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

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CLINICAL GUIDELINES

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American Society of Hematology 2023 guidelines for management of venous thromboembolism: thrombophilia testing

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Background: Hereditary and acquired thrombophilia are risk factors for venous thromboembolism (VTE). Whether testing helps guide management decisions is controversial.

Objective: These evidence-based guidelines from the American Society of Hematology (ASH) intend to support decision making about thrombophilia testing.

Methods: ASH formed a multidisciplinary guideline panel covering clinical and methodological expertise and minimizing bias from conflicts of interest. The McMaster University GRADE Centre provided logistical support, performed systematic reviews, and created evidence profiles and evidence-to-decision tables. The Grading of Recommendations Assessment, Development, and Evaluation approach (GRADE) was used. Recommendations were subject to public comment.

Results: The panel agreed on 23 recommendations regarding thrombophilia testing and associated management. Nearly all recommendations are based on very low certainty in the evidence due to modeling assumptions.

Conclusions: The panel issued a strong recommendation against testing the general population before starting combined oral contraceptives (COCs) and conditional recommendations for thrombophilia testing in the following scenarios: (a) patients with VTE associated with nonsurgical major transient or hormonal risk factors; (b) patients with cerebral or splanchnic venous thrombosis, in settings where anticoagulation would otherwise be discontinued; (c) individuals with a family history of antithrombin, protein C, or protein S deficiency when considering thromboprophylaxis for minor provoking risk factors and for guidance to avoid COCs/hormone replacement therapy; (d) pregnant women with a family history of high-risk thrombophilia types; and (e) patients with cancer at low or intermediate risk of thrombosis and with a family history of VTE. For all other questions, the panel provided conditional recommendations against testing for thrombophilia.

Summary of recommendations

For each of the clinical questions for patients with venous thromboembolism (VTE), the panel compared 2 scenarios: (a) thrombophilia testing and subsequent indefinite anticoagulation of only the individuals

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Data are available through ASH/McMaster University GRADE Centre.

The full-text version of this article contains a data supplement.

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)

Example: PICO question

"Should thrombolytic therapy in addition to anticoagulation vs. anticoagulation alone be used for patients with extensive proximal DVT??"

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

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

	STRONG Recommendation ("The panel recommends…")	**CONDITIONAL Recommendation** ("The panel suggests…")
For patients	Most individuals would want the intervention.	A majority would want the intervention, but many would not.
For clinicians	Most individuals should receive the intervention.	Different choices will be appropriate for different patients, depending on their values and preferences. Use **shared decision making**.

Grading the quality of evidence

Introduction

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

Advantages	Disadvantages
Improved risk stratification of VTE	Risk of false negatives (missed diagnosis) and false positives (overdiagnosis)
Guides treatment and prevention of VTE	Potential for physical, psychological, or financial harm to patients

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

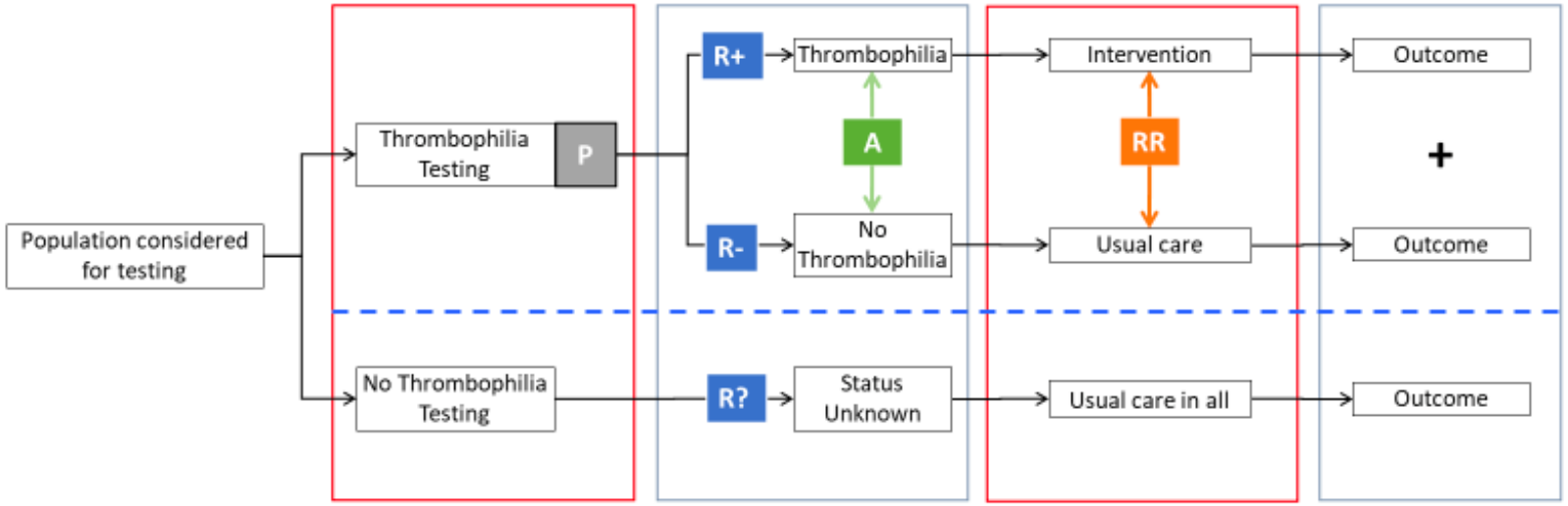
For each clinical question, the panel compared two scenarios:

