Treatment of Venous Thromboembolism: Thrombophilia Testing

An Educational Slide Set

American Society of Hematology Guidelines for the Management of Venous Thromboembolism: Thrombophilia Testing

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Clinical Guidelines

American Society of Hematology 2023 Guidelines for Management of Venous Thromboembolism: Thrombophilia Testing

ASH Clinical Practice Guidelines on VTE

1. Prevention of VTE in Surgical Hospitalized Patients
2. Prevention of VTE in Medical Hospitalized Patients
3. Diagnosis of VTE
4. Optimal Management of Anticoagulant Therapy
5. Heparin-Induced Thrombocytopenia (HIT)
6. VTE in the Context of Pregnancy
7. **Thrombophilia Testing**
8. Treatment of Pediatric VTE
9. Treatment of Acute VTE (DVT and PE)
10. Prevention and Treatment of VTE in Patients with Cancer
11. Anticoagulation in Patients with COVID-19
12. Adaptation of ASH Management of VTE Guidelines for Latin America
How were these ASH guidelines developed?

**PANEL FORMATION**
Each guideline panel was formed following these key criteria:
- Balance of expertise (including disciplines beyond hematology, and patients)
- Close attention to minimization and management of COI

**CLINICAL QUESTIONS**
20-30 clinically-relevant questions generated in PICO format (population, intervention, comparison, outcome)

**EVIDENCE SYNTHESIS**
Evidence summary generated for each PICO question via systematic review of health effects plus:
- Resource use
- Feasibility
- Acceptability
- Equity
- Patient values and preferences

Example: PICO question
“Should thrombolytic therapy in addition to anticoagulation vs. anticoagulation alone be used for patients with extensive proximal DVT??”

**MAKING RECOMMENDATIONS**
Recommendations made by guideline panel members based on evidence for all factors.

ASH guidelines are reviewed annually by expert work groups convened by ASH. Resources, such as this slide set, derived from guidelines that require updating are removed from the ASH website.
How patients and clinicians should use these recommendations

<table>
<thead>
<tr>
<th>STRONG Recommendation</th>
<th>CONDITIONAL Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For patients</strong></td>
<td></td>
</tr>
<tr>
<td>Most individuals would want the intervention.</td>
<td>A majority would want the intervention, but many would not.</td>
</tr>
<tr>
<td><strong>For clinicians</strong></td>
<td></td>
</tr>
<tr>
<td>Most individuals should receive the intervention.</td>
<td>Different choices will be appropriate for different patients, depending on their values and preferences. Use shared decision making.</td>
</tr>
</tbody>
</table>
Grading the quality of evidence

- Low (or Very Low)
- Moderate
- Strong
Introduction

Thrombophilia: acquired or hereditary conditions with higher-than-normal risk of VTE
Thrombophilia testing has several potential advantages and disadvantages:

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved risk stratification</td>
<td>Risk of false negatives (missed diagnosis) and false positives (overdiagnosis)</td>
</tr>
<tr>
<td>of VTE</td>
<td></td>
</tr>
<tr>
<td>Guides treatment and prevention of VTE</td>
<td>Potential for physical, psychological, or financial harm to patients</td>
</tr>
</tbody>
</table>

Guideline purpose: Provide evidence-based recommendations about whether thrombophilia testing and tailoring management based on results, improves patient-important outcomes.
Objectives

By the end of the session, you should be able to:

1. Review the prevalence and risks associated with hereditary thrombophilia
2. Describe when thrombophilia testing may be indicated in patients with symptomatic VTE
3. Describe recommendations for thrombophilia testing in asymptomatic patients with a family history of VTE/thrombophilia
For each clinical question, the panel compared two scenarios:

**Thrombophilia Testing** Intervention in only the individuals found to have the thrombophilia

**No thrombophilia Testing** Usual care in all individuals

Depending on the specific question, for patients positive for thrombophilia, interventions include:
- Indefinite Anticoagulation
- Thromboprophylaxis
- Avoidance of Thrombotic Risk Factor
Treatment (anticoagulation) effect

For example, in a patient with a history of a provoked VTE, where stopping anticoagulation is usual care:

