Klinische implicaties van trombofilie

Saskia Middeldorp, M.D.
Venous thrombosis and pulmonary embolism

- 35,000 patients per year in The Netherlands
- 25-50% postthrombotic syndrome
- 25-30% recurs in the next 10 years
- Case fatality rate 5%
Hereditary thrombophilia

Increases the risk for venous thrombosis

- Deficiencies of natural anticoagulants
  - antithrombin, protein C, protein S

- Gain of function mutations
  - factor V Leiden (FVL, APC resistance)
  - prothrombin 20210A mutation

- Elevated plasma levels of coagulation factors
  - factor VIII:c

Slightly associated with pregnancy complications

No association with arterial diseases
Objectives of testing

• (To have an explanation)

• To reduce morbidity and mortality
  
  In patients with venous thrombosis or pulmonary embolism
  • Modified treatment
  • Modified prophylaxis during high risk situations
  • Other preventive measures

Primary prevention in relatives

Middeldorp NTvG 2001; Cohn Sem Thromb Haemost 2007
Thromophilia and the risk of recurrent VTE

Factor V Leiden:
OR 1.4 (1.1-1.8)

Prothrombin mutation:
OR 1.4 (0.9-2.0)

Marchetti, Thromb Haemost 2000; Vink, J Thromb Haemost 2003
Thrombophilia and the risk of recurrent VTE

- Thrombophilia versus clinical risk factors

Baglin, Lancet 2003
Aims of E. Dekker Stipend (2003T038)

Assessing the usefulness of screening for hereditary thrombophilia

1. To survey the current practice of thrombophilia testing in the Netherlands
2. To assess the effect of testing for thrombophilia on the risk of recurrent VT
3. To prepare a trial that provides grade 1 level of evidence on the usefulness of testing

funded by the Netherlands Heart Foundation
Acknowledgements

- Nederlandse Hartstichting
- ZonMw

AMC Amsterdam
- Harry Büller
- Michiel Coppens
- Jos Reijnders
- Danny Cohn

Trombosediensten Amsterdam, Leiden en Rotterdam

Nostradamus onderzoekers

LUMC Leiden
- Frits Rosendaal
- Carine Doggen
- Team MEGA studie

Sanquin Amsterdam
- Jan van Mourik
- Karel Eckmann

funded by the Netherlands Heart Foundation
Indications for thrombophilia testing

• Survey in The Netherlands (2003-2004)
• Consecutive orders from November 1st 2003 at Sanquin Laboratories
• Mailed 2000 questionnaires to ordering physicians
• Response rate 63% (n=1132)
• Collection period 126 days
  • ≈ 5500-6000 orders/year

Coppens J Throm Haemost 2007
<table>
<thead>
<tr>
<th>Specialization</th>
<th>Total (%)</th>
<th>VTE (%)</th>
<th>Arterial (%)</th>
<th>Obstetric (%)</th>
<th>Family (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal medicine</td>
<td>37</td>
<td>68</td>
<td>21</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>Gynecology</td>
<td>20</td>
<td>6</td>
<td>&lt; 1</td>
<td>95</td>
<td>7</td>
</tr>
<tr>
<td>Neurology</td>
<td>15</td>
<td>2</td>
<td>58</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>General practitioners</td>
<td>14</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>65</td>
</tr>
<tr>
<td>Pulmonologists</td>
<td>6</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Surgeons</td>
<td>5</td>
<td>3</td>
<td>14</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>&lt; 1</td>
<td>5</td>
</tr>
</tbody>
</table>
## Consequences of tests

<table>
<thead>
<tr>
<th>Management consequences</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient management influenced by tests</td>
<td>71</td>
</tr>
<tr>
<td>Management implications present in this patient</td>
<td>23</td>
</tr>
<tr>
<td>Management implications only if thrombophilia was present</td>
<td>48</td>
</tr>
<tr>
<td>Nature of management decisions (≥ 1 answer possible)</td>
<td></td>
</tr>
<tr>
<td>Altered duration of anticoagulant treatment</td>
<td>10</td>
</tr>
<tr>
<td>Intensified prophylaxis in high-risk episodes</td>
<td>12</td>
</tr>
<tr>
<td>Lifestyle changes (including withholding oral contraceptives)</td>
<td>11</td>
</tr>
<tr>
<td>Frequency of patient contact</td>
<td>2</td>
</tr>
<tr>
<td>Additional testing in family members</td>
<td>6</td>
</tr>
<tr>
<td>Not specified</td>
<td>43</td>
</tr>
<tr>
<td><strong>No influence on patient management</strong></td>
<td>24</td>
</tr>
<tr>
<td>Uncertain</td>
<td>5</td>
</tr>
</tbody>
</table>
# Drawbacks of testing: psychological impact

<table>
<thead>
<tr>
<th>Table 2 Methodology: used measurements and points in time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Heilman 2003 [19]</td>
</tr>
<tr>
<td>Lindqvist 2003 [20]</td>
</tr>
<tr>
<td>Bank 2004 [21]</td>
</tr>
<tr>
<td>Van Korlaar 2005 [22]</td>
</tr>
<tr>
<td>Saaenko 2006 [23]</td>
</tr>
<tr>
<td>Legnani 2006 [24]</td>
</tr>
</tbody>
</table>

*Reported in correspondence by the authors; †self-reported by participants.
**Drawbacks of testing: costs**

<table>
<thead>
<tr>
<th>Description</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full thrombophilia panel (excluding LAC/ACA)</td>
<td>150 (?)</td>
</tr>
<tr>
<td>Consultation with an expert</td>
<td>200</td>
</tr>
<tr>
<td><strong>Total/patient</strong></td>
<td>350</td>
</tr>
</tbody>
</table>

**Spin-off costs**

<table>
<thead>
<tr>
<th>Description</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultation of 4 first degree relatives</td>
<td>800</td>
</tr>
<tr>
<td>Lab costs targeted testing (4x 25)</td>
<td>100</td>
</tr>
<tr>
<td>Intensified prophylaxis for 3 weeks (life-time estimation, 2x)</td>
<td>300</td>
</tr>
<tr>
<td><strong>Total/4 relatives</strong></td>
<td>1200</td>
</tr>
</tbody>
</table>

**TOTAL** 1550
Costs €

- Our survey
  - 126 days
  - Only regional care providers in The Netherlands
  - Partial thrombophilia screen in approx 50%
- 1000 * € 75 = 75,000
- 1000 * € 150 = 150,000
- Total costs € 225,000
- Annual (this lab only!): approx € 650,000

- Is it worthwhile? Does it reduce recurrent VTE?
Effect of testing on the risk of recurrent VT

- Case-cohort study of patients with recurrent VT
  - Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) (NHS 98.113)
  - >5000 cases with first VT or PE, > 5000 controls
  - 1999-2004

- 197 cases with recurrent VT during follow-up
- 324 controls matched for age, sex, year of first VT and region
Work load

- Selecting cases with recurrent VT from three anticoagulation clinics
- Selecting controls from the database
- Retrieving medical records from > 600 patients in 15 hospitals
  - Diagnosis verification
  - Thrombophilia testing yes/no
- Exposure: tested for thrombophilia after first VT
- Outcome: recurrent VT
Results

• Recurrent VT patients
  • 35% had been tested at the time of first VT

• Patients free from recurrence
  • 30% had been tested at the time of first VT

• Who were tested?
  • Women > men
  • Young > old
  • Positive family history of VT > no family history
  • Idiopathic or hormone-related > provoked by surgery/trauma
## Effect of testing on recurrent risk

<table>
<thead>
<tr>
<th></th>
<th>% tested</th>
<th></th>
<th>OR for recurrent VT (tested vs not-tested)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recurrent VT (cases)</td>
<td>No recurrent VT (controls)</td>
<td></td>
</tr>
<tr>
<td>all</td>
<td>35</td>
<td>30</td>
<td>1.2 (0.8-1.8)</td>
</tr>
<tr>
<td>women</td>
<td>41</td>
<td>35</td>
<td>1.4 (0.7-2.9)</td>
</tr>
<tr>
<td>First VT with OC use</td>
<td>60</td>
<td>32</td>
<td>3.4 (1.3-8.6)</td>
</tr>
<tr>
<td>Positive family history for VT</td>
<td>47</td>
<td>39</td>
<td>1.5 (0.7-3.1)</td>
</tr>
</tbody>
</table>
**NOSTRADAMUS study - design**

- randomisatie
  - wel trombofilieonderzoek
    - geen trombofilie
      - uitlokkende factor aanwezig: 3 maanden antistollingstherapie
    - wel trombofilie
      - uitlokkende factor aanwezig: 6 maanden antistollingstherapie
  - geen trombofilieonderzoek
    - idiopathisch: 6 maanden antistollingstherapie
Has the issue now been settled?

- Huge amount of money spent on testing
- No therapeutic consequences (observational evidence)
- Grade 1 evidence unlikely to ever become available

BRIEVEN AAN DE REDACTIE

Vroegtijdige beëindiging van het onderzoek naar het nut van trombofiliests bij een eerste veneuze trombo-embolie: het NOSTRADAMUS-onderzoek

D.M.Cohn en S.Middeldorp

Zie ook de artikelen op bl. 2053, 2057, 2062, 2065 en 2077.

Cohn, NTvG 2008
Family testing

• (To have an explanation)

• To reduce morbidity and mortality

   In patients with venous thrombosis or pulmonary embolism
   • Modified treatment
   • Modified prophylaxis during high risk situations
   • Other preventive measures

Primary prevention in relatives
Interaction between FVL and oral contraceptive use

How does this translate to absolute risk?

- Overall (annual)
- Per high risk situation (including oral contraceptives)
- The setting matters
  - Family history of VTE?
Relatives of patients with a known defect – FV Leiden

437 relatives of FVL + patients

All VTE

470 asymptomatic FVL carriers

Annual risk for spontaneous VTE 0.26% (0.07-0.65)

### Solid risk estimates for high risk situations

- **Setting of VTE family history**

<table>
<thead>
<tr>
<th>Incidences of first VTE in individuals who have inherited thrombophilia</th>
<th>Antithrombin, protein S, or protein C deficiency (%)/year</th>
<th>Factor V Leiden (0.7–2.8) [89]</th>
<th>Prothrombin 20210A (0.1–1.1) [91]</th>
<th>Elevated FVIII:c levels (%)/episode</th>
<th>Mild hyperhomocysteinemia (%)/year of use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (%)/year</td>
<td>1.5 (0.7–2.8) [89]</td>
<td>0.5 (0.1–1.3) [24,90]</td>
<td>0.4 (0.1–1.1) [91]</td>
<td>1.3 (0.5–2.7) [92]</td>
<td>0.2 (0.1–0.3) [93]</td>
</tr>
<tr>
<td>Surgery/trauma/immobilization (%)/episode</td>
<td>8.1 (4.5–13.2) [24]</td>
<td>1.8 (0.7–4.0) [23,24]</td>
<td>1.6 (0.5–3.8) [25]</td>
<td>1.2 (0.4–2.8) [15]</td>
<td>0.9 (0.1–3.4) [93]</td>
</tr>
<tr>
<td>Pregnancy (%)/pregnancy</td>
<td>4.1 (1.7–8.3) [24]</td>
<td>2.1 (0.7–4.9) [23,24]</td>
<td>2.3 (0.8–5.3) [25]</td>
<td>1.3 (0.4–3.4) [15]</td>
<td>0.5 (0.0–2.6) [93]</td>
</tr>
<tr>
<td>During pregnancy</td>
<td>1.2 (0.3–4.2)</td>
<td>0.4 (0.1–2.4)</td>
<td>0.5 (0.1–2.6)</td>
<td>0.3 (0.1–1.8)</td>
<td>0.0 (0.0–1.8)</td>
</tr>
<tr>
<td>Puerperium</td>
<td>3.0 (1.3–6.7)</td>
<td>1.7 (0.7–4.3)</td>
<td>1.9 (0.7–4.7)</td>
<td>1.0 (0.3–2.9)</td>
<td>0.5 (0.0–2.6)</td>
</tr>
<tr>
<td>Oral contraceptive use (%)/year of use</td>
<td>4.3 (1.4–9.7) [24]</td>
<td>0.5 (0.1–1.4) [23,24]</td>
<td>0.2 (0.0–0.9) [25]</td>
<td>0.6 (0.2–1.5) [15]</td>
<td>0.1 (0.0–0.7) [93]</td>
</tr>
</tbody>
</table>

General conclusion

• No indication for thrombophilia testing of relatives
  • Potential exception: women who intend to become pregnant or are ambivalent to use oral contraceptives
  • Beware of false reassurance!

• Think before you test, and counsel
Pregnancy loss

Recurrent miscarriage prevalent
- 0.5-1% of couples (3 or more)
- 3% of couples (2 or more)

Revised nomenclature (2005)
- Recurrent miscarriage
  - 3 early consecutive losses or 2 late pregnancy losses
- Early or late pregnancy loss
  - Before or after 12 weeks gestation
  - Ultrasound criteria

Rai, Lancet 2006; Farquharson, Hum Reprod 2005; “Miscarriage” Rachel Dolezal
### Associations

#### Family studies

<table>
<thead>
<tr>
<th>Thrombophilia defect</th>
<th>Sporadic miscarriage OR</th>
<th>Recurrent miscarriage OR</th>
<th>Intra-uterine fetal death OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT, PC, or PS deficiency</td>
<td>2.0</td>
<td>2.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Factor V Leiden mutation</td>
<td>1.0</td>
<td>2.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Prothrombin 20210A mutation</td>
<td>1.3</td>
<td>0.9</td>
<td>-</td>
</tr>
<tr>
<td>Homozygous defects or combinations of defects</td>
<td>0.8</td>
<td>-</td>
<td>14.3</td>
</tr>
<tr>
<td>Mild hyperhomocysteinemia</td>
<td>0.8</td>
<td>1.1</td>
<td>-</td>
</tr>
<tr>
<td>Elevated FVIII:c levels</td>
<td>1.2</td>
<td>1.1</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thrombophilia defect</th>
<th>Sporadic miscarriage OR</th>
<th>Recurrent miscarriage OR</th>
<th>Intra-uterine fetal death OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus anticoagulant</td>
<td>3.0</td>
<td>7.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Anticardiolipin antibodies</td>
<td>3.4</td>
<td>3.6 - 5.1</td>
<td>3.3</td>
</tr>
<tr>
<td>AT deficiency</td>
<td>1.5</td>
<td>0.9</td>
<td>7.6 (0.3-196)</td>
</tr>
<tr>
<td>PC deficiency</td>
<td>1.4</td>
<td>1.6</td>
<td>3.1</td>
</tr>
<tr>
<td>PS deficiency</td>
<td>Heterogeneous data</td>
<td>14.7 (1.0-218.0)</td>
<td>7.4 (1.3-42.8) 20.1 (3.7-109.2)</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>1.7</td>
<td>2.0</td>
<td>2.1 - 3.3</td>
</tr>
<tr>
<td>Prothrombin 20210A</td>
<td>2.1</td>
<td>2.3 - 2.7</td>
<td>2.3 – 2.7</td>
</tr>
<tr>
<td>Homozygous / combined defects</td>
<td>2.7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>6.3</td>
<td>2.7 – 4.2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Effect of heparin in thrombophilia - more observations

EPCOT cohort study
131 pregnant women with hereditary thrombophilia
  • No thrombosis prophylaxis n=48 (9 prior fetal loss)
    • Live birth rate 67-79% with/without fetal loss history
  • With thrombosis prophylaxis started early n=21
    • Live birth rate 76%

Single center Dutch study
37 women with AT/C/S deficiency, mainly asymptomatic
  • No thrombosis prophylaxis n=11
    • Live birth rate 55%
  • With thrombosis prophylaxis n=26
    • Live birth rate 100%

Recent trials – none with placebo or no treatment

Gris (Blood 2004)
• At least 1 single late fetal loss and thrombophilia
• LMWH versus aspirin

Live-enox (Brenner, JTH 2005)
• Women with at least 3 losses 1\textsuperscript{st} trimester, 2 2\textsuperscript{nd} trimester, or 1 IUFD (3\textsuperscript{rd} trimester) and hereditary thrombophilia
• 2 doses of LMWH
Ongoing trials

**TIPPS study** (M. Rodger, Canada)
- Recurrent fetal loss and other pregnancy complications + thrombophilia
- No treatment vs LMWH

**ALIFE study** (S. Middeldorp, The Netherlands)
- Recurrent fetal loss - unexplained or with hereditary thrombophilia
- Placebo (for aspirin) vs aspirin vs aspirin + LMWH

**SPIN study** (P. Clark, UK)
- Recurrent fetal loss - unexplained
- No treatment vs aspirin + LMWH

**HAPPY study** (I. Martinelli, Italy)
- Pregnancy complications
- No treatment vs LMWH
Conclusions

- Patients with VTE
- Family testing
- Pregnancy complications (recurrent miscarriage)

Thrombophilia testing only serves limited purpose and should not be performed on a routine basis

Middeldorp & Van Hylckama Vlieg, Br J Haematol 2008