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:

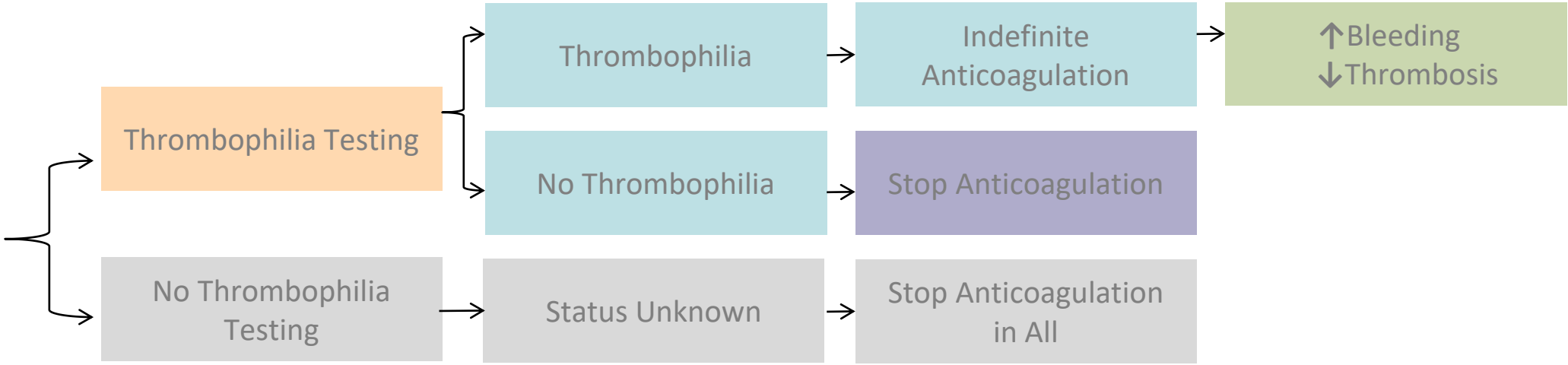
- Indefinite Anticoagulation
- Thromboprophylaxis
- Avoidance of Thrombotic Risk Factor



Prevalence	**Thrombophilia prevalence**
Incidence Risk	**Risk of Outcomes in thrombophilia positive (R+), negative (R-), and unknown status (R?)**
Association	**Association (RR/OR) of thrombophilia status with Outcomes**
RR of Intervention	**Relative effect of the Intervention vs. No intervention / Usual care**

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

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

*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

Usual Care

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)

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

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)

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

Quality of Evidence (GRADE): Low or Very Low Moderate High

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)

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

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)

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

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

	Base Risk of VTE Recurrence (1st year)	Treatment Risk for Major Bleeding	Recommended Strategy for Thrombophilia Testing
Unprovoked	High (10%)	0.5-1.5%	Do Not Test (indefinite anticoagulation in all)
Unusual Site	Intermediate (2.7%-3.8%)		Do Not Test (indefinite anticoagulation in all) OR Test (indefinite anticoagulant therapy in patients with thrombophilia)
Provoked (non-surgical)	Intermediate (5%)		Test (indefinite anticoagulant therapy in patients with thrombophilia)
Provoked (surgical)	Low (1%)		Do Not Test (primary short-term anticoagulation in all)

