Thrombophilia Testing and Management

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HTRS workshop
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Off-label product use discussion:  NONE
A 32-year-old man is seen for evaluation for a possible hypercoagulable state. His father was recently diagnosed with heterozygous factor V Leiden mutation following an episodes of unprovoked venous thromboembolic disease. The patient is concerned with his own risk of thrombosis. Medical history is negative, with no venous thromboembolism.
Your poll will show here

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A 28-year-old woman presents with a 2-day history of right leg pain and swelling. Medical history is unremarkable. Her only medication is an estrogen-progestin oral contraceptive pill. She is diagnosed with a proximal deep venous thrombosis; there was no preceding trauma, surgery, immobility or long-distance travel. Anticoagulant therapy with low-molecular-weight heparin and warfarin is initiated. A thrombophilia evaluation is ordered, which includes factor V Leiden and prothrombin G20210A genetic testing; protein C, S, and antithrombin activities; lupus anticoagulant; and anticardiolipin and anti-β₂-glycoprotien-I antibody testing.
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A 63 year old otherwise healthy man undergoes left hip replacement surgery for osteoarthritis. He is making a good recovery, but 2 weeks after the surgery he develops left leg swelling and pain and is diagnosed with a proximal left leg DVT. How long should he be treated with anticoagulation?
Your poll will show here

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or
Open poll in your web browser
Introduction / The Basics
Hi Dr Moll,

I need your recommendations about a 56 yr old man; 2013: R leg DVT + PE. Heterozygous FVL/Leiden. Long-term warfarin?

Thanks!

With warm regards,

......
1. Define the clot

   R leg proximal DVT, unprovoked

2. List the VTE risk factors: (a) …, (b) …, (c) …

   (a) OCP, (b) BMI, (c) hetero FVL
How Long to Treat With Anticoagulation?

Conglomerate decision of:

1. Risk of recurrent VTE
   (a)...., (b)...., (c) ..... 

2. Risk for Bleeding
   (a)...., (b)...., (c) ..... 

3. Patient preference


Warfarin “Hate Factor”

Blood Thinner “Dislike Factor”
Case

- 27 yr old woman
- PE and prox + distal DVT

VTE risk factors:
  a) OCP (estrogen/progestin)
  b) BMI > 30.

**Question:** How long to treat with anticoagulation?
VTE due to major transient risk factor

Woman with VTE on hormones
Non-major transient risk factor

Woman with unprovoked VTE
- DVT
- PE

Man with unprovoked VTE
- DVT
- PE

Recurrence Triangle

VTE due to major transient risk factor

Woman with VTE on hormones
Non-major transient risk factor

Woman with unprovoked VTE
- DVT
- PE

Man with unprovoked VTE
- DVT
- PE

Strong Thrombophilia

D-dimer

3 months

Long-term

Cumulative VTE Recurrence Rate

<table>
<thead>
<tr>
<th></th>
<th>1 year</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 %</td>
<td>3 %</td>
<td></td>
</tr>
<tr>
<td>6 % *</td>
<td>15 %</td>
<td></td>
</tr>
<tr>
<td>10 %</td>
<td>30 %</td>
<td></td>
</tr>
</tbody>
</table>


*[Douketis J et al. BMJ 2011;342:d813]*
• 3.6 % of recurrent VTE are fatal
• 10 % of major bleeds are fatal

Thus:
If risk of recurrence ≥ 3x higher than risk of major bleed =
long-term anticoagulation.

Consequences of a recurrent VTE or a major bleed

The most important consequence of a recurrent VTE or a major bleed is that it may be fatal. In prospective studies, case fatality has been estimated as 3.6% for a recurrent VTE and 11.3% for a major bleed on a VKA. There is uncertainty about these estimates. Fatal PE may occur more often outside of prospective studies because early detection and treatment of recurrent DVT and PE is less likely, and the 11.3% estimate for the case fatality of major bleeding is based on data from initial rather than extended therapy. Also, because a recurrence is 3 times as likely to be a PE if the initial event was a PE rather than a DVT, case fatality for recurrent VTE may be substantially higher (perhaps double) when the initial VTE was a PE.

Nonfatal events are also important: (1) PE, DVT, and bleeding are distressing for patients and costly; (2) recurrent DVT, especially in the same leg, increases risk and severity of the postthrombotic syndrome (PTS); and (3) recurrent PE may cause chronic cardiopulmonary impairment.