In providing a recommendation, the panel considered:
- Risk of bleeding vs. recurrent thrombosis
- Cost & burden of thrombophilia testing/anticoagulant treatment
- Patient preferences
### Thrombophilia testing in patients with VTE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence, Median % (Min-Max)</th>
<th>RR for VTE Recurrence - Positive vs Negative (95% CI)</th>
<th>Treatment effect for VTE recurrence, RR (95% CI)</th>
<th>Treatment effect for major bleeding, RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Thrombophilia</td>
<td>38.0 (21.6-59.5)</td>
<td>1.65 (1.28-2.47)</td>
<td>0.15 (0.10-0.23)</td>
<td>2.17 (1.40-3.35)</td>
</tr>
<tr>
<td><strong>Low Risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVL Heterozygous</td>
<td>17.5 (4.1-34.8)</td>
<td>1.36 (1.19-1.57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td>6.1 (1.4-16.3)</td>
<td>1.34 (1.05-1.71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVL Homozygous</td>
<td>1.5 (0.3-3.1)</td>
<td>2.10 (1.09-4.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithrombin (AT) Deficiency*</td>
<td>2.2 (0.2-8.7)</td>
<td>2.07 (1.50-2.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein C (PC) Deficiency*</td>
<td>2.5 (0.7-8.6)</td>
<td>2.13 (1.26-3.59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein S (PS) Deficiency *</td>
<td>2.3 (0.7-7.3)</td>
<td>1.30 (0.87-1.94)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Results influenced by hormone use, timing of testing and anticoagulation*
Case 1: Unprovoked VTE

52 year old male

Past Medical History: None

Diagnosis: Unprovoked symptomatic right leg DVT

Treatment: He has been treated with anticoagulation for 3 months without any bleeding concerns
Indefinite antithrombotic therapy is suggested in most individuals with unprovoked VTE (Treatment of VTE ASH guideline)

Thrombophilia testing strategy would mean that patients without thrombophilia would stop anticoagulant therapy (potential for more thrombosis and less bleeding)

What management strategy do you suggest?

a. No thrombophilia testing and indefinite anticoagulation

b. Thrombophilia testing and stop anticoagulation in patients without thrombophilia
Recommendation 1

In patients with unprovoked VTE who have completed primary short term treatment, the ASH guideline panel suggests not to perform thrombophilia testing to guide the duration of anticoagulant treatment (conditional recommendation, low certainty)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Impact of thrombophilia testing strategy per 1000 patients (620 fewer patients treated with indefinite anticoagulation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>42 more VTE recurrences (ranging from 17 to 67)</td>
</tr>
<tr>
<td>Major Bleeding - Low Risk</td>
<td>4 fewer major bleeds (ranging from 1 to 9)</td>
</tr>
<tr>
<td>(0.5% per year)</td>
<td></td>
</tr>
<tr>
<td>Major Bleeding – High Risk</td>
<td>11 fewer major bleeds (ranging from 2 to 28)</td>
</tr>
<tr>
<td>(1.5% per year)</td>
<td></td>
</tr>
</tbody>
</table>

Quality of Evidence (GRADE): Low or Very Low
Case 2: Provoked VTE

35-year-old female

**Past Medical History**: Hypertension

**Past Surgical History**: Appendectomy

**Diagnosis**: Pulmonary embolism on post-operative day 21 following appendectomy

**Treatment**: She is started on anticoagulation and referred for outpatient assessment
Usual Care

Individuals with VTE provoked by surgery discontinue anticoagulant therapy after primary treatment (Treatment of VTE ASH guideline)

Thrombophilia testing strategy would mean that patients with thrombophilia would receive indefinite anticoagulant therapy (potential for less thrombosis and more bleeding)

What management strategy do you suggest?

a. No thrombophilia testing, treat for 3 months and stop anticoagulation

b. Thrombophilia testing and indefinite anticoagulation only in patients with thrombophilia
Recommendation 2

In patients with VTE provoked by surgery who have completed primary short-term treatment, the ASH guideline panel suggests not to perform thrombophilia testing to determine the duration of anticoagulation treatment (conditional recommendation, very low certainty of evidence).

