Thrombophilia Testing and Optimal Duration of Anticoagulation for Patients with Venous Thromboembolism

Gregory Piazza, MD, MS
Assistant Professor of Medicine
Harvard Medical School
Staff Physician, Cardiovascular Division
Brigham and Women’s Hospital
September 29, 2016

Objectives
1. Review the epidemiology of thrombophilias
2. Highlight the implications of thrombophilia on venous thromboembolism (VTE) risk, women’s health, and disease recurrence
3. Discuss "when, why, and how" to perform thrombophilia testing
4. Understand how thrombophilia testing impacts the determination of optimal duration of anticoagulation

Thrombophilia: Prevalence

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>General Population (%)</th>
<th>Patients with 1st VTE (%)</th>
<th>Family History of Thrombosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>3-7</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>Prothrombin Gene Mutation</td>
<td>1-3</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>5-10</td>
<td>10-25</td>
<td>?</td>
</tr>
<tr>
<td>Antiphospholipid Antibodies</td>
<td>0-7</td>
<td>5-15</td>
<td>?</td>
</tr>
<tr>
<td>Protein C Deficiency</td>
<td>0.2-0.4</td>
<td>3</td>
<td>6-8</td>
</tr>
<tr>
<td>Antithrombin Deficiency</td>
<td>0.02</td>
<td>1</td>
<td>4-8</td>
</tr>
<tr>
<td>Protein S Deficiency</td>
<td>?</td>
<td>1-2</td>
<td>3-13</td>
</tr>
</tbody>
</table>

Rosendaal FR. Semin Hematol 1997;34:171

What Would You Do?

- A 21-year-old woman is referred from her college health center for evaluation of possible OCP use.
- The patient’s mother suffered PE during her first pregnancy and her older sister had a DVT on an OCP.
- The patient has never suffered a thrombotic event.
- Her mother and sister were never tested for thrombophilias because their physician felt “it would not assist with management of venous thromboembolism.”
Thrombophilia and Conventional Risk Factors: US DVT Registry

Goldhaber SZ and Tapson VF. Am J Cardiol 2004;93:259

Thrombophilia Testing in the Real World: Lessons from RIETE

- N = 21,367 consecutive patients with symptomatic VTE.
- Thrombophilia testing was performed in 21%.
- Thrombophilia was detected in 32%.
- The rate of thrombophilia was similar in patients with idiopathic VTE and those with provoked events.


Why Test for Thrombophilias?
- Determine optimal agent or duration of anticoagulation
- Predict risk of VTE recurrence
- Determine optimal intensity of thromboprophylaxis
- Assess VTE risk with pregnancy or hormonal contraception/replacement therapy
- Identify at-risk family members

Other Reasons for Thrombophilia Testing
- Patients and families expect/request it.
- Referring clinicians expect/request it.
- Peers expect it.
- Evaluation is considered incomplete without it, especially from a “specialist”

A Philosophic Approach to Thrombophilia Testing

“Kitchen Sink”
- Run all available tests

Selective
- Obtain only tests that impact therapy OR for which there is intellectual curiosity

No Testing
- Defer testing because it will not impact therapy

Thrombophilia: the “Big Three”

Factor V Leiden
- Activated protein C resistance
- Genetic test

Prothrombin Gene Mutation 20210
- Genetic test

Antiphospholipid Antibodies
- Anti-cardiolipin antibodies
- Lupus anticoagulant
- Anti-beta 2 glycoprotein-1 antibodies
- Anti-prothrombin antibody

**Can be drawn in the setting of acute thrombosis or anticoagulation.**
**Thrombophilias: High-Yield vs. Low-Yield**

**High-Yield**
- Factor V Leiden
- Prothrombin Gene Mutation
- Antiphospholipid Antibodies
- Protein C, S, antithrombin
- Homocysteine
- Factors VIII, IX, and XI
- Fibrinogen
- PAI-1
- MTHFR gene mutation

**Low-Yield**

**Classifying Major Thrombophilias**

<table>
<thead>
<tr>
<th>Table 1. Thrombophilia Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombophilia</td>
</tr>
<tr>
<td>Factor V Leiden</td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
</tr>
<tr>
<td>Protein C deficiency</td>
</tr>
<tr>
<td>Protein S deficiency</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
</tr>
</tbody>
</table>

Piazza G. Circulation 2014; 130:283

**High-Risk Thrombophilias**
- Deficiency of antithrombin, protein C, or protein S
- Homozygosity for factor V Leiden or prothrombin gene mutation 20210
- Compound heterozygosity for factor V Leiden and prothrombin gene mutation
- Elevated antiphospholipid antibodies

**Factor V Leiden**
- Guanine-to-adenine substitution at nucleotide 1,691 results in a glutamine instead of arginine at amino acid residue 506.
- Factor V becomes resistant to cleavage by activated protein C.

