ASH Draft Recommendations for Thrombophilia Testing

INTRODUCTION

Public comment period occurs after recommendations are formed but before ASH organizational approval of the guidelines. Comments collected during the open comment period are provided to the guideline panel for review prior to finalizing the guidelines.

These draft recommendations are not final and therefore are not intended for use or citation.

To submit comments on the draft recommendations, please visit https://hematology.questionpro.com/t/AMvCYZnX2B

The public comment period for these draft recommendations closes on **July 30, 2021.**

RECOMMENDATIONS

- Recommendation 1: After completion of primary treatment for patients with any type of symptomatic VTE, the ASH guideline panel suggests not testing for thrombophilia to guide the duration of anticoagulant treatment, and using indefinite anticoagulant treatment in all patients (conditional recommendation based on very low certainty of the evidence about effects).

  Remarks:

  - A strategy with testing for thrombophilia would mean that positive patients would receive indefinite anticoagulant treatment, and negative patients would stop anticoagulant treatment.
  - Thrombosis experts would consider the population "with any VTE" virtual more than real, as the circumstances (unprovoked vs provoked) are usually easy to assess and very useful to stratify the risk of VTE recurrence and hence, would guide treatment decisions. However, in general clinical practice, which is the setting where thrombophilia testing is frequently performed, VTE is often managed regardless of circumstances qualifying the VTE as provoked or unprovoked (any VTE).
  - This recommendation refers to testing for inherited and acquired types of thrombophilia.

- Recommendation 2: After completion of primary treatment in patients with unprovoked symptomatic VTE, the ASH guideline panel suggests not testing for thrombophilia to guide the duration of anticoagulant treatment, and using indefinite anticoagulant treatment in all patients (conditional recommendation based on very low certainty of the evidence about effects).

  Remarks:

  - A strategy with testing for thrombophilia would mean that positive patients would receive indefinite anticoagulant treatment, and negative patients would stop anticoagulant treatment.
  - This recommendation refers to testing for inherited and acquired types of thrombophilia.

- Recommendation 3: After completion of primary treatment for patients with symptomatic VTE provoked by surgery, the ASH guideline panel suggests not testing for thrombophilia to guide the duration of anticoagulant treatment, and stopping anticoagulant treatment in all patients (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:

- A strategy with testing for thrombophilia would mean that positive patients would receive indefinite anticoagulant treatment, and negative patients negative would stop anticoagulant treatment.
- This recommendation refers to testing for inherited and acquired types of thrombophilia.

- Recommendation 4: After completion of primary treatment for patients with a symptomatic VTE provoked by a non-surgical major transient risk factor, the ASH guideline panel suggests testing for thrombophilia and indefinite anticoagulant treatment in positive patients over no testing for thrombophilia and stopping anticoagulant treatment in all patients (conditional recommendation based on very low certainty of the evidence about effects)

Remarks:

- Non-surgical major transient risk factors: e.g. confined to bed in hospital for at least 3 days with an acute illness ("bathroom privileges only"), or a combination of minor transient risk factors such as admission to hospital for less than 3 days with an acute illness, confined to bed out of hospital for at least 3 days with an acute illness, or leg injury associated with decreased mobility for at least 3 days. (See Table 3 in the ASH 2020 guidelines for treatment of DVT and PE).
- A strategy with testing for thrombophilia would mean that positive patients would receive indefinite anticoagulant treatment, and negative patients would stop anticoagulant treatment.
- This recommendation refers to testing for inherited and acquired types of thrombophilia.

- Recommendation 5: After completion of primary treatment for women with a symptomatic VTE provoked by pregnancy or postpartum, the ASH guideline panel suggests testing for thrombophilia and indefinite anticoagulant treatment in positive women over no testing for thrombophilia and stopping anticoagulant treatment in all women (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:

- A strategy with testing for thrombophilia would mean that positive women would receive indefinite anticoagulant treatment, and negative women negative would stop anticoagulant treatment.
- This recommendation refers to testing for inherited and acquired types of thrombophilia.

- Recommendation 6: After completion of primary treatment for women with a symptomatic VTE associated with use of combined oral contraceptives, the ASH guideline panel suggests testing for thrombophilia and indefinite anticoagulant treatment in positive women over no testing for thrombophilia and stopping anticoagulant treatment in all women (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:

- A strategy with testing for thrombophilia would mean that positive women would receive indefinite anticoagulant treatment, and negative women would stop anticoagulant treatment.
- This recommendation refers to testing for inherited and acquired types of thrombophilia.

- Recommendation 7: After completion of primary treatment for patients with cerebral venous thrombosis, the ASH guideline panel suggests testing for thrombophilia and indefinite anticoagulant treatment in positive patients over no testing for thrombophilia and stopping anticoagulant treatment in all patients (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:

- A strategy with testing for thrombophilia would mean that positive patients would receive indefinite anticoagulant treatment, and negative patients would stop anticoagulant treatment.
- This recommendation refers to testing for inherited and acquired types of thrombophilia.
- This recommendation addresses settings where the standard of care for cerebral venous thrombosis patients is stopping anticoagulant treatment; the ASH guideline panel provides a separate recommendation for settings where the standard of care is indefinite anticoagulant treatment (Q7.A.1).

- **Recommendation 8: After completion of primary treatment for patients with cerebral venous thrombosis, the ASH guideline panel suggests not testing for thrombophilia to guide the duration of anticoagulant treatment, and using indefinite anticoagulant treatment in all patients (conditional recommendation based on very low certainty of the evidence about effects).**

Remarks:

- A strategy with testing for thrombophilia would mean that positive patients would receive indefinite anticoagulant treatment, and negative patients would stop anticoagulant treatment.
- This recommendation refers to testing for inherited and acquired types of thrombophilia.
- This recommendation addresses settings where the standard of care for cerebral venous thrombosis patients is indefinite anticoagulant treatment; the ASH guideline panel provides a separate recommendation for settings where the standard of care is stopping anticoagulant treatment (Q7.A.2).

- **Recommendation 9: After completion of primary treatment for patients with splanchnic venous thrombosis, the ASH guideline panel suggests testing for thrombophilia and indefinite anticoagulant treatment in positive patients over no testing for thrombophilia and stopping anticoagulant treatment in all patients (conditional recommendation based on very low certainty of the evidence about effects).**

Remarks:

- A strategy with testing for thrombophilia would mean that positive patients would receive indefinite anticoagulant treatment, and negative patients would stop anticoagulant treatment.
- This recommendation refers to testing for inherited and acquired types of thrombophilia.
- This recommendation addresses settings where the standard of care for splanchnic venous thrombosis patients is stopping anticoagulant treatment; the ASH guideline panel provides a separate recommendation for settings where the standard of care is indefinite anticoagulant treatment (Q7.B.1).

- **Recommendation 10: After completion of primary treatment for patients with splanchnic venous thrombosis, the ASH guideline panel suggests not testing for thrombophilia to guide the duration of anticoagulant treatment, and using indefinite anticoagulant treatment in all patients (conditional recommendation based on very low certainty of the evidence about effects).**

Remarks:

- A strategy with testing for thrombophilia would mean that positive patients would receive indefinite anticoagulant treatment, and negative patients would stop anticoagulant treatment.
- This recommendation refers to testing for inherited and acquired types of thrombophilia.

- This recommendation addresses settings where the standard of care for splanchnic venous thrombosis patients is indefinite anticoagulant treatment; the ASH guideline panel provides a separate recommendation for settings where the standard of care is stopping anticoagulant treatment (Q7.B.2).

- Recommendation 11:
  - *Factor V Leiden or prothrombin mutation*

    In first- and second-degree relatives of patients with VTE and known factor V Leiden or prothrombin mutation (low risk thrombophilia types), and who have a minor provoking risk factor for VTE, the ASH guideline panel suggests not testing for any hereditary thrombophilia to guide thromboprophylaxis, and not using thromboprophylaxis in all relatives (conditional recommendation based on very low certainty in the evidence about effects)
  - *Antithrombin, protein C, or protein S deficiency*

    In first- and second-degree relatives of patients with VTE and known antithrombin, protein C, or protein S deficiency (high risk thrombophilia types), and who have a minor provoking risk factor for VTE, the ASH guideline panel suggests testing for any hereditary thrombophilia and thromboprophylaxis in relatives positive for thrombophilia over no testing for thrombophilia and no thromboprophylaxis in all relatives (conditional recommendation based on very low certainty in the evidence about effects)

    Remarks:

    - A strategy with testing for any hereditary thrombophilia would mean that positive relatives receive thromboprophylaxis, and negative relatives would receive no thromboprophylaxis.
    - These recommendations do not address homozygous defects, or combinations of thrombophilia types.
    - These recommendations refer to testing for any inherited type of thrombophilia. A separate question in this guideline addressed selective testing only for the known familial thrombophilia type in this population, and the resulting recommendations are the same.

- Recommendation 12:
  - *Factor V Leiden or prothrombin mutation*

    In first- and second-degree relatives of patients with VTE and known factor V Leiden or prothrombin mutation (low risk thrombophilia), and who have a minor provoking risk factor for VTE, the ASH guideline panel suggests not testing for the known familial thrombophilia to guide thromboprophylaxis, and not using thromboprophylaxis in all relatives (conditional recommendation based on very low certainty in the evidence about effects)
  - *Antithrombin, protein C, or protein S deficiency*

    In first- and second-degree relatives of patients with VTE and known antithrombin, protein C, or protein S deficiency (high risk thrombophilia), and who have a minor provoking risk factor for VTE, the ASH guideline panel suggests testing for the known familial thrombophilia and thromboprophylaxis in.

    Remarks:

    - A strategy with selective testing for the known familial thrombophilia type would mean that positive relatives would receive thromboprophylaxis, and negative relatives would receive no thromboprophylaxis.
    - These recommendations do not address homozygous defects, or combinations of thrombophilia types.
    - These recommendations refer to selective testing for the known familial thrombophilia type. A separate question in this guideline addressed testing for any hereditary thrombophilia type in this population, and the resulting recommendations are the same.

- Recommendation 13: In first- and second-degree relatives of patients with VTE and unknown thrombophilia status, and who have a minor provoking risk factor for VTE, the ASH guideline panel suggests not testing for any hereditary thrombophilia to guide thromboprophylaxis, and not using thromboprophylaxis in all relatives (conditional recommendation based on very low certainty in the evidence about effects)

  Remarks:

  - Thrombophilia testing may be considered if relatives had multiple family members with a VTE, if the family member with VTE was of young age, with patient preference, and in settings where testing incurs a low cost.
  - A strategy with testing for any hereditary thrombophilia would mean that positive relatives receive thromboprophylaxis, and negative relatives would receive no thromboprophylaxis.
  - These recommendations do not address homozygous defects, or combinations of thrombophilia types.

- Recommendation 14:
  - *Factor V Leiden or prothrombin mutation in first- and second- degree relatives*

    In first- and second-degree relatives of patients with known factor V Leiden or prothrombin mutation (low risk thrombophilia) but no history of VTE, and who have a minor provoking risk factor for VTE, the ASH guideline panel suggests not testing for the known familial thrombophilia to guide thromboprophylaxis, and not using thromboprophylaxis in all relatives (conditional recommendation based on very low certainty in the evidence about effects)
  - *Antithrombin, protein C, or protein S deficiency in first-degree relatives*

    In first-degree relatives of patients with known antithrombin, protein C, or protein S deficiency (high risk thrombophilia) but no history of VTE, and who have a minor provoking risk factor for VTE, the ASH guideline panel suggests testing for the known familial thrombophilia and thromboprophylaxis in relatives positive for thrombophilia over not testing for thrombophilia and no thromboprophylaxis in all relatives (conditional recommendation based on very low certainty in the evidence about effects).
  - *Antithrombin, protein C, or protein S deficiency in second-degree relatives*

    In second-degree relatives of patients with known antithrombin, protein C, or protein S deficiency (high risk thrombophilia) but no history of VTE, and who have a minor provoking risk factor for VTE, the ASH guideline panel suggests either testing for the known familial thrombophilia and thromboprophylaxis in relatives positive for thrombophilia or not testing for thrombophilia and not using thromboprophylaxis in all relatives (conditional recommendation based on very low certainty in the evidence about effects).

  Remarks:

  - A strategy with selective testing for the known familial thrombophilia type would mean that positive relatives would receive thromboprophylaxis, and negative relatives would receive no thromboprophylaxis.
  - These recommendations do not address homozygous defects, or combinations of thrombophilia types.

- Recommendation 15: In women from the general population who are considering using combined oral contraceptives (COC), the ASH guideline panel recommends not testing for any hereditary thrombophilia to guide prescription of COC (strong recommendation based on low certainty in the evidence about effects).

  Remarks:

  - Women with risk factors for VTE, such as familial VTE and/or thrombophilia, are at higher risk of VTE. Other recommendations in this guideline address thrombophilia testing in these populations.

- Recommendation 16: In women from the general population who are considering using hormone replacement therapy (HRT), the ASH guideline panel suggests not testing for any hereditary thrombophilia to guide prescription of HRT (conditional recommendation based on low certainty in the evidence about effects).

  Remarks:

  - Women with risk factors for VTE, such as familial VTE and/or thrombophilia, are at higher risk of VTE. Other recommendations in this guideline address thrombophilia testing in these populations.

- Recommendation 17: In women with a family history of VTE and unknown thrombophilia in the family who are considering using combined oral contraceptives (COC), the ASH guideline panel suggests not testing for any hereditary thrombophilia to guide prescription of COC (conditional recommendation based on very low certainty in the evidence about effects)

  Remarks:

  - Women with a family history of VTE and a known thrombophilia in the family are at higher risk for testing positive for thrombophilia and are therefore at higher risk for VTE. Another recommendation in this guideline addresses thrombophilia testing in this population.

- Recommendation 18: In women with a family history of VTE and unknown thrombophilia in the family who are considering using hormone replacement therapy (HRT), the ASH guideline panel suggests not testing for any hereditary thrombophilia to guide prescription of HRT (conditional recommendation based on very low certainty in the evidence about effects)

  Remarks:

  - Women with a family history of VTE and a known thrombophilia in the family are at higher risk for testing positive for thrombophilia and are therefore at higher risk for VTE. Another recommendation in this guideline addresses thrombophilia testing in this population.

- Recommendation 19:
  - *Factor V Leiden or prothrombin mutation*

    In first- and second-degree relatives of patients with VTE and known factor V Leiden or prothrombin mutation in the family (low risk thrombophilia), the ASH guideline panel suggests not testing for the known familial thrombophilia to guide prescription of COC (conditional recommendation based on very low certainty in the evidence about effects)
  - *Antithrombin, protein C, or protein S deficiency*

    In first- and second-degree relatives of patients with VTE and known antithrombin, protein C or protein S deficiency in the family (high risk thrombophilia), the ASH guideline panel suggests testing for the known familial thrombophilia and avoidance of COC in women positive for thrombophilia over no testing for thrombophilia and COC in all women (conditional recommendation based on very low certainty in the evidence about effects).

  Remarks:

  - A strategy with selective testing for the known familial thrombophilia would mean that positive women would avoid COC, and negative women would use COC.
  - These recommendations do not address homozygous defects, or combinations of thrombophilia types.

- Recommendation 20:
  - *Factor V Leiden or prothrombin mutation*

    In first- and second-degree relatives of patients with VTE and known factor V Leiden or prothrombin mutation in the family (low risk thrombophilia), the ASH guideline panel suggests not testing for the known familial thrombophilia to guide prescription of HRT (conditional recommendation based on very low certainty in the evidence about effects)
  - *Antithrombin, protein C, or protein S deficiency*

    In first- and second-degree relatives of patients with VTE and known antithrombin, protein C or protein S deficiency in the family (high risk thrombophilia), the ASH guideline panel suggests testing for the known familial thrombophilia and avoidance of HRT in women for thrombophilia over no testing for thrombophilia and HRT in all women (conditional recommendation based on very low certainty in the evidence about effects).

    Remarks:

    - A strategy with selective testing for the known familial thrombophilia would mean that positive women would avoid HRT, and negative women would use HRT.
    - These recommendations do not address homozygous defects, or combinations of thrombophilia types.
- Recommendation 21:
  - *Homozygous factor V Leiden, combination of factor V Leiden and prothrombin mutation, or antithrombin deficiency in first-degree relatives:*

    In first-degree relatives of patients with VTE and known homozygous factor V Leiden, combination of factor V Leiden and prothrombin mutation, or antithrombin deficiency in the family, the ASH guideline panel suggests testing for the known familial thrombophilia and antepartum thromboprophylaxis in first-degree relatives positive for thrombophilia over no testing for thrombophilia and no antepartum thromboprophylaxis in all first-degree relatives (conditional recommendation based on very low certainty in the evidence about effects)
  - *Combination of factor V Leiden and prothrombin mutation, or antithrombin deficiency in second-degree relatives:*

    In second-degree relatives of patients with VTE and known combination of factor V Leiden and prothrombin mutation, or antithrombin deficiency in the family, the ASH guideline panel suggests testing for the known familial thrombophilia and antepartum thromboprophylaxis in second-degree relatives positive for thrombophilia over no testing for thrombophilia and no antepartum thromboprophylaxis in all second-degree relatives (conditional recommendation based on very low certainty in the evidence about effects)
  - *Protein C or protein S deficiency in first- and second-degree relatives:*

    In first- and second-degree relatives of patients with VTE and known protein C or protein S deficiency in the family, the ASH guideline panel suggests either testing for the known familial thrombophilia and antepartum thromboprophylaxis in relatives positive for thrombophilia or not testing for thrombophilia and no antepartum thromboprophylaxis in all relatives (conditional recommendation based on very low certainty in the evidence about effects)

    Remarks:

    - Pharmacological thromboprophylaxis based on antepartum thrombophilia testing is often continued postpartum.
    - Conditions can include the duration and burden of the treatment, which involves injections, and patient preference.
    - A strategy with selective testing for the known familial thrombophilia type would mean that positive relatives would receive thromboprophylaxis, and negative relatives would receive no thromboprophylaxis.

- For homozygous FVL, these recommendations only concern siblings, not children. Management of second-degree relatives was not addressed.
- These recommendations do not address heterozygous FVL or PT mutation alone, as the ASH guidelines on the management of VTE in the context of pregnancy suggest not to prescribe thromboprophylaxis in these patients, and patient outcomes would not be affected by thrombophilia testing.

- Recommendation 22:
  - *Homozygous factor V Leiden, combination of factor V Leiden and prothrombin mutation, antithrombin, protein C, or protein S deficiency in first-degree relatives:*

    In first-degree relatives of patients with VTE and known homozygous factor V Leiden, combination of factor V Leiden and prothrombin mutation, antithrombin deficiency, protein C deficiency, or protein S deficiency in the family, the ASH guideline panel suggests testing for the known familial thrombophilia and postpartum thromboprophylaxis in first-degree relatives positive for thrombophilia over no testing for thrombophilia and no postpartum thromboprophylaxis in all first-degree relatives (conditional recommendation based on very low certainty in the evidence about effects)
  - *Combination of factor V Leiden and prothrombin mutation, or antithrombin deficiency in second-degree relatives:*

    In second-degree relatives of patients with VTE and known combination of factor V Leiden and prothrombin mutation, or antithrombin deficiency in the family, the ASH guideline panel suggests testing for the known familial thrombophilia and postpartum thromboprophylaxis in second-degree relatives positive for thrombophilia over no testing for thrombophilia and no postpartum thromboprophylaxis in all second-degree relatives (conditional recommendation based on very low certainty in the evidence about effects)
  - *Protein C or protein S deficiency in first- and second-degree relatives:*

    In first- and second-degree relatives of patients with VTE and known protein C or protein S deficiency in the family, the ASH guideline panel suggests either testing for the known familial thrombophilia and postpartum thromboprophylaxis in relatives positive for thrombophilia or not testing for thrombophilia and no postpartum thromboprophylaxis in all relatives (conditional recommendation based on very low certainty in the evidence about effects)

    Remarks:

    - Pharmacological thromboprophylaxis postpartum continues until 6 weeks after delivery.
    - Conditions can include the duration and burden of the treatment, which involves injections, and patient preference.
    - A strategy with selective testing for the known familial thrombophilia type would mean that positive relatives would receive thromboprophylaxis, and negative relatives would receive no thromboprophylaxis.
    - For homozygous FVL, these recommendations only concern siblings, not children. Management of second-degree relatives was not addressed.
    - These recommendations do not address heterozygous FVL or PT mutation alone, as the ASH guidelines on the management of VTE in the context of pregnancy suggest not to prescribe thromboprophylaxis in these patients, and patient outcomes would not be affected by thrombophilia testing.

- Recommendation 23: In ambulatory cancer patients without a personal history of VTE, and who are first-degree relatives of a patient with VTE and are at low or intermediate risk for VTE, the ASH guideline panel suggests testing for any hereditary thrombophilia and thromboprophylaxis in positive patients over no testing for thrombophilia and no thromboprophylaxis in all patients (conditional recommendation based on very low certainty of the evidence about effects):

  Remarks:

- This question only addresses patients at low or intermediate risk for VTE. The ASH VTE guidelines on prevention and treatment in patients with cancer suggest using direct oral anticoagulant prophylaxis in all ambulatory cancer patients with high VTE risk.
- Patient preference is an important condition to consider, as it can be an added burden for cancer patients in terms of undergoing the thrombophilia test, knowing the positive test result, and receiving additional medication
- A strategy with testing for any hereditary thrombophilia would mean that positive relatives receive thromboprophylaxis, and negative relatives would receive no thromboprophylaxis.
- This recommendation does not address homozygous defects, or combinations of thrombophilia types.

QUESTION

Should thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia vs. no thrombophilia testing and indefinite anticoagulant treatment in all be used for patients with any type of symptomatic venous thromboembolism who completed primary treatment?

