graph showing vascular occlusive episodes per PCV range]

<table>
<thead>
<tr>
<th>PCV</th>
<th>0.40-0.44</th>
<th>0.45-0.49</th>
<th>0.50-0.54</th>
<th>0.55-0.59</th>
<th>≥0.60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio of episodes to yr w PCV</td>
<td>1/50</td>
<td>12/130</td>
<td>24/105</td>
<td>13/39</td>
<td>6/8</td>
</tr>
<tr>
<td>Episodes/10y</td>
<td>0.20</td>
<td>0.92</td>
<td>2.29</td>
<td>3.33</td>
<td>7.5</td>
</tr>
</tbody>
</table>

Pearson TC, Lancet 1979:1219-1221
“The results of this study indicate that P.C.V. should be maintained at less than 0.45 in primary proliferative polycythaemia.”
Impact of Hct on clinical outcome in a retrospective study of 226 PV patients

An Hct >0.48 was associated with shorter OS and shorter time to thrombosis in multivariate analysis

Is the recommended hematocrit target in PV evidence-based?

“YES”(*)

• There are compelling information concerning the relationships between Hct, blood viscosity and hemorehology
• There are intriguing clinical observations in PV (BUT: retrospective study design, small numbers, statistical issues)

• In summary, we still LACK a prospective, controlled, randomized trial of the value of Hct level control for the risk of thrombosis in polycythemia vera

(*) Italian short aphorism meaning “nor YES nor NO”