**Distribution of Factor V Leiden**

<table>
<thead>
<tr>
<th>Population</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>5.3%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2.2%</td>
</tr>
<tr>
<td>Native American</td>
<td>1.2%</td>
</tr>
<tr>
<td>African American</td>
<td>1.2%</td>
</tr>
<tr>
<td>Asian</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

Ridker PM, et al. JAMA 1997;277:1305

**Age and Factor V Leiden: Physicians' Health Study**

Age and Factor V Leiden: Physicians' Health Study

**Prothrombin Gene Mutation**

- Guanine-to-adenine substitution at nucleotide 20210 in the 3' untranslated region of the prothrombin gene.
- Heterozygous carriers have 30% higher plasma prothrombin levels than normals.
- Heterozygotes have a 4-fold increase in the risk of VTE.


**Homocysteinemia and VTE**

![Graph showing plasma homocysteine levels and VTE risk]


**Antiphospholipid Antibodies in Patients with VTE**

![Graph showing recurrence and death rates with ACLA positive and ACLA negative]


**Thrombophilia and 1st VTE**

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>RR of 1st VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>2-10</td>
</tr>
<tr>
<td>Prothrombin Gene Mutation</td>
<td>2-6</td>
</tr>
<tr>
<td>Factor V Leiden/Prothrombin Gene Mutation (compound heterozygote)</td>
<td>20</td>
</tr>
<tr>
<td>Protein C Deficiency</td>
<td>6.5-31</td>
</tr>
<tr>
<td>Protein S Deficiency</td>
<td>2-36</td>
</tr>
<tr>
<td>Antithrombin Deficiency</td>
<td>5-40</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>2-4</td>
</tr>
<tr>
<td>Antiphospholipid Antibodies</td>
<td>3-11</td>
</tr>
</tbody>
</table>

http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/hematology-oncology/hypercoagulable-states/#t0010

**Contraception and Thrombophilia**

- Estrogen-based oral contraceptive pills (OCPs) in patients with thrombophilia are associated with a 20-to-40-fold increase in the risk of VTE.
- The increased risk of VTE appears to be highest around the time of OCP initiation and within the first 6 months.

Interaction of OCPs and Factor V Leiden


Considering VTE Risk When Choosing an OCP

- 2nd generation OCPs with low-dose estrogen and progestins such as levonorgestrel are the safest combination formulations.
- Reducing the estrogen component from 50 mcg to 30-40 mcg reduces VTE risk.
- Estrogen dose reduction to 20-30 mcg decreases VTE risk further.
- “Morning after” pill: usually progesterone-only; no increased VTE risk.

Safe Alternatives to Combination OCPs

Progestin-Only Pill
- “Mini-pill”
- Has not been associated with VTE

Mirena IUD
- Releases ~20 mcg of levonorgestrel daily
- Has not been associated with VTE

Copper IUD
- No hormonal component

Miscarriage and Thrombophilia

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous factor V Leiden</td>
<td>3-fold</td>
<td>2-fold</td>
</tr>
<tr>
<td>Heterozygous factor V Leiden</td>
<td>2-fold</td>
<td>2-fold</td>
</tr>
<tr>
<td>Heterozygous prothrombin gene mutation</td>
<td>2-fold</td>
<td>3-fold</td>
</tr>
<tr>
<td>Anticardiolipin antibody</td>
<td>3-fold</td>
<td>3-fold</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>3-fold</td>
<td>1-fold</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>1-fold</td>
<td>8-fold</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>2-fold</td>
<td>3-fold</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>4-fold</td>
<td>20-fold</td>
</tr>
</tbody>
</table>