VTE due to major transient risk factor

Woman with VTE on hormones
Non-major transient risk factor

Woman with unprovoked VTE
• DVT
• PE

Man with unprovoked VTE
• DVT
• PE

Fatality

1 of 1,250
3% Recurrent VTE

1 of 600
6% DVT

1 of 170
15% PE

1 of 80
30% Strong Thrombophilia

## “Strong” Thrombophilias

<table>
<thead>
<tr>
<th>No.</th>
<th>Condition</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>APLA syndrome</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Antithrombin deficiency</td>
<td>Yes</td>
</tr>
<tr>
<td>3.</td>
<td>Protein C deficiency</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Protein S deficiency</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Homozygous factor V Leiden</td>
<td>yes / no</td>
</tr>
<tr>
<td>6.</td>
<td>Homozygous II20210 mutation</td>
<td>unknown</td>
</tr>
<tr>
<td>7.</td>
<td>Heterozygous FVL plus heterozygous II20210</td>
<td>yes / no</td>
</tr>
</tbody>
</table>

[Segal J et al. JAMA 2009; 301:2472-85]
[Lijfering WM et al. Circulation 2010;121:1706-12]
Individual Thrombophilias…

...Key Points
Obesity and VTE Risk

![Graph showing the relationship between BMI and odds ratio for VTE risk. The x-axis represents BMI categories: <20, ≥20 and <22.5, ≥22.5 and <25, ≥25 and <27.5, ≥27.5 and <30, ≥30 and <32.5, ≥32.5 and <35, ≥35. The y-axis represents the odds ratio, ranging from 0.0 to 3.5. Each category shows an increase in odds ratio as BMI increases.]

# Inherited and Acquired Thrombophilias

**Most common**
- Factor V Leiden
- Prothrombin 20210

**Classics**
- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency

**Acquired**
- Antiphospholipid antibodies (ACA, LA, anti-\(\beta_2\)-GPI)
- ↑ Homocysteine, MTHFR
- ↑ Fibrinogen, factor VIII, IX, XI

**Others**
- PAI-1, tPA levels and polymorphisms
- CBC, CD55/59, JAK-2
Prevalences

- Factor V Leiden, heterozygous: 1 : 20
- II20210 mutation, heterozygous: 1 : 50
- Protein C deficiency 1 : 500
- Protein S deficiency 1 : 500
- Antithrombin deficiency 1 : 5,000
- Homozygous protein C deficiency 1 : 250,000
- Homozygous FVL 1 : 1,600
- Hetero FVL + hetero II20210 1 : 1,000
- Homozygous II20210 1 : 10,000

## Risk of 1\textsuperscript{st} VTE with thrombophilias

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Relative risk increase for first VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>No thrombophilia</td>
<td>Reference group</td>
</tr>
<tr>
<td>II\textsubscript{20210}, hetero</td>
<td>3.8 (95% CI 3.0-4.9)</td>
</tr>
<tr>
<td>FVL, heterozygous</td>
<td>4.9 (95% CI 4.1-5.9)</td>
</tr>
<tr>
<td>II\textsubscript{20210}, homozygous</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>FVL, homozygous</td>
<td>18 (95% CI 4.1-41)</td>
</tr>
<tr>
<td>Hetero II\textsubscript{20210} PLUS hetero FVL</td>
<td>20 (95% CI 11.1-36.1)</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>30.6 (95% CI 26.9-55.3)</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>24.1 (95% CI 13.7-42.4)</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>28.2 (95% CI 13.5-58.6)</td>
</tr>
</tbody>
</table>

Risk of **Recurrent** VTE with Thrombophilias

1. II20210, hetero: 1.45
   (95% CI 0.96-2.21)
   
   FVL, hetero: 1.56
   (95% CI 1.14-2.12)

   [Segal J et al. JAMA 2009; 301:2472-85]

2. FVL, homo: 2.65
   (95% CI 1.18-5.97)
   
   FVL, homo: 1.2
   (95% CI 0.5-2.6)

   [Segal J et al. JAMA 2009; 301:2472-85; meta-analysis]
   [Lijfering WM et al. Circulation 2010;121:1706-12]

3. FVL + II2010: 4.81
   (95% CI 0.50-46.3)
   
   FVL + II2010: 1.0
   (95% CI 0.6-1.9)