POPULATION:	patients with any type of symptomatic venous thromboembolism who completed primary treatment
INTERVENTION:	thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia
COMPARISON:	no thrombophilia testing and indefinite anticoagulant treatment in all
MAIN OUTCOMES:	Recurrent VTE; Major Bleeding - Low Risk (0.5% per year); Major Bleeding - High Risk (1.5% per year);
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Thrombophilia, either acquired or inherited, can be identified in many patients presenting with venous thromboembolism (VTE). The currently most commonly tested inherited thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. Thrombophilia testing is often performed in patients with VTE, particularly if they are young, have recurrent episodes, have thrombosis at unusual sites, or have a positive family history for VTE. Although testing patients with VTE has a high chance of finding a positive test result, the relevant question and aim of the current guideline is to assess whether thrombophilia testing and tailoring management to the test result would improve patient important outcomes. This question addresses whether thrombophilia testing and subsequent definite duration of anticoagulant treatment in patients negative for thrombophilia improves patient-important outcomes in patients with (any type of) VTE, as compared with no thrombophilia testing and treating all patients with indefinite anticoagulant treatment. Since no randomized controlled trials have addressed this question, we used a modeling approach based on observational evidence for baseline risk of patient-important outcomes, prevalence of thrombophilia and associated risk of recurrent events with thrombophilia, and RCTs based evidence for the effect of indefinite anticoagulation on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Thrombosis experts would consider the population with “any VTE” more virtual than real, as the circumstances (unprovoked vs provoked) are usually easy to assess and very useful to stratify the risk of VTE recurrence. However, in general clinical practice, which is the setting where thrombophilia testing is frequently performed, VTEs can be managed regardless of circumstances qualifying the VTE as provoked or unprovoked (any VTE).	Although this seems a resolved question for thrombosis experts, it is still considered a priority for physicians who are not thrombosis experts.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Evidence Profile.	Desirable effect = avoiding major bleeding. Major bleedings would be avoided in patients who are negative for thrombophilia by not extending their anticoagulant treatment.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	See Evidence Profile.	Undesirable effect = allowing VTE recurrence. VTE recurrences would be allowed to happen in patients who are negative for thrombophilia by not extending their anticoagulant treatment.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows using a scale from 0 (worst possible scenario, usually death), to 1 (best possible scenario, usually perfect health):** **Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(1, 2, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3) **Gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off)(2, 3) **Minor intracranial bleeding event:** 0.75 (standard gamble)(2)	The panel considered that clinicians may value avoiding major bleeding more (they do not want to cause harm), while patients may value avoiding VTE events more (they may prefer avoiding a recurrence of blood clots).

	Major intracranial bleeding event: 0.15 (standard gamble)(2) **Anticoagulant therapy** Patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome.(3) Patients would favor efficacy and safety over convenience of route of administration.(6) Also, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events.(7, 6, 8)	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		No studies assessed indefinite anticoagulation as life-long treatment. The panel observed that the appraisal of the comparison of the two interventions (testing and treating positives vs treating all) was limited by the absence of studies comparing extended anticoagulation as life-long treatment versus no anticoagulation, which the panel had to extrapolate.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	Intervention Costs: **Test (source)** / Approximate Cost (2005) / Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016) / **(14/12/2016) £1 = $1,27** **Full Blood Count** £2.55 £3.29 **$4,18** **Protein C** £11.67 £15.5 **$19,12** **Free Protein S** £11.67 £15.5 **$19,12** **Antithrombin** £11.67 £15.5 **$19,12** **APCR** £10.73 £13.84 **$17,58** **Factor V Leiden** £85.00 £109.65 **$141,45** **Prothrombin gene mutation** £85.00 £109.65 **$141,45** **Lupus Anticoagulant** £10.73 £13.84 **$17,58** **Antiphospholipid antibodies** £12.30 £15.87 **$20,15** **Anti Beta-2 GP1 antibody** £9.50 £12.25 **$15,81** **The potential cost of a full thrombophilia screen** £250.82, £323.56 **$410,92** Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx **Cost of the health outcomes:**(9) - **Recurrent VTE:** 11,000 to 15,000 USD - **Major bleeding:** 11,000 to 22,000 USD **Cost of interventions:**(10) - **Dabigatran:** Cost per month: $300.44–$600.88 USD - **Rivaroxaban:** Cost per month: $300.42–$600.84 USD - **Apixaban:** Cost per month: $300.44–$600.88	**The panel considered the following cost ranges:** - Cost for testing: $400 -$2,000 per patient - Cost for treatment: $1,000-$ 4,500 per patient per year In assessing the resources required the panel considered that the intervention (testing and treating only patients positive for thrombophilia) added the cost for testing all patients but "saved" the cost of treatment avoided in the patients negative for thrombophilia. The panel did not consider the costs for recurrent clots or for bleeding events.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	Three studies evaluated the cost-effectiveness of thrombophilia testing and different management strategies in patients with a first venous thromboembolism.(11, 12, 13) All three studies found thrombophilia testing cost-effective, although the uncertainty was high in general due to prevalence of mutation and the variability in the recurrence rate (which depends on the type of thrombophilia), risk of adverse events such as major haemorrhage, age or efficacy of the anticoagulant therapy, among others. Cost per quality-adjusted life year (QALY) for the testing and treatment strategies varied between the 3 studies and in sensitivity analyses (Simpson 2009: approximately £20,000/QALY for patients with PE or DVT; Marchetti 2001: $13,624/QALY for any VTE, Eckman 2002: $16,823/QALY for any VTE) One study evaluated thrombophilia testing using a panel of thrombophilia tests that included Factor V Leiden, Prothrombin G20210A, APC resistance, Protein C, Protein S, antithrombin levels, antiphospholipid antibodies and homocysteine levels, dysfibrinogenaemia, and levels of factor VIII, factor IX and factor XI.(13) Another cost-effectiveness study included only screening for FVL and G20210A prothrombin mutations,(11) and the third study included testing for FVL mutation.(12)	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(14)	The panel considered that the health system/service coverage will be the main aspect affecting the health equity. The US is an example where promotion of testing that is not covered by insurance would generate inequities, i.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies	Research studies suggested the following regarding acceptability and barriers associated with testing and treatment:	The panel considered testing acceptable for many doctors, although maybe not for all.

○ Don't know	**Patients**: A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(15) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(16) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers**: A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(17) **Payers**: At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	Patients are in general willing to undergo thrombophilia testing when testing is proposed by their doctor.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation. External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across

	significant proportion of thrombophilia testing was inappropriately performed.(18) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending.(19) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(20) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(21) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(22)	laboratories.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies

	JUDGEMENT						
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

After completion of primary treatment for patients with any type of symptomatic VTE, the ASH guideline panel suggests not testing for thrombophilia to guide the duration of anticoagulant treatment, and using indefinite anticoagulant treatment in all patients (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:

- A strategy with testing for thrombophilia would mean that positive patients would receive indefinite anticoagulant treatment, and negative patients would stop anticoagulant treatment.

- Thrombosis experts would consider the population “with any VTE” virtual more than real, as the circumstances (unprovoked vs provoked) are usually easy to assess and very useful to stratify the risk of VTE recurrence and hence, would guide treatment decisions. However, in general clinical practice, which is the setting where thrombophilia testing is frequently performed, VTE is often managed regardless of circumstances qualifying the VTE as provoked or unprovoked (any VTE).

- This recommendation refers to testing for inherited and acquired types of thrombophilia.

Justification

The panel's main consideration in supporting this recommendation is that the increase in the risk of VTE recurrence in patients negative for thrombophilia outweighs the decrease in the risk of major bleeding and does not justify testing and limiting anticoagulant treatment duration.

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation.

Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

This recommendation is primarily aimed at providers who are not thrombosis experts. Such providers are suggested to avoid requesting thrombophilia screening for their patients. For patients known to have had a provoked or unprovoked VTE, we refer to the separate recommendations in these patients.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

The most impactful research in this field would be around educational interventions aiming at reducing the number of cases in which providers were to decide about duration of anticoagulation without properly classifying VTE as provoked or unprovoked.

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
7. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
8. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
9. Grosse, S. D., Nelson, R. E., Nyarko, K. A., Richardson, L. C., Raskob, G. E.. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res; Jan 2016.
10. Biskupiak, J., Ghate, S. R., Jiao, T., Brixner, D.. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. J Manag Care Pharm; Nov-Dec 2013.
11. Marchetti, M., Quaglini, S., Barosi, G.. Cost-effectiveness of screening and extended anticoagulation for carriers of both factor V Leiden and prothrombin G20210A. Qjm; Jul 2001.
12. Eckman, M. H., Singh, S. K., Erban, J. K., Kao, G.. Testing for factor V Leiden in patients with pulmonary or venous thromboembolism: a cost-effectiveness analysis. Med Decis Making; Mar-Apr 2002.
13. Simpson, E. L., Stevenson, M. D., Rawdin, A., Papaioannou, D.. Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis. Health Technol Assess; Jan 2009.
14. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
15. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
16. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
17. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
18. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
19. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
20. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
21. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
22. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In patients with any type of symptomatic venous thromboembolism who completed primary treatment, should thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia compared to no thrombophilia testing and indefinite anticoagulant treatment in all be used?

Setting:

Bibliography: See reference list and footnotes.[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Recurrent VTE (assessed with: any DVT or PE)									
25 [a,b,c,d,e,f,g]	observational studies	not serious	not serious	serious [h]	serious [i]	none	When testing 1,000 patients who completed primary treatment of symptomatic VTE for any type of thrombophilia and only treating the 380 positives with indefinite anticoagulation (ranging from 216 to 595), 43 VTE recurrences will occur per year (ranging from 30 to 57). When not testing 1,000 patients for thrombophilia and treating all of them with indefinite anticoagulation, 11 VTE recurrences will occur per year (95% CI: 8 to 17). Therefore, a thrombophilia testing strategy is associated with 620 fewer patients treated with indefinite anticoagulation (ranging from 405 to 784) and **32 more VTE recurrences (ranging from 12 to 50)** per 1,000 patients per year compared with a no testing strategy. [j]	⨁◯◯◯ VERY LOW	CRITICAL
Major Bleeding - Low Risk (0.5% per year)[k]									
32 [c,d,l,m,n]	observational studies	not serious	not serious	serious [o]	not serious	none	When testing 1,000 patients who completed primary treatment of symptomatic VTE, and who are at low risk of major bleeding, for any type of thrombophilia and only treating the 380 positives with indefinite anticoagulation (ranging from 216 to 595), 7 major bleedings will occur per year (ranging from 6 to 8). When not testing 1,000 patients for thrombophilia and treating all of them with indefinite anticoagulation, 11 major bleedings will occur per year (95% CI: 7-17). Therefore, a thrombophilia testing strategy is associated with 620 fewer patients treated with indefinite anticoagulation (ranging from 405 to 784) and **4 fewer major bleedings (ranging from 1 to 9)** per 1,000 patients per year compared with a no testing strategy. [p]	⨁◯◯◯ VERY LOW	CRITICAL
Major Bleeding - High Risk (1.5% per year)[q]									
32 [c,d,l,m,r]	observational studies	not serious	not serious	serious [o]	serious [i]	none	When testing 1,000 patients who completed primary treatment of symptomatic VTE, and who are at high risk of major bleeding, for any type of thrombophilia and only treating the 380 positives with indefinite anticoagulation (ranging from 216 to 595), 22 major bleedings will occur per year (ranging from 19 to 23). When not testing 1,000 patients for thrombophilia and treating all of them with indefinite anticoagulation, 33 major bleedings will occur per year (95% CI: 21-50). Therefore, a thrombophilia testing strategy is associated with 620 fewer patients treated with indefinite anticoagulation (ranging from 405 to 784) and **11 fewer major bleedings (ranging from 2 to 28)** per 1,000 patients per year compared with a no testing strategy. [s]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

a. Number of studies used in calculations: Overall risk for VTE recurrence, 1 systematic review; Prevalence, 20 studies; Risk association for thrombophilia positive versus negative, 6 studies (all also reported Prevalence); Extended anticoagulation effect, 4 RCTs

b. Overall risk for VTE recurrence: Carrier 2010

c. Thrombophilia prevalence, used for calculation: Bezemer 2009, Cebi 2009, Di Minno 2014, Garcia-Fuster 2005, Heit 2010, Kearon 1999, Kearon 2018, Lim 2017, Mello 2010, Meyer 2015, Olie 2011, Palareti 2003, Prandoni 2007, Roldan 2009, Rossi 2008, Santamaria 2005, Schattner 1997, Schulman 2006, Sundquist 2015, Weingarz 2015

d. Prevalence of specific thrombophilia types, used to verify calculation estimate: Ahmad 2016, Ahmad 2016, Ahmad 2017, Asim 2017, Baarslag 2004, Baglin 2003, Brouwer 2009, Bruwer 2016, Christiansen 2005, De Stefano 1999, De Stefano 2006, Eichinger 1999, Eichinger 2002, Eischer 2017, Gonzalez-Porras 2006, Heijboer 1990, Hirmerova 2014, Hoibraaten 2000, Kearon 2008, Laczkovics 2007, Lee 2017, Lijfering 2010, Lindmarker 1999, Marcucci 2003, Mateo 1997, Miles 2001, Ridker 1995, Rodger 2008, Roupie 2016, Rupa-Matysek 2014, Simioni 2000, Sonnevi 2013, Strandberg 2007, Sveinsdottir 2012, The Procare group 2003, Wahlander 2006

e. Thrombophilia positive vs negative risk association, used for calculation: Kearon, 1999, Kearon 2018, Mello 2010, Santamaria 2005, Schulman 2006, Weingarz 2015

f. Risk association for specific thrombophilia types, used to verify calculation estimate: Baglin 2003, Brouwer 2009, Christiansen 2005, De Stefano 1999, De Stefano 2006, Di Minno 2014, Eichinger 2002, Gonzalez-Porras 2006, Hoibraaten 2000, Lijfering 2010, Lindmarker 1999, Marcucci 2003, Miles 2001, Palareti 2003, Prandoni 2007, Ridker 1995, Rodger 2008, Schattner 1997, Simioni 2000, Strandberg 2007, Wahlander 2006

g. Effect of extended anticoagulation treatment, used in calculation: Agnelli 2013, Bauersachs 2010, Schulman 2003, Schulman 2013

h. The effect was indirectly calculated using separate studies for thrombophilia prevalence, relative risk of thrombophilia positives vs negatives, and the effect of treatment

i. There is a clinically important difference between the smallest and largest possible effect of the testing strategy.

j. Based on the following estimates: Overall risk for VTE recurrence, 75 per 1,000; Prevalence of any thrombophilia, 38.0% (min 21.6 - max 59.5); Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 1.65 (95%CI: 1.28-2.47); Relative risk of VTE recurrence with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.15 (0.10-0.23). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

k. Among RCTs assessing the effect of extended treatment against limited treatment, the lowest observed rate of major bleeding with limited treatment was 0.5% (Agnelli 2001)

l. Number of studies used in calculations: Overall risk, 1 RCT; Prevalence, 20 studies; Extended anticoagulation effect, 11 RCTs

m. Effect of extended anticoagulation treatment, used in calculation: Agnelli 2001, Agnelli 2003, Agnelli 2013, Bauersachs 2010, Couturaud 2015, Eischer 2009, Kearon 1999, Palareti 2006, Ridker 2003, Schulman 2003, Schulman 2013

n. Overall risk for Major bleeding: Agnelli 2001

o. The effect was indirectly calculated using separate studies for thrombophilia prevalence and the effect of treatment

p. Based on the following estimates: Overall risk for Major bleeding of 5 per 1,000; Prevalence of any thrombophilia, 38.0% (21.6-59.5); Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 2.17 (1.40-3.35). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the smallest treatment effect (lower CI).

q. Among RCTs assessing the effect of extended treatment against limited treatment, the highest observed rate of major bleeding with limited treatment was 1.5% (Agnelli 2013)

r. Overall risk for Major bleeding: Agnelli 2013

s. Based on the following estimates: Overall risk for Major bleeding of 15 per 1,000; Prevalence of any thrombophilia, 38.0% (21.6-59.5); Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 2.17 (1.40-3.35). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the smallest treatment effect (lower CI).

References

1. Agnelli, G., Buller, H. R., Cohen, A., Curto, M., Gallus, A. S., Johnson, M., Porcari, A., Raskob, G. E., Weitz, J. I., Investigators, Amplify-Ext. Apixaban for extended treatment of venous thromboembolism. N Engl J Med; Feb 21 2013.

2. Agnelli, G., Prandoni, P., Becattini, C., Silingardi, M., Taliani, M. R., Miccio, M., Imberti, D., Poggio, R., Ageno, W., Pogliani, E., Porro, F., Zonzin, P., Warfarin Optimal Duration Italian Trial, Investigators. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med; Jul 1 2003.

3. Agnelli, G., Prandoni, P., Santamaria, M. G., Bagatella, P., Iorio, A., Bazzan, M., Moia, M., Guazzaloca, G., Bertoldi, A., Tomasi, C., Scannapieco, G., Ageno, W., Warfarin Optimal Duration Italian Trial, Investigators. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med; Jul 19 2001.

4. Ahmad, A., Sundquist, K., Zoller, B., Dahlback, B., Svensson, P. J., Sundquist, J., Memon, A. A.. Identification of polymorphisms in Apolipoprotein M gene and their relationship with risk of recurrent venous thromboembolism. Thromb Haemost; Aug 30 2016.

5. Asim, M., Al-Thani, H., El-Menyar, A.. Recurrent Deep Vein Thrombosis After the First Venous Thromboembolism Event: A Single-Institution Experience. Med Sci Monit; May 20 2017.

6. Baarslag, H. J., Koopman, M. M., Hutten, B. A., Linthorst Homan, M. W., Buller, H. R., Reekers, J. A., van Beek, E. J.. Long-term follow-up of patients with suspected deep vein thrombosis of the upper extremity: survival, risk factors and post-thrombotic syndrome. Eur J Intern Med; Dec 2004.

7. Baglin, T., Luddington, R., Brown, K., Baglin, C.. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet; Aug 16 2003.

8. Bezemer, I. D., van der Meer, F. J., Eikenboom, J. C., Rosendaal, F. R., Doggen, C. J.. The value of family history as a risk indicator for venous thrombosis. Archives of Internal Medicine; Mar 23 2009.

9. Brouwer, J. L., Lijfering, W. M., Ten Kate, M. K., Kluin-Nelemans, H. C., Veeger, N. J., van der Meer, J.. High long-term absolute risk of recurrent venous thromboembolism in patients with hereditary deficiencies of protein S, protein C or antithrombin. Thromb Haemost; Jan 2009.

10. Bruwer, G., Limperger, V., Kenet, G., Klostermeier, U. C., Shneyder, M., Degenhardt, F., Finckh, U., Heller, C., Holzhauer, S., Trappe, R., Kentouche, K., Knoefler, R., Kurnik, K., Krumpel, A., Lauten, M., Manner, D., Mesters, R., Junker, R., Nowak-Gottl, U.. Impact of high risk thrombophilia status on recurrence among children and adults with VTE: An observational multicenter cohort study. Blood Cells Mol Dis; Nov 2016.

11. Carrier, M., Le Gal, G., Wells, P. S., Rodger, M. A.. Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. Ann Intern Med; May 4 2010.

12. Cebi, N., Tanriverdi, S.. Aetiology of deep vein thrombosis in 63 turkish patients. Turkish Journal of Medical Sciences; April 2009.

13. Christiansen, S. C., Cannegieter, S. C., Koster, T., Vandenbroucke, J. P., Rosendaal, F. R.. Thrombophilia, clinical factors, and recurrent venous thrombotic events. Jama; May 18 2005.

14. Couturaud, F., Sanchez, O., Pernod, G., Mismetti, P., Jego, P., Duhamel, E., Provost, K., dit Sollier, C. B., Presles, E., Castellant, P., Parent, F., Salaun, P. Y., Bressollette, L., Nonent, M., Lorillon, P., Girard, P., Lacut, K., Guegan, M., Bosson, J. L., Laporte, S., Leroyer, C., Decousus, H., Meyer, G., Mottier, D., Investigators, Padis-Pe. Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism: The PADIS-PE Randomized Clinical Trial. Jama; Jul 7 2015.

15. De Stefano, V., Martinelli, I., Mannucci, P. M., Paciaroni, K., Chiusolo, P., Casorelli, I., Rossi, E., Leone, G.. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med; Sep 9 1999.

16. De Stefano, V., Simioni, P., Rossi, E., Tormene, D., Za, T., Pagnan, A., Leone, G.. The risk of recurrent venous thromboembolism in patients with inherited deficiency of natural anticoagulants antithrombin, protein C and protein S. Haematologica; May 2006.

17. Di Minno, M. N., Dentali, F., Lupoli, R., Ageno, W.. Mild antithrombin deficiency and risk of recurrent venous thromboembolism: a prospective cohort study. Circulation; Jan 28 2014.

18. Eichinger, S., Minar, E., Hirschl, M., Bialonczyk, C., Stain, M., Mannhalter, C., Stumpflen, A., Schneider, B., Lechner, K., Kyrle, P. A.. The risk of early recurrent venous thromboembolism after oral anticoagulant therapy in patients with the G20210A transition in the prothrombin gene. Thromb Haemost; Jan 1999.

19. Eichinger, S., Weltermann, A., Mannhalter, C., Minar, E., Bialonczyk, C., Hirschl, M., Schonauer, V., Lechner, K., Kyrle, P. A.. The risk of recurrent venous thromboembolism in heterozygous carriers of factor V Leiden and a first spontaneous venous thromboembolism. Archives of Internal Medicine; Nov 11 2002.

20. Eischer, L., Kammer, M., Traby, L., Kyrle, P. A., Eichinger, S.. Risk of cancer after anticoagulation in patients with unprovoked venous thromboembolism: an observational cohort study. Journal of Thrombosis and Haemostasis; July 2017.

21. Eischer, L., Gartner, V., Schulman, S., Kyrle, P. A., Eichinger, S., investigators, Aurec-Fviii. 6 versus 30 months anticoagulation for recurrent venous thrombosis in patients with high factor VIII. Ann Hematol; May 2009.

22. Garcia-Fuster, M. J., Forner, M. J., Fernandez, C., Gil, J., Vaya, A., Maldonado, L.. Long-term prospective study of recurrent venous thromboembolism in patients younger than 50 years. Pathophysiol Haemost Thromb; 2005.

23. Gonzalez-Porras, J. R., Garcia-Sanz, R., Alberca, I., Lopez, M. L., Balanzategui, A., Gutierrez, O., Lozano, F., San Miguel, J.. Risk of recurrent venous thrombosis in patients with G20210A mutation in the prothrombin gene or factor V Leiden mutation. Blood Coagul Fibrinolysis; Jan 2006.

24. Group, The,Procare. Is recurrent venous thromboembolism more frequent in homozygous patients for the factor V Leiden mutation than in heterozygous patients?. Blood Coagulation and Fibrinolysis; September 2003.

25. Heijboer, H., Brandjes, D. P., Buller, H. R., Sturk, A., ten Cate, J. W.. Deficiencies of coagulation-inhibiting and fibrinolytic proteins in outpatients with deep-vein thrombosis. N Engl J Med; Nov 29 1990.