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Impact of thrombophilia testing strategy per 1000 patients (380 more patients treated with indefinite anticoagulation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>4 fewer VTE recurrences (ranging from 2 to 7)</td>
</tr>
<tr>
<td>Major Bleeding - Low Risk (0.5% per year)</td>
<td>2 more major bleeds (ranging from 0 to 7)</td>
</tr>
<tr>
<td>Major Bleeding - High Risk (1.5% per year)</td>
<td>7 more major bleeds (ranging from 1 to 21)</td>
</tr>
</tbody>
</table>

Quality of Evidence (GRADE): Low or Very Low
Case 3: Pregnancy

24-year-old female, G1P0, 35+3 weeks gestation

Past Medical History: None

Diagnosis: Left leg DVT after presenting with a 2-day history of increasing left leg swelling and pain

Treatment: She is started on anticoagulation and referred for outpatient assessment
Usual Care

Individuals with VTE provoked by pregnancy will discontinue anticoagulant therapy after primary treatment (Treatment of VTE ASH guideline)

Thrombophilia testing strategy would mean that patients with thrombophilia would receive indefinite anticoagulant therapy (potential for less thrombosis and more bleeding)

What management plan do you suggest?

a. No thrombophilia testing, treat for 3 months and stop anticoagulation

b. Thrombophilia testing and indefinite anticoagulation only in patients with thrombophilia
Case 4: Non-Surgical Major Transient Risk Factor

64-year-old male

**Past Medical History:** None

**Medications:** Naproxen PRN

**Diagnosis:** Left leg DVT diagnosed on day 3 of admission for pneumonia. While in hospital he is relatively immobile, only getting up to use the washroom

**Treatment:** He is started on anticoagulation and referred for outpatient assessment
Usual Care

Individuals with VTE provoked by non-surgical major transient risk factors will discontinue anticoagulant therapy after primary treatment (Treatment of VTE ASH guideline)

Thrombophilia testing strategy would mean that patients with thrombophilia would receive indefinite anticoagulant treatment (potential for less thrombosis and more bleeding)

What management plan do you suggest?

a. No thrombophilia testing, treat for 3 months and stop anticoagulation

b. Thrombophilia testing and indefinite anticoagulation only in patients with thrombophilia
**Recommendations 3-5**

In patients with VTE provoked by a **non-surgical major transient risk factor, combined oral contraceptives, pregnancy or postpartum** who have completed primary short-term treatment, the panel suggests **testing for thrombophilia to guide anticoagulant treatment duration** (conditional recommendation, very low certainty)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Impact of thrombophilia testing strategy per 1000 patients (380 more patients treated with indefinite anticoagulation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>21 fewer VTE recurrences (ranging from 10 to 35)</td>
</tr>
<tr>
<td>Major Bleeding - Low Risk (0.5% per year)</td>
<td>2 more major bleeds (ranging from 0 to 7)</td>
</tr>
<tr>
<td>Major Bleeding - High Risk (1.5% per year)</td>
<td>7 more major bleeds (ranging from 1 to 21)</td>
</tr>
</tbody>
</table>

Quality of Evidence (GRADE): Low or Very Low 🟥  Moderate 🟠  High 🟢
American Society of Hematology 2020 Guidelines
(Treatment of VTE)

Transient Risk Factors (resolve after provoked VTE)

Major Risk Factor
• Surgery, gen anesthesia > 30 min
• Confined to hospital bed ≥ 3 days with acute illness
• Cesarean section

Minor Risk Factor
• Estrogen therapy (OCP, HRT)
• Pregnancy, puerperium
• Confined to bed out of hospital ≥ 3 days with acute illness
• Leg injury, reduced mobility ≥ 3 days

Chronic (Persistent) Risk Factors (persistent after VTE occurs)

• Active cancer (ongoing chemo; recurrent or progressive disease)
• Inflammatory bowel disease
• Autoimmune disorder (e.g., antiphospholipid syndrome, rheumatoid arthritis)
• Chronic infection
• Chronic immobility (e.g., spinal cord injury)
Case 5: Unusual site thrombosis

44-year-old male assessed in follow up

Past Medical History: Hypertension

Diagnosis: Unprovoked cerebral venous thrombosis diagnosed 2 years earlier

Treatment: In discussion with the patient, you have decided to continue with indefinite anticoagulation
Guidelines are indecisive on duration of anticoagulation for unusual site VTE.

Thrombophilia testing strategy impact is dependent on clinicians' usual care.

