Hereditary thrombophilia and venous thromboembolism:
Guidelines for a rational use

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BHS course 01-12-14
Thrombophilia

Inherited or acquired hemostastic abnormalities which may lead to venous thrombo-embolic complications
Most common thrombophilia tests

- **Hereditary**
  - Antithrombin deficiency
  - Protein C deficiency
  - Protein S deficiency
  - Factor V Leiden mutation
  - Factor II G20210A mutation
  - FVIII ? (raises with age, inflammation, cancer…)

- **Acquired**
  - Antiphospholipid syndrome
Other factors or polymorphisms can be tested

Factor XIII V34L
MTHFR C677T
β-fibrinogen –455G>A
PAI1 4G/5G
HPA1a/b
ApoB R3500Q

«Slight increased potential of cardiovascular and/or venous diseases »
Uncertain clinical implications
Weak association with VTE for some of them
Knowledge of hereditary thrombophilia?

- For the prevention of VTE in asymptomatic patients?
- To adapt the anticoagulant therapy?
- Cost-effective?
- Reassure the patient <-> unnecessary anxiety
- Problems to obtain life insurance in asymptomatic patient
- Predict recurrence of VTE?
- Decision for contraception?
- Prevention during pregnancy?
Recommendations on Testing for Thrombophilia in Venous Thromboembolic Disease

A French Consensus Guideline

Pernod et al. J Mal Vasc 2009;34:156

Clinical Guidelines for testing for heritable thrombophilia


Is thrombophilia testing useful

Middeldorp S. ASH Education Book 2011
1) Can the detection of thrombophilia help in explaining the occurrence of an episode of VTE?

2) Is there any value in testing for thrombophilia in asymptomatic patients with a family history of VTE?

3) Can the detection of thrombophilia help in better assessing the risk of recurrence after a VTE event?

4) Will the testing for thrombophilia influence the anticoagulant therapy?
Thrombophilia testing after a 1st episode of VTE

Thrombophilia testing is often considered in patients with VTE, particularly if they are young, have recurrent episodes, have thrombosis at unusual sites, or have a positive family history for the disease. However, this may lead to an increased yield of testing, but will a positive test modify management?

- Very high frequency of some mutations (FVL and *FII)
- However only a few of these individuals will have a VTE (Langlois and Well’s 2003)
- VTE occurs most of the time in association with environmental risk factors
# Prevalence of thrombophilia and relative risk for various clinical manifestations

<table>
<thead>
<tr>
<th></th>
<th>Antithrombin deficiency</th>
<th>Protein C deficiency</th>
<th>Protein S deficiency</th>
<th>Factor V Leiden</th>
<th>Prothrombin 20210A mutation</th>
<th>Lupus anticoagulant*</th>
<th>Anti-cardiolipin antibodies*</th>
<th>Anti-β2 GPI antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence in the general population</td>
<td>0.02%</td>
<td>0.2%</td>
<td>0.03%-0.13%</td>
<td>3.7%</td>
<td>0.7%-4%</td>
<td>1%-8 %</td>
<td>5</td>
<td>3.4</td>
</tr>
<tr>
<td>Relative risk for a first venous thrombosis</td>
<td>5-10</td>
<td>4-6.5</td>
<td>1-10</td>
<td>3.5</td>
<td>2.3</td>
<td>3-10</td>
<td>0.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Relative risk for recurrent venous thrombosis</td>
<td>1.9-2.6</td>
<td>1.4-1.8</td>
<td>1.0-1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>2-6</td>
<td>1-6</td>
<td></td>
</tr>
<tr>
<td>Relative risk for arterial thrombosis</td>
<td>No association</td>
<td>No consistent association</td>
<td>No consistent association</td>
<td>1.3</td>
<td>0.9</td>
<td>10</td>
<td>1.5-10</td>
<td></td>
</tr>
<tr>
<td>Relative risk for pregnancy complications</td>
<td>1.3-3.6</td>
<td>1.3-3.6</td>
<td>1.3-3.6</td>
<td>1.0-2.6</td>
<td>0.9-1.3</td>
<td>No consistent data</td>
<td>No consistent data</td>
<td></td>
</tr>
</tbody>
</table>
« These observations suggest that the presence of a biological thrombophilia is not a sufficient explanation in itself for the development of a VTE event (level 2) »
However