26. Heit, J. A., Beckman, M. G., Bockenstedt, P. L., Grant, A. M., Key, N. S., Kulkarni, R., Manco-Johnson, M. J., Moll, S., Ortel, T. L., Philipp, C. S., Thrombosis, C.,D.,C., Hemostasis Centers, Research, Prevention, Network. Comparison of characteristics from White- and Black-Americans with venous thromboembolism: a cross-sectional study. Am J Hematol; Jul 2010.

27. Hirmerova, J., Seidlerova, J., Subrt, I.. The association of factor V Leiden with various clinical patterns of venous thromboembolism-the factor V Leiden paradox. Qjm; Sep 2014.

28. Hoibraaten, E., Qvigstad, E., Arnesen, H., Larsen, S., Wickstrom, E., Sandset, P. M.. Increased risk of recurrent venous thromboembolism during hormone replacement therapy--results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). Thromb Haemost; Dec 2000.

29. Investigators, Einstein, Bauersachs, R., Berkowitz, S. D., Brenner, B., Buller, H. R., Decousus, H., Gallus, A. S., Lensing, A. W., Misselwitz, F., Prins, M. H., Raskob, G. E., Segers, A., Verhamme, P., Wells, P., Agnelli, G., Bounameaux, H., Cohen, A., Davidson, B. L., Piovella, F., Schellong, S.. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med; Dec 23 2010.

30. Kearon, C., Gent, M., Hirsh, J., Weitz, J., Kovacs, M. J., Anderson, D. R., Turpie, A. G., Green, D., Ginsberg, J. S., Wells, P., MacKinnon, B., Julian, J. A.. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med; Mar 25 1999.

31. Kearon, C., Julian, J. A., Kovacs, M. J., Anderson, D. R., Wells, P., Mackinnon, B., Weitz, J. I., Crowther, M. A., Dolan, S., Turpie, A. G., Geerts, W., Solymoss, S., van Nguyen, P., Demers, C., Kahn, S. R., Kassis, J., Rodger, M., Hambleton, J., Gent, M., Ginsberg, J. S., Investigators, Elate. Influence of thrombophilia on risk of recurrent venous thromboembolism while on warfarin: results from a randomized trial. Blood; Dec 1 2008.

32. Kearon, C., Parpia, S., Spencer, F. A., Baglin, T., Stevens, S. M., Bauer, K. A., Lentz, S. R., Kessler, C. M., Douketis, J. D., Moll, S., Kaatz, S., Schulman, S., Connors, J. M., Ginsberg, J. S., Spadafora, L., Bhagirath, V., Liaw, P. C., Weitz, J. I., Julian, J. A.. Antiphospholipid antibodies and recurrent thrombosis after a first unprovoked venous thromboembolism. Blood; May 10 2018.

33. Laczkovics, C., Grafenhofer, H., Kaider, A., Quehenberger, P., Simanek, R., Mannhalter, C., Lechner, K., Pabinger, I.. Risk of recurrence after a first venous thromboembolic event in young women. Haematologica; Sep 2007.

34. Lee, S. Y., Kim, E. K., Kim, M. S., Shin, S. H., Chang, H., Jang, S. Y., Kim, H. J., Kim, D. K.. The prevalence and clinical manifestation of hereditary thrombophilia in Korean patients with unprovoked venous thromboembolisms. PLoS ONE [Electronic Resource]; 2017.

35. Lijfering, W. M., Middeldorp, S., Veeger, N. J., Hamulyak, K., Prins, M. H., Buller, H. R., van der Meer, J.. Risk of recurrent venous thrombosis in homozygous carriers and double heterozygous carriers of factor V Leiden and prothrombin G20210A. Circulation; Apr 20 2010.

36. Lim, H. Y., Chua, C. C., Tacey, M., Sleeman, M., Donnan, G., Nandurkar, H., Ho, P.. Venous thromboembolism management in Northeast Melbourne: how does it compare to international guidelines and data?. Intern Med J; Sep 2017.

37. Lindmarker, P., Schulman, S., Sten-Linder, M., Wiman, B., Egberg, N., Johnsson, H.. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. DURAC Trial Study Group. Duration of Anticoagulation. Thromb Haemost; May 1999.

38. Marcucci, R., Liotta, A. A., Cellai, A. P., Rogolino, A., Gori, A. M., Giusti, B., Poli, D., Fedi, S., Abbate, R., Prisco, D.. Increased plasma levels of lipoprotein(a) and the risk of idiopathic and recurrent venous thromboembolism. Am J Med; Dec 1 2003.

39. Mateo, J., Oliver, A., Borrell, M., Sala, N., Fontcuberta, J.. Laboratory evaluation and clinical characteristics of 2,132 consecutive unselected patients with venous thromboembolism--results of the Spanish Multicentric Study on Thrombophilia (EMET-Study). Thromb Haemost; Mar 1997.

40. Mello, T. B., Orsi, F. L., Montalvao, S. A., Ozelo, M. C., de Paula, E. V., Annichinno-Bizzachi, J. M.. Long-term prospective study of recurrent venous thromboembolism in a Hispanic population. Blood Coagul Fibrinolysis; Oct 2010.

41. Meyer, M. R., Witt, D. M., Delate, T., Johnson, S. G., Fang, M., Go, A., Clark, N. P.. Thrombophilia testing patterns amongst patients with acute venous thromboembolism. Thromb Res; Dec 2015.

42. Miles, J. S., Miletich, J. P., Goldhaber, S. Z., Hennekens, C. H., Ridker, P. M.. G20210A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. J Am Coll Cardiol; Jan 2001.

43. Olie, V., Plu-Bureau, G., Conard, J., Horellou, M. H., Canonico, M., Scarabin, P. Y.. Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. Menopause; May 2011.

44. Palareti, G., Cosmi, B., Legnani, C., Tosetto, A., Brusi, C., Iorio, A., Pengo, V., Ghirarduzzi, A., Pattacini, C., Testa, S., Lensing, A. W., Tripodi, A., Investigators, Prolong. D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med; Oct 26 2006.

45. Palareti, G., Legnani, C., Cosmi, B., Valdre, L., Lunghi, B., Bernardi, F., Coccheri, S.. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation; Jul 22 2003.

46. Prandoni, P., Noventa, F., Ghirarduzzi, A., Pengo, V., Bernardi, E., Pesavento, R., Iotti, M., Tormene, D., Simioni, P., Pagnan, A.. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica; Feb 2007.

47. Ridker, P. M., Miletich, J. P., Stampfer, M. J., Goldhaber, S. Z., Lindpaintner, K., Hennekens, C. H.. Factor V Leiden and risks of recurrent idiopathic venous thromboembolism. Circulation; Nov 15 1995.

48. Rodger, M. A., Kahn, S. R., Wells, P. S., Anderson, D. A., Chagnon, I., Le Gal, G., Solymoss, S., Crowther, M., Perrier, A., White, R., Vickars, L., Ramsay, T., Betancourt, M. T., Kovacs, M. J.. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. Cmaj; Aug 26 2008.

49. Roldan, V., Lecumberri, R., Munoz-Torrero, J. F., Vicente, V., Rocha, E., Brenner, B., Monreal, M., Investigators, Riete. Thrombophilia testing in patients with venous thromboembolism. Findings from the RIETE registry. Thromb Res; Jun 2009.

50. Roupie, A. L., Dossier, A., Goulenok, T., Perozziello, A., Papo, T., Sacre, K.. First venous thromboembolism in admitted patients younger than 50years old. Eur J Intern Med; Oct 2016.

51. Rossi, E., Za, T., Ciminello, A., Leone, G., De Stefano, V.. The risk of symptomatic pulmonary embolism due to proximal deep venous thrombosis differs in patients with different types of inherited thrombophilia. Thromb Haemost; Jun 2008.

52. Rupa-Matysek, J., Gil, L., Wojtasinska, E., Ciepluch, K., Lewandowska, M., Komarnicki, M.. The relationship between mean platelet volume and thrombosis recurrence in patients diagnosed with antiphospholipid syndrome. Rheumatol Int; Nov 2014.

53. Santamaria, M. G., Agnelli, G., Taliani, M. R., Prandoni, P., Moia, M., Bazzan, M., Guazzaloca, G., Ageno, W., Bertoldi, A., Silingardi, M., Tomasi, C., Ambrosio, G. B., Warfarin Optimal Duration Italian Trial, Investigators. Thrombophilic abnormalities and recurrence of venous thromboembolism in patients treated with standardized anticoagulant treatment. Thromb Res; 2005.

54. Schattner, A., Kasher, I., Berrebi, A.. Causes and outcome of deep-vein thrombosis in otherwise-healthy patients under 50 years. Qjm; Apr 1997.

55. Schulman, S., Kearon, C., Kakkar, A. K., Schellong, S., Eriksson, H., Baanstra, D., Kvamme, A. M., Friedman, J., Mismetti, P., Goldhaber, S. Z., Investigators, Re-Medy,Trial, Investigators, Re-Sonate,Trial. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med; Feb 21 2013.

56. Schulman, S., Lindmarker, P., Holmstrom, M., Larfars, G., Carlsson, A., Nicol, P., Svensson, E., Ljungberg, B., Viering, S., Nordlander, S., Leijd, B., Jahed, K., Hjorth, M., Linder, O., Beckman, M.. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. Journal of Thrombosis & Haemostasis; Apr 2006.

57. Schulman, S., Wahlander, K., Lundstrom, T., Clason, S. B., Eriksson, H., Investigators, Thrive,Iii. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. N Engl J Med; Oct 30 2003.

58. Simioni, P., Prandoni, P., Lensing, A. W., Manfrin, D., Tormene, D., Gavasso, S., Girolami, B., Sardella, C., Prins, M., Girolami, A.. Risk for subsequent venous thromboembolic complications in carriers of the prothrombin or the factor V gene mutation with a first episode of deep-vein thrombosis. Blood; Nov 15 2000.

59. Sonnevi, K., Tchaikovski, S. N., Holmstrom, M., Antovic, J. P., Bremme, K., Rosing, J., Larfars, G.. Obesity and thrombin-generation profiles in women with venous thromboembolism. Blood Coagul Fibrinolysis; Jul 2013.

60. Strandberg, K., Svensson, P. J., Ohlin, A. K.. Venous thromboembolism in carriers of the Factor V Leiden mutation and in patients without known thrombophilic risk factor; prediction of recurrence and APC-PCI complex concentration and/or soluble thrombomodulin antigen and activity. Thromb Res; 2007.

61. Sundquist, K., Sundquist, J., Svensson, P. J., Zoller, B., Memon, A. A.. Role of family history of venous thromboembolism and thrombophilia as predictors of recurrence: a prospective follow-up study. Journal of Thrombosis & Haemostasis; Dec 2015.

62. Sveinsdottir, S. V., Saemundsson, Y., Isma, N., Gottsater, A., Svensson, P. J.. Evaluation of recurrent venous thromboembolism in patients with Factor V Leiden mutation in heterozygous form. Thromb Res; Sep 2012.

63. Vitovec, M., Golan, L., Roztocil, K., Linhart, A.. The development of persistent thrombotic masses in patients with deep venous thrombosis randomized to long-term anticoagulation treatment. Vasa; Aug 2009.

64. Wahlander, K., Eriksson, H., Lundstrom, T., Billing Clason, S., Wall, U., Nystrom, P., Wessman, P., Schulman, S., Investigators, Thrive,Iii. Risk of recurrent venous thromboembolism or bleeding in relation to thrombophilic risk factors in patients receiving ximelagatran or placebo for long-term secondary prevention of venous thromboembolism. Br J Haematol; Apr 2006.

65. Weingarz, L., Schindewolf, M., Schwonberg, J., Hecking, C., Wolf, Z., Erbe, M., Lindhoff-Last, E., Linnemann, B.. Thrombophilia and risk of VTE recurrence according to the age at the time of first VTE manifestation. Vasa; Jul 2015.

QUESTION

Should thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia vs. no thrombophilia testing and indefinite anticoagulant treatment in all be used for patients with unprovoked symptomatic venous thromboembolism who completed primary treatment?

POPULATION:	patients with unprovoked symptomatic venous thromboembolism who completed primary treatment
INTERVENTION:	thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia
COMPARISON:	no thrombophilia testing and indefinite anticoagulant treatment in all
MAIN OUTCOMES:	Recurrent VTE; Major bleeding - Low risk (0.5% per year); Major bleeding - High risk (1.5% per year);
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Thrombophilia, either acquired or inherited, can be identified in many patients presenting with venous thromboembolism (VTE). The currently most commonly tested inherited thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. The current guideline aims to assess whether identifying patients positive for one or more of these defects allows management options which reduce patient important outcomes. Usually, indefinite duration anticoagulant treatment is considered in patients with unprovoked VTE, due to the high risk of VTE recurrence. In this setting, thrombophilia testing might be considered to identify patients at lower risk of VTE recurrence, particularly in older patients, those without single or multiple previous episodes of provoked thrombosis, or having a negative family history of VTE. The question is whether a negative test result should alter usual anticoagulant management. This question addresses whether thrombophilia testing and subsequent definite duration of anticoagulant treatment in patients negative for thrombophilia improves patient important outcomes in patients with unprovoked VTE, as compared with no thrombophilia testing and treating all patients with indefinite duration anticoagulant treatment. Since no randomized controlled trials have addressed this question, we used a modeling approach based on observational evidence for baseline risk of patient-important outcomes, prevalence of thrombophilia and increased risk of events associated with thrombophilia, and RCTs based evidence for the effect of indefinite anticoagulation on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Evidence Profile.	Desirable effect = avoiding major bleeding. Major bleedings would be avoided in patients who are negative for thrombophilia by not extending their anticoagulation treatment. The panel considered the reduction of major bleeding in patients at Low risk of bleeding (0.5% per year), which would be the majority of the population, to be Small. In patients at High risk of bleeding (1.5% per year) this effect was considered to be Moderate.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	See Evidence Profile.	Undesirable effect = allowing VTE recurrence. VTE recurrences would be allowed to happen in patients who are negative for thrombophilia by not extending their anticoagulation treatment. The panel considered the 4.2% per year increase in VTE recurrence to be Moderate, using a 5.0% per year as a threshold to consider the effect Large.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows using a scale from 0 (worst possible scenario, usually death), to 1 (best possible scenario, usually perfect health): Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(1, 2, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3) **Gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off)(2, 3) **Minor intracranial bleeding event:** 0.75 (standard gamble)(2) **Major intracranial bleeding event:** 0.15 (standard gamble)(2) **Anticoagulant therapy** Patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome.(3) Patients would favor efficacy and safety over convenience of route of administration.(6) Also, patients would like to avoid adverse events but most of them are “not afraid of” the adverse events.(6, 7, 8)	The panel considered that clinicians may value avoiding major bleeding more (they do not want to cause harm), while patients may value avoiding VTE events more (they may prefer avoiding a recurrence of blood clots).

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		No studies assessed indefinite anticoagulation as life-long treatment. The panel observed that the appraisal of the comparison of the two interventions (testing and treating positives vs treating all) was limited by the absence of studies comparing extended anticoagulation as life-long treatment versus no anticoagulation, which the panel had to extrapolate.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	Intervention Costs: **Test (source)** / Approximate Cost (2005) / Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016) / **(14/12/2016) £1 = $1,27** **Full Blood Count** £2.55 £3.29 **$4,18** **Protein C** £11.67 £15.5 **$19,12** **Free Protein S** £11.67 £15.5 **$19,12** **Antithrombin** £11.67 £15.5 **$19,12** **APCR** £10.73 £13.84 **$17,58** **Factor V Leiden** £85.00 £109.65 **$141,45** **Prothrombin gene mutation** £85.00 £109.65 **$141,45** **Lupus Anticoagulant** £10.73 £13.84 **$17,58** **Antiphospholipid antibodies** £12.30 £15.87 **$20,15** **Anti Beta-2 GP1 antibody** £9.50 £12.25 **$15,81** **The potential cost of a full thrombophilia screen** £250.82, £323.56 **$410,92** Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx **Cost of the health outcomes:**(9) - Recurrent VTE: 11,000 to 15,000 USD - Major bleeding: 11,000 to 22,000 USD **Cost of interventions:**(10) - Dabigatran: Cost per month: $300.44–$600.88 USD - Rivaroxaban: Cost per month: $300.42–$600.84 USD - Apixaban: Cost per month: $300.44–$600.88	**The panel considered the following cost ranges:** - Cost for testing: $400 -$2,000 per patient - Cost for treatment: $1,000-$ 4,500 per patient per year In assessing the resources required the panel considered that the intervention (testing and treating only patients positive for thrombophilia) added the cost for testing all patients but "saved" the cost of treatment avoided in the patients negative for thrombophilia. The panel did not consider the costs for recurrent clots or for bleeding events.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	In a **cost-effectiveness** analysis using a Markov state transition model, strategies of testing or not testing for hypercoagulable state followed by anticoagulation for 6 to 36 months were compared in patients with idiopathic deep vein thrombosis. Testing followed by 24 months of anticoagulation in patients with hypercoagulable condition was more cost-effective ($54,820; 23,76 QALY) than usual care (6 months of anticoagulation without testing ($55,260; 23,72 QALY).(11) **Cost-effectiveness** analysis, using a decision analysis, with a Markov state transition model, the strategies that explored testing patients who have survived a 1st venous thromboembolic event for the factor V Leiden mutation:(12) 1) Standard anticoagulant therapy for 6 months without testing: $10,392 2) Testing and treating all patients found to have the factor V leiden mutation with 3 years (36 months) of anticoagulation therapy : $9,676 3) Testing and treating all carriers with lifelong anticoagulation therapy: $13,179 Sensitivity analysis (Constant risk model of recurrent VTE): favored the 3rd strategy. Marginal cost-effectiveness ratio was highly dependent on the rate of recurrent VTE, the risk of major hemorrhage, prevalence of factor V Leiden, patient age, and the efficacy of anticoagulation therapy. The results of the cost analysis indicated that **reduced or eliminated FVL and PG mutation testing in patients with a first unprovoked VTE is likely to result in cost savings** for jurisdictions that currently fund these tests. The magnitude of savings is dependent on a number of factors that may vary across jurisdictions including test costs and the extent to which clinicians modify the duration of anticoagulation therapy after VTE based on test results in current clinical practice.(13)	The evidence shows that testing might be cost-effective when comparing with stopping the treatment, but the magnitude of the effect varies across studies.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia	The panel considered that the health system/service coverage/access to care will be the main aspect affecting health equity. USA is an example where promotion of testing that is not covered by insurance would generate inequities. I.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies.

	(factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(14)	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Research studies suggested the following regarding acceptability and barriers associated with testing and treatment: **Patients**: A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(15) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(16) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers**: A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(17) **Payers**: At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	The panel considered testing acceptable for many doctors, although maybe not for all. Patients are in general willing to undergo thrombophilia testing when testing is proposed by their doctor.

Feasibility

Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(18) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending.(19) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombobin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(20) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(21) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(22)	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation. External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know

	JUDGEMENT						
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

After completion of primary treatment in patients with unprovoked symptomatic VTE, the ASH guideline panel suggests not testing for thrombophilia to guide the duration of anticoagulant treatment, and using indefinite anticoagulant treatment in all patients (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:

- A strategy with testing for thrombophilia would mean that positive patients would receive indefinite anticoagulant treatment, and negative patients would stop anticoagulant treatment.

- This recommendation refers to testing for inherited and acquired types of thrombophilia.

Justification

The panel's main consideration in supporting this recommendation is that the increase in the risk of VTE recurrence in patients negative for thrombophilia outweighs the decrease in the risk of major bleeding and does not justify testing and limiting anticoagulant treatment duration.

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation. Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

Randomized controlled trials comparing testing vs no testing would be ideal but have shown to be difficult to perform.(Cohn 2008, Cohn 2012) The second best option would be pragmatic non-randomized controlled studies comparing in patients with unprovoked VTE the clinical outcomes of non-tested patients undergoing life-long treatment and tested patients treated according to the test results.(Coppens 2008)

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
7. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
8. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
9. Grosse, S. D., Nelson, R. E., Nyarko, K. A., Richardson, L. C., Raskob, G. E.. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res; Jan 2016.
10. Biskupiak, J., Ghate, S. R., Jiao, T., Brixner, D.. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. J Manag Care Pharm; Nov-Dec 2013.
11. Auerbach, A. D., Sanders, G. D., Hambleton, J.. Cost-effectiveness of testing for hypercoagulability and effects on treatment strategies in patients with deep vein thrombosis. Am J Med; Jun 15 2004.
12. Eckman, M. H., Singh, S. K., Erban, J. K., Kao, G.. Testing for factor V Leiden in patients with pulmonary or venous thromboembolism: a cost-effectiveness analysis. Med Decis Making; Mar-Apr 2002.
13. CADTH, . Effectiveness of Factor V Leiden and Prothrombin Mutation Testing in Patients Presenting With a First Unprovoked Venous Thromboembolic Episode: A Systematic Review and Economic Analysis. 2015.
14. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
15. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
16. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
17. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
18. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
19. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
20. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
21. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
22. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In patients with unprovoked symptomatic venous thromboembolism who completed primary treatment, should thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia compared to no thrombophilia testing and indefinite anticoagulant treatment in all be used?