Pregnancy and Thrombophilia

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Prevalence</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden mutation</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Heterozygous</td>
<td>20-70</td>
<td>9</td>
</tr>
<tr>
<td>Homozygous</td>
<td>0.2-0.5</td>
<td>14</td>
</tr>
<tr>
<td>Prothrombin G20210A mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterozygous</td>
<td>2.0</td>
<td>7</td>
</tr>
<tr>
<td>Homozygous</td>
<td>Raw</td>
<td>24</td>
</tr>
<tr>
<td>Antithrombin deficiency (&gt;80% activity)</td>
<td>&lt;0.1-0.4</td>
<td>5</td>
</tr>
<tr>
<td>Protein C deficiency (&lt;75% activity)</td>
<td>0.2-0.3</td>
<td>1</td>
</tr>
<tr>
<td>Protein S deficiency (&lt;60% activity)</td>
<td>&lt;0.1-0.1</td>
<td>3</td>
</tr>
</tbody>
</table>

Table I: Estimated Prevalence of Congenital Thrombophilia and Its Associated Risk of Thromboembolism during Pregnancy in a Caucasian Population.8


Pregnancy and Thrombophilia


Thrombophilia and Complicated Pregnancy

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Complication (n = 110)</th>
<th>Normal (n = 110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>20%</td>
<td>6%</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>22%</td>
<td>8%</td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>Protein C, S, or antithrombin deficiency</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>Anticardiolipin antibody</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Any thrombophilia</td>
<td>65%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Pregnancy and Thrombophilia:

High Relative Risk of VTE

<table>
<thead>
<tr>
<th>Thrombophilia*</th>
<th>VTE Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>9-fold</td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td>15-fold</td>
</tr>
<tr>
<td>Factor V Leiden and prothrombin gene mutation</td>
<td>107-fold</td>
</tr>
</tbody>
</table>

*Could be heterozygous or homozygous


Low Absolute Risk of VTE

<table>
<thead>
<tr>
<th>Thrombophilia*</th>
<th>VTE Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>0.2%</td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td>0.5%</td>
</tr>
<tr>
<td>Factor V Leiden and prothrombin gene mutation</td>
<td>4.6%</td>
</tr>
</tbody>
</table>

*Could be heterozygous or homozygous


VTE in Pregnancy: Pathophysiology

↑resistance to activated protein C
↑fibrinogen, PAI-1
↑venous capacitance
↑FI,II,VII,VIII, IX,X
↓mobility
↓Protein S

Thrombophilia and Infertility

Hypercoagulability

Bates SM, et al. CHEST 2012;141:e691s

Inherited Thrombophilias and Recurrent Pregnancy Loss: Meta-Analysis


Prevalence of Thrombophilia in Infertile Women Undergoing IVF

Guidelines for Thrombophilia Evaluation

Table III American College of Obstetricians and Gynecologists Practice Bulletin does not recommend screening all women but selects individuals.

- History of previous thrombosis
- Unexplained fetal death >10 weeks (even one)
- Premature birth <34 weeks (even one)
- History of eclampsia or severe pre-eclampsia
- History of 3 or more unexplained miscarriages before 10 weeks

Check JH. Am J Reprod Immunol 2012;67:326

Does Thrombophilia Predict VTE Recurrence?

**Probable**
- Antiphospholipid Antibodies
- Protein C, Protein S, or Antithrombin Deficiency

**Not**
- Factor V Leiden
- Prothrombin Gene Mutation

Recurrence Risk: Leiden Thrombophilia Study

- N = 474 patients with 1st VTE (average follow-up of 7 years).
- Extensive thrombophilia testing performed:
  - Factor V Leiden
  - Protein C, S, and antithrombin
  - Homocysteine
  - Fibrinogen
  - Factors VIII, IX, and XI


Recurrence Risk: Factor V Leiden and Prothrombin Gene Mutation

<table>
<thead>
<tr>
<th>Table I</th>
<th>Risk of Recurrent Venous Thrombosis in Individuals With Fibrinogen Deficiency</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Male/Female</td>
<td>Factor V Leiden</td>
</tr>
<tr>
<td>18-39</td>
<td>5/5</td>
<td>1.0 (Ref)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>5/5</td>
<td>1.2 (0.8-1.6)</td>
</tr>
<tr>
<td>Controls</td>
<td>5/5</td>
<td>1.0 (Ref)</td>
</tr>
</tbody>
</table>


