Zin en onzin van trombofiliescreening

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Disclosures for Saskia Middeldorp

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Outline

- Inherited thrombophilia
- Antiphospholipid syndrome (APS)
- To test or not to test? What do the guidelines say?

Panel

- Factor V Leiden
- Protrombine G20210A mutatie (F2 of FII mutatie)
- Antitrombine activiteit
- Proteine C activiteit
- Proteine S activiteit
- Lupus anticoagulans
- Anticardiolipine antistoffen IgG en IgM
- Antibeta2 glycoproteine antistoffen IgG en IgM

Inherited thrombophilia

Table 1. Prevalence of inherited thrombophilia and relative risk estimates for various clinical manifestations

	Antithrombin deficiency	Protein C deficiency	Protein S deficiency	Factor V Leiden	Prothrombin 20210A mutation
Prevalence in the general population*	0.02%	0.2%	0.03%-0.13%	3%-7%	0.7%-4%
Prevalence in consecutive patients with VTE*	1%	3%	2%	20%	5%
Relative risk for a first VTE†	5-10	4-6.5	1-10	3-5	2-3
Relative risk for recurrent VTE	1.9-2.6	1.4-1.8	1.0-1.4	1.4	1.4
Relative risk for arterial thrombosis	No association	No consistent association	No consistent association	1.3	0.9
Relative risk for pregnancy complications	1.3-3.6	1.3-3.6	1.3-3.6	1.0-2.6	0.9-1.3

Middeldorp, Hematology Am Soc Hematol Educ Program 2016

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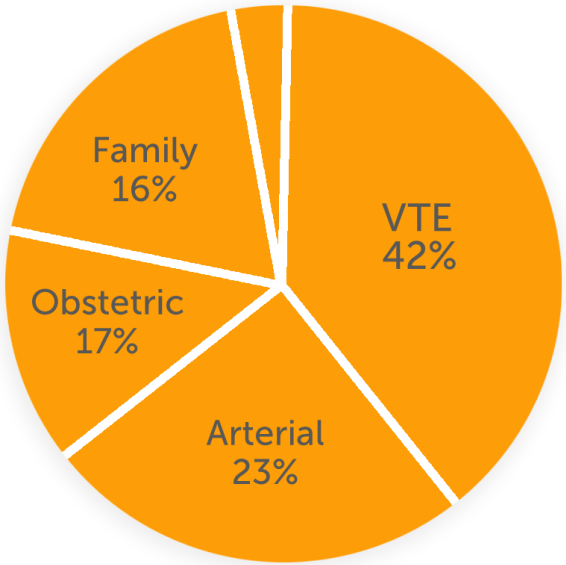
Widespread testing (in the past)

No change in management in 24%

BUT

A lot of people with known thrombophilia…



Coppens J Thromb Haemost 2007

Is it useful to test?

Population

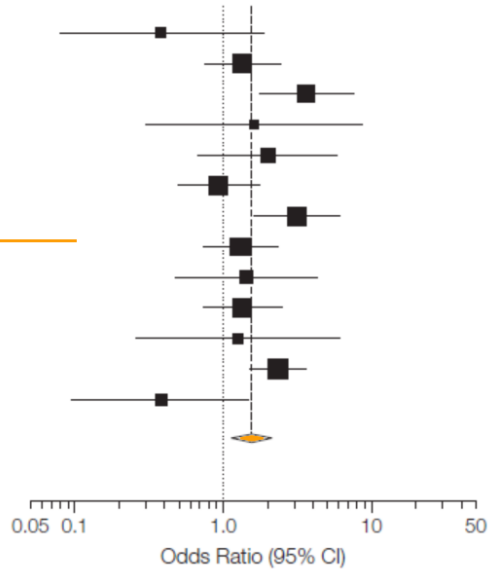
- Patients with VTE
- Relatives of patients with VTE
- Women with pregnancy complications

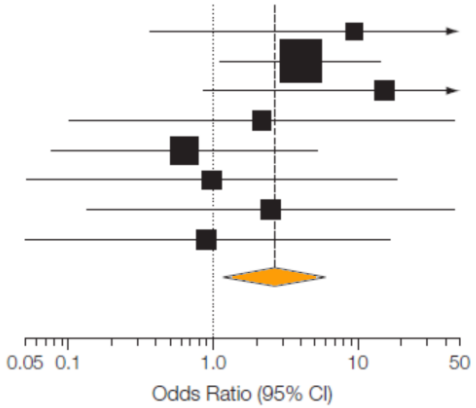
Outcome

- Recurrent VTE
- First VTE
- Pregnancy outcome (live birth)

Risk of recurrent VTE with FV Leiden

Factor V Leiden heterozygous OR 1.56





Factor V Leiden homozygous OR 2.65

Segal, JAMA 2009

Do these risk increases change treatment?