Setting:

Bibliography: See reference list and footnotes.[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Recurrent VTE (assessed with: any DVT or PE)									
25 [a,b,c,d,e,f,g]	observational studies	not serious	serious	serious [h]	serious [i]	none	When testing 1,000 patients who completed primary treatment of unprovoked symptomatic VTE for any type of thrombophilia and only treating the 380 positives with indefinite anticoagulation (ranging from 216 to 595), 57 VTE recurrences will occur per year (ranging from 40 to 77). When not testing 1,000 patients for thrombophilia and treating all of them with indefinite anticoagulation, 15 VTE recurrences will occur per year (95% CI: 10 to 23). Therefore, a thrombophilia testing strategy is associated with 620 fewer patients treated with indefinite anticoagulation (ranging from 405 to 784) and **42 more VTE recurrences (ranging from 17 to 67)** per 1,000 patients per year compared with a no testing strategy. [j]	⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding - Low risk (0.5% per year)[k]									
32 [c,d,l,m,n]	observational studies	not serious	not serious	serious [o]	not serious	none	When testing 1,000 patients who completed primary treatment of unprovoked symptomatic VTE, and who are at low risk of major bleeding, for any type of thrombophilia and only treating the 380 positives with indefinite anticoagulation (ranging from 216 to 595), 7 major bleedings will occur per year (ranging from 6 to 8). When not testing 1,000 patients for thrombophilia and treating all of them with indefinite anticoagulation, 11 major bleedings will occur per year (95% CI: 7-17). Therefore, a thrombophilia testing strategy is associated with 620 fewer patients treated with indefinite anticoagulation (ranging from 405 to 784) and **4 fewer major bleedings (ranging from 1 to 9)** per 1,000 patients per year compared with a no testing strategy. [p]	⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding - High risk (1.5% per year)[q]									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
32 [c,d,l,m,r]	observational studies	not serious	not serious	serious [o]	serious [i]	none	When testing 1,000 patients who completed primary treatment of unprovoked symptomatic VTE, and who are at high risk of major bleeding, for any type of thrombophilia and only treating the 380 positives with indefinite anticoagulation, (ranging from 216 to 595), 22 major bleedings will occur per year (ranging from 19 to 23). When not testing 1,000 patients for thrombophilia and treating all of them with indefinite anticoagulation, 33 major bleedings will occur per year (95% CI: 21-50). Therefore, a thrombophilia testing strategy is associated with 620 fewer patients treated with indefinite anticoagulation (ranging from 405 to 784) and **11 fewer major bleedings (ranging from 2 to 28)** per 1,000 patients per year compared with a no testing strategy. [s]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE recurrence, 1 systematic review; Prevalence, 20 studies; Risk association for thrombophilia positive versus negative, 6 studies (all also reported Prevalence); Extended anticoagulation effect, 4 RCTs

b. Overall risk for VTE recurrence: Khan 2019

c. Thrombophilia prevalence, used for calculation: Bezemer 2009, Cebi 2009, Di Minno 2014, Garcia-Fuster 2005, Heit 2010, Kearon 1999, Kearon 2018, Lim 2017, Mello 2010, Meyer 2015, Olie 2011, Palareti 2003, Prandoni 2007, Roldan 2009, Rossi 2008, Santamaria 2005, Schattner 1997, Schulman 2006, Sundquist 2015, Weingarz 2015

d. Prevalence of specific thrombophilia types, used to verify calculation estimate: Ahmad 2016, Ahmad 2016, Ahmad 2017, Asim 2017, Baarslag 2004, Baglin 2003, Brouwer 2009, Bruwer 2016, Christiansen 2005, De Stefano 1999, De Stefano 2006, Eichinger 1999, Eichinger 2002, Eischer 2017, Gonzalez-Porras 2006, Heijboer 1990, Hirmerova 2014, Hoibraaten 2000, Kearon 2008, Laczkovics 2007, Lee 2017, Lijfering 2010, Lindmarker 1999, Marcucci 2003, Mateo 1997, Miles 2001, Ridker 1995, Rodger 2008, Roupie 2016, Rupa-Matysek 2014, Simioni 2000, Sonnevi 2013, Strandberg 2007, Sveinsdottir 2012, The Procare group 2003, Wahlander 2006

e. Thrombophilia positive vs negative risk association, used for calculation: Kearon, 1999, Kearon 2018, Mello 2010, Santamaria 2005, Schulman 2006, Weingarz 2015

f. Risk association for specific thrombophilia types, used to verify calculation estimate: Baglin 2003, Brouwer 2009, Christiansen 2005, De Stefano 1999, De Stefano 2006, Di Minno 2014, Eichinger 2002, Gonzalez-Porras 2006, Hoibraaten 2000, Lijfering 2010, Lindmarker 1999, Marcucci 2003, Miles 2001, Palareti 2003, Prandoni 2007, Ridker 1995, Rodger 2008, Schattner 1997, Simioni 2000, Strandberg 2007, Wahlander 2006

g. Effect of extended anticoagulation treatment, used in calculation: Agnelli 2013, Bauersachs 2010, Schulman 2003, Schulman 2013

h. The effect was indirectly calculated using separate studies for thrombophilia prevalence, relative risk of thrombophilia positives vs negatives, and the effect of treatment.

i. There is a clinically important difference between the smallest and largest possible effect of the testing strategy.

j. Based on the following estimates: Overall risk for VTE recurrence, 100 per 1,000; Prevalence of any thrombophilia, 38.0% (min 21.6 - max 59.5); Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 1.65 (95%CI: 1.28-2.47); Relative risk of VTE recurrence with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.16 (0.11-0.22). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

k. Among RCTs assessing the effect of extended treatment against limited treatment, the lowest observed rate of major bleeding with limited treatment was 0.5% (Agnelli 2001)

l. Number of studies used in calculations: Overall risk, 1 RCT; Prevalence, 20 studies; Extended anticoagulation effect, 11 RCTs

m. Effect of extended anticoagulation treatment, used in calculation: Agnelli 2001, Agnelli 2003, Agnelli 2013, Bauersachs 2010, Couturaud 2015, Eischer 2009, Kearon 1999, Palareti 2006, Ridker 2003, Schulman 2003, Schulman 2013

n. Overall risk for Major bleeding: Agnelli 2001

o. The effect was indirectly calculated using separate studies for thrombophilia prevalence and the effect of treatment.

p. Based on the following estimates: Overall risk for Major bleeding of 5 per 1,000; Prevalence of any thrombophilia, 38.0% (21.6-59.5); Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 2.17 (1.40-3.35). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the smallest treatment effect (lower CI).

q. Among RCTs assessing the effect of extended treatment against limited treatment, the highest observed rate of major bleeding with limited treatment was 1.5% (Agnelli 2013)

r. Overall risk for Major bleeding: Agnelli 2013

s. Based on the following estimates: Overall risk for Major bleeding of 15 per 1,000; Prevalence of any thrombophilia, 38.0% (21.6-59.5); Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 2.21 (1.42-3.44). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the smallest treatment effect (lower CI).

References

1. Agnelli, G., Buller, H. R., Cohen, A., Curto, M., Gallus, A. S., Johnson, M., Porcari, A., Raskob, G. E., Weitz, J. I., Investigators, Amplify-Ext. Apixaban for extended treatment of venous thromboembolism. N Engl J Med; Feb 21 2013.

2. Agnelli, G., Prandoni, P., Becattini, C., Silingardi, M., Taliani, M. R., Miccio, M., Imberti, D., Poggio, R., Ageno, W., Pogliani, E., Porro, F., Zonzin, P., Warfarin Optimal Duration Italian Trial, Investigators. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med; Jul 1 2003.

3. Agnelli, G., Prandoni, P., Santamaria, M. G., Bagatella, P., Iorio, A., Bazzan, M., Moia, M., Guazzaloca, G., Bertoldi, A., Tomasi, C., Scannapieco, G., Ageno, W., Warfarin Optimal Duration Italian Trial, Investigators. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med; Jul 19 2001.

4. Ahmad, A., Sundquist, K., Zoller, B., Dahlback, B., Svensson, P. J., Sundquist, J., Memon, A. A.. Identification of polymorphisms in Apolipoprotein M gene and their relationship with risk of recurrent venous thromboembolism. Thromb Haemost; Aug 30 2016.

5. Asim, M., Al-Thani, H., El-Menyar, A.. Recurrent Deep Vein Thrombosis After the First Venous Thromboembolism Event: A Single-Institution Experience. Med Sci Monit; May 20 2017.

6. Baarslag, H. J., Koopman, M. M., Hutten, B. A., Linthorst Homan, M. W., Buller, H. R., Reekers, J. A., van Beek, E. J.. Long-term follow-up of patients with suspected deep vein thrombosis of the upper extremity: survival, risk factors and post-thrombotic syndrome. Eur J Intern Med; Dec 2004.

7. Baglin, T., Luddington, R., Brown, K., Baglin, C.. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet; Aug 16 2003.

8. Bezemer, I. D., van der Meer, F. J., Eikenboom, J. C., Rosendaal, F. R., Doggen, C. J.. The value of family history as a risk indicator for venous thrombosis. Archives of Internal Medicine; Mar 23 2009.

9. Brouwer, J. L., Lijfering, W. M., Ten Kate, M. K., Kluin-Nelemans, H. C., Veeger, N. J., van der Meer, J.. High long-term absolute risk of recurrent venous thromboembolism in patients with hereditary deficiencies of protein S, protein C or antithrombin. Thromb Haemost; Jan 2009.

10. Bruwer, G., Limperger, V., Kenet, G., Klostermeier, U. C., Shneyder, M., Degenhardt, F., Finckh, U., Heller, C., Holzhauer, S., Trappe, R., Kentouche, K., Knoefler, R., Kurnik, K., Krumpel, A., Lauten, M., Manner, D., Mesters, R., Junker, R., Nowak-Gottl, U.. Impact of high risk thrombophilia status on recurrence among children and adults with VTE: An observational multicenter cohort study. Blood Cells Mol Dis; Nov 2016.

11. Cebi, N., Tanriverdi, S.. Aetiology of deep vein thrombosis in 63 turkish patients. Turkish Journal of Medical Sciences; April 2009.

12. Christiansen, S. C., Cannegieter, S. C., Koster, T., Vandenbroucke, J. P., Rosendaal, F. R.. Thrombophilia, clinical factors, and recurrent venous thrombotic events. Jama; May 18 2005.

13. Couturaud, F., Sanchez, O., Pernod, G., Mismetti, P., Jego, P., Duhamel, E., Provost, K., dit Sollier, C. B., Presles, E., Castellant, P., Parent, F., Salaun, P. Y., Bressollette, L., Nonent, M., Lorillon, P., Girard, P., Lacut, K., Guegan, M., Bosson, J. L., Laporte, S., Leroyer, C., Decousus, H., Meyer, G., Mottier, D., Investigators, Padis-Pe. Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism: The PADIS-PE Randomized Clinical Trial. Jama; Jul 7 2015.

14. De Stefano, V., Martinelli, I., Mannucci, P. M., Paciaroni, K., Chiusolo, P., Casorelli, I., Rossi, E., Leone, G.. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med; Sep 9 1999.

15. De Stefano, V., Simioni, P., Rossi, E., Tormene, D., Za, T., Pagnan, A., Leone, G.. The risk of recurrent venous thromboembolism in patients with inherited deficiency of natural anticoagulants antithrombin, protein C and protein S. Haematologica; May 2006.

16. Di Minno, M. N., Dentali, F., Lupoli, R., Ageno, W.. Mild antithrombin deficiency and risk of recurrent venous thromboembolism: a prospective cohort study. Circulation; Jan 28 2014.

17. Eichinger, S., Minar, E., Hirschl, M., Bialonczyk, C., Stain, M., Mannhalter, C., Stumpflen, A., Schneider, B., Lechner, K., Kyrle, P. A.. The risk of early recurrent venous thromboembolism after oral anticoagulant therapy in patients with the G20210A transition in the prothrombin gene. Thromb Haemost; Jan 1999.

18. Eichinger, S., Weltermann, A., Mannhalter, C., Minar, E., Bialonczyk, C., Hirschl, M., Schonauer, V., Lechner, K., Kyrle, P. A.. The risk of recurrent venous thromboembolism in heterozygous carriers of factor V Leiden and a first spontaneous venous thromboembolism. Archives of Internal Medicine; Nov 11 2002.

19. Eischer, L., Kammer, M., Traby, L., Kyrle, P. A., Eichinger, S.. Risk of cancer after anticoagulation in patients with unprovoked venous thromboembolism: an observational cohort study. Journal of Thrombosis and Haemostasis; July 2017.

20. Eischer, L., Gartner, V., Schulman, S., Kyrle, P. A., Eichinger, S., investigators, Aurec-Fviii. 6 versus 30 months anticoagulation for recurrent venous thrombosis in patients with high factor VIII. Ann Hematol; May 2009.

21. Garcia-Fuster, M. J., Forner, M. J., Fernandez, C., Gil, J., Vaya, A., Maldonado, L.. Long-term prospective study of recurrent venous thromboembolism in patients younger than 50 years. Pathophysiol Haemost Thromb; 2005.

22. Gonzalez-Porras, J. R., Garcia-Sanz, R., Alberca, I., Lopez, M. L., Balanzategui, A., Gutierrez, O., Lozano, F., San Miguel, J.. Risk of recurrent venous thrombosis in patients with G20210A mutation in the prothrombin gene or factor V Leiden mutation. Blood Coagul Fibrinolysis; Jan 2006.

23. Group, The,Procare. Is recurrent venous thromboembolism more frequent in homozygous patients for the factor V Leiden mutation than in heterozygous patients?. Blood Coagulation and Fibrinolysis; September 2003.

24. Heijboer, H., Brandjes, D. P., Buller, H. R., Sturk, A., ten Cate, J. W.. Deficiencies of coagulation-inhibiting and fibrinolytic proteins in outpatients with deep-vein thrombosis. N Engl J Med; Nov 29 1990.

25. Heit, J. A., Beckman, M. G., Bockenstedt, P. L., Grant, A. M., Key, N. S., Kulkarni, R., Manco-Johnson, M. J., Moll, S., Ortel, T. L., Philipp, C. S., Thrombosis, C.,D.,C., Hemostasis Centers, Research, Prevention, Network. Comparison of characteristics from White- and Black-Americans with venous thromboembolism: a cross-sectional study. Am J Hematol; Jul 2010.

26. Hirmerova, J., Seidlerova, J., Subrt, I.. The association of factor V Leiden with various clinical patterns of venous thromboembolism-the factor V Leiden paradox. Qjm; Sep 2014.

27. Hoibraaten, E., Qvigstad, E., Arnesen, H., Larsen, S., Wickstrom, E., Sandset, P. M.. Increased risk of recurrent venous thromboembolism during hormone replacement therapy--results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). Thromb Haemost; Dec 2000.

28. Investigators, Einstein, Bauersachs, R., Berkowitz, S. D., Brenner, B., Buller, H. R., Decousus, H., Gallus, A. S., Lensing, A. W., Misselwitz, F., Prins, M. H., Raskob, G. E., Segers, A., Verhamme, P., Wells, P., Agnelli, G., Bounameaux, H., Cohen, A., Davidson, B. L., Piovella, F., Schellong, S.. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med; Dec 23 2010.

29. Kearon, C., Gent, M., Hirsh, J., Weitz, J., Kovacs, M. J., Anderson, D. R., Turpie, A. G., Green, D., Ginsberg, J. S., Wells, P., MacKinnon, B., Julian, J. A.. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med; Mar 25 1999.

30. Kearon, C., Julian, J. A., Kovacs, M. J., Anderson, D. R., Wells, P., Mackinnon, B., Weitz, J. I., Crowther, M. A., Dolan, S., Turpie, A. G., Geerts, W., Solymoss, S., van Nguyen, P., Demers, C., Kahn, S. R., Kassis, J., Rodger, M., Hambleton, J., Gent, M., Ginsberg, J. S., Investigators, Elate. Influence of thrombophilia on risk of recurrent venous thromboembolism while on warfarin: results from a randomized trial. Blood; Dec 1 2008.

31. Kearon, C., Parpia, S., Spencer, F. A., Baglin, T., Stevens, S. M., Bauer, K. A., Lentz, S. R., Kessler, C. M., Douketis, J. D., Moll, S., Kaatz, S., Schulman, S., Connors, J. M., Ginsberg, J. S., Spadafora, L., Bhagirath, V., Liaw, P. C., Weitz, J. I., Julian, J. A.. Antiphospholipid antibodies and recurrent thrombosis after a first unprovoked venous thromboembolism. Blood; May 10 2018.

32. Khan, F., Rahman, A., Carrier, M., Kearon, C., Weitz, J. I., Schulman, S., Couturaud, F., Eichinger, S., Kyrle, P. A., Becattini, C., Agnelli, G., Brighton, T. A., Lensing, A. W. A., Prins, M. H., Sabri, E., Hutton, B., Pinede, L., Cushman, M., Palareti, G., Wells, G. A., Prandoni, P., Buller, H. R., Rodger, M. A., Collaborators, Marvelous. Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: systematic review and meta-analysis. Bmj; Jul 24 2019.

33. Laczkovics, C., Grafenhofer, H., Kaider, A., Quehenberger, P., Simanek, R., Mannhalter, C., Lechner, K., Pabinger, I.. Risk of recurrence after a first venous thromboembolic event in young women. Haematologica; Sep 2007.

34. Lee, S. Y., Kim, E. K., Kim, M. S., Shin, S. H., Chang, H., Jang, S. Y., Kim, H. J., Kim, D. K.. The prevalence and clinical manifestation of hereditary thrombophilia in Korean patients with unprovoked venous thromboembolisms. PLoS ONE [Electronic Resource]; 2017.

35. Lijfering, W. M., Middeldorp, S., Veeger, N. J., Hamulyak, K., Prins, M. H., Buller, H. R., van der Meer, J.. Risk of recurrent venous thrombosis in homozygous carriers and double heterozygous carriers of factor V Leiden and prothrombin G20210A. Circulation; Apr 20 2010.

36. Lim, H. Y., Chua, C. C., Tacey, M., Sleeman, M., Donnan, G., Nandurkar, H., Ho, P.. Venous thromboembolism management in Northeast Melbourne: how does it compare to international guidelines and data?. Intern Med J; Sep 2017.

37. Lindmarker, P., Schulman, S., Sten-Linder, M., Wiman, B., Egberg, N., Johnsson, H.. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. DURAC Trial Study Group. Duration of Anticoagulation. Thromb Haemost; May 1999.

38. Marcucci, R., Liotta, A. A., Cellai, A. P., Rogolino, A., Gori, A. M., Giusti, B., Poli, D., Fedi, S., Abbate, R., Prisco, D.. Increased plasma levels of lipoprotein(a) and the risk of idiopathic and recurrent venous thromboembolism. Am J Med; Dec 1 2003.

39. Mateo, J., Oliver, A., Borrell, M., Sala, N., Fontcuberta, J.. Laboratory evaluation and clinical characteristics of 2,132 consecutive unselected patients with venous thromboembolism--results of the Spanish Multicentric Study on Thrombophilia (EMET-Study). Thromb Haemost; Mar 1997.

40. Mello, T. B., Orsi, F. L., Montalvao, S. A., Ozelo, M. C., de Paula, E. V., Annichinno-Bizzachi, J. M.. Long-term prospective study of recurrent venous thromboembolism in a Hispanic population. Blood Coagul Fibrinolysis; Oct 2010.

41. Meyer, M. R., Witt, D. M., Delate, T., Johnson, S. G., Fang, M., Go, A., Clark, N. P.. Thrombophilia testing patterns amongst patients with acute venous thromboembolism. Thromb Res; Dec 2015.

42. Miles, J. S., Miletich, J. P., Goldhaber, S. Z., Hennekens, C. H., Ridker, P. M.. G20210A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. J Am Coll Cardiol; Jan 2001.

43. Olie, V., Plu-Bureau, G., Conard, J., Horellou, M. H., Canonico, M., Scarabin, P. Y.. Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. Menopause; May 2011.

44. Palareti, G., Cosmi, B., Legnani, C., Tosetto, A., Brusi, C., Iorio, A., Pengo, V., Ghirarduzzi, A., Pattacini, C., Testa, S., Lensing, A. W., Tripodi, A., Investigators, Prolong. D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med; Oct 26 2006.

45. Palareti, G., Legnani, C., Cosmi, B., Valdre, L., Lunghi, B., Bernardi, F., Coccheri, S.. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation; Jul 22 2003.

46. Prandoni, P., Noventa, F., Ghirarduzzi, A., Pengo, V., Bernardi, E., Pesavento, R., Iotti, M., Tormene, D., Simioni, P., Pagnan, A.. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica; Feb 2007.

47. Ridker, P. M., Miletich, J. P., Stampfer, M. J., Goldhaber, S. Z., Lindpaintner, K., Hennekens, C. H.. Factor V Leiden and risks of recurrent idiopathic venous thromboembolism. Circulation; Nov 15 1995.

48. Rodger, M. A., Kahn, S. R., Wells, P. S., Anderson, D. A., Chagnon, I., Le Gal, G., Solymoss, S., Crowther, M., Perrier, A., White, R., Vickars, L., Ramsay, T., Betancourt, M. T., Kovacs, M. J.. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. Cmaj; Aug 26 2008.

49. Roldan, V., Lecumberri, R., Munoz-Torrero, J. F., Vicente, V., Rocha, E., Brenner, B., Monreal, M., Investigators, Riete. Thrombophilia testing in patients with venous thromboembolism. Findings from the RIETE registry. Thromb Res; Jun 2009.

50. Roupie, A. L., Dossier, A., Goulenok, T., Perozziello, A., Papo, T., Sacre, K.. First venous thromboembolism in admitted patients younger than 50years old. Eur J Intern Med; Oct 2016.

51. Rossi, E., Za, T., Ciminello, A., Leone, G., De Stefano, V.. The risk of symptomatic pulmonary embolism due to proximal deep venous thrombosis differs in patients with different types of inherited thrombophilia. Thromb Haemost; Jun 2008.

52. Rupa-Matysek, J., Gil, L., Wojtasinska, E., Ciepluch, K., Lewandowska, M., Komarnicki, M.. The relationship between mean platelet volume and thrombosis recurrence in patients diagnosed with antiphospholipid syndrome. Rheumatol Int; Nov 2014.

53. Santamaria, M. G., Agnelli, G., Taliani, M. R., Prandoni, P., Moia, M., Bazzan, M., Guazzaloca, G., Ageno, W., Bertoldi, A., Silingardi, M., Tomasi, C., Ambrosio, G. B., Warfarin Optimal Duration Italian Trial, Investigators. Thrombophilic abnormalities and recurrence of venous thromboembolism in patients treated with standardized anticoagulant treatment. Thromb Res; 2005.

54. Schattner, A., Kasher, I., Berrebi, A.. Causes and outcome of deep-vein thrombosis in otherwise-healthy patients under 50 years. Qjm; Apr 1997.

55. Schulman, S., Kearon, C., Kakkar, A. K., Schellong, S., Eriksson, H., Baanstra, D., Kvamme, A. M., Friedman, J., Mismetti, P., Goldhaber, S. Z., Investigators, Re-Medy,Trial, Investigators, Re-Sonate,Trial. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med; Feb 21 2013.

56. Schulman, S., Lindmarker, P., Holmstrom, M., Larfars, G., Carlsson, A., Nicol, P., Svensson, E., Ljungberg, B., Viering, S., Nordlander, S., Leijd, B., Jahed, K., Hjorth, M., Linder, O., Beckman, M.. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. Journal of Thrombosis & Haemostasis; Apr 2006.