- Some of these biological thrombophilia are strong risk factors (high frequency of VTE in these patients) and play an important role in the development of a VTE, without sometimes a clear other risk factor associated.
- Best example is AT deficiency type 1: at age of 50 yrs most subjects will have a VTE event.
Summary

• Associated to environemental risk factors, thrombophilia plays a role in the occurrence of a first VTE

• Some hereditary thrombophilias (AT deficiency, combined thrombophilias or homozygous) are at high risk of idiopathic VTE

• Indiscriminate testing for heritable thrombophilia in unselected patients presenting with a first episode of venous thrombosis is not indicated (1B).
1) Can the detection of thrombophilia help in explaining the occurrence of an episode of VTE?

2) Is there any value in testing for thrombophilia in asymptomatic patients with a family history of VTE?

3) Can the detection of thrombophilia help in better assessing the risk of recurrence after a VTE event?
Thrombotic risk in family members

In families with hereditary thrombophilia, the relatives who do not carry the mutations AT, PC, PS, FVL and *FII seem also to have a higher risk of VTE than that of the general population.

Risk of false reassurance

Inheritable thrombophilia and 1\textsuperscript{st} VTE

Prospective study of 382 relatives from 84 probands with a 1\textsuperscript{st} VTE and AT, PC or PS deficiency

✓ Deficient subjects were advised to use thrombo-prophylaxis during exogenous risk factors and avoid OC

<table>
<thead>
<tr>
<th>Annual incidence of VTE</th>
<th>Deficient relatives</th>
<th>Non-deficient relatives</th>
<th>Adjusted hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.53% (1.00-2.34)</td>
<td>0.29% (0.13-0.64)</td>
<td>7.0 (2.7-18.0)</td>
</tr>
<tr>
<td>Unprovoked</td>
<td>0.95%</td>
<td>0.05%</td>
<td>22.3 (p = 0.003)</td>
</tr>
<tr>
<td>Provoked</td>
<td>0.58%</td>
<td>0.24% (0.13-0.64)</td>
<td>2.8 (p = 0.08)</td>
</tr>
</tbody>
</table>

Mahmoodi BK et al. \textit{JTH} 2010:8:1193
Thrombophilia screening in relatives of patients with a first VTE (retrospective cohort study, n = 2479)

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Annual incidence of VTE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVLeiden</td>
<td>0.49% (0.39-0.60)</td>
</tr>
<tr>
<td>FIIG20210A</td>
<td>0.34% (0.22-0.49)</td>
</tr>
<tr>
<td>AT deficiency</td>
<td>1.77 % (1.14-2.6)</td>
</tr>
<tr>
<td>PC deficiency</td>
<td>1.52% (1.06-2.11)</td>
</tr>
<tr>
<td>PS deficiency</td>
<td>1.90% (1.32-2.64)</td>
</tr>
</tbody>
</table>
• AT deficiency should be tested in asymptomatic relatives (grade B)

• Same approach for other strong risk factors such as PC, PS, homozygous FVL and *FII as well as double heterozygous FVL and *FII cases (grade C)

• A family study in case of isolated heterozygous FVL or FII in the index case is not indicated 1B (can be considered case by case)
It is proposed to test the relatives mainly for the thrombophilia marker identified in the index case. Asymptomatic family members may benefit from preventive measures in case of a thrombophilia marker is present.
Some situations where there is a thrombotic risk

• Oral contraceptive
• Hormone replacement therapy
• Pregnancy
<table>
<thead>
<tr>
<th>Event</th>
<th>Antithrombin, protein C, or protein S deficiency</th>
<th>Factor V Leiden, heterozygous</th>
<th>Prothrombin 20210A mutation</th>
<th>Factor V Leiden, homozygous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall, %/year (95% CI)</td>
<td>1.5 (0.7-2.8)</td>
<td>0.5 (0.1-1.3)</td>
<td>0.4 (0.1-1.1)</td>
<td>1.8 (0.1-4.0)*</td>
</tr>
<tr>
<td>Surgery, trauma, or immobilization, %/episode (95% CI)†</td>
<td>8.1% (4.5-13.2)</td>
<td>1.8 (0.7-4.0)</td>
<td>1.6 (0.5-3.8)</td>
<td></td>
</tr>
<tr>
<td>Pregnancy, %/pregnancy (95% CI)</td>
<td>4.1 (1.7-8.3)</td>
<td>2.1 (0.7-4.9)</td>
<td>2.3 (0.8-5.3)</td>
<td>16.3‡</td>
</tr>
<tr>
<td>During pregnancy, % (95% CI)</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>7.0‡</td>
</tr>
<tr>
<td>Postpartum period, % (95% CI)</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>9.3‡</td>
</tr>
<tr>
<td>Oral contraceptive use, %/year of use (95% CI)</td>
<td>4.3 (1.4-9.7)</td>
<td>0.5 (0.1-1.4)</td>
<td>0.2 (0.0-0.9)</td>
<td></td>
</tr>
</tbody>
</table>

Middeldorp S. *ASH Education Book 2011*
Recommendations

- Before prescription of OC, testing for thrombophilia should be considered in case of AT deficiency (grade B), and a treatment with oestroprogestatives is contraindicated if AT deficiency is detected.

- In general the recommendation is the same for PC or PS deficiencies or double heterozygous FVL and *FII or homozygous (grade C).

- In case of isolated heterozygous FVL or *FII a family study is debatable and should be considered case by case (possibility to prescribe another OC).
In all cases, if genetic thrombophilia is identified in the index case and tests of the asymptomatic relative prove negative, the informative quality of the family, and thus the risks conferred by the family history alone should be taken into account in the decision to use oestroprogestative CO (grade B).
Family studies before prescription of HRT

Same thinking as for CO but the risk is $x \ 10$ at this age

Esther study: FVL or *FII increases $x \ 25$ the risk of VTE when oral HRT is given but no increase with transdermal HRT


So there is little data to support testing for thrombophilia prior to the prescription of HRT in an asymptomatic woman with a family history of VTE, and testing is not recommended (expert agreement)
VTE and pregnancy

<table>
<thead>
<tr>
<th>Condition</th>
<th>VTE risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control women</td>
<td>1/1500</td>
</tr>
<tr>
<td>Heterozygous FVL</td>
<td>1/500</td>
</tr>
<tr>
<td>Heterozygous *FII</td>
<td>1/200</td>
</tr>
<tr>
<td>Heterozygous VL and *II</td>
<td>1/20</td>
</tr>
<tr>
<td>Homozygous VL or *II</td>
<td>1/10</td>
</tr>
<tr>
<td>AT deficiency</td>
<td>1/3</td>
</tr>
</tbody>
</table>

Greer IA et al. *NEJM* 2000;342:424
Recommendation

- It is recommended to propose testing to asymptomatic women of childbearing age in the case of familial history of VTE linked to AT, PC or PS deficiency, homozygous or double heterozygous FVL/*FII (grade B).

- Such testing is of questionable value in cases of heterozygous FVL or *FII in the absence of clear evidence justifying prophylactic medication throughout pregnancy and postpartum.
9.2.1. For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation (OR around 30) AND have a positive family history for VTE, we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or VKAs targeted at INR 2.0 to 3.0 rather than no prophylaxis (Grade 2B)

Bates et al. *Chest* 2012;141:e691s
9.2.2. For pregnant women with all other thrombophilias (OR around 5 or 5/1000 pregnancies) and no prior VTE who have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis (Grade 2C)……

Bates et al. Chest 2012;141:e691s
1) Can the detection of thrombophilia help in explaining the occurrence of an episode of VTE?

2) Is there any value in testing for thrombophilia in asymptomatic patients with a family history of VTE?

3) Can the detection of thrombophilia help in better assessing the risk of recurrence after a VTE event?
Particular risk factors for VTE recurrence

- Idiopathic event
- Permanent risk factor (cancer, etc.)
- Male sex (3x more than women)
- Post-thrombotic syndrome
- Raised D-dimer after completing anticoagulation
- Thrombophilia
Idiopathic vs provoked VTE: the major determinant of recurrence

Risk for a recurrence much higher (2-10%/yr) than for a 1st event (0.1%/yr)

After surgery, risk of recurrence around 2%/year

In the absence of a provocative risk factor (i.e. idiopathic or unprovoked VTE), the risk of recurrence is around 10%/year
Age

Very important risk factor for a first VTE event: 70% of patients are > 60 years old and 25% > 80 years

Naess et al. J Thromb Haemost 2007;5 692

Very low impact of FVL on the risk of VTE after 60 yrs

Couturaud et al. Thromb Haemost 2008;99:793
Family history

Considered also as a RF of recurrence but caution since a) often no precise diagnosis and b) definition of family history inadequate.

Should only be taken into account the 1\textsuperscript{st} degree family members (children, parents, siblings) and consider a family history informative only if at least two 1\textsuperscript{st} degree family members have had a documented VTE (level 4)
Recurrence in subjects with congenital thrombophilia

Thrombophilic alterations and altered D-Dimer
Hazard ratio = 8.34
(95%CI: 2.72-17.43)

Thrombophilic alterations and normal D-Dimer

## Inheritable thrombophilia and recurrence

<table>
<thead>
<tr>
<th>VTE</th>
<th>FV&lt;sub&gt;Leiden&lt;/sub&gt; and FII&lt;sub&gt;G20210A&lt;/sub&gt;</th>
<th>AT, PC and PS deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative recurrence rate</td>
<td>7% after 2 years</td>
<td>19% after 2 years</td>
</tr>
<tr>
<td></td>
<td>11% after 5 years</td>
<td>40% after 5 years</td>
</tr>
<tr>
<td></td>
<td>25% after 10 years</td>
<td>55% after 10 years</td>
</tr>
<tr>
<td>Annual incidence rate</td>
<td>2.25% (1.52-3.21)</td>
<td>6.23% (4.31-8.70)</td>
</tr>
<tr>
<td>Median age at recurrence</td>
<td>43 years (21-85 years)</td>
<td>36 years (20-75 years)</td>
</tr>
</tbody>
</table>

Lijfering WM et al. *Blood* 2009;113:5314
In principle, the duration of the anticoagulant therapy should be determined by a clinical assessment risk (2-3% per year) of major bleeding under VKA and the clinical benefit (less recurrence of VTE) under long term anticoagulation.

In a majority of patients, this assessment will not require or be informed by testing for thrombophilia.

Kearon et al, 2008
Recommendations

1. The determination of whether the VTE was provoked or not is fundamental in the assessment of the risk of recurrence, irrelevant of any knowledge of possible thrombophilia (grade A).

2. In cases of a first episode of VTE after 60 years, it is recommended not to undertake tests for thrombophilia (grade B).

3. In case of a first episode before 60 years:
   - when the VTE was unprovoked, tests for thrombophilia are recommended (grade C).
   - when the VTE occurred following major triggering circumstances (grade B) and in the absence of family data (grade C), tests for thrombophilia should not be systematically performed.
Limitations of these tests

It is not because a thrombophilia work-up is normal that the person is not at risk of recurrence and on the opposite an anomaly does not imply that the person is at risk.
When to perform a thrombophilia screening?

- At any time
  - genetic tests
- Do not perform
  - PC, PS if patient under VKA
  - aCL, anti-\(\beta\)2GPI and PS in the acute phase of VTE
  - PS if pregnancy, CO, HRT and infection or inflammation