Table 11 Categorization of risk factors for venous thromboembolism based on the risk of recurrence over the long-term

Estimated risk for long-term recurrence[a]	Risk factor category for index PE[b]	Examples[b]
Low (<3% per year)	Major transient or reversible factors associated with >10-fold increased risk for the index VTE event (compared to patients without the risk factor)	• Surgery with general anaesthesia for >30 min • Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness • Trauma with fractures
Intermediate (3–8% per year)	Transient or reversible factors associated with ≤10-fold increased risk for first (index) VTE	• Minor surgery (general anaesthesia for <30 min) • Admission to hospital for <3 days with an acute illness • Oestrogen therapy/contraception • Pregnancy or puerperium • Confined to bed out of hospital for ≥3 days with an acute illness • Leg injury (without fracture) associated with reduced mobility for ≥3 days • Long-haul flight
	Non-malignant persistent risk factors	• Inflammatory bowel disease • Active autoimmune disease
	No identifiable risk factor	
High (>8% per year)		• Active cancer • One or more previous episodes of VTE in the absence of a major transient or reversible factor • Antiphospholipid antibody syndrome

Konstantinides, ESC guidelines 2019

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Doe geen onderzoek naar een erfelijke stollingsafwijking bij een eerste trombose of embolie.

De uitkomst van dit stollingsonderzoek zal de behandeling niet beïnvloeden. Daarnaast voorkomt het onnodig screenen en onrust bij de patiënt en de familie als er sprake is van een positieve uitslag. Het niet doen van dit onderzoek is patiëntvriendelijk en kosten-besparend.

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Thrombophilia

Nostradamus study

to test or not to test

No randomized controlled trials

Cohn, Cochrane Database 2012

Tested?

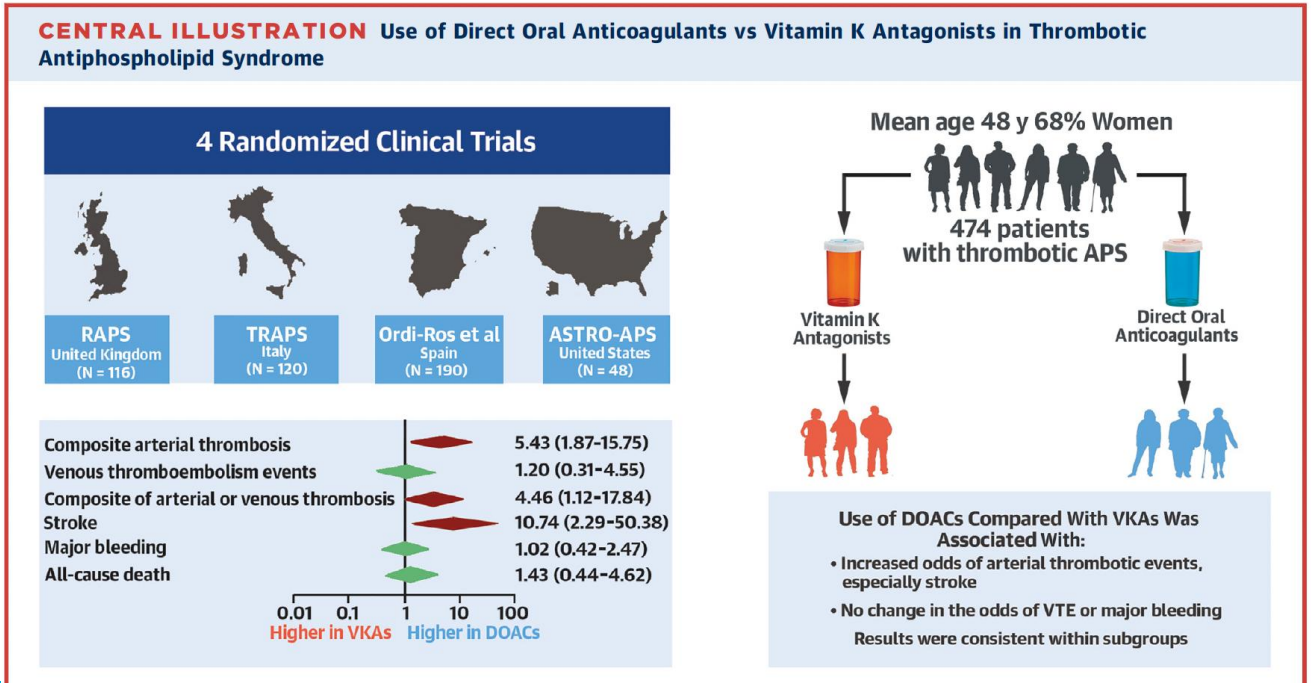
Recurrent VTE 35%

No recurrent VTE 30%

Coppens, J Thromb Haemost 2007

What about antiphospholipid syndrome (APS)?

- Potential therapeutic management consequence in VTE patients with APS



Khairani et all, J Am Coll Cardiol 2023

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What do the guidelines say?

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

Saskia Middeldorp,[1] Eddy Lang,[10] Steph[en] Yuan Zhang,[1,2] Wo[j] James,[9] [Pet]er G. Karam,[2,3]

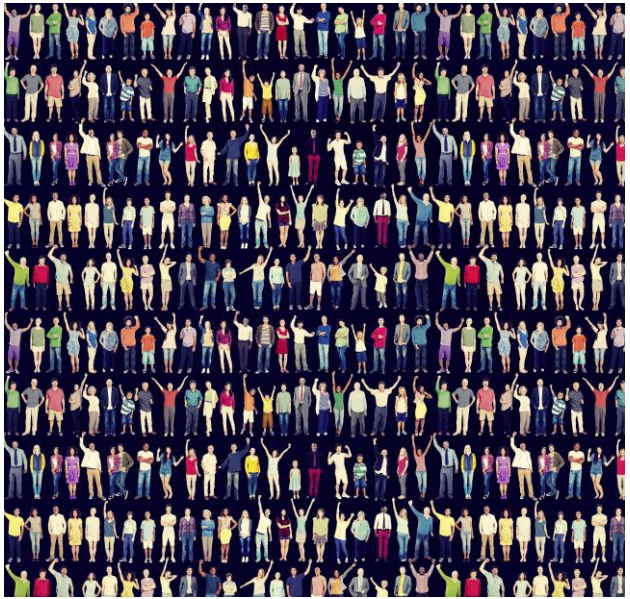
An Educational Slide Set
American Society of Hematology Guidelines for the Management of Venous Thromboembolism: Thrombophilia Testing

Slide set authors:
Taylor Dear MD (University of Toronto)
Nicole Relke MD (University of Toronto)
Zachary Liederman MD MScCH (University of Toronto)

Objectives of the ASH guideline

- To provide evidence-based recommendations about whether thrombophilia testing and tailoring management based on results,improves patient-important outcomes

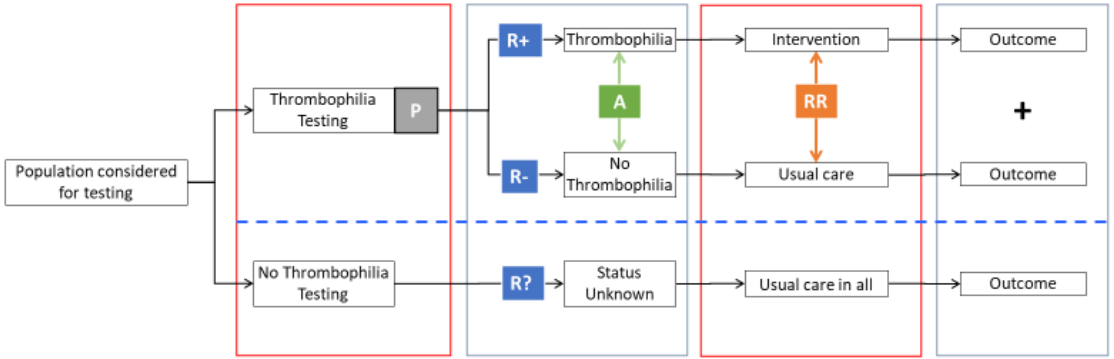
- On a group level



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



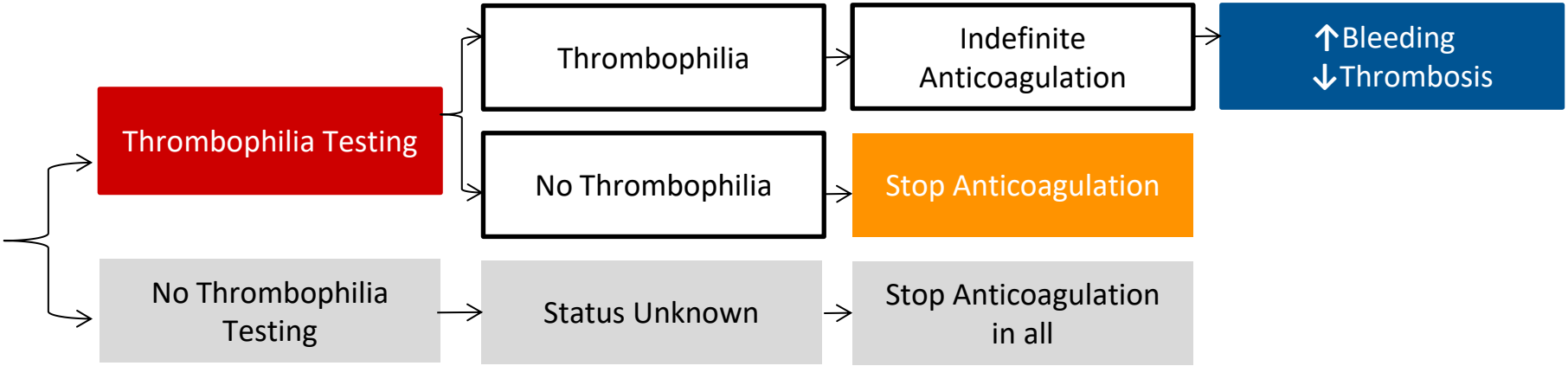
Prevalence	Thrombophilia prevalence
Incidence Risk	Risk of Outcomes in thrombophilia positive (R+), negative (R-), and unknown status (R?)
Association	Association (RR/OR) of thrombophilia status with Outcomes
RR of Intervention	Relative effect of the Intervention vs. No intervention / Usual care

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 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

Thresholds to suggest testing

Reduction of VTE (recurrence or first-time)

- Trivial: < 5 per 1000 patients/individuals tested
- **Small: 5 to 20 per 1000 patients/individuals tested**
- **Moderate: 20 to 50 per 1000 patients/individuals tested**

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)

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

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

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 🟢

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 all hereditary thrombophilia types

Selective Thrombophilia Testing: testing for a specific thrombophilia type (i.e. family testing)

Case 7: Combined Oral Contraceptive (COC) pill or Hormone Replacement Therapy (HRT) use

22-year-old woman

She would like to start the combined oral contraceptive pill for pregnancy prevention

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

Family History: Mother has a history of DVT. Her sister recently had 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

Case 8: Women who are planning pregnancy

26-year-old female is planning to become pregnant, and 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 choose?

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)	

*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

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

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

In Summary: which recommendations may change your practice?

Suggestion to test – only if it would change management!

1. Patients with VTE associated with non-surgical risk factor (including hormones)
2. Patients with unusual site thrombosis *if* the plan is to stop anticoagulation after 3 to 6 months.
3. Individuals with a family history of high-risk thrombophilia and VTE
4. Ambulatory cancer patients undergoing systemic therapy with a family history of VTE who are at low to moderate thrombosis risk

Limitations of the evidence used in this guideline

- No RCTs on thrombophilia testing
- Prevalence of thrombophilia varies between populations
- Indirect evidence from modeling about consequences of thrombophilia testing
- Analyses done in isolation from other risk stratification strategies

Implementation of guidelines?

Lots of controversy about these guidelines

- APS question (VKA vs. DOAC) not prioritized at time of guideline developement

- ? Protocols are easier than personalized medicine

Take home points

- Inherited thrombophilia is prevalent
- Consider the context of testing
- Think before you test – but it provides room for personalized medicine
  - Particularly for high risk thrombophilias
  - Young women in the family (oral contraceptives, pregnancy)