57. Schulman, S., Wahlander, K., Lundstrom, T., Clason, S. B., Eriksson, H., Investigators, Thrive,Iii. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. N Engl J Med; Oct 30 2003.

58. Simioni, P., Prandoni, P., Lensing, A. W., Manfrin, D., Tormene, D., Gavasso, S., Girolami, B., Sardella, C., Prins, M., Girolami, A.. Risk for subsequent venous thromboembolic complications in carriers of the prothrombin or the factor V gene mutation with a first episode of deep-vein thrombosis. Blood; Nov 15 2000.

59. Sonnevi, K., Tchaikovski, S. N., Holmstrom, M., Antovic, J. P., Bremme, K., Rosing, J., Larfars, G.. Obesity and thrombin-generation profiles in women with venous thromboembolism. Blood Coagul Fibrinolysis; Jul 2013.

60. Strandberg, K., Svensson, P. J., Ohlin, A. K.. Venous thromboembolism in carriers of the Factor V Leiden mutation and in patients without known thrombophilic risk factor; prediction of recurrence and APC-PCI complex concentration and/or soluble thrombomodulin antigen and activity. Thromb Res; 2007.

61. Sundquist, K., Sundquist, J., Svensson, P. J., Zoller, B., Memon, A. A.. Role of family history of venous thromboembolism and thrombophilia as predictors of recurrence: a prospective follow-up study. Journal of Thrombosis & Haemostasis; Dec 2015.

62. Sveinsdottir, S. V., Saemundsson, Y., Isma, N., Gottsater, A., Svensson, P. J.. Evaluation of recurrent venous thromboembolism in patients with Factor V Leiden mutation in heterozygous form. Thromb Res; Sep 2012.

63. Vitovec, M., Golan, L., Roztocil, K., Linhart, A.. The development of persistent thrombotic masses in patients with deep venous thrombosis randomized to long-term anticoagulation treatment. Vasa; Aug 2009.

64. Wahlander, K., Eriksson, H., Lundstrom, T., Billing Clason, S., Wall, U., Nystrom, P., Wessman, P., Schulman, S., Investigators, Thrive,Iii. Risk of recurrent venous thromboembolism or bleeding in relation to thrombophilic risk factors in patients receiving ximelagatran or placebo for long-term secondary prevention of venous thromboembolism. Br J Haematol; Apr 2006.

65. Weingarz, L., Schindewolf, M., Schwonberg, J., Hecking, C., Wolf, Z., Erbe, M., Lindhoff-Last, E., Linnemann, B.. Thrombophilia and risk of VTE recurrence according to the age at the time of first VTE manifestation. Vasa; Jul 2015.

QUESTION

Should thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia vs. no thrombophilia testing and stopping anticoagulant treatment in all be used for patients with symptomatic venous thromboembolism provoked by surgery who completed primary treatment?

POPULATION:	patients with symptomatic venous thromboembolism provoked by surgery who completed primary treatment
INTERVENTION:	thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia
COMPARISON:	no thrombophilia testing and stopping anticoagulant treatment in all
MAIN OUTCOMES:	Recurrent VTE; Major bleeding - Low (0.5% per year); Major bleeding - High (1.5% per year);
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Thrombophilia, either acquired or inherited, can be identified in many patients presenting with venous thromboembolism (VTE). The currently most commonly tested inherited thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. The current guideline aims to assess whether identifying patients positive for one or more of these defects allows management options which reduce patient important outcomes. Usually, 3 months of anticoagulant treatment is considered sufficient in the setting of VTE provoked by surgery (within 1 month of surgery), due to the low risk of VTE recurrence. In this setting, thrombophilia testing might be considered to identify patients at higher risk of VTE recurrence, particularly in young patients, those with recurrent episodes of provoked thrombosis, or having a positive family history for VTE or thrombophilia. Although testing patients with provoked VTE may have a moderate chance of finding a positive test result, the true question is whether a positive test result should alter anticoagulant management. This question addresses whether thrombophilia testing and subsequent indefinite duration of anticoagulant treatment in patients positive for thrombophilia improves patient important outcomes in patients with VTE provoked by surgery, as compared with no thrombophilia testing and treating all patients with definite duration anticoagulant treatment. Since no randomized controlled trials have addressed this question, we used a modeling approach based on observational evidence for baseline risk of patient-important outcomes, prevalence of thrombophilia and increase in the risk of associated events with thrombophilia, and RCTs based evidence for the effect of extended anticoagulation on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Evidence Profile.	Desirable effect = preventing VTE recurrence. VTE recurrences would be avoided in patients who are positive for thrombophilia by extending their anticoagulation treatment. The panel considered a reduction in VTE recurrence of 5% to be the threshold to consider the effect Large, and a 2% reduction to be Small in the overall population of interest. However, the panel also discussed that a 2% reduction may be considered Large in subgroups that are at lower risk, such as young women.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	See Evidence Profile.	Undesirable effect = causing major bleeding. Major bleedings would be caused in patients who are positive for thrombophilia by extending their anticoagulation treatment.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows using a scale from 0 (worst possible scenario, usually death), to 1 (best possible scenario, usually perfect health):** **Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(1, 2, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3) **Gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off)(2, 3) **Minor intracranial bleeding event:** 0.75 (standard gamble)(2) **Major intracranial bleeding event:** 0.15 (standard gamble)(2) **Anticoagulant therapy** Patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome.(3) Patients would favor efficacy and safety over convenience of route of administration.(6) Also, patients would like to avoid adverse events but most of them are “not afraid of” the adverse events.(6, 7, 8)	The panel considered that clinicians may value avoiding major bleeding more (they do not want to cause harm), while patients may value avoiding VTE events more (they may prefer avoiding a recurrence of blood clots).

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel discussed to choose between 'Does not favor either the intervention or the comparison' and 'Probably favors the comparison'. No studies assessed extended anticoagulation as life-long treatment. No studies assessed indefinite anticoagulation as life-long treatment. The panel observed that the appraisal of the comparison of the two interventions (testing and treating positives vs treating none) was limited by the absence of studies comparing extended anticoagulation as life-long treatment versus no anticoagulation, which the panel had to extrapolate.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		**The panel considered the following cost ranges:** - Cost for testing: $400 -$2,000 per patient - Cost for treatment: $1,000-$ 4,500 per patient per year In assessing the resources required the panel considered that the intervention added the cost for testing all patients and treating the patients positive for thrombophilia. The panel did not consider the costs for recurrent clots or for bleeding events.

Intervention Costs:

Test (source)	Approximate Cost (2005)	Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016)	(14/12/2016) £1 = $1,27
Full Blood Count	£2.55	£3.29	$4,18
Protein C	£11.67	£15.5	$19,12
Free Protein S	£11.67	£15.5	$19,12
Antithrombin	£11.67	£15.5	$19,12
APCR	£10.73	£13.84	$17,58
Factor V Leiden	£85.00	£109.65	$141,45
Prothrombin gene mutation	£85.00	£109.65	$141,45
Lupus Anticoagulant	£10.73	£13.84	$17,58
Antiphospholipid antibodies	£12.30	£15.87	$20,15
Anti Beta-2 GP1 antibody	£9.50	£12.25	$15,81
The potential cost of a full thrombophilia screen	£250.82,	£323.56	$410,92

Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx

Cost of the health outcomes:(9)

- **Recurrent VTE:** 11,000 to 15,000 USD

- **Major bleeding:** 11,000 to 22,000 USD

Cost of interventions:(10)

- **Dabigatran:** Cost per month: $300.44–$600.88 USD

- **Rivaroxaban:** Cost per month: $300.42–$600.84 USD

- **Apixaban:** Cost per month: $300.44–$600.88

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	Three studies evaluated the cost-effectiveness of thrombophilia testing and different management strategies in patients with a first venous thromboembolism.(11, 12, 13) All three studies found thrombophilia testing cost-effective, although the uncertainty was high in general due to prevalence of mutation and the variability in the recurrence rate (which depends on the type of thrombophilia), risk of adverse events such as major haemorrhage, age or efficacy of the anticoagulant therapy, among others. Cost per quality-adjusted life year (QALY) for the testing and treatment strategies varied between the 3 studies and in sensitivity analyses (Simpson 2009: approximately £20,000/QALY for patients with PE or DVT; Marchetti 2001: $13,624/QALY for any VTE, Eckman 2002: $16,823/QALY for any VTE) One study evaluated thrombophilia testing using a panel of thrombophilia tests that included Factor V Leiden, Prothrombin G20210A, APC resistance, Protein C, Protein S, antithrombin levels, antiphospholipid antibodies and homocysteine levels, dysfibrinogenaemia, and levels of factor VIII, factor IX and factor XI.(13) Another cost-effectiveness study included only screening for FVL and G20210A prothrombin mutations,(11) and the third study included testing for FVL mutation.(12)	The panel made this judgment based on extrapolation of cost-effectiveness evidence for patients with any type of VTE, as shown here.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(14)	The panel considered that the health system/service coverage/access to care will be the main aspect affecting health equity. USA is an example where promotion of testing that is not covered by insurance would generate inequities. I.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies. Also, the additional cost for indefinite anticoagulant treatment of the patients positive for thrombophilia may or may not be covered.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Research studies suggested the following regarding acceptability and barriers associated with testing and treatment:	The panel considered testing acceptable for many doctors, although maybe not for all. Patients are in general willing to undergo thrombophilia testing when testing is proposed by their doctor.

	Patients: A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(15) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(16) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers**: A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(17) **Payers**: At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(18)	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation. External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories.

	Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending.(19) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(20) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(21) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(22)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know

	JUDGEMENT						
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

After completion of primary treatment for patients with symptomatic VTE provoked by surgery, the ASH guideline panel suggests not testing for thrombophilia to guide the duration of anticoagulant treatment, and stopping anticoagulant treatment in all patients (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:

- A strategy with testing for thrombophilia would mean that positive patients would receive indefinite anticoagulant treatment, and negative patients negative would stop anticoagulant treatment.

- This recommendation refers to testing for inherited and acquired types of thrombophilia.

Justification

The panel considered that thrombophilia testing and extending anticoagulant treatment in thrombophilia positives likely has limited benefit in terms of prevention of VTE recurrence that does not outweigh the risk of major bleeding in patients at low risk, and may not justify the costs of extended anticoagulant treatment.

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation. Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

Randomized controlled trials comparing testing vs no testing would be ideal but have shown to be difficult to perform.(Cohn 2008, Cohn 2012) The second best option would be pragmatic non-randomized controlled studies comparing in patients with VTE provoked by surgery the clinical outcomes of non-tested patients undergoing definite treatment and tested patients treated according to the test results.(Coppens 2008)

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
7. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
8. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
9. Grosse, S. D., Nelson, R. E., Nyarko, K. A., Richardson, L. C., Raskob, G. E.. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res; Jan 2016.
10. Biskupiak, J., Ghate, S. R., Jiao, T., Brixner, D.. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. J Manag Care Pharm; Nov-Dec 2013.
11. Marchetti, M., Quaglini, S., Barosi, G.. Cost-effectiveness of screening and extended anticoagulation for carriers of both factor V Leiden and prothrombin G20210A. Qjm; Jul 2001.
12. Eckman, M. H., Singh, S. K., Erban, J. K., Kao, G.. Testing for factor V Leiden in patients with pulmonary or venous thromboembolism: a cost-effectiveness analysis. Med Decis Making; Mar-Apr 2002.
13. Simpson, E. L., Stevenson, M. D., Rawdin, A., Papaioannou, D.. Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis. Health Technol Assess; Jan 2009.
14. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
15. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
16. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
17. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
18. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
19. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
20. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
21. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
22. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In patients with symptomatic venous thromboembolism provoked by surgery who completed primary treatment, should thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia compared to no thrombophilia testing and stopping anticoagulant treatment in all be used?

Setting:

Bibliography: See reference list and footnotes.[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Recurrent VTE (assessed with: any DVT or PE)									
25 [a,b,c,d,e,f,g]	observational studies	not serious	not serious	very serious [h]	not serious	none	When testing 1,000 patients who completed primary treatment of symptomatic VTE provoked by surgery for any type of thrombophilia, and treating the 380 positives with indefinite anticoagulation (ranging from 216 to 595), 6 VTE recurrences will occur per year (ranging from 3 to 8). When not testing 1,000 patients for thrombophilia and stopping treatment in all of them, 10 VTE recurrences will occur per year. Therefore, a thrombophilia testing strategy is associated with 380 more patients treated with indefinite anticoagulation (ranging from 216 to 595) and **4 fewer VTE recurrences (ranging from 2 to 7)** per 1,000 patients per year compared with a no testing strategy. [i]	⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding - Low (0.5% per year)[j]									
32 [c,d,k,l,m]	observational studies	not serious	not serious	serious [n]	not serious	none	When testing 1,000 patients who completed primary treatment of symptomatic VTE provoked by surgery, and who are at low risk of major bleeding, for any type of thrombophilia, and treating the 380 positives with indefinite anticoagulation (ranging from 216 to 595), 7 major bleedings will occur per year (ranging from 5 to 12). When not testing 1,000 patients for thrombophilia and stopping treatment in all of them, 5 major bleedings will occur per year. Therefore, a thrombophilia testing strategy is associated with 380 more patients treated with indefinite anticoagulation and **2 more major bleedings (ranging from 0 to 7)** per 1,000 patients per year compared with a no testing strategy. [o]	⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding - High (1.5% per year)[p]									
32 [c,d,k,l,q]	observational studies	not serious	not serious	serious [n]	not serious	none	When testing 1,000 patients who completed primary treatment of symptomatic VTE provoked by surgery, and who are at high risk of major bleeding, for any type of thrombophilia, and treating the 380 positives with indefinite anticoagulation (ranging from 216 to 595), 22 major bleedings will occur per year (ranging from 16 to 36). When not testing 1,000 patients for thrombophilia and stopping treatment in all of them, 15 major bleedings will occur per year. Therefore, a thrombophilia testing strategy is associated with 380 more patients treated with indefinite anticoagulation and **7 more major bleedings (ranging from 1 to 21)** per 1,000 patients per year compared with a no testing strategy. [r]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE recurrence, 1 systematic review; Prevalence, 20 studies; Risk association for thrombophilia positive versus negative, 6 studies (all also reported Prevalence); Extended anticoagulation effect, 4 RCTs

b. Overall risk for VTE recurrence: Iorio 2010

c. Thrombophilia prevalence, used for calculation: Bezemer 2009, Cebi 2009, Di Minno 2014, Garcia-Fuster 2005, Heit 2010, Kearon 1999, Kearon 2018, Lim 2017, Mello 2010, Meyer 2015, Olie 2011, Palareti 2003, Prandoni 2007, Roldan 2009, Rossi 2008, Santamaria 2005, Schattner 1997, Schulman 2006, Sundquist 2015, Weingarz 2015

d. Prevalence of specific thrombophilia types, used to verify calculation estimate: Ahmad 2016, Ahmad 2016, Ahmad 2017, Asim 2017, Baarslag 2004, Baglin 2003, Brouwer 2009, Bruwer 2016, Christiansen 2005, De Stefano 1999, De Stefano 2006, Eichinger 1999, Eichinger 2002, Eischer 2017, Gonzalez-Porras 2006, Heijboer 1990, Hirmerova 2014, Hoibraaten 2000, Kearon 2008, Laczkovics 2007, Lee 2017, Lijfering 2010, Lindmarker 1999, Marcucci 2003, Mateo 1997, Miles 2001, Ridker 1995, Rodger 2008, Roupie 2016, Rupa-Matysek 2014, Simioni 2000, Sonnevi 2013, Strandberg 2007, Sveinsdottir 2012, The Procare group 2003, Wahlander 2006

e. Thrombophilia positive vs negative risk association, used for calculation: Kearon, 1999, Kearon 2018, Mello 2010, Santamaria 2005, Schulman 2006, Weingarz 2015

f. Risk association for specific thrombophilia types, used to verify calculation estimate: Baglin 2003, Brouwer 2009, Christiansen 2005, De Stefano 1999, De Stefano 2006, Di Minno 2014, Eichinger 2002, Gonzalez-Porras 2006, Hoibraaten 2000, Lijfering 2010, Lindmarker 1999, Marcucci 2003, Miles 2001, Palareti 2003, Prandoni 2007, Ridker 1995, Rodger 2008, Schattner 1997, Simioni 2000, Strandberg 2007, Wahlander 2006

g. Effect of extended anticoagulation treatment, used in calculation: Agnelli 2013, Bauersachs 2010, Schulman 2003, Schulman 2013

h. The effect was indirectly calculated using evidence from an indirect population (patients with any type of VTE), and using separate studies for thrombophilia prevalence, relative risk of thrombophilia positives vs negatives, and the effect of treatment.

i. Based on the following estimates: Overall risk for VTE recurrence, 10 per 1,000; Prevalence of any thrombophilia, 38.0% (min 21.6 - max 59.5); Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 1.65 (95%CI: 1.28-2.47); Relative risk of VTE recurrence with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.15 (0.10-0.23). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, upper CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI)

j. Among RCTs assessing the effect of extended treatment against limited treatment, the lowest observed rate of major bleeding with limited treatment was 0.5% (Agnelli 2001)

k. Number of studies used in calculations: Overall risk, 1 RCT; Prevalence, 20 studies; Extended anticoagulation effect, 11 RCTs

l. Effect of extended anticoagulation treatment, used in calculation: Agnelli 2001, Agnelli 2003, Agnelli 2013, Bauersachs 2010, Couturaud 2015, Eischer 2009, Kearon 1999, Palareti 2006, Ridker 2003, Schulman 2003, Schulman 2013

m. Overall risk for Major bleeding: Agnelli 2001

n. The effect was indirectly calculated using separate studies for thrombophilia prevalence and the effect of treatment.

o. Based on the following estimates: Overall risk for Major bleeding of 5 per 1,000; Prevalence of any thrombophilia, 38.0% (21.6-59.5); Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 2.17 (1.40-3.35). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the smallest treatment effect (lower CI).

p. Among RCTs assessing the effect of extended treatment against limited treatment, the highest observed rate of major bleeding with limited treatment was 1.5% (Agnelli 2013)

q. Overall risk for Major bleeding: Agnelli 2013

r. Based on the following estimates: Overall risk for Major bleeding of 15 per 1,000; Prevalence of any thrombophilia, 38.0% (21.6-59.5); Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 2.17 (1.40-3.35). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the smallest treatment effect (lower CI).

References

1. Agnelli, G., Buller, H. R., Cohen, A., Curto, M., Gallus, A. S., Johnson, M., Porcari, A., Raskob, G. E., Weitz, J. I., Investigators, Amplify-Ext. Apixaban for extended treatment of venous thromboembolism. N Engl J Med; Feb 21 2013.

2. Agnelli, G., Prandoni, P., Becattini, C., Silingardi, M., Taliani, M. R., Miccio, M., Imberti, D., Poggio, R., Ageno, W., Pogliani, E., Porro, F., Zonzin, P., Warfarin Optimal Duration Italian Trial, Investigators. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med; Jul 1 2003.

3. Agnelli, G., Prandoni, P., Santamaria, M. G., Bagatella, P., Iorio, A., Bazzan, M., Moia, M., Guazzaloca, G., Bertoldi, A., Tomasi, C., Scannapieco, G., Ageno, W., Warfarin Optimal Duration Italian Trial, Investigators. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med; Jul 19 2001.

4. Ahmad, A., Sundquist, K., Zoller, B., Dahlback, B., Svensson, P. J., Sundquist, J., Memon, A. A.. Identification of polymorphisms in Apolipoprotein M gene and their relationship with risk of recurrent venous thromboembolism. Thromb Haemost; Aug 30 2016.

5. Asim, M., Al-Thani, H., El-Menyar, A.. Recurrent Deep Vein Thrombosis After the First Venous Thromboembolism Event: A Single-Institution Experience. Med Sci Monit; May 20 2017.

6. Baarslag, H. J., Koopman, M. M., Hutten, B. A., Linthorst Homan, M. W., Buller, H. R., Reekers, J. A., van Beek, E. J.. Long-term follow-up of patients with suspected deep vein thrombosis of the upper extremity: survival, risk factors and post-thrombotic syndrome. Eur J Intern Med; Dec 2004.

7. Baglin, T., Luddington, R., Brown, K., Baglin, C.. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet; Aug 16 2003.

8. Bezemer, I. D., van der Meer, F. J., Eikenboom, J. C., Rosendaal, F. R., Doggen, C. J.. The value of family history as a risk indicator for venous thrombosis. Archives of Internal Medicine; Mar 23 2009.

9. Brouwer, J. L., Lijfering, W. M., Ten Kate, M. K., Kluin-Nelemans, H. C., Veeger, N. J., van der Meer, J.. High long-term absolute risk of recurrent venous thromboembolism in patients with hereditary deficiencies of protein S, protein C or antithrombin. Thromb Haemost; Jan 2009.

10. Bruwer, G., Limperger, V., Kenet, G., Klostermeier, U. C., Shneyder, M., Degenhardt, F., Finckh, U., Heller, C., Holzhauer, S., Trappe, R., Kentouche, K., Knoefler, R., Kurnik, K., Krumpel, A., Lauten, M., Manner, D., Mesters, R., Junker, R., Nowak-Gottl, U.. Impact of high risk thrombophilia status on recurrence among children and adults with VTE: An observational multicenter cohort study. Blood Cells Mol Dis; Nov 2016.

11. Cebi, N., Tanriverdi, S.. Aetiology of deep vein thrombosis in 63 turkish patients. Turkish Journal of Medical Sciences; April 2009.

12. Christiansen, S. C., Cannegieter, S. C., Koster, T., Vandenbroucke, J. P., Rosendaal, F. R.. Thrombophilia, clinical factors, and recurrent venous thrombotic events. Jama; May 18 2005.

13. Couturaud, F., Sanchez, O., Pernod, G., Mismetti, P., Jego, P., Duhamel, E., Provost, K., dit Sollier, C. B., Presles, E., Castellant, P., Parent, F., Salaun, P. Y., Bressollette, L., Nonent, M., Lorillon, P., Girard, P., Lacut, K., Guegan, M., Bosson, J. L., Laporte, S., Leroyer, C., Decousus, H., Meyer, G., Mottier, D., Investigators, Padis-Pe. Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism: The PADIS-PE Randomized Clinical Trial. Jama; Jul 7 2015.

14. De Stefano, V., Martinelli, I., Mannucci, P. M., Paciaroni, K., Chiusolo, P., Casorelli, I., Rossi, E., Leone, G.. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med; Sep 9 1999.