Recurrence Risk: Leiden Thrombophilia Study

<table>
<thead>
<tr>
<th>Table II</th>
<th>Recurrence Rates for Fibrinogen Deficiency in 474 Patients</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anomaly</td>
<td>No. of Recurrences</td>
<td>Incidence Rate (95% CI)</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>20</td>
<td>50 (9.0-20.7)</td>
</tr>
<tr>
<td>Protein C, S, and Antithrombin Deficiency</td>
<td>20</td>
<td>45 (9.0-20.7)</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>20</td>
<td>50 (9.0-20.7)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>20</td>
<td>50 (9.0-20.7)</td>
</tr>
<tr>
<td>Factors VIII, IX, and XI</td>
<td>20</td>
<td>50 (9.0-20.7)</td>
</tr>
</tbody>
</table>


STEP 1: When to Test?

- VTE in young patients
- Unprovoked or recurrent VTE
- Strong family history of VTE
- Recurrent pregnancy loss

Consider Testing
STEP 2: Why to Test?

- Test Duration or intensity of anticoagulation
- Choice of anticoagulant
- Risk of hormonal therapies (e.g., OCPs)
- Family screening
- Duration or intensity of anticoagulation
- Patient request

STEP 3: How to Test?

**Initial Thrombophilia Evaluation**

- Factor V Leiden
- Prothrombin Gene Mutation
- Antiphospholipid Antibodies

**Secondary Evaluation**

- Protein C Deficiency
- Protein S Deficiency
- Antithrombin Deficiency

"Can be drawn in the setting of acute thrombosis or anticoagulation.

Piazza G. Circulation 2014; 130:283

Cost-effectiveness of Thrombophilia Testing for DVT: Markov Model

- Thrombophilia testing followed by 24 months of anticoagulation in DVT patients with a hypercoagulable condition was more cost-effective ($54,820; 23.76 QALYs) than usual care (6 months of anticoagulation without testing) ($55,260; 23.72 QALYs).

- All thrombophilias tested were common enough and associated with a sufficient recurrence risk to justify inclusion in a test panel.

- 24 months of initial anticoagulation was preferred (<$50,000/QALY) for most conditions, whereas lifetime anticoagulation was preferred for patients with antiphospholipid antibodies ($2928/QALY) or homozygous factor V Leiden ($3804/QALY).


Thrombophilia Testing in the High-Risk: Meta-Analysis and Cost-Effectiveness


Tips for Thrombophilia Testing

- Follow a stepwise strategy for thrombophilia testing that considers the when to test, why to test, and how to test.

- Focus on the highest yield thrombophilia tests first.

- Deferring testing for protein C, protein S, and antithrombin because low levels do not necessarily indicate true thrombophilia in the setting of acute thrombosis and anticoagulation.

- Remind patients that a negative thrombophilia evaluation does not exclude thrombophilia since there are many hypercoagulable conditions that have yet to be identified and for which testing does not exist.

- Deferring thrombophilia testing to the outpatient visit when there will be more time for discussion and when the patient will have recovered psychologically from the acute event.

Piazza G. Circulation 2014; 130:283

Patient Education

- Cardiology Patient Page (pdf FREE) at Circulation Online

http://circ.ahajournals.org/content/130/2/e9.long
Discussion Case
• A 67-year-old man with diabetes and hypertension presents to the Emergency Department with sudden onset dyspnea on exertion and pleuritic pain.

• He denies recent surgery, trauma, or immobility.

• On physical examination, he is tachycardic to 110 bpm, normotensive at 116/72 mmHg, and hypoxemic with an O₂ saturation of 88% on room air.

His ECG shows sinus tachycardia.

His complete blood count and chemistries are normal, but his cardiac troponin T is elevated to 0.4 ng/mL.

He undergoes CT angiography to assess for PE.

Optimal Duration of Anticoagulation

Acute PE
- Provoked
- Indeterminate
- Unprovoked
- Cancer

Assess individual risk of VTE recurrence
- Consider indefinite anticoagulation if low bleeding risk
- Consider prolonged anticoagulation as long as cancer is active

Clinical risk factors:
- Past/family history of VTE
- Obesity
- Chronic medical conditions (COPD, heart failure, inflammatory disorders)
- Obesity
- Chronic immobilization

Additional risk factors:
- Elevated D-dimer levels after discontinuing anticoagulation

Goldhaber SZ and Piazza G. Circulation 2011;123:864

Impact of Gender of VTE Recurrence


Increased Risk of Recurrence with Unprovoked VTE


Antithrombotic Therapy for VTE Disease

Kearon C, et al. CHEST 2012; 141: e419S
Prevention of Recurrent Unprovoked VTE

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Recurrent VTE**</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREVENT</td>
<td>Warfarin, INR 1.5-2 vs. placebo</td>
<td>64%</td>
</tr>
<tr>
<td>ELATE</td>
<td>Warfarin, INR 2.3 vs. INR 1.5-2</td>
<td>63%</td>
</tr>
<tr>
<td>THRIVE III</td>
<td>Ximelagatran vs. placebo</td>
<td>84%</td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>Rivaroxaban vs. placebo</td>
<td>82%</td>
</tr>
<tr>
<td>AMPLIFY-EXT</td>
<td>Apixaban vs. placebo</td>
<td>81%</td>
</tr>
<tr>
<td>RE-SONATE</td>
<td>Dabigatran vs. placebo</td>
<td>50%</td>
</tr>
<tr>
<td>RE-MEDY</td>
<td>Dabigatran vs. warfarin, INR 2.3</td>
<td>Non-inferior</td>
</tr>
</tbody>
</table>

**Regardless of thrombophilia status

Goldhaber SZ and Piazza G. Circulation 2011;123:664

Low-Dose Aspirin for Secondary Prevention of VTE

<table>
<thead>
<tr>
<th>Study</th>
<th>Warfarin, INR 1.5-2 vs. placebo</th>
<th>↓64%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELATE</td>
<td>Warfarin, INR 2.3 vs. INR 1.5-2</td>
<td>↓63%</td>
</tr>
<tr>
<td>THRIVE III</td>
<td>Ximelagatran vs. placebo</td>
<td>↓84%</td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>Rivaroxaban vs. placebo</td>
<td>↓82%</td>
</tr>
<tr>
<td>AMPLIFY-EXT</td>
<td>Apixaban vs. placebo</td>
<td>↓81%</td>
</tr>
<tr>
<td>RE-SONATE</td>
<td>Dabigatran vs. placebo</td>
<td>↓50%</td>
</tr>
<tr>
<td>RE-MEDY</td>
<td>Dabigatran vs. warfarin, INR 2.3</td>
<td>Non-inferior</td>
</tr>
</tbody>
</table>

**Regardless of thrombophilia status

Goldhaber SZ and Piazza G. Circulation 2011;123:664

Low-Dose Aspirin for Secondary Prevention of VTE

Goldhaber SZ and Piazza G. Circulation 2011;123:664

D-Dimer and Recurrence after Unprovoked VTE


Long-Term Impact of VTE on Mortality

Søgaard KK, et al. Circulation 2014;130:829

Cancer and Risk of VTE Recurrence


HR 3.2 (95% CI, 1.9-5.4)
VTE and the Risk of Cancer Diagnosis


CLOT Trial: Dalteparin Monotherapy vs. Warfarin


CATCH Trial: Tinzaparin vs Warfarin for VTE in Patients with Cancer

Lee AYY, et al. JAMA. 2015;314:677

NOACs in VTE Patients with Cancer: Meta-analysis

Vedovati MC, et al. CHEST 2015;146:475

Lifestyle Modification

Weight Reduction
Exercise
Increase Fish, Fruit, and Vegetable Intake/Decrease Red Meat Consumption
Tobacco Cessation
Stress Reduction

Piazza G and Goldhaber SZ. Circulation 2010;121:2146

Take-Home Points

- Although thrombophilia is frequently emphasized in the literature, traditional VTE risk factors (such as cancer) are much more prevalent.

- While thrombophilias have important implications for the risk of an initial VTE event and for women’s health, their impact on VTE recurrence is limited.

- The decision to test for thrombophilias must take into account the clinical setting (“when to test”) and how management might be impacted ("why to test").

- Optimal duration of anticoagulation depends on assessment of the patient’s risk of VTE recurrence, especially the circumstances of the initial event.
What Would You Do?

- A 21-year-old woman is referred from her college Health Center for evaluation of possible OCP use.

- The patient’s mother suffered PE during her first pregnancy and her older sister had a DVT on an OCP.

- The patient has never suffered a thrombotic event.

- Her mother and sister were never tested for thrombophilies because their physician felt “it would not assist with management of venous thromboembolism.”