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

	RR for 1st VTE - Positive vs Negative (95% CI)	Treatment effect for VTE occurrence, RR (95% CI)	Treatment effect for major bleeding, RR (95% CI)
Low Risk		0.54 (0.32-0.91)	2.09 (1.33-3.27)
FVL Heterozygous	2.71 (2.06-3.56)		
Prothrombin (PT) Mutation	2.35 (1.46-3.78)		
High Risk			
Antithrombin (AT) Deficiency	12.17 (5.45-27.17)		
Protein C (PC) Deficiency	7.47 (2.81-19.81)		
Protein S (PS) Deficiency	5.98 (2.45-14.57)		

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)

Outcomes	Impact of thrombophilia testing strategy in first degree relatives of patients with VTE per 1000 episodes (142 more patients receive thromboprophylaxis)
Recurrent VTE	2.16 fewer VTE (0.02 to 5.66)
Major Bleeding	0.62 more major bleeds (0.13 to 1.82)

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)

Family History	Impact of selective thrombophilia strategy in first degree relatives of patients with VTE per 1000 episodes (500 more patients treated with thromboprophylaxis)	
	VTE	Major Bleeding
Low Risk		2.18 more bleeds (0.66 to 4.54)
FVL Heterozygous	5.04 fewer VTE (0.91 to 7.96)	
Prothrombin mutation	4.84 fewer VTE (0.80 to 8.07)	
High Risk		
Antithrombin Deficiency	21.25 fewer VTE (3.80 to 32.79)	
Protein C Deficiency	20.28 fewer VTE (3.32 to 32.37)	
Protein S Deficiency	19.79 fewer VTE (3.20 to 31.82)	

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)

Family History	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)*	
	COC	HRT
Low Risk		
FVL Heterozygous	4.57 fewer VTE (3.75 to 5.55)	1.36 fewer VTE (0.21 to 1.96)
Prothrombin mutation	4.38 fewer VTE (3.76 to 4.90)	2.20 fewer VTE (0.25 to 4.79)
High Risk		
Antithrombin Deficiency	19.39 fewer VTE (15.30 to 23.90)	6.45 fewer VTE (0.77 to 13.49)
Protein C Deficiency	13.84 fewer VTE (11.34 to 15.45)	4.94 fewer VTE (0.60 to 10.12)
Protein S Deficiency	10.49 fewer (8.71 to 11.48)	3.92 fewer VTE (0.47 to 7.87)

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)

Family History	Impact of selective thrombophilia testing strategy per 1000 pregnancies (Antepartum thromboprophylaxis used in 250-500* more pregnancies)	
Homozygous FVL	19.35 fewer VTE (12.16 to 24.14)	1.05 fewer bleeds (1.52 fewer to 3.50 more)
Combination of FVL and PGM	9.05 fewer VTE (4.63 to 12.33)	
Antithrombin deficiency	9.70 fewer VTE (5.90 to 11.97)	2.09 fewer bleeds (3.04 fewer to 7.01 more)
Protein C deficiency	2.02 fewer VTE (0.82 to 2.66)	
Protein S deficiency	3.94 fewer VTE (1.34 to 5.32)	

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 prophylaxisO

*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

Quality of Evidence (GRADE): Low or Very Low ● Moderate ● High ●

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)

Family History	Impact of thrombophilia strategy per 1000 pregnancies (Postpartum thromboprophylaxis used in 250-500* more pregnancies)	
Homozygous FVL	19.35 fewer VTE (12.16 to 24.14)	1.06 fewer bleeds (3.51 fewer to 10.07 more)
Combination of FVL and PGM	9.05 fewer VTE (4.63 to 12.33)	
Antithrombin deficiency	9.70 fewer VTE (5.90 to 11.97)	0.53 fewer bleeds (1.76 fewer to 5.03 more)
Protein C deficiency	2.02 fewer VTE (0.82 to 2.66)	
Protein S deficiency	3.94 fewer VTE (1.34 to 5.32)	

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

*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

Quality of Evidence (GRADE): Low or Very Low ● Moderate ● High ●

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)	
	VTE	**Major Bleeding**
Low Risk for VTE	6.85 fewer VTE (23.37 fewer to 0.16 more)	0.33 more bleeds (0.10 fewer to 2.02 more)
Intermediate Risk for VTE	9.04 fewer VTE (30.85 fewer to 0.21 more)	0.74 more bleeds (0.22 fewer to 4.49 more)

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