15. De Stefano, V., Simioni, P., Rossi, E., Tormene, D., Za, T., Pagnan, A., Leone, G.. The risk of recurrent venous thromboembolism in patients with inherited deficiency of natural anticoagulants antithrombin, protein C and protein S. Haematologica; May 2006.

16. Di Minno, M. N., Dentali, F., Lupoli, R., Ageno, W.. Mild antithrombin deficiency and risk of recurrent venous thromboembolism: a prospective cohort study. Circulation; Jan 28 2014.

17. Eichinger, S., Minar, E., Hirschl, M., Bialonczyk, C., Stain, M., Mannhalter, C., Stumpflen, A., Schneider, B., Lechner, K., Kyrle, P. A.. The risk of early recurrent venous thromboembolism after oral anticoagulant therapy in patients with the G20210A transition in the prothrombin gene. Thromb Haemost; Jan 1999.

18. Eichinger, S., Weltermann, A., Mannhalter, C., Minar, E., Bialonczyk, C., Hirschl, M., Schonauer, V., Lechner, K., Kyrle, P. A.. The risk of recurrent venous thromboembolism in heterozygous carriers of factor V Leiden and a first spontaneous venous thromboembolism. Archives of Internal Medicine; Nov 11 2002.

19. Eischer, L., Gartner, V., Schulman, S., Kyrle, P. A., Eichinger, S., investigators, Aurec-Fviii. 6 versus 30 months anticoagulation for recurrent venous thrombosis in patients with high factor VIII. Ann Hematol; May 2009.

20. Eischer, L., Kammer, M., Traby, L., Kyrle, P. A., Eichinger, S.. Risk of cancer after anticoagulation in patients with unprovoked venous thromboembolism: an observational cohort study. Journal of Thrombosis and Haemostasis; July 2017.

21. Garcia-Fuster, M. J., Forner, M. J., Fernandez, C., Gil, J., Vaya, A., Maldonado, L.. Long-term prospective study of recurrent venous thromboembolism in patients younger than 50 years. Pathophysiol Haemost Thromb; 2005.

22. Gonzalez-Porras, J. R., Garcia-Sanz, R., Alberca, I., Lopez, M. L., Balanzategui, A., Gutierrez, O., Lozano, F., San Miguel, J.. Risk of recurrent venous thrombosis in patients with G20210A mutation in the prothrombin gene or factor V Leiden mutation. Blood Coagul Fibrinolysis; Jan 2006.

23. Group, The,Procare. Is recurrent venous thromboembolism more frequent in homozygous patients for the factor V Leiden mutation than in heterozygous patients?. Blood Coagulation and Fibrinolysis; September 2003.

24. Heijboer, H., Brandjes, D. P., Buller, H. R., Sturk, A., ten Cate, J. W.. Deficiencies of coagulation-inhibiting and fibrinolytic proteins in outpatients with deep-vein thrombosis. N Engl J Med; Nov 29 1990.

25. Heit, J. A., Beckman, M. G., Bockenstedt, P. L., Grant, A. M., Key, N. S., Kulkarni, R., Manco-Johnson, M. J., Moll, S., Ortel, T. L., Philipp, C. S., Thrombosis, C.,D.,C., Hemostasis Centers, Research, Prevention, Network. Comparison of characteristics from White- and Black-Americans with venous thromboembolism: a cross-sectional study. Am J Hematol; Jul 2010.

26. Hirmerova, J., Seidlerova, J., Subrt, I.. The association of factor V Leiden with various clinical patterns of venous thromboembolism-the factor V Leiden paradox. Qjm; Sep 2014.

27. Hoibraaten, E., Qvigstad, E., Arnesen, H., Larsen, S., Wickstrom, E., Sandset, P. M.. Increased risk of recurrent venous thromboembolism during hormone replacement therapy--results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). Thromb Haemost; Dec 2000.

28. Investigators, Einstein, Bauersachs, R., Berkowitz, S. D., Brenner, B., Buller, H. R., Decousus, H., Gallus, A. S., Lensing, A. W., Misselwitz, F., Prins, M. H., Raskob, G. E., Segers, A., Verhamme, P., Wells, P., Agnelli, G., Bounameaux, H., Cohen, A., Davidson, B. L., Piovella, F., Schellong, S.. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med; Dec 23 2010.

29. Iorio, A., Kearon, C., Filippucci, E., Marcucci, M., Macura, A., Pengo, V., Siragusa, S., Palareti, G.. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. Archives of Internal Medicine; Oct 25 2010.

30. Kearon, C., Gent, M., Hirsh, J., Weitz, J., Kovacs, M. J., Anderson, D. R., Turpie, A. G., Green, D., Ginsberg, J. S., Wells, P., MacKinnon, B., Julian, J. A.. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med; Mar 25 1999.

31. Kearon, C., Julian, J. A., Kovacs, M. J., Anderson, D. R., Wells, P., Mackinnon, B., Weitz, J. I., Crowther, M. A., Dolan, S., Turpie, A. G., Geerts, W., Solymoss, S., van Nguyen, P., Demers, C., Kahn, S. R., Kassis, J., Rodger, M., Hambleton, J., Gent, M., Ginsberg, J. S., Investigators, Elate. Influence of thrombophilia on risk of recurrent venous thromboembolism while on warfarin: results from a randomized trial. Blood; Dec 1 2008.

32. Kearon, C., Parpia, S., Spencer, F. A., Baglin, T., Stevens, S. M., Bauer, K. A., Lentz, S. R., Kessler, C. M., Douketis, J. D., Moll, S., Kaatz, S., Schulman, S., Connors, J. M., Ginsberg, J. S., Spadafora, L., Bhagirath, V., Liaw, P. C., Weitz, J. I., Julian, J. A.. Antiphospholipid antibodies and recurrent thrombosis after a first unprovoked venous thromboembolism. Blood; May 10 2018.

33. Laczkovics, C., Grafenhofer, H., Kaider, A., Quehenberger, P., Simanek, R., Mannhalter, C., Lechner, K., Pabinger, I.. Risk of recurrence after a first venous thromboembolic event in young women. Haematologica; Sep 2007.

34. Lee, S. Y., Kim, E. K., Kim, M. S., Shin, S. H., Chang, H., Jang, S. Y., Kim, H. J., Kim, D. K.. The prevalence and clinical manifestation of hereditary thrombophilia in Korean patients with unprovoked venous thromboembolisms. PLoS ONE [Electronic Resource]; 2017.

35. Lijfering, W. M., Middeldorp, S., Veeger, N. J., Hamulyak, K., Prins, M. H., Buller, H. R., van der Meer, J.. Risk of recurrent venous thrombosis in homozygous carriers and double heterozygous carriers of factor V Leiden and prothrombin G20210A. Circulation; Apr 20 2010.

36. Lim, H. Y., Chua, C. C., Tacey, M., Sleeman, M., Donnan, G., Nandurkar, H., Ho, P.. Venous thromboembolism management in Northeast Melbourne: how does it compare to international guidelines and data?. Intern Med J; Sep 2017.

37. Lindmarker, P., Schulman, S., Sten-Linder, M., Wiman, B., Egberg, N., Johnsson, H.. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. DURAC Trial Study Group. Duration of Anticoagulation. Thromb Haemost; May 1999.

38. Marcucci, R., Liotta, A. A., Cellai, A. P., Rogolino, A., Gori, A. M., Giusti, B., Poli, D., Fedi, S., Abbate, R., Prisco, D.. Increased plasma levels of lipoprotein(a) and the risk of idiopathic and recurrent venous thromboembolism. Am J Med; Dec 1 2003.

39. Mateo, J., Oliver, A., Borrell, M., Sala, N., Fontcuberta, J.. Laboratory evaluation and clinical characteristics of 2,132 consecutive unselected patients with venous thromboembolism--results of the Spanish Multicentric Study on Thrombophilia (EMET-Study). Thromb Haemost; Mar 1997.

40. Mello, T. B., Orsi, F. L., Montalvao, S. A., Ozelo, M. C., de Paula, E. V., Annichinno-Bizzachi, J. M.. Long-term prospective study of recurrent venous thromboembolism in a Hispanic population. Blood Coagul Fibrinolysis; Oct 2010.

41. Meyer, M. R., Witt, D. M., Delate, T., Johnson, S. G., Fang, M., Go, A., Clark, N. P.. Thrombophilia testing patterns amongst patients with acute venous thromboembolism. Thromb Res; Dec 2015.

42. Miles, J. S., Miletich, J. P., Goldhaber, S. Z., Hennekens, C. H., Ridker, P. M.. G20210A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. J Am Coll Cardiol; Jan 2001.

43. Olie, V., Plu-Bureau, G., Conard, J., Horellou, M. H., Canonico, M., Scarabin, P. Y.. Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. Menopause; May 2011.

44. Palareti, G., Cosmi, B., Legnani, C., Tosetto, A., Brusi, C., Iorio, A., Pengo, V., Ghirarduzzi, A., Pattacini, C., Testa, S., Lensing, A. W., Tripodi, A., Investigators, Prolong. D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med; Oct 26 2006.

45. Prandoni, P., Noventa, F., Ghirarduzzi, A., Pengo, V., Bernardi, E., Pesavento, R., Iotti, M., Tormene, D., Simioni, P., Pagnan, A.. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica; Feb 2007.

46. Ridker, P. M., Miletich, J. P., Stampfer, M. J., Goldhaber, S. Z., Lindpaintner, K., Hennekens, C. H.. Factor V Leiden and risks of recurrent idiopathic venous thromboembolism. Circulation; Nov 15 1995.

47. Rodger, M. A., Kahn, S. R., Wells, P. S., Anderson, D. A., Chagnon, I., Le Gal, G., Solymoss, S., Crowther, M., Perrier, A., White, R., Vickars, L., Ramsay, T., Betancourt, M. T., Kovacs, M. J.. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. Cmaj; Aug 26 2008.

48. Roldan, V., Lecumberri, R., Munoz-Torrero, J. F., Vicente, V., Rocha, E., Brenner, B., Monreal, M., Investigators, Riete. Thrombophilia testing in patients with venous thromboembolism. Findings from the RIETE registry. Thromb Res; Jun 2009.

49. Rossi, E., Za, T., Ciminello, A., Leone, G., De Stefano, V.. The risk of symptomatic pulmonary embolism due to proximal deep venous thrombosis differs in patients with different types of inherited thrombophilia. Thromb Haemost; Jun 2008.

50. Roupie, A. L., Dossier, A., Goulenok, T., Perozziello, A., Papo, T., Sacre, K.. First venous thromboembolism in admitted patients younger than 50years old. Eur J Intern Med; Oct 2016.

51. Rupa-Matysek, J., Gil, L., Wojtasinska, E., Ciepluch, K., Lewandowska, M., Komarnicki, M.. The relationship between mean platelet volume and thrombosis recurrence in patients diagnosed with antiphospholipid syndrome. Rheumatol Int; Nov 2014.

52. Santamaria, M. G., Agnelli, G., Taliani, M. R., Prandoni, P., Moia, M., Bazzan, M., Guazzaloca, G., Ageno, W., Bertoldi, A., Silingardi, M., Tomasi, C., Ambrosio, G. B., Warfarin Optimal Duration Italian Trial, Investigators. Thrombophilic abnormalities and recurrence of venous thromboembolism in patients treated with standardized anticoagulant treatment. Thromb Res; 2005.

53. Schattner, A., Kasher, I., Berrebi, A.. Causes and outcome of deep-vein thrombosis in otherwise-healthy patients under 50 years. Qjm; Apr 1997.

54. Schulman, S., Kearon, C., Kakkar, A. K., Schellong, S., Eriksson, H., Baanstra, D., Kvamme, A. M., Friedman, J., Mismetti, P., Goldhaber, S. Z., Investigators, Re-Medy,Trial, Investigators, Re-Sonate,Trial. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med; Feb 21 2013.

55. Schulman, S., Lindmarker, P., Holmstrom, M., Larfars, G., Carlsson, A., Nicol, P., Svensson, E., Ljungberg, B., Viering, S., Nordlander, S., Leijd, B., Jahed, K., Hjorth, M., Linder, O., Beckman, M.. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. Journal of Thrombosis & Haemostasis; Apr 2006.

56. Schulman, S., Wahlander, K., Lundstrom, T., Clason, S. B., Eriksson, H., Investigators, Thrive,Iii. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. N Engl J Med; Oct 30 2003.

57. Simioni, P., Prandoni, P., Lensing, A. W., Manfrin, D., Tormene, D., Gavasso, S., Girolami, B., Sardella, C., Prins, M., Girolami, A.. Risk for subsequent venous thromboembolic complications in carriers of the prothrombin or the factor V gene mutation with a first episode of deep-vein thrombosis. Blood; Nov 15 2000.

58. Sonnevi, K., Tchaikovski, S. N., Holmstrom, M., Antovic, J. P., Bremme, K., Rosing, J., Larfars, G.. Obesity and thrombin-generation profiles in women with venous thromboembolism. Blood Coagul Fibrinolysis; Jul 2013.

59. Strandberg, K., Svensson, P. J., Ohlin, A. K.. Venous thromboembolism in carriers of the Factor V Leiden mutation and in patients without known thrombophilic risk factor; prediction of recurrence and APC-PCI complex concentration and/or soluble thrombomodulin antigen and activity. Thromb Res; 2007.

60. Sundquist, K., Sundquist, J., Svensson, P. J., Zoller, B., Memon, A. A.. Role of family history of venous thromboembolism and thrombophilia as predictors of recurrence: a prospective follow-up study. Journal of Thrombosis & Haemostasis; Dec 2015.

61. Sveinsdottir, S. V., Saemundsson, Y., Isma, N., Gottsater, A., Svensson, P. J.. Evaluation of recurrent venous thromboembolism in patients with Factor V Leiden mutation in heterozygous form. Thromb Res; Sep 2012.

62. Vitovec, M., Golan, L., Roztocil, K., Linhart, A.. The development of persistent thrombotic masses in patients with deep venous thrombosis randomized to long-term anticoagulation treatment. Vasa; Aug 2009.

63. Wahlander, K., Eriksson, H., Lundstrom, T., Billing Clason, S., Wall, U., Nystrom, P., Wessman, P., Schulman, S., Investigators, Thrive,Iii. Risk of recurrent venous thromboembolism or bleeding in relation to thrombophilic risk factors in patients receiving ximelagatran or placebo for long-term secondary prevention of venous thromboembolism. Br J Haematol; Apr 2006.

64. Weingarz, L., Schindewolf, M., Schwonberg, J., Hecking, C., Wolf, Z., Erbe, M., Lindhoff-Last, E., Linnemann, B.. Thrombophilia and risk of VTE recurrence according to the age at the time of first VTE manifestation. Vasa; Jul 2015.

65. Palareti, G., Legnani, C., Cosmi, B., Valdre, L., Lunghi, B., Bernardi, F., Coccheri, S.. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation; Jul 22 2003.

QUESTION

Should thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia vs. no thrombophilia testing and stopping anticoagulant treatment in all be used for patients with symptomatic venous thromboembolism provoked by a non-surgical major transient risk factor who completed primary treatment?

POPULATION:	patients with symptomatic venous thromboembolism provoked by a non-surgical major transient risk factor who completed primary treatment
INTERVENTION:	thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia
COMPARISON:	no thrombophilia testing and stopping anticoagulant treatment in all
MAIN OUTCOMES:	Recurrent VTE; Major Bleeding - Low (0.5% per year); Major Bleeding - High (1.5% per year);
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Thrombophilia, either acquired or inherited, can be identified in many patients presenting with venous thromboembolism (VTE). The currently most commonly tested inherited thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. The current guideline aims to assess whether identifying patients positive for one or more of these defects allows management options which reduce patient important outcomes. Usually, 3 months of anticoagulant treatment is considered sufficient in the setting of VTE provoked by non-surgical major transient risk factors, due to the low risk of VTE recurrence. In this setting, thrombophilia testing might be considered to identify patients at higher risk of VTE recurrence, particularly in young patients, those with recurrent episodes of provoked thrombosis, or having a positive family history for VTE or thrombophilia. Although testing patients with provoked VTE may have a moderate chance of finding a positive test result, the true question is whether a positive test result should alter anticoagulant management. This question addresses whether thrombophilia testing and subsequent indefinite duration of anticoagulant treatment in patients positive for thrombophilia improves patient important outcomes in patients with VTE provoked by non-surgical major transient risk factors, as compared with no thrombophilia testing and treating all patients with definite duration anticoagulant treatment. Since no randomized controlled trials have addressed this question, we used a modeling approach based on observational evidence for baseline risk of patient-important outcomes, prevalence of thrombophilia and increase in the risk of associated events with thrombophilia, and RCTs based evidence for the effect of extended anticoagulation on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes		

○ Varies ○ Don't know		

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Evidence Profile.	Desirable effect = preventing VTE recurrence. VTE recurrences would be avoided in patients who are positive for thrombophilia by extending their anticoagulation treatment. The panel considered a reduction in VTE recurrence of 5% to be the threshold to consider the effect Large, and a 2% reduction to be Small in the overall population of interest. However, the panel also discussed that a 2% reduction may be considered Large in subgroups that are at lower risk, such as young women.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	See Evidence Profile.	Undesirable effect = causing major bleeding. Major bleedings would be caused in patients who are positive for thrombophilia as a side effect of extending their anticoagulation treatment. The panel considered the increase in major bleeding to be in between Small and Trivial.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows using a scale from 0 (worst possible scenario, usually death), to 1 (best possible scenario, usually perfect health):** **Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(1, 2, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3) **Gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off)(2, 3) **Minor intracranial bleeding event:** 0.75 (standard gamble)(2) **Major intracranial bleeding event:** 0.15 (standard gamble)(2)	The panel considered that clinicians may value avoiding major bleeding more (they do not want to cause harm), while patients may value avoiding VTE events more (they may prefer avoiding a recurrence of blood clots).

	Anticoagulant therapy Patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome.(3) Patients would favor efficacy and safety over convenience of route of administration.(6) Also, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events.(6, 7, 8)	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		No studies assessed indefinite anticoagulation as life-long treatment. The panel observed that the appraisal of the comparison of the two interventions (testing and treating positives vs treating none) was limited by the absence of studies comparing indefinite anticoagulation as life-long treatment versus no anticoagulation, which the panel had to extrapolate.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		**The panel considered the following cost ranges:** - Cost for testing: $400 -$2,000 per patient - Cost for treatment: $1,000-$ 4,500 per patient per year In assessing the resources required the panel considered that the intervention added the cost for testing all patients and treating the patients positive for thrombophilia. The panel did not consider the costs for recurrent clots or for bleeding events.

Intervention Costs:

Test (source)	Approximate Cost (2005)	Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016)	(14/12/2016) £1 = $1,27
Full Blood Count	£2.55	£3.29	$4,18
Protein C	£11.67	£15.5	$19,12
Free Protein S	£11.67	£15.5	$19,12
Antithrombin	£11.67	£15.5	$19,12
APCR	£10.73	£13.84	$17,58
Factor V Leiden	£85.00	£109.65	$141,45
Prothrombin gene mutation	£85.00	£109.65	$141,45
Lupus Anticoagulant	£10.73	£13.84	$17,58
Antiphospholipid antibodies	£12.30	£15.87	$20,15
Anti Beta-2 GP1 antibody	£9.50	£12.25	$15,81
The potential cost of a full thrombophilia screen	£250.82,	£323.56	$410,92

Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx

Cost of the health outcomes:(9)

- **Recurrent VTE:** 11,000 to 15,000 USD

- **Major bleeding:** 11,000 to 22,000 USD

Cost of interventions:(10)

- **Dabigatran:** Cost per month: $300.44–$600.88 USD

- **Rivaroxaban:** Cost per month: $300.42–$600.84 USD

- **Apixaban:** Cost per month: $300.44–$600.88

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	Three studies evaluated the cost-effectiveness of thrombophilia testing and different management strategies in patients with a first venous thromboembolism.(11, 12, 13) All three studies found thrombophilia testing cost-effective, although the uncertainty was high in general due to prevalence of mutation and the variability in the recurrence rate (which depends on the type of thrombophilia), risk of adverse events such as major haemorrhage, age or efficacy of the anticoagulant therapy, among others. Cost per quality-adjusted life year (QALY) for the testing and treatment strategies varied between the 3 studies and in sensitivity analyses (Simpson 2009: approximately £20,000/QALY for patients with PE or DVT; Marchetti 2001: $13,624/QALY for any VTE, Eckman 2002: $16,823/QALY for any VTE) One study evaluated thrombophilia testing using a panel of thrombophilia tests that included Factor V Leiden, Prothrombin G20210A, APC resistance, Protein C, Protein S, antithrombin levels, antiphospholipid antibodies and homocysteine levels, dysfibrinogenaemia, and levels of factor VIII, factor IX and factor XI.(13) Another cost-effectiveness study included only screening for FVL and G20210A prothrombin mutations,(11) and the third study included testing for FVL mutation.(12)	The panel made this judgment based on extrapolation of cost-effectiveness evidence for patients with any type of VTE, as shown here.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(14)	The panel considered that the health system/service coverage/access to care will be the main aspect affecting health equity. USA is an example where promotion of testing that is not covered by insurance would generate inequities. I.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies. Also, the additional cost for indefinite anticoagulant treatment of the patients positive for thrombophilia may or may not be covered.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies	Research studies suggested the following regarding acceptability and barriers associated with testing and treatment:	The panel considered testing acceptable for many doctors, although maybe not for all. Patients are in general willing to undergo thrombophilia testing when testing is proposed by their doctor.

○ Don't know	**Patients**: A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(15) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(16) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers**: A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(17) **Payers**: At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(18) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation. External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories.

	overspending.(19) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombobin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(20) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(21) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(22)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

After completion of primary treatment for patients with a symptomatic VTE provoked by a non-surgical major transient risk factor, the ASH guideline panel suggests testing for thrombophilia and indefinite anticoagulant treatment in positive patients over no testing for thrombophilia and stopping anticoagulant treatment in all patients (conditional recommendation based on very low certainty of the evidence about effects)

Remarks:

- Non-surgical major transient risk factors: e.g. confined to bed in hospital for at least 3 days with an acute illness (“bathroom privileges only”), or a combination of minor transient risk factors such as admission to hospital for less than 3 days with an acute illness, confined to bed out of hospital for at least 3 days with an acute illness, or leg injury associated with decreased mobility for at least 3 days. (See Table 3 in the ASH 2020 guidelines for treatment of DVT and PE).