Primary short term treatment only planned – patients with thrombophilia would receive indefinite anticoagulant treatment (potential for less thrombosis and more bleeding).

Indefinite anticoagulation planned – patients without thrombophilia would stop anticoagulant therapy (potential for more thrombosis and less bleeding).

The patient is interested in thrombophilia testing.

**What management plan do you suggest?**

a. No thrombophilia testing and indefinite anticoagulation

b. Thrombophilia testing and stop anticoagulation if negative
Recommendations 7-8

In patients with Cerebral Venous Thrombosis who have completed primary short-term treatment, the panel suggests testing for thrombophilia to guide anticoagulant treatment duration only if anticoagulation would be discontinued otherwise (conditional recommendation, very low certainty).

### Impact of thrombophilia testing strategy per 1000 patients

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Primary treatment only planned (436 more patients treated with indefinite anticoagulation)</th>
<th>Indefinite anticoagulant therapy planned (564 fewer patients treated with indefinite anticoagulation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>18 fewer VTE recurrences (14 to 23)</td>
<td>14 more VTE recurrences (10 to 18)</td>
</tr>
<tr>
<td>Major Bleeding - Low Risk</td>
<td>3 more major bleeds (1 to 5)</td>
<td>3 fewer major bleeds (1 to 7)</td>
</tr>
<tr>
<td>Major Bleeding - High Risk</td>
<td>8 more major bleeds (3 to 16)</td>
<td>10 fewer major bleeds (3 to 20)</td>
</tr>
</tbody>
</table>

### Additional factors may influence thrombophilia testing/ treatment and were not included in analysis

- Provoked vs. unprovoked
- Additional thrombophilia (e.g. JAK 2 mutation)

Quality of Evidence (GRADE): Low or Very Low  ▢ Moderate  ▢ High
Summary of Thrombophilia Testing Strategy for Patients with VTE

<table>
<thead>
<tr>
<th>Base Risk of VTE Recurrence (1st year)</th>
<th>Treatment Risk for Major Bleeding</th>
<th>Recommended Strategy for Thrombophilia Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unprovoked</td>
<td>High (10%)</td>
<td>Do Not Test (indefinite anticoagulation in all)</td>
</tr>
<tr>
<td>Unusual Site</td>
<td>Intermediate (2.7%-3.8%)</td>
<td>Do Not Test (indefinite anticoagulation in all) OR Test (indefinite anticoagulant therapy in patients with thrombophilia)</td>
</tr>
<tr>
<td>Provoked (non-surgical)</td>
<td>Intermediate (5%)</td>
<td>Test (indefinite anticoagulant therapy in patients with thrombophilia)</td>
</tr>
<tr>
<td>Provoked (surgical)</td>
<td>Low (1%)</td>
<td>Do Not Test (primary short-term anticoagulation in all)</td>
</tr>
</tbody>
</table>

Intermediate Risk of recurrent thrombosis: Testing can tip the balance towards indefinite anticoagulation (thrombophilia positive recurrent VTE risk > bleeding risk)

High or Low Risk of recurrent thrombosis: Testing does not cross treatment thresholds (i.e. for unprovoked VTE, recurrent VTE risk > bleeding risk regardless of thrombophilia test results)
Introduction to thrombophilia testing in individuals with a family history of VTE and/or thrombophilia

In families with VTE, the panel examined patient outcomes from testing asymptomatic individuals (relatives) for thrombophilia

The panel considered two scenarios:
1. Known specific thrombophilia in affected family member (proband)
   - Selective thrombophilia testing
2. Unknown thrombophilia status
   - Panel thrombophilia testing

When outcomes were similar, the panel favored selective over panel testing
### Thrombophilia testing in individuals with family history of VTE

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Treatment effect for VTE occurrence, RR (95% CI)</th>
<th>Treatment effect for major bleeding, RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVL Heterozygous</td>
<td>2.71 (2.06-3.56)</td>
<td></td>
</tr>
<tr>
<td>Prothrombin (PT) Mutation</td>
<td>2.35 (1.46-3.78)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High Risk</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin (AT) Deficiency</td>
<td>12.17 (5.45-27.17)</td>
<td>2.09 (1.33-3.27)</td>
</tr>
<tr>
<td>Protein C (PC) Deficiency</td>
<td>7.47 (2.81-19.81)</td>
<td></td>
</tr>
<tr>
<td>Protein S (PS) Deficiency</td>
<td>5.98 (2.45-14.57)</td>
<td></td>
</tr>
</tbody>
</table>

**Panel Testing:** testing for APLA and all hereditary thrombophilia types

**Selective Thrombophilia Testing:** testing for a specific thrombophilia type (i.e. family testing)
Case 6: Family history of VTE and minor provoking risk factor

22-year-old female is assessed as an outpatient following a severe high grade ankle sprain being managed non-operatively. Non-weightbearing and immobilization are recommended for the next 10 days

Past Medical History: None

Medications: None

Family History: Mother has a history of DVT. To her knowledge, her mother has not been tested for thrombophilia
Usual Care

No thromboprophylaxis for medical outpatients with minor provoking risk factors for VTE (Prophylaxis for Medical Patients ASH guideline)

Thrombophilia testing strategy would mean that individuals with thrombophilia would receive thromboprophylaxis for a minor provoking factor (potential for less thrombosis and more bleeding)

What management plan do you suggest?

a. No thrombophilia testing and no thromboprophylaxis
b. Thrombophilia testing and start anticoagulant thromboprophylaxis if positive
Recommendation 13

In individuals with a minor risk factor who have a family history of VTE and unknown thrombophilia status, suggest not to perform thrombophilia testing to guide thromboprophylaxis (conditional recommendation, very low certainty)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Impact of thrombophilia testing strategy in first degree relatives of patients with VTE per 1000 episodes (142 more patients receive thromboprophylaxis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>2.16 fewer VTE (0.02 to 5.66)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>0.62 more major bleeds (0.13 to 1.82)</td>
</tr>
</tbody>
</table>

Recommendations assume no time delay for testing

Quality of Evidence (GRADE): Low or Very Low  •  Moderate  •  High
## Recommendations 11-12

In individuals with a minor provoking risk factor who have a family history of VTE and known thrombophilia, suggest thrombophilia testing to guide thromboprophylaxis for high risk thrombophilia but not low risk thrombophilia (conditional recommendation, very low certainty)

<table>
<thead>
<tr>
<th>Family History</th>
<th>Impact of selective thrombophilia strategy in first degree relatives of patients with VTE per 1000 episodes (500 more patients treated with thromboprophylaxis)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VTE</td>
</tr>
<tr>
<td>Low Risk</td>
<td></td>
</tr>
<tr>
<td>FVL Heterozygous</td>
<td>5.04 fewer VTE (0.91 to 7.96)</td>
</tr>
<tr>
<td>Prothrombin mutation</td>
<td>4.84 fewer VTE (0.80 to 8.07)</td>
</tr>
<tr>
<td>High Risk</td>
<td></td>
</tr>
<tr>
<td>Antithrombin Deficiency</td>
<td>21.25 fewer VTE (3.80 to 32.79)</td>
</tr>
<tr>
<td>Protein C Deficiency</td>
<td>20.28 fewer VTE (3.32 to 32.37)</td>
</tr>
<tr>
<td>Protein S Deficiency</td>
<td>19.79 fewer VTE (3.20 to 31.82)</td>
</tr>
</tbody>
</table>

Quality of Evidence (GRADE): Low or Very Low 🟥 Moderate 🟢 High 🟡
Case 7: Combined Oral Contraceptive (COC) pill or Hormone Replacement Therapy (HRT) use

The same patient is re-referred 2 years later. She would like to start the combined oral contraceptive pill for pregnancy prevention.

Her past medical history is unchanged and she is not on any regular medications.

Since the initial visit, her sister developed an unprovoked PE and was found to have Protein C Deficiency.
Thrombophilia testing strategy would mean that individuals with thrombophilia would avoid COC and HRT (potential for less thrombosis)

She is looking to start combined oral contraceptive pill for prevention of pregnancy.

**What management plan do you suggest?**

a. No thrombophilia testing and start COC

b. Thrombophilia testing and suggest against COC if positive
# Recommendations 19-20

In individuals with a **family history of VTE and known thrombophilia**, suggest **selective thrombophilia testing to guide COC or HRT for high risk thrombophilia only** (conditional recommendation, very low certainty)

<table>
<thead>
<tr>
<th>Family History</th>
<th>Impact of selective thrombophilia testing strategy on VTE episodes per 1000 women who are first degree relatives of patients with VTE / year (500 fewer using COC or HRT)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>COC</td>
</tr>
<tr>
<td><strong>Low Risk</strong></td>
<td></td>
</tr>
<tr>
<td>FVL Heterozygous</td>
<td>4.57 fewer VTE (3.75 to 5.55)</td>
</tr>
<tr>
<td>Prothrombin mutation</td>
<td>4.38 fewer VTE (3.76 to 4.90)</td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td></td>
</tr>
<tr>
<td>Antithrombin Deficiency</td>
<td>19.39 fewer VTE (15.30 to 23.90)</td>
</tr>
<tr>
<td>Protein C Deficiency</td>
<td>13.84 fewer VTE (11.34 to 15.45)</td>
</tr>
<tr>
<td>Protein S Deficiency</td>
<td>10.49 fewer (8.71 to 11.48)</td>
</tr>
</tbody>
</table>

Quality of Evidence (GRADE): Low or Very Low  📸  Moderate  📸  High  📸
Recommendations 15-18

In individuals from the **general population** suggest **not to perform thrombophilia testing** to guide the use of COC (strong recommendation, low certainty) or HRT (conditional recommendation, low certainty)

In individuals with a **family history of VTE and unknown thrombophilia**, suggest **not to perform thrombophilia testing** to guide the use of COC or HRT (conditional recommendation, very low certainty)

| Impact of thrombophilia testing strategy on VTE per 1000 women / year (69-142 fewer using COC or HRT)* |
|---|---|
| | COC | HRT |
| General Population | 0.26 fewer VTE (0.09 to 0.65) | 0.29 fewer VTE (0.01 to 1.98) |
| Family History of VTE (1st degree) and Unknown Thrombophilia | 1.17 fewer VTE (0.06 to 1.55) | 0.94 fewer VTE (0.01 to 5.16) |

The potential harms of hormone avoidance fall outside the guidelines scope but may include unwanted pregnancies and postmenopausal symptoms.

Quality of Evidence (GRADE): Low or Very Low Moderate High
Case 8: Women who are planning pregnancy

26 year old female is planning to become pregnant, and was referred for a family history of VTE and FVL. The patient has not undergone testing for thrombophilia, and she has no history of VTE

Past Medical History: None

Medications: None

Family History: Sister has a history of DVT and is homozygous for FVL
Usual Care

No antepartum or postpartum thromboprophylaxis for women with no or 1 clinical risk factor (Pregnancy ASH guideline)

Thrombophilia testing strategy would mean that patients with thrombophilia would receive antepartum and/or postpartum thromboprophylaxis (potential for less thrombosis and more bleeding)

She is planning a pregnancy.

What management plan do you recommend?

a. Test for all inherited thrombophilias (FVL, PGM, Protein C / S, ATIII) and start thromboprophylaxis if positive
b. No inherited thrombophilia testing and do not start thromboprophylaxis

c. Selective thrombophilia testing (FVL only) and start thromboprophylaxis if FVL homozygous
### Recommendation 21

In women with a **family history of VTE and homozygous FVL, combination of FVL and PGM, or antithrombin deficiency in the family**, suggest **testing for the known familial thrombophilia and antepartum thromboprophylaxis in women with the same familial thrombophilia** (conditional recommendation, very low certainty)

<table>
<thead>
<tr>
<th>Family History</th>
<th>Impact of selective thrombophilia testing strategy per 1000 pregnancies (Antepartum thromboprophylaxis used in 250-500* more pregnancies)</th>
<th>Quality of Evidence (GRADE): Low or Very Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous FVL</td>
<td>19.35 fewer VTE (12.16 to 24.14)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Combination of FVL and PGM</td>
<td>9.05 fewer VTE (4.63 to 12.33)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>9.70 fewer VTE (5.90 to 11.97)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>2.02 fewer VTE (0.82 to 2.66)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>3.94 fewer VTE (1.34 to 5.32)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

In women with a family history of VTE and known protein C or S deficiency in the family, the panel suggests either testing or not testing to guide antepartum prophylaxis.

*250 more pregnancies for family history of homozygous FVL or combination of FVL and PGM; 500 more pregnancies for family history of antithrombin deficiency, protein C deficiency or protein S deficiency*
Recommendation 22

In women with a family history of VTE and a high risk thrombophilia (including combination of FVL and PGM), suggest testing for the known familial thrombophilia and postpartum thromboprophylaxis in women with the same familial thrombophilia (conditional recommendation, very low certainty)

<table>
<thead>
<tr>
<th>Family History</th>
<th>Impact of thrombophilia strategy per 1000 pregnancies (Postpartum thromboprophylaxis used in 250-500* more pregnancies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous FVL</td>
<td>19.35 fewer VTE (12.16 to 24.14)</td>
</tr>
<tr>
<td>Combination of FVL and PGM</td>
<td>9.05 fewer VTE (4.63 to 12.33)</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>9.70 fewer VTE (5.90 to 11.97)</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>2.02 fewer VTE (0.82 to 2.66)</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>3.94 fewer VTE (1.34 to 5.32)</td>
</tr>
</tbody>
</table>

*250 more pregnancies for family history of homozygous FVL or combination of FVL and PGM; 500 more pregnancies for family history of antithrombin deficiency, protein C deficiency or protein S deficiency

ASH guidelines on the management of VTE in pregnancy suggest against postpartum thromboprophylaxis to prevent a first VTE in individuals with FVL heterozygosity or PGM
Case 9: Patients with cancer and family history VTE

65 year old man from home with stage II head and neck cancer is seen in clinic before starting systemic chemotherapy

Past Medical History: Hypertension

Medications: Ramipril

Family History: Brother has a history of pulmonary embolism
Usual Care

No thromboprophylaxis for ambulatory cancer patients receiving systemic therapy at low to intermediate risk of thrombosis (Prevention and Treatment in Patients with Cancer ASH Guideline)

Thrombophilia testing strategy would mean that patients with thrombophilia would receive thromboprophylaxis (potential for less thrombosis and more bleeding)

What management plan do you recommend before starting systemic chemotherapy?

a. No thrombophilia testing and do not start thromboprophylaxis

b. Testing for hereditary thrombophilia and thromboprophylaxis if positive
Recommendation 23

In ambulatory cancer patients receiving systemic therapy who have a family history of VTE and are at low or intermediate risk for VTE, the panel suggests testing for hereditary thrombophilia and starting thromboprophylaxis if positive (conditional, very low certainty)

Impact of thrombophilia testing strategy per 1000 patients who are first degree relatives of patients with VTE/6 months (142 more patients receive thromboprophylaxis)

<table>
<thead>
<tr>
<th>VTE</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk for VTE</td>
<td>6.85 fewer VTE (23.37 fewer to 0.16 more)</td>
</tr>
<tr>
<td>Intermediate Risk for VTE</td>
<td>9.04 fewer VTE (30.85 fewer to 0.21 more)</td>
</tr>
</tbody>
</table>

ASH VTE Cancer guidelines suggest using direct oral anticoagulant (DOAC) prophylaxis in all ambulatory cancer patients receiving systemic therapy with high VTE risk

Quality of Evidence (GRADE): Low or Very Low 🟠 Moderate 🟡 High 🟢
Other guideline recommendations that were not directly covered in this session

Thrombophilia testing for:

- Unspecified VTE (Recommendation 6)
- Splanchnic vein thrombosis (Recommendations 9-10)
- Family history of thrombophilia but no family history of VTE to prevent VTE associated with minor risk factors (Recommendation 14)
Future Priorities for Research

• Risk of recurrent VTE and its association with prognostic variables
• Optimal duration of anticoagulant therapy after acute cerebral venous thrombosis or acute splanchnic venous thrombosis
• Large implementation studies comparing the impact (outcomes rates) among management strategies involving thrombophilia testing
• Online calculator for specific thrombophilia defects incorporating localized prevalence values
In Summary: Back to Our Objectives

1. Review the prevalence and risks associated with hereditary thrombophilia
2. Describe when thrombophilia testing may be indicated in patients with symptomatic VTE
3. Describe recommendations for thrombophilia testing in asymptomatic patients with a family history of VTE/thrombophilia