   [Segal J et al. JAMA 2009; 301:2472-85; meta-analysis]
   [Lijfering WM et al. Circulation 2010;121:1706-12]

4. II20210, homo: insufficient data
Risk of Recurrent VTE with Thrombophilias

Protein C
Protein S
Antithrombin

2.8 (95 % CI 2.0 – 4.0)

[Liifering WM et al. Circulation 2010;121:1706-12]

APLA: 1.41 (95 % CI 0.99-2.00)
ACA: 1.53 (95 % CI 0.76-3.11)
LA: 2.83 (95 % CI 0.83-9.64)

APLA syndrome: ~2.0

[Kearon C et al; Chest 2012;141:e419S-494S]
Protein C, S and Antithrombin Deficiency

**Acquired deficiency:**
- Liver disease (C, S, AT)
- Warfarin therapy (C, S)
- Estrogens, pregnancy (S)
- Inflammatory diseases (S)
- Heparin therapy (AT)
- Acute thrombosis (S, AT)

**How do you test?**
- C, S, AT activity
- free S antigen
- >100 mutations

**Practical point:**
- Always question the diagnosis!

**How do you treat?**
- Consider AT concentrate
- Severe neonatal C deficiency: protein C concentrate
Antiphospholipid Antibody Testing

I) Antibody test (ELISA)
- anticardiolipin
- anti-β2-glycoprotein I
- antiphosphatidylserine
- antiphosphatidylcholine
- antiphosphatidylethanolamine

II) Functional test
- lupus anticoagulant (inhibitor)

Antiphospholipid Antibodies

- Up to 10% of pts with APLA syndrome only positive for anti-\(\beta_2\)-GP I


- \(\beta_2\)-GP-I Ab may be more specific for APLA syndrome

- Not yet recommended that anti-\(\beta_2\)-GP-I Ab test replaces ACA


- IgG and IgM recommended (for ACA and anti-\(\beta_2\)-GP-I Ab);
  - if neg: test for IgA.


- “Testing for IgA Abs is NOT recommended”

Antiphospholipid Antibodies
Updated Sapporo Criteria for APS (2006):

- Clinical criteria:
  - Vascular thrombosis
  - Pregnancy morbidity

- Laboratory criteria*:
  - Anticardiolipin antibodies (IgG or IgM) (medium or high titer: >40 GPL/MPL or >99th percentile)
  - Anti-β₂-glycoprotein I antibodies (IgG or IgM) (>99th percentile)
  - LA

*2 or more occasions, >12 wks apart.

• “APLA syndrome”: question the diagnosis
• ≥ moderately high titers of ACA (≥40 U/mL)
• Include anti-\(\beta_2\)-GP-I antibody testing
• Test outside the acute event
• Repeat APLA testing (3 months apart)
• Know the LA tests and their interpretation

• Role of IgA antibodies unclear.
**Conclusions:**

1. LA stronger and more definitive risk factor for thrombosis than ACA.
2. Risk for thrombosis is highest if positive APLA by multiple assays.

**APLA: Risk for 1st Thrombosis**

- ACA +; anti-\(\beta_2\)-GP-I +; LA +
Are APLA a Risk Factor for Recurrent VTE?

Systematic Review

- 8 eligible studies
- All had important methodologic limitations.
- “We judged the overall quality of the evidence as very low”.

Conclusion

- Although it appears that pos. APLA predict ↑’d risk of VTE recurrence, the strength of this association is uncertain.