- A strategy with testing for thrombophilia would mean that positive patients would receive indefinite anticoagulant treatment, and negative patients would stop anticoagulant treatment.

- This recommendation refers to testing for inherited and acquired types of thrombophilia.

Justification

The panel considered that thrombophilia testing and extending anticoagulant treatment in thrombophilia positives is likely producing benefit in terms of prevention of VTE recurrence that outweighs the risk of major bleeding in patients at low risk of bleeding, and may justify the costs of indefinite anticoagulant treatment.

Subgroup considerations

The decision to test for thrombophilia may depend on the strength of the provoking factor, and whether VTE occurred despite thromboprophylaxis.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation. Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

Randomized controlled trials comparing testing vs no testing would be ideal but have shown to be difficult to perform.(Cohn 2008, Cohn 2012) The second best option would be pragmatic non-randomized controlled studies comparing in patients with VTE provoked by a non-surgical major transient risk factor the clinical outcomes of non-tested patients undergoing definite treatment and tested patients treated according to the test results.(Coppens 2008)

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
7. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
8. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
9. Grosse, S. D., Nelson, R. E., Nyarko, K. A., Richardson, L. C., Raskob, G. E.. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res; Jan 2016.
10. Biskupiak, J., Ghate, S. R., Jiao, T., Brixner, D.. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. J Manag Care Pharm; Nov-Dec 2013.
11. Marchetti, M., Quaglini, S., Barosi, G.. Cost-effectiveness of screening and extended anticoagulation for carriers of both factor V Leiden and prothrombin G20210A. Qjm; Jul 2001.
12. Eckman, M. H., Singh, S. K., Erban, J. K., Kao, G.. Testing for factor V Leiden in patients with pulmonary or venous thromboembolism: a cost-effectiveness analysis. Med Decis Making; Mar-Apr 2002.
13. Simpson, E. L., Stevenson, M. D., Rawdin, A., Papaioannou, D.. Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis. Health Technol Assess; Jan 2009.
14. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
15. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
16. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
17. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
18. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
19. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
20. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
21. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
22. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In patients with symptomatic venous thromboembolism provoked by a non-surgical major transient risk factor who completed primary treatment, should thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia compared to no thrombophilia testing and stopping anticoagulant treatment in all be used?

Setting:

Bibliography: See reference list and footnotes.[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Recurrent VTE (assessed with: any DVT or PE)									
25 [a,b,c,d,e,f,g]	observational studies	not serious	not serious	serious [h]	serious [i]	none	When testing 1,000 patients who completed primary treatment of symptomatic VTE provoked by a non-surgical major transient risk factor for any type of thrombophilia, and treating the 380 positives with indefinite anticoagulation (ranging from 216 to 595), 29 VTE recurrences will occur per year (ranging from 15 to 40). When not testing 1,000 patients for thrombophilia and stopping treatment in all of them, 50 VTE recurrences will occur per year. Therefore, a thrombophilia testing strategy is associated with 380 more patients treated with indefinite anticoagulation (ranging from 216 to 595) and **21 fewer VTE recurrences (ranging from 10 to 35)** per 1,000 patients per year compared with a no testing strategy. [j]	⨁◯◯◯ VERY LOW	CRITICAL
Major Bleeding - Low (0.5% per year)[k]									
32 [c,d,l,m,n]	observational studies	not serious	not serious	very serious [o]	not serious	none	When testing 1,000 patients with symptomatic VTE provoked by a non-surgical major transient risk factor who are at low risk of major bleeding for any type of thrombophilia, and treating the 380 positives with indefinite anticoagulation (ranging from 216 to 595), 7 major bleedings will occur per year (ranging from 5 to 12). When not testing 1,000 patients for thrombophilia and stopping treatment in all of them, 5 major bleedings will occur per year. Therefore, a thrombophilia testing strategy is associated with 380 more patients treated with indefinite anticoagulation (ranging from 216 to 595) and **2 more major bleedings (ranging from 0 to 7)** per 1,000 patients per year compared with a no testing strategy. [p]	⨁◯◯◯ VERY LOW	CRITICAL
Major Bleeding - High (1.5% per year)[q]									
32 [c,d,l,m,r]	observational studies	not serious	not serious	serious [o]	serious [i]	none	When testing 1,000 patients with symptomatic VTE provoked by a non-surgical major transient risk factor who are at high risk of major bleeding for any type of thrombophilia, and treating the 380 positives with indefinite anticoagulation (ranging from 216 to 595), 22 major bleedings will occur per year (ranging from 16 to 36). When not testing 1,000 patients for thrombophilia and stopping treatment in all of them, 15 major bleedings will occur per year. Therefore, a thrombophilia testing strategy is associated with 380 more patients treated with indefinite anticoagulation (ranging from 216 to 595) and **7 more major bleedings (ranging from 1 to 21)** per 1,000 patients per year compared with a no testing strategy. [s]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE recurrence, 1 systematic review; Prevalence, 20 studies; Risk association for thrombophilia positive versus negative, 6 studies (all also reported Prevalence); Extended anticoagulation effect, 4 RCTs

b. Overall risk for VTE recurrence: Iorio 2010

c. Thrombophilia prevalence, used for calculation: Bezemer 2009, Cebi 2009, Di Minno 2014, Garcia-Fuster 2005, Heit 2010, Kearon 1999, Kearon 2018, Lim 2017, Mello 2010, Meyer 2015, Olie 2011, Palareti 2003, Prandoni 2007, Roldan 2009, Rossi 2008, Santamaria 2005, Schattner 1997, Schulman 2006, Sundquist 2015, Weingarz 2015

d. Prevalence of specific thrombophilia types, used to verify calculation estimate: Ahmad 2016, Ahmad 2016, Ahmad 2017, Asim 2017, Baarslag 2004, Baglin 2003, Brouwer 2009, Bruwer 2016, Christiansen 2005, De Stefano 1999, De Stefano 2006, Eichinger 1999, Eichinger 2002, Eischer 2017, Gonzalez-Porras 2006, Heijboer 1990, Hirmerova 2014, Hoibraaten 2000, Kearon 2008, Laczkovics 2007, Lee 2017, Lijfering 2010, Lindmarker 1999, Marcucci 2003, Mateo 1997, Miles 2001, Ridker 1995, Rodger 2008, Roupie 2016, Rupa-Matysek 2014, Simioni 2000, Sonnevi 2013, Strandberg 2007, Sveinsdottir 2012, The Procare group 2003, Wahlander 2006

e. Thrombophilia positive vs negative risk association, used for calculation: Kearon, 1999, Kearon 2018, Mello 2010, Santamaria 2005, Schulman 2006, Weingarz 2015

f. Risk association for specific thrombophilia types, used to verify calculation estimate: Baglin 2003, Brouwer 2009, Christiansen 2005, De Stefano 1999, De Stefano 2006, Di Minno 2014, Eichinger 2002, Gonzalez-Porras 2006, Hoibraaten 2000, Lijfering 2010, Lindmarker 1999, Marcucci 2003, Miles 2001, Palareti 2003, Prandoni 2007, Ridker 1995, Rodger 2008, Schattner 1997, Simioni 2000, Strandberg 2007, Wahlander 2006

g. Effect of extended anticoagulation treatment, used in calculation: Agnelli 2013, Bauersachs 2010, Schulman 2003, Schulman 2013

h. The effect was indirectly calculated using evidence from an indirect population (patients with any type of VTE), and using separate studies for thrombophilia prevalence, relative risk of thrombophilia positives vs negatives, and the effect of treatment

i. There is a clinically important difference between the smallest and largest possible effect of the testing strategy

j. Based on the following estimates: Overall risk for VTE recurrence, 50 per 1,000; Prevalence of any thrombophilia, 38.0% (min 21.6 - max 59.5); Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 1.65 (95%CI: 1.28-2.47); Relative risk of VTE recurrence with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.15 (0.10-0.23). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, upper CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

k. Among RCTs assessing the effect of extended treatment against limited treatment, the lowest observed rate of major bleeding with limited treatment was 0.5% (Agnelli 2001)

l. Number of studies used in calculations: Overall risk, 1 RCT; Prevalence, 20 studies; Extended anticoagulation effect, 11 RCTs

m. Effect of extended anticoagulation treatment, used in calculation: Agnelli 2001, Agnelli 2003, Agnelli 2013, Bauersachs 2010, Couturaud 2015, Eischer 2009, Kearon 1999, Palareti 2006, Ridker 2003, Schulman 2003, Schulman 2013

n. Overall risk for Major bleeding: Agnelli 2001

o. The effect was indirectly calculated using separate studies for thrombophilia prevalence and the effect of treatment

p. Based on the following estimates: Overall risk for Major bleeding of 5 per 1,000; Prevalence of any thrombophilia, 38.0% (21.6-59.5); Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 2.17 (1.40-3.35). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the smallest treatment effect (lower CI).

q. Among RCTs assessing the effect of extended treatment against limited treatment, the highest observed rate of major bleeding with limited treatment was 1.5% (Agnelli 2013)

r. Overall risk for Major bleeding: Agnelli 2013

s. Based on the following estimates: Overall risk for Major bleeding of 15 per 1,000; Prevalence of any thrombophilia, 38.0% (21.6-59.5); Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 2.17 (1.40-3.35). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the smallest treatment effect (lower CI).

References

1. Agnelli, G., Buller, H. R., Cohen, A., Curto, M., Gallus, A. S., Johnson, M., Porcari, A., Raskob, G. E., Weitz, J. I., Investigators, Amplify-Ext. Apixaban for extended treatment of venous thromboembolism. N Engl J Med; Feb 21 2013.

2. Agnelli, G., Prandoni, P., Becattini, C., Silingardi, M., Taliani, M. R., Miccio, M., Imberti, D., Poggio, R., Ageno, W., Pogliani, E., Porro, F., Zonzin, P., Warfarin Optimal Duration Italian Trial, Investigators. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med; Jul 1 2003.

3. Agnelli, G., Prandoni, P., Santamaria, M. G., Bagatella, P., Iorio, A., Bazzan, M., Moia, M., Guazzaloca, G., Bertoldi, A., Tomasi, C., Scannapieco, G., Ageno, W., Warfarin Optimal Duration Italian Trial, Investigators. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med; Jul 19 2001.

4. Ahmad, A., Sundquist, K., Zoller, B., Dahlback, B., Svensson, P. J., Sundquist, J., Memon, A. A.. Identification of polymorphisms in Apolipoprotein M gene and their relationship with risk of recurrent venous thromboembolism. Thromb Haemost; Aug 30 2016.

5. Asim, M., Al-Thani, H., El-Menyar, A.. Recurrent Deep Vein Thrombosis After the First Venous Thromboembolism Event: A Single-Institution Experience. Med Sci Monit; May 20 2017.

6. Baarslag, H. J., Koopman, M. M., Hutten, B. A., Linthorst Homan, M. W., Buller, H. R., Reekers, J. A., van Beek, E. J.. Long-term follow-up of patients with suspected deep vein thrombosis of the upper extremity: survival, risk factors and post-thrombotic syndrome. Eur J Intern Med; Dec 2004.

7. Baglin, T., Luddington, R., Brown, K., Baglin, C.. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet; Aug 16 2003.

8. Bezemer, I. D., van der Meer, F. J., Eikenboom, J. C., Rosendaal, F. R., Doggen, C. J.. The value of family history as a risk indicator for venous thrombosis. Archives of Internal Medicine; Mar 23 2009.

9. Brouwer, J. L., Lijfering, W. M., Ten Kate, M. K., Kluin-Nelemans, H. C., Veeger, N. J., van der Meer, J.. High long-term absolute risk of recurrent venous thromboembolism in patients with hereditary deficiencies of protein S, protein C or antithrombin. Thromb Haemost; Jan 2009.

10. Bruwer, G., Limperger, V., Kenet, G., Klostermeier, U. C., Shneyder, M., Degenhardt, F., Finckh, U., Heller, C., Holzhauer, S., Trappe, R., Kentouche, K., Knoefler, R., Kurnik, K., Krumpel, A., Lauten, M., Manner, D., Mesters, R., Junker, R., Nowak-Gottl, U.. Impact of high risk thrombophilia status on recurrence among children and adults with VTE: An observational multicenter cohort study. Blood Cells Mol Dis; Nov 2016.

11. Cebi, N., Tanriverdi, S.. Aetiology of deep vein thrombosis in 63 turkish patients. Turkish Journal of Medical Sciences; April 2009.

12. Christiansen, S. C., Cannegieter, S. C., Koster, T., Vandenbroucke, J. P., Rosendaal, F. R.. Thrombophilia, clinical factors, and recurrent venous thrombotic events. Jama; May 18 2005.

13. Couturaud, F., Sanchez, O., Pernod, G., Mismetti, P., Jego, P., Duhamel, E., Provost, K., dit Sollier, C. B., Presles, E., Castellant, P., Parent, F., Salaun, P. Y., Bressollette, L., Nonent, M., Lorillon, P., Girard, P., Lacut, K., Guegan, M., Bosson, J. L., Laporte, S., Leroyer, C., Decousus, H., Meyer, G., Mottier, D., Investigators, Padis-Pe. Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism: The PADIS-PE Randomized Clinical Trial. Jama; Jul 7 2015.

14. De Stefano, V., Martinelli, I., Mannucci, P. M., Paciaroni, K., Chiusolo, P., Casorelli, I., Rossi, E., Leone, G.. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med; Sep 9 1999.

15. De Stefano, V., Simioni, P., Rossi, E., Tormene, D., Za, T., Pagnan, A., Leone, G.. The risk of recurrent venous thromboembolism in patients with inherited deficiency of natural anticoagulants antithrombin, protein C and protein S. Haematologica; May 2006.

16. Di Minno, M. N., Dentali, F., Lupoli, R., Ageno, W.. Mild antithrombin deficiency and risk of recurrent venous thromboembolism: a prospective cohort study. Circulation; Jan 28 2014.

17. Eichinger, S., Minar, E., Hirschl, M., Bialonczyk, C., Stain, M., Mannhalter, C., Stumpflen, A., Schneider, B., Lechner, K., Kyrle, P. A.. The risk of early recurrent venous thromboembolism after oral anticoagulant therapy in patients with the G20210A transition in the prothrombin gene. Thromb Haemost; Jan 1999.

18. Eichinger, S., Weltermann, A., Mannhalter, C., Minar, E., Bialonczyk, C., Hirschl, M., Schonauer, V., Lechner, K., Kyrle, P. A.. The risk of recurrent venous thromboembolism in heterozygous carriers of factor V Leiden and a first spontaneous venous thromboembolism. Archives of Internal Medicine; Nov 11 2002.

19. Eischer, L., Kammer, M., Traby, L., Kyrle, P. A., Eichinger, S.. Risk of cancer after anticoagulation in patients with unprovoked venous thromboembolism: an observational cohort study. Journal of Thrombosis and Haemostasis; July 2017.

20. Eischer, L., Gartner, V., Schulman, S., Kyrle, P. A., Eichinger, S., investigators, Aurec-Fviii. 6 versus 30 months anticoagulation for recurrent venous thrombosis in patients with high factor VIII. Ann Hematol; May 2009.

21. Garcia-Fuster, M. J., Forner, M. J., Fernandez, C., Gil, J., Vaya, A., Maldonado, L.. Long-term prospective study of recurrent venous thromboembolism in patients younger than 50 years. Pathophysiol Haemost Thromb; 2005.

22. Gonzalez-Porras, J. R., Garcia-Sanz, R., Alberca, I., Lopez, M. L., Balanzategui, A., Gutierrez, O., Lozano, F., San Miguel, J.. Risk of recurrent venous thrombosis in patients with G20210A mutation in the prothrombin gene or factor V Leiden mutation. Blood Coagul Fibrinolysis; Jan 2006.

23. Group, The,Procare. Is recurrent venous thromboembolism more frequent in homozygous patients for the factor V Leiden mutation than in heterozygous patients?. Blood Coagulation and Fibrinolysis; September 2003.

24. Heijboer, H., Brandjes, D. P., Buller, H. R., Sturk, A., ten Cate, J. W.. Deficiencies of coagulation-inhibiting and fibrinolytic proteins in outpatients with deep-vein thrombosis. N Engl J Med; Nov 29 1990.

25. Heit, J. A., Beckman, M. G., Bockenstedt, P. L., Grant, A. M., Key, N. S., Kulkarni, R., Manco-Johnson, M. J., Moll, S., Ortel, T. L., Philipp, C. S., Thrombosis, C.,D.,C., Hemostasis Centers, Research, Prevention, Network. Comparison of characteristics from White- and Black-Americans with venous thromboembolism: a cross-sectional study. Am J Hematol; Jul 2010.

26. Hirmerova, J., Seidlerova, J., Subrt, I.. The association of factor V Leiden with various clinical patterns of venous thromboembolism-the factor V Leiden paradox. Qjm; Sep 2014.

27. Hoibraaten, E., Qvigstad, E., Arnesen, H., Larsen, S., Wickstrom, E., Sandset, P. M.. Increased risk of recurrent venous thromboembolism during hormone replacement therapy--results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). Thromb Haemost; Dec 2000.

28. Investigators, Einstein, Bauersachs, R., Berkowitz, S. D., Brenner, B., Buller, H. R., Decousus, H., Gallus, A. S., Lensing, A. W., Misselwitz, F., Prins, M. H., Raskob, G. E., Segers, A., Verhamme, P., Wells, P., Agnelli, G., Bounameaux, H., Cohen, A., Davidson, B. L., Piovella, F., Schellong, S.. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med; Dec 23 2010.

29. Iorio, A., Kearon, C., Filippucci, E., Marcucci, M., Macura, A., Pengo, V., Siragusa, S., Palareti, G.. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. Archives of Internal Medicine; Oct 25 2010.

30. Kearon, C., Gent, M., Hirsh, J., Weitz, J., Kovacs, M. J., Anderson, D. R., Turpie, A. G., Green, D., Ginsberg, J. S., Wells, P., MacKinnon, B., Julian, J. A.. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med; Mar 25 1999.

31. Kearon, C., Julian, J. A., Kovacs, M. J., Anderson, D. R., Wells, P., Mackinnon, B., Weitz, J. I., Crowther, M. A., Dolan, S., Turpie, A. G., Geerts, W., Solymoss, S., van Nguyen, P., Demers, C., Kahn, S. R., Kassis, J., Rodger, M., Hambleton, J., Gent, M., Ginsberg, J. S., Investigators, Elate. Influence of thrombophilia on risk of recurrent venous thromboembolism while on warfarin: results from a randomized trial. Blood; Dec 1 2008.

32. Kearon, C., Parpia, S., Spencer, F. A., Baglin, T., Stevens, S. M., Bauer, K. A., Lentz, S. R., Kessler, C. M., Douketis, J. D., Moll, S., Kaatz, S., Schulman, S., Connors, J. M., Ginsberg, J. S., Spadafora, L., Bhagirath, V., Liaw, P. C., Weitz, J. I., Julian, J. A.. Antiphospholipid antibodies and recurrent thrombosis after a first unprovoked venous thromboembolism. Blood; May 10 2018.

33. Laczkovics, C., Grafenhofer, H., Kaider, A., Quehenberger, P., Simanek, R., Mannhalter, C., Lechner, K., Pabinger, I.. Risk of recurrence after a first venous thromboembolic event in young women. Haematologica; Sep 2007.

34. Lee, S. Y., Kim, E. K., Kim, M. S., Shin, S. H., Chang, H., Jang, S. Y., Kim, H. J., Kim, D. K.. The prevalence and clinical manifestation of hereditary thrombophilia in Korean patients with unprovoked venous thromboembolisms. PLoS ONE [Electronic Resource]; 2017.

35. Lijfering, W. M., Middeldorp, S., Veeger, N. J., Hamulyak, K., Prins, M. H., Buller, H. R., van der Meer, J.. Risk of recurrent venous thrombosis in homozygous carriers and double heterozygous carriers of factor V Leiden and prothrombin G20210A. Circulation; Apr 20 2010.

36. Lim, H. Y., Chua, C. C., Tacey, M., Sleeman, M., Donnan, G., Nandurkar, H., Ho, P.. Venous thromboembolism management in Northeast Melbourne: how does it compare to international guidelines and data?. Intern Med J; Sep 2017.

37. Lindmarker, P., Schulman, S., Sten-Linder, M., Wiman, B., Egberg, N., Johnsson, H.. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. DURAC Trial Study Group. Duration of Anticoagulation. Thromb Haemost; May 1999.

38. Marcucci, R., Liotta, A. A., Cellai, A. P., Rogolino, A., Gori, A. M., Giusti, B., Poli, D., Fedi, S., Abbate, R., Prisco, D.. Increased plasma levels of lipoprotein(a) and the risk of idiopathic and recurrent venous thromboembolism. Am J Med; Dec 1 2003.

39. Mateo, J., Oliver, A., Borrell, M., Sala, N., Fontcuberta, J.. Laboratory evaluation and clinical characteristics of 2,132 consecutive unselected patients with venous thromboembolism--results of the Spanish Multicentric Study on Thrombophilia (EMET-Study). Thromb Haemost; Mar 1997.

40. Mello, T. B., Orsi, F. L., Montalvao, S. A., Ozelo, M. C., de Paula, E. V., Annichinno-Bizzachi, J. M.. Long-term prospective study of recurrent venous thromboembolism in a Hispanic population. Blood Coagul Fibrinolysis; Oct 2010.

41. Meyer, M. R., Witt, D. M., Delate, T., Johnson, S. G., Fang, M., Go, A., Clark, N. P.. Thrombophilia testing patterns amongst patients with acute venous thromboembolism. Thromb Res; Dec 2015.

42. Miles, J. S., Miletich, J. P., Goldhaber, S. Z., Hennekens, C. H., Ridker, P. M.. G20210A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. J Am Coll Cardiol; Jan 2001.

43. Olie, V., Plu-Bureau, G., Conard, J., Horellou, M. H., Canonico, M., Scarabin, P. Y.. Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. Menopause; May 2011.

44. Palareti, G., Cosmi, B., Legnani, C., Tosetto, A., Brusi, C., Iorio, A., Pengo, V., Ghirarduzzi, A., Pattacini, C., Testa, S., Lensing, A. W., Tripodi, A., Investigators, Prolong. D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med; Oct 26 2006.

45. Palareti, G., Legnani, C., Cosmi, B., Valdre, L., Lunghi, B., Bernardi, F., Coccheri, S.. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation; Jul 22 2003.

46. Prandoni, P., Noventa, F., Ghirarduzzi, A., Pengo, V., Bernardi, E., Pesavento, R., Iotti, M., Tormene, D., Simioni, P., Pagnan, A.. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica; Feb 2007.

47. Ridker, P. M., Miletich, J. P., Stampfer, M. J., Goldhaber, S. Z., Lindpaintner, K., Hennekens, C. H.. Factor V Leiden and risks of recurrent idiopathic venous thromboembolism. Circulation; Nov 15 1995.

48. Rodger, M. A., Kahn, S. R., Wells, P. S., Anderson, D. A., Chagnon, I., Le Gal, G., Solymoss, S., Crowther, M., Perrier, A., White, R., Vickars, L., Ramsay, T., Betancourt, M. T., Kovacs, M. J.. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. Cmaj; Aug 26 2008.

49. Roldan, V., Lecumberri, R., Munoz-Torrero, J. F., Vicente, V., Rocha, E., Brenner, B., Monreal, M., Investigators, Riete. Thrombophilia testing in patients with venous thromboembolism. Findings from the RIETE registry. Thromb Res; Jun 2009.

50. Roupie, A. L., Dossier, A., Goulenok, T., Perozziello, A., Papo, T., Sacre, K.. First venous thromboembolism in admitted patients younger than 50years old. Eur J Intern Med; Oct 2016.

51. Rossi, E., Za, T., Ciminello, A., Leone, G., De Stefano, V.. The risk of symptomatic pulmonary embolism due to proximal deep venous thrombosis differs in patients with different types of inherited thrombophilia. Thromb Haemost; Jun 2008.

52. Rupa-Matysek, J., Gil, L., Wojtasinska, E., Ciepluch, K., Lewandowska, M., Komarnicki, M.. The relationship between mean platelet volume and thrombosis recurrence in patients diagnosed with antiphospholipid syndrome. Rheumatol Int; Nov 2014.

53. Santamaria, M. G., Agnelli, G., Taliani, M. R., Prandoni, P., Moia, M., Bazzan, M., Guazzaloca, G., Ageno, W., Bertoldi, A., Silingardi, M., Tomasi, C., Ambrosio, G. B., Warfarin Optimal Duration Italian Trial, Investigators. Thrombophilic abnormalities and recurrence of venous thromboembolism in patients treated with standardized anticoagulant treatment. Thromb Res; 2005.

54. Schattner, A., Kasher, I., Berrebi, A.. Causes and outcome of deep-vein thrombosis in otherwise-healthy patients under 50 years. Qjm; Apr 1997.

55. Schulman, S., Kearon, C., Kakkar, A. K., Schellong, S., Eriksson, H., Baanstra, D., Kvamme, A. M., Friedman, J., Mismetti, P., Goldhaber, S. Z., Investigators, Re-Medy,Trial, Investigators, Re-Sonate,Trial. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med; Feb 21 2013.

56. Schulman, S., Lindmarker, P., Holmstrom, M., Larfars, G., Carlsson, A., Nicol, P., Svensson, E., Ljungberg, B., Viering, S., Nordlander, S., Leijd, B., Jahed, K., Hjorth, M., Linder, O., Beckman, M.. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. Journal of Thrombosis & Haemostasis; Apr 2006.

57. Schulman, S., Wahlander, K., Lundstrom, T., Clason, S. B., Eriksson, H., Investigators, Thrive,Iii. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. N Engl J Med; Oct 30 2003.

58. Simioni, P., Prandoni, P., Lensing, A. W., Manfrin, D., Tormene, D., Gavasso, S., Girolami, B., Sardella, C., Prins, M., Girolami, A.. Risk for subsequent venous thromboembolic complications in carriers of the prothrombin or the factor V gene mutation with a first episode of deep-vein thrombosis. Blood; Nov 15 2000.

59. Sonnevi, K., Tchaikovski, S. N., Holmstrom, M., Antovic, J. P., Bremme, K., Rosing, J., Larfars, G.. Obesity and thrombin-generation profiles in women with venous thromboembolism. Blood Coagul Fibrinolysis; Jul 2013.

60. Strandberg, K., Svensson, P. J., Ohlin, A. K.. Venous thromboembolism in carriers of the Factor V Leiden mutation and in patients without known thrombophilic risk factor; prediction of recurrence and APC-PCI complex concentration and/or soluble thrombomodulin antigen and activity. Thromb Res; 2007.

61. Sundquist, K., Sundquist, J., Svensson, P. J., Zoller, B., Memon, A. A.. Role of family history of venous thromboembolism and thrombophilia as predictors of recurrence: a prospective follow-up study. Journal of Thrombosis & Haemostasis; Dec 2015.

62. Sveinsdottir, S. V., Saemundsson, Y., Isma, N., Gottsater, A., Svensson, P. J.. Evaluation of recurrent venous thromboembolism in patients with Factor V Leiden mutation in heterozygous form. Thromb Res; Sep 2012.

63. Vitovec, M., Golan, L., Roztocil, K., Linhart, A.. The development of persistent thrombotic masses in patients with deep venous thrombosis randomized to long-term anticoagulation treatment. Vasa; Aug 2009.

64. Wahlander, K., Eriksson, H., Lundstrom, T., Billing Clason, S., Wall, U., Nystrom, P., Wessman, P., Schulman, S., Investigators, Thrive,Iii. Risk of recurrent venous thromboembolism or bleeding in relation to thrombophilic risk factors in patients receiving ximelagatran or placebo for long-term secondary prevention of venous thromboembolism. Br J Haematol; Apr 2006.

65. Weingarz, L., Schindewolf, M., Schwonberg, J., Hecking, C., Wolf, Z., Erbe, M., Lindhoff-Last, E., Linnemann, B.. Thrombophilia and risk of VTE recurrence according to the age at the time of first VTE manifestation. Vasa; Jul 2015.

QUESTION

Should thrombophilia testing and subsequent indefinite anticoagulant treatment in women positive for thrombophilia and stopping anticoagulant treatment in women negative for thrombophilia vs. no thrombophilia testing and stopping anticoagulant treatment in all be used for women with VTE provoked by pregnancy or postpartum who completed primary treatment?

POPULATION:	women with VTE provoked by pregnancy or postpartum who completed primary treatment
INTERVENTION:	thrombophilia testing and subsequent indefinite anticoagulant treatment in women positive for thrombophilia and stopping anticoagulant treatment in women negative for thrombophilia
COMPARISON:	no thrombophilia testing and stopping anticoagulant treatment in all
MAIN OUTCOMES:	Recurrent VTE; Major bleeding - Low risk (0.5% per year); Major bleeding - High risk (1.5% per year);
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Thrombophilia, either acquired or inherited, can be identified in many patients presenting with venous thromboembolism (VTE). The currently most commonly tested inherited thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. The current guideline aims to assess whether identifying patients positive for one or more of these defects allows management options which reduce patient important outcomes. Usually, 3 months of anticoagulant treatment is considered sufficient in the setting of VTE provoked by pregnancy or postpartum, due to the low risk of VTE recurrence. In this setting, thrombophilia testing might be considered to identify patients at higher risk of VTE recurrence, particularly in young patients, those with recurrent episodes of provoked thrombosis, or having a positive family history for VTE or thrombophilia. Although testing patients with provoked VTE may have a moderate chance of finding a positive test result, the true question is whether a positive test result should alter anticoagulant management. This question addresses whether thrombophilia testing and subsequent indefinite duration of anticoagulant treatment in patients positive for thrombophilia improves patient important outcomes in patients with VTE provoked by pregnancy or postpartum as compared with no thrombophilia testing and treating all patients with definite duration anticoagulant treatment. Since no randomized controlled trials have addressed this question, we used a modeling approach based on observational evidence for baseline risk of patient-important outcomes, prevalence of thrombophilia and increase in the risk of associated events with thrombophilia, and RCTs based evidence for the effect of extended anticoagulation on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies	The risk of VTE is increased during pregnancy because of physiological changes in the coagulation system, and other physical changes, such as stasis in large veins of the lower extremities from uterine compression and the delivery process. In pregnancy, the risk of VTE is increased in women who have certain inherited (and acquired) thrombophilias and	

○ Don't know	in those with multiple thrombophilic defects. Data suggest that at least 50 percent of women with VTE during pregnancy have an acquired or inherited thrombophilia.(Marik 2008) All thrombophilias, however, do not confer equivalent degrees of risk for thrombotic complications during pregnancy.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Evidence Profile.	Desirable effect = preventing VTE recurrence. VTE recurrences would be avoided in patients who are positive for thrombophilia by extending their anticoagulation treatment. As for patients with VTE provoked by a non-surgical major non-transient risk factors, the panel considered a reduction in VTE recurrence of 5% to be the threshold to consider the effect Large, and a 2% reduction to be Small in the overall population of interest. However, the panel also discussed that a 2% reduction may be considered Large in subgroups that are at lower risk, such as young women.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	See Evidence Profile.	Undesirable effect = causing major bleeding. Major bleedings would be caused in patients who are positive for thrombophilia by extending their anticoagulation treatment. The panel considered the increase in major bleeding to be Trivial in most women who are at low risk of bleeding, but Small in those at high risk.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows using a scale from 0 (worst possible scenario, usually death), to 1 (best possible scenario, usually perfect health):** **Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(1, 2, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3) **Gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off)(2, 3) **Minor intracranial bleeding event:** 0.75 (standard gamble)(2) **Major intracranial bleeding event:** 0.15 (standard gamble)(2)	The panel considered that clinicians may value avoiding major bleeding more (they do not want to cause harm), while patients may value avoiding VTE events more (they may prefer avoiding a recurrence of blood clots).

	Anticoagulant therapy Patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome.(3) Patients would favor efficacy and safety over convenience of route of administration.(6) Also, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events.(6, 7, 8)	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		No studies assessed indefinite anticoagulation as life-long treatment. The panel observed that the appraisal of the comparison of the two interventions (testing and treating positives vs treating none) was limited by the absence of studies comparing extended anticoagulation as life-long treatment versus no anticoagulation, which the panel had to extrapolate.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		**The panel considered the following cost ranges:** - Cost for testing: $400 -$2,000 per patient - Cost for treatment: $1,000-$ 4,500 per patient per year In assessing the resources required the panel considered that the intervention added the cost for testing all patients and treating the patients positive for thrombophilia. The panel did not consider the costs for recurrent clots or for bleeding events.

Intervention Costs:

Test (source)	Approximate Cost (2005)	Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016)	(14/12/2016) £1 = $1,27
Full Blood Count	£2.55	£3.29	**$4,18**
Protein C	£11.67	£15.5	**$19,12**
Free Protein S	£11.67	£15.5	**$19,12**
Antithrombin	£11.67	£15.5	**$19,12**
APCR	£10.73	£13.84	**$17,58**
Factor V Leiden	£85.00	£109.65	**$141,45**
Prothrombin gene mutation	£85.00	£109.65	**$141,45**
Lupus Anticoagulant	£10.73	£13.84	**$17,58**
Antiphospholipid antibodies	£12.30	£15.87	**$20,15**
Anti Beta-2 GP1 antibody	£9.50	£12.25	**$15,81**
The potential cost of a full thrombophilia screen	£250.82,	£323.56	**$410,92**

Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx

Cost of the health outcomes:(9)

- **Recurrent VTE:** 11,000 to 15,000 USD

- **Major bleeding:** 11,000 to 22,000 USD

Cost of interventions:(10)

- **Dabigatran:** Cost per month: $300.44–$600.88 USD

- **Rivaroxaban:** Cost per month: $300.42–$600.84 USD

- **Apixaban:** Cost per month: $300.44–$600.88

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No specific CEA studies were identified for testing in women with VTE provoked by pregnancy or post-partum.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(11)	The panel considered that the health system/service coverage/access to care will be the main aspect affecting health equity. USA is an example where promotion of testing that is not covered by insurance would generate inequities. I.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies. Also, the additional cost for indefinite anticoagulant treatment of the women positive for thrombophilia may or may not be covered.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Research studies suggested the following regarding acceptability and barriers associated with testing and treatment: **Patients**: A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(12)	The panel considered testing acceptable for many doctors, although maybe not for all. Patients are in general willing to undergo thrombophilia testing when testing is proposed by their doctor.

	Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(13) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers**: A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(14) **Payers**: At present, thrombophilia testing is discouraged and in some health care settings not reimbursed. **Pregnancy specific research evidence**: Four studies assessed several categories of acceptability depicted as compliance / adherence of different interventions for the prevention of thromboembolism during delivery(15, 16), adherence to enoxaparin(17), and for adherence to guidelines recommendations in general in obstetric patient population.(18) Compliance or acceptability was deemed rather adequate for postnatal thromboprophylaxis (83%), enoxaparin (93%) and for guidelines in obstetric patients in general (69%).	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation.

	months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(19) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending.(20) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(21) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(22) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(23)	External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the	Probably favors the intervention	Favors the intervention	Varies	**No included studies**

	JUDGEMENT						
			comparison				
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

After completion of primary treatment for women with a symptomatic VTE provoked by pregnancy or postpartum, the ASH guideline panel suggests testing for thrombophilia and indefinite anticoagulant treatment in positive women over no testing for thrombophilia and stopping anticoagulant treatment in all women (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:

- A strategy with testing for thrombophilia would mean that positive women would receive indefinite anticoagulant treatment, and negative women negative would stop anticoagulant treatment.

- This recommendation refers to testing for inherited and acquired types of thrombophilia.

Justification

The panel considered that thrombophilia testing and extending anticoagulant treatment in thrombophilia positives is likely producing benefit in terms of prevention of VTE recurrence that outweighs the risk of major bleeding in patients at low risk of bleeding, and may justify the costs of indefinite anticoagulant treatment.

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation. Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

Considering the limited specific data in women with VTE provoked by pregnancy or postpartum, research needed to provide reliable estimates for the prevalence of thrombophilia, risk of VTE recurrence, and cost-effectiveness of testing.

Randomized controlled trials comparing testing vs no testing would be ideal but have shown to be difficult to perform.(Cohn 2008; Cohn Cochrane review 2012) The second best option would be a pragmatic non-randomized controlled study comparing tested and non-tested patients with VTE.(Coppens 2008)

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
7. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
8. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
9. Grosse, S. D., Nelson, R. E., Nyarko, K. A., Richardson, L. C., Raskob, G. E.. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res; Jan 2016.
10. Biskupiak, J., Ghate, S. R., Jiao, T., Brixner, D.. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. J Manag Care Pharm; Nov-Dec 2013.
11. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
12. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
13. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
14. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
15. Hordern, C. E., Bircher, C. W., Prosser-Snelling, E. C., Fraser, F. K., Smith, R. P.. Patient compliance with postnatal thromboprophylaxis: An observational study. J Obstet Gynaecol; 2015.
16. Guimicheva, B., Czuprynska, J., Arya, R.. The prevention of pregnancy-related venous thromboembolism. Br J Haematol; Jan 2015.
17. Patel, J. P., Auyeung, V., Patel, R. K., Marsh, M. S., Green, B., Arya, R., Davies, J. G.. Women's views on and adherence to low-molecular-weight heparin therapy during pregnancy and the puerperium. Journal of Thrombosis & Haemostasis; Dec 2012.
18. Cregan, A., Higgins, J. R., O'Shea, S.. Implementation of thromboprophylaxis guidelines. Ir Med J; Mar 2013.
19. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
20. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
21. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
22. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
23. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In women with VTE provoked by pregnancy or postpartum who completed primary treatment, should thrombophilia testing and subsequent indefinite anticoagulant treatment in women positive for thrombophilia and stopping anticoagulant treatment in women negative for thrombophilia compared to no thrombophilia testing and stopping anticoagulant treatment in all be used?

Setting:

Bibliography: See reference list and footnotes. [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Recurrent VTE (assessed with: any DVT or PE)									
25 [a,b,c,d,e,f,g]	observational studies	not serious	not serious	very serious [h]	serious [i]	none	When testing 1,000 women who completed primary treatment of VTE provoked by pregnancy or postpartum for any type of thrombophilia, and treating the 380 positives with indefinite anticoagulation (ranging from 216 to 595), 29 VTE recurrences will occur per year (ranging from 15 to 40). When not testing 1,000 women for thrombophilia and stopping treatment in all of them, 50 VTE recurrences will occur per year. Therefore, a thrombophilia testing strategy is associated with 380 more women treated with indefinite anticoagulation (ranging from 216 to 595) and **21 fewer VTE recurrences (ranging from 10 to 35)** per 1,000 patients per year compared with a no testing strategy. [j]	⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding - Low risk (0.5% per year)[k]									
32 [c,d,l,m,n]	observational studies	not serious	not serious	serious [o]	not serious	none	When testing 1,000 women who completed primary treatment of VTE provoked by pregnancy or postpartum, and who are at low risk of major bleeding, for any type of thrombophilia, and treating the 380 positives with indefinite anticoagulation (ranging from 216 to 595), 7 major bleedings will occur per year (ranging from 5 to 12). When not testing 1,000 women for thrombophilia and stopping treatment in all of them, 5 major bleedings will occur per year. Therefore, a thrombophilia testing strategy is associated with 380 more women treated with indefinite anticoagulation (ranging from 216 to 595) and **2 more major bleedings (ranging from 0 to 7)** per 1,000 patients per year compared with a no testing strategy. [p]	⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding - High risk (1.5% per year)[q]									
32 [c,d,l,m,r]	observational studies	not serious	not serious	serious [o]	serious [i]	none	When testing 1,000 women who completed primary treatment of VTE provoked by pregnancy or postpartum, and who are at high risk of major bleeding, for any type of thrombophilia, and treating the 380 positives with indefinite anticoagulation (ranging from 216 to 595), 22 major bleedings will occur per year (ranging from 16 to 32). When not testing 1,000 women for thrombophilia and stopping treatment in all of them, 15 major bleedings will occur per year. Therefore, a thrombophilia testing strategy is associated with 380 more women treated with indefinite anticoagulation (ranging from 216 to 595) and **7 more major bleedings (ranging from 1 to 21)** per 1,000 patients per year compared with a no testing strategy. [s]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE recurrence, 1 systematic review; Prevalence, 20 studies; Risk association for thrombophilia positive versus negative, 6 studies (all also reported Prevalence); Extended anticoagulation effect, 4 RCTs

b. Overall risk for VTE recurrence: Iorio 2010

c. Thrombophilia prevalence, used for calculation: Bezemer 2009, Cebi 2009, Di Minno 2014, Garcia-Fuster 2005, Heit 2010, Kearon 1999, Kearon 2018, Lim 2017, Mello 2010, Meyer 2015, Olie 2011, Palareti 2003, Prandoni 2007, Roldan 2009, Rossi 2008, Santamaria 2005, Schattner 1997, Schulman 2006, Sundquist 2015, Weingarz 2015

d. Prevalence of specific thrombophilia types, used to verify calculation estimate: Ahmad 2016, Ahmad 2016, Ahmad 2017, Asim 2017, Baarslag 2004, Baglin 2003, Brouwer 2009, Bruwer 2016, Christiansen 2005, De Stefano 1999, De Stefano 2006, Eichinger 1999, Eichinger 2002, Eischer 2017, Gonzalez-Porras 2006, Heijboer 1990, Hirmerova 2014, Hoibraaten 2000, Kearon 2008, Laczkovics 2007, Lee 2017, Lijfering 2010, Lindmarker 1999, Marcucci 2003, Mateo 1997, Miles 2001, Ridker 1995, Rodger 2008, Roupie 2016, Rupa-Matysek 2014, Simioni 2000, Sonnevi 2013, Strandberg 2007, Sveinsdottir 2012, The Procare group 2003, Wahlander 2006

e. Thrombophilia positive vs negative risk association, used for calculation: Kearon, 1999, Kearon 2018, Mello 2010, Santamaria 2005, Schulman 2006, Weingarz 2015

f. Risk association for specific thrombophilia types, used to verify calculation estimate: Baglin 2003, Brouwer 2009, Christiansen 2005, De Stefano 1999, De Stefano 2006, Di Minno 2014, Eichinger 2002, Gonzalez-Porras 2006, Hoibraaten 2000, Lijfering 2010, Lindmarker 1999, Marcucci 2003, Miles 2001, Palareti 2003, Prandoni 2007, Ridker 1995, Rodger 2008, Schattner 1997, Simioni 2000, Strandberg 2007, Wahlander 2006

g. Effect of extended anticoagulation treatment, used in calculation: Agnelli 2013, Bauersachs 2010, Schulman 2003, Schulman 2013

h. The effect was indirectly calculated using evidence from an indirect population (patients with a symptomatic VTE provoked by a non-surgical major transient risk factor), and using separate studies for thrombophilia prevalence, relative risk of thrombophilia positives vs negatives, and the effect of treatment

i. There is a clinically important difference between the smallest and largest possible effect of the testing strategy

j. Based on the following estimates: Overall risk for VTE recurrence, 50 per 1,000; Prevalence of any thrombophilia, 38.0% (min 21.6 - max 59.5); Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 1.65 (95%CI: 1.28-2.47); Relative risk of VTE recurrence with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.15 (0.10-0.23). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, upper CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

k. Among RCTs assessing the effect of extended treatment against limited treatment, the lowest observed rate of major bleeding with limited treatment was 0.5% (Agnelli 2001)

l. Number of studies used in calculations: Overall risk, 1 RCT; Prevalence, 20 studies; Extended anticoagulation effect, 11 RCTs

m. Effect of extended anticoagulation treatment, used in calculation: Agnelli 2001, Agnelli 2003, Agnelli 2013, Bauersachs 2010, Couturaud 2015, Eischer 2009, Kearon 1999, Palareti 2006, Ridker 2003, Schulman 2003, Schulman 2013

n. Overall risk for Major bleeding: Agnelli 2001

o. The effect was indirectly calculated using separate studies for thrombophilia prevalence and the effect of treatment

p. Based on the following estimates: Overall risk for Major bleeding of 5 per 1,000; Prevalence of any thrombophilia, 38.0% (21.6-59.5); Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 2.17 (1.40-3.35). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the smallest treatment effect (lower CI).

q. Among RCTs assessing the effect of extended treatment against limited treatment, the highest observed rate of major bleeding with limited treatment was 1.5% (Agnelli 2013)

r. Overall risk for Major bleeding: Agnelli 2013

s. Based on the following estimates: Overall risk for Major bleeding of 15 per 1,000; Prevalence of any thrombophilia, 38.0% (21.6-59.5); Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 2.17 (1.40-3.35). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the smallest treatment effect (lower CI).

References

1. Agnelli, G., Buller, H. R., Cohen, