Is C2 Disease Progressive?

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I Have No Disclosures Relevant To This Presentation

The Epidemiology of CVD

- Cross sectional sample of 3072 subjects
- CVD Prevalence

Factors Associated with CVD Progression
Kostas T, J Vasc Surg 2010

- 5 yr follow up of 73 asymptomatic limbs after unilateral vein surgery
- 32% of limbs with increase in C class by ≥ 2
- Factors associated with clinical deterioration
  - Standing > 4 hrs (p ≤ 0.001)
  - BMI ≥ 30 (p ≤ 0.001)
  - Non-compliance with elastic stockings (p ≤ 0.001)

<table>
<thead>
<tr>
<th>Initial Class</th>
<th>C0</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>C4</th>
</tr>
</thead>
<tbody>
<tr>
<td>C0</td>
<td>5</td>
<td>10</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>6</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C2</td>
<td>2</td>
<td>2</td>
<td></td>
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</tbody>
</table>

The Progression of 1° CVD
The Bonn Vein Study II, Rabe E, in press

- 6.6 year follow-up of Bonn I participants
- 2% per year progression to CVI (C3 – C6)
- Risk factors for progression
  - Age
  - Arterial Hypertension
  - Obesity

<table>
<thead>
<tr>
<th>C2 n (%)</th>
<th>C3 n (%)</th>
<th>C4a n (%)</th>
<th>C4b n (%)</th>
<th>C5 n (%)</th>
<th>C6 n (%)</th>
<th>Any n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C0-C1 (1226)</td>
<td>101 (8.3)</td>
<td>99 (8.1)</td>
<td>22 (1.8)</td>
<td>1 (0.1)</td>
<td>3 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>C2 (149)</td>
<td>28 (18.6)</td>
<td>14 (9.6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>C3 (264)</td>
<td>9 (4.4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C4 (135)</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C5 (32)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

CVD Progression
Pacific Vascular Symposium 6, J Vasc Surg 2010

- Most patients with CVD do not progress to C4 – 6
- Advanced CVD is a multifactorial disease
  - Age
  - Obesity
  - Gender
  - Hypertension
  - Occupation
  - HFE polymorphisms
  - AT deficiency
- Number needed to prevent 1 ulcer (NNT) is low and will likely remain unknown
Could a Randomized Trial Be Done?

- Theoretical randomized trial to reduce progression from C1-2 to C3-6 by 50%
  - Observation only
  - Superficial venous intervention
- Assumptions
  - 2% per year progression
  - 5 year reduction in progression from 10% to 5%
  - Alpha error = 0.5, 80% power
  - 20% loss to follow-up
- 440 patients per group
- 1056 patients required
- Estimated cost $10 - $20 million

Genetic Factors in CVD Progression
Gemmati, J Vasc Surg 2009

- Multiple postulated single nucleotide polymorphisms (SNPs)
  - Iron metabolism
    - HFE (hemochromatosis protein)
    - Ferroportin gene (FPN)
  - Wound healing (MMP12)
  - Coagulation (Factor XIII, protective)
- DNA array genotyping in 638 subjects
  - 333 C3 – C6 patients
  - 305 healthy controls

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>VLDL Risk</th>
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</thead>
<tbody>
<tr>
<td>HFE</td>
<td>C282Y</td>
<td>6 – 7X</td>
</tr>
<tr>
<td>FPN</td>
<td>8GG</td>
<td>5X</td>
</tr>
<tr>
<td>MMP12</td>
<td>R2AA</td>
<td>2X</td>
</tr>
</tbody>
</table>

Demographic & Environmental Factors
- Age
- Gender
- Obesity

Factor XIII
- Unidentified Factors

Conclusions
- Disease progression is a multifactorial process
  - Venous disease may be the promoting factor
  - Other deterministic factors
    - Environmental & demographic factors
    - Genetic factors
- Attributing progression to venous disease alone is overly simplistic
- The value of prophylactic intervention for unselected C2 – 3 disease is unlikely to be demonstrated
- Factors determining progression to C4 – 6 disease need to be better elucidated