1. Are APLA a risk factor for recurrent VTE? “They appear to be!”

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>APLA Events</th>
<th>APLA Total</th>
<th>No APLA Events</th>
<th>No APLA Total</th>
<th>Weight</th>
<th>Risk Ratio (M-H, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginsberg 1995</td>
<td>2</td>
<td>11</td>
<td>6</td>
<td>34</td>
<td>5.1%</td>
<td>1.03 [0.24, 4.39]</td>
</tr>
<tr>
<td>Kearon 1999</td>
<td>4</td>
<td>6</td>
<td>12</td>
<td>71</td>
<td>13.5%</td>
<td>3.94 [1.83, 8.48]</td>
</tr>
<tr>
<td>Kearon 2004</td>
<td>1</td>
<td>17</td>
<td>6</td>
<td>124</td>
<td>2.7%</td>
<td>1.22 [0.16, 9.49]</td>
</tr>
<tr>
<td>Rodger 2008</td>
<td>56</td>
<td>384</td>
<td>31</td>
<td>235</td>
<td>25.0%</td>
<td>1.11 [0.74, 1.66]</td>
</tr>
<tr>
<td>Schulman 2006</td>
<td>38</td>
<td>116</td>
<td>194</td>
<td>694</td>
<td>30.1%</td>
<td>1.17 [0.88, 1.56]</td>
</tr>
<tr>
<td>Taliani 2009</td>
<td>3</td>
<td>6</td>
<td>76</td>
<td>291</td>
<td>12.3%</td>
<td>1.91 [0.84, 4.36]</td>
</tr>
<tr>
<td>Wahlander 2005</td>
<td>5</td>
<td>48</td>
<td>49</td>
<td>465</td>
<td>11.3%</td>
<td>0.99 [0.41, 2.36]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>588</td>
<td></td>
<td>1914</td>
<td></td>
<td>100.0%</td>
<td><strong>1.41 [0.99, 2.00]</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>109</td>
<td></td>
<td>374</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau²</td>
<td>0.08</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.96, df = 6 (P = 0.09); I² = 45%</td>
</tr>
<tr>
<td>Test for overall effect: Z</td>
<td>1.92 (P = 0.06)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2.** Relative risks for recurrent VTE after stopping anticoagulant therapy with APLA vs without APLA. M-H, Mantel–Haenszel. [Garcia D et al. Blood 2013;122:817-824]
Risk for Recurrent Thrombosis

2. Which of the APLA best predicts recurrent VTE?

### Lupus Anticoagulant (LA)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Lupus Anticoagulant</th>
<th>No APLA</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginsberg 1995</td>
<td>2/9</td>
<td>6/34</td>
<td>1.33 [0.22, 8.08]</td>
</tr>
<tr>
<td>Kearon 1999</td>
<td>2/3</td>
<td>12/71</td>
<td>9.63 [0.82, 117.35]</td>
</tr>
<tr>
<td>Kearon 2004</td>
<td>1/7</td>
<td>6/124</td>
<td>3.28 [0.34, 31.74]</td>
</tr>
</tbody>
</table>

Total (95% CI) 19/229 100.0% 2.83 [0.83, 9.64]

Heterogeneity: $\tau^2 = 0.00, \Chi^2 = 1.66, df = 2 (P = 0.44), I^2 = 0$

Test for overall effect: $Z = 1.66 (P = 0.10)$

### Anti-Cardiolipin Antibody (ACA)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ACLA Positive</th>
<th>No APLA</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kearon 1999</td>
<td>2/3</td>
<td>12/71</td>
<td>3.94 [1.52, 10.22]</td>
</tr>
<tr>
<td>Schulman 2006</td>
<td>38/116</td>
<td>194/694</td>
<td>1.17 [0.88, 1.56]</td>
</tr>
<tr>
<td>Wahlander 2005</td>
<td>5/48</td>
<td>49/465</td>
<td>0.99 [0.41, 2.36]</td>
</tr>
</tbody>
</table>

Total (95% CI) 167/1230 100.0% 1.53 [0.76, 3.11]

Heterogeneity: $\tau^2 = 0.26, \Chi^2 = 6.29, df = 2 (P = 0.04), I^2 = 68$

Test for overall effect: $Z = 1.18 (P = 0.24)$
Homocysteine, MTHFR

- MTHFR C677T, homozygous TT, or A1298C
- **May** have higher homocysteine levels
- **Not** a risk factor for thrombosis or pregnancy complications

---

**Practical point:**
Don’t Test for MTHFR.

**Practical point:**
Test for homocysteine?– no good indication.

MTHFR=methylenetetrahydrofolate reductase

[Klerk M. JAMA. 2002;288:2023-2031]
[Rey E. Lancet. 2003;361:901-908]
[ACOG Bulletin #124, 2011]
Why you shouldn’t know too much about your own genes

By Carolyn Johnson  September 11 at 9:30 AM  Follow @carolynyjohnson

The potential harms of people seeking out information about MTHFR may seem relatively small. People may pay for genetic tests or supplements that they do not need, and perhaps that money would be better spent on a gym membership or hiking boots, said Muin Khoury, the director of the office of public health genomics at the Centers for Disease Control and Prevention. But
Other Thrombophilias

- Elevation of factor VIII
- Elevations of fibrinogen, factors II, IX, XI
- Fibrinolysis abnormalities:
  - Plasminogen deficiency
  - Decreased tPA levels and polymorphisms
  - Elevated PAI-1 level and polymorphisms
  - Elevated TAFI levels
- Myeloproliferative disorders (JAK-2 mutation)
- Paroxysmal nocturnal hemoglobinuria (CD55/59)

tPA=tissue plasminogen activator; PAI-1=plasminogen activator inhibitor 1; TAFI=thrombin activatable fibrinolysis inhibitor.
Unexplained Arterial Thrombosis

“Unexplained” arterial clots – considerations and laboratory work-up

A. Is arteriosclerosis the underlying problem?
   - Arteriosclerotic changes demonstrated on imaging studies (on CT or other radiologic imaging) or on pathology specimens?
   - Arteriosclerosis risk factors present?
     - Cigarette smoking
     - High blood pressure
     - High LDL (low density lipoprotein)
     - Low HDL (high density lipoprotein)
     - Diabetes mellitus
     - Family history of arterial problems (heart attack relatives (less than 50 years of age)

B. Is there a cardioembolic source?
   - Atrial fibrillation - Holter monitor to be done.
   - Patent foramen ovale (PFO) - cardiac echo (TTE-transthoracic echocardiography, TTE is normal, obtain a swallow echo (TEE-transesophageal echocardiography)

C. Other causes
   - Is the patient on estrogen therapy (contraceptive pill, menopause therapy)?
   - Does the patient use cocaine or amphetamine steroids?
   - Is there evidence for Buerger’s disease (does patient smoke) – or chronic venous disease (does patient have symptoms suggestive of a chronic venous condition)?
   - Were anatomic abnormalities seen in the artery leading to the ischemic area (web, fibromuscular dysplasia, dissection, vasculitis, external compression)?
   - Does patient have evidence of a rheumatologic or autoimmune disease (arthritis, skin rashes, etc.) – consider laboratory work-up for vasculitis and immune disorder

D. Thrombophilia work-up
   - Hemoglobin and platelet count
   - Antiphospholipid antibodies
     - Anti-cardiolipin IgG and IgM antibodies
     - Anti-β2-glycoprotein-I IgG and IgM antibodies
     - Lupus anticoagulant
   - Protein C activity
   - Protein S activity and/or free protein S antigen
   - Antithrombin activity
   - Homocysteine (to rule homocysteinemia)
   - Lipoprotein(a)
   - Factor V Leiden and prothrombin 20210 mutation (purpose of testing is to detect the homozygous or double heterozygous state)
   - Do not test for MTHFR polymorphisms

1. Arteriosclerosis documented or risk factors present?
2. Cardioembolic source?
3. Other causes (hormones, cocaine, vasculitis, etc?)
4. Thrombophilia?

http://professionalsblog.clotconnect.org/2011/01/31/unexplained-arterial-thrombosis-causes-thrombophilia-testing

Arterial Thrombosis

**FVL:** OR **1.21** (95% CI, 0.99-1.49)

**II20210:** OR **1.32** (95% CI, OR 1.03-1.69)

[Kim RJ et al. *Am Heart J* 2003;146:948-957]

**Protein C and S deficiency**
- <55 yrs: **4.7-fold** (95% CI 1.5-4.2)
- >55 yrs: **1.1-fold** (95% CI 1.1-18.3)

**Antithrombin deficiency**
- “Not a risk factor”

How to best treat (secondary prevention?)

1. Anti-platelet therapy?
2. Anticoagulant?
3. Both together?

The more information, the better – even though we don’t have all the answers.
Whom to Test for Thrombophilia?
Whom to Test for Thrombophilia?

**Background:**

3 reasons to consider testing:

1. “Does it influence length of anticoagulation decision?”
2. “Does it have consequences for patient’s family members?”
3. Wish of patient and MD to “understand” why clot happened
Whom to Test for Thrombophilia?

- Everybody
- Any pt with VTE
- Any pt with spontan. VTE
- Young pt
- Young pt with FHx
- Nobody

Ultra-liberal  Arch-conservative
Whom to Test for Thrombophilia?

Europ Genetics Foundation, Mediterranean League on Thromboembolism, Internat. Union of Angiology, etc., 2005

CAP, 2002

Am Coll Med Geneticists, 2001

Thrombosis Interest Group of Canada 2006

EGAPP 2011

Br Committee for Standards in Haematol, 2010

ACF, 2016

[Baglin T. Br J Hematol 2010;Jan 28;Epub ahead of print]
[van Cott EM et al. Arch Pathol Lab Med 2002;126:1281-1295]
[Grody WW. Genetics in Medicine 2001;3:139-148]
[Mant M. www.tigc.org/eguidelines/hypercoagstates.htm]
[Nicolaides AN. International Angiology 2005;24:1-26]
[EGAPP. Genetics in Medicine 2011;13 (1)67-76]
[Stevens S et al. J Thromb Thrombolys 2016]
Whom to Test

- Controversial
- Recent guideline: ACF 2016
- Guidelines in development: ASH 2016/2017


- Terminology used:
  - “testing can be considered”
  - “benefit of testing unclear”
  - “lack of evidence that testing impacts clinical outcomes”
- Cost, mis-interpretation
1. Only the professional knowledgeable about the 4Ps should test.
   - Patient selection
   - Pretest counseling
   - Proper lab test interpretation
   - Provision of education and advice

2. Do not test while patient is on an anticoagulant.
3. Do not test during acute thrombotic episode.
4. Do not test a hospitalized patient.

In Whom to Consider Testing

1. DVT/PE, intermediate risk recurrence
2. VTE in unusual locations, unprovoked
3. Arterial thrombosis, unexplained
4. Pregnancy loss(es), unexplained
5. VTE: Patient requests testing
6. Family members (if “strong thrombophilia” in index pt)
Choosing Wisely® Campaign

Whom NOT to test

Recommend against thrombophilia testing in pts with VTE associated with major transient risk factor.

What to Test?
# Inherited and Acquired Thrombophilias

**Most common**
- Factor V Leiden
- Prothrombin 20210

**Classics**
- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency
- Antiphospholipid antibodies (ACA, LA, anti-β2-GPI)

**Acquired**
- ↑ Homocysteine, MTHFR
- ↑ Fibrinogen, factor VIII, IX, XI

**Others**
- PAI-1, tPA levels and polymorphisms
- CBC, CD55/59, JAK-2

### Influence of Anticoagulants on Thrombophilia Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Acute thrombosis</th>
<th>Unfractionated heparin</th>
<th>Low molecular weight heparin</th>
<th>Vitamin K antagonists</th>
<th>DOACs</th>
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</thead>
<tbody>
<tr>
<td>Factor V Leiden genetic test</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Reliable</td>
</tr>
<tr>
<td>APC resistance assay</td>
<td>Reliable&lt;sup&gt;a&lt;/sup&gt;</td>
<td>???&lt;sup&gt;a&lt;/sup&gt;</td>
<td>???&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Reliable&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Unreliable&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>Prothrombin G20210A genetic test</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Reliable</td>
</tr>
<tr>
<td>Protein C activity</td>
<td>???&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Low</td>
<td>Elevated&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Protein C antigen</td>
<td>???&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Low</td>
<td>Reliable</td>
</tr>
<tr>
<td>Protein S activity</td>
<td>May be low</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Low</td>
<td>Elevated&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Protein S antigen</td>
<td>May be low</td>
<td>May be low</td>
<td>May be low</td>
<td>May be elevated&lt;sup&gt;h&lt;/sup&gt;</td>
<td>Elevated&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>Antithrombin activity</td>
<td>May be low</td>
<td>???&lt;sup&gt;e&lt;/sup&gt;</td>
<td>???&lt;sup&gt;e&lt;/sup&gt;</td>
<td>???&lt;sup&gt;e&lt;/sup&gt;</td>
<td>False positive&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>Accurate&lt;sup&gt;d&lt;/sup&gt;</td>
<td>???&lt;sup&gt;e&lt;/sup&gt;</td>
<td>???&lt;sup&gt;e&lt;/sup&gt;</td>
<td>???&lt;sup&gt;e&lt;/sup&gt;</td>
<td>False positive&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anticardiolipin antibodies</td>
<td>Accurate&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Reliable</td>
</tr>
<tr>
<td>Anti-B&lt;sub&gt;2&lt;/sub&gt;-glycoprotein-I antibodies</td>
<td>Accurate&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Reliable</td>
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<tr>
<td>Homocysteine</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Reliable</td>
<td>Reliable</td>
</tr>
</tbody>
</table>

Which Family Members to Test for Thrombophilia
Which Family Members to Screen for Thrombophilia?

- Having a 1st degree relative with VTE, increases a family member’s risk for VTE.

- Increased risk is irrespective of presence of FVL or prothrombin 20210:
  - Positive family history but no FVL or prothrombin 20210: OR 2.6 (95% CI, 1.7-3.8)
  - Positive family history plus FVL or prothrombin 20210: OR 3.6 (95% CI, 1.2-4.0)

## Which Family Members to Consider for Thrombophilia Screening?

<table>
<thead>
<tr>
<th>Proband’s thrombophilia</th>
<th>Male Family Member</th>
<th>Female Family Member</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sons</td>
<td>Brothers</td>
</tr>
<tr>
<td>Hetero FVL or hetero prothrombin 20210</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Homo FVL or homo prothrombin 20210</td>
<td>no</td>
<td>reasonable</td>
</tr>
<tr>
<td>Double hetero</td>
<td>reasonable</td>
<td>reasonable</td>
</tr>
<tr>
<td>C, S, AT</td>
<td>reasonable</td>
<td>reasonable</td>
</tr>
</tbody>
</table>

“reasonable” because: consider LMWH with airline travel, cast, non-major surgery; prolonged after major surgeries.

“yes” because: advise against estrogen contraceptives/hormone therapy; give antepartum and postpartum anticoagulation.
Anticoagulation in Pregnancy Complications

“Whether anticoagulant therapy prevents recurrent miscarriage in women with inherited thrombophilia is controversial – inconsistent results from trials.”

[Middeldorp S. Hematology 2014; ASH Education Program:393-399]
• “Some asymptomatic women of fertile age”:
  • may choose ante- and postpartum VTE prophylaxis
  • may choose not to take hormonal contraceptives


• Benefit of testing and of LMWH treatment if thrombophilia found is unclear.
• Enroll patients into trials; or: non-evidence-based decision.
Contraceptive Options in Thrombosis / Thrombophilia

Estrogen combination pill
- 3rd generation
- 2nd generation

Injectable progestins
- Depot preparation
- Rod

Progestin pill (minipill)

Progestin-releasing IUDs

Non-hormonal methods

Summary

1. Often little/no evidence of benefit of testing

2. Whom to test? Terminology: “Consider”, not “recommend”

3. When to test: At 3 months; not acutely, not inpatient, not while on anticoagulation.

4. Cave: Interpretation of test results while on anticoagulation
Summary: In Whom Do I consider Testing?

1. DVT/PE, intermediate risk recurrence
2. VTE in unusual locations, unprovoked
3. Arterial thrombosis, unexplained
4. Pregnancy loss, unexplained
5. VTE: Patient requests testing
6. Family members (if “strong thrombophilia” in index pt)
A 32-year-old man is seen for evaluation for a possible hypercoagulable state. His father was recently diagnosed with heterozygous factor V Leiden mutation following an episodes of unprovoked venous thromboembolic disease. The patient is concerned with his own risk of thrombosis. Medical history is negative, with no venous thromboembolism.
Your poll will show here

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A 28-year-old woman presents with a 2-day history of right leg pain and swelling. Medical history is unremarkable. Her only medication is an estrogen-progestin oral contraceptive pill. She is diagnosed with a proximal deep venous thrombosis; there was no preceding trauma, surgery, immobility or long-distance travel. Anticoagulant therapy with low-molecular-weight heparin and warfarin is initiated. A thrombophilia evaluation is ordered, which includes factor V Leiden and prothrombin G20210A genetic testing; protein C, S, and antithrombin activities; lupus anticoagulant; and anticardiolipin and anti-β₂-glycoprotien-I antibody testing.
Your poll will show here

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or
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A 63 year old otherwise healthy man undergoes left hip replacement surgery for osteoarthritis. He is making a good recovery, but 2 weeks after the surgery he develops left leg swelling and pain and is diagnosed with a proximal left leg DVT. How long should he be treated with anticoagulation?
Your poll will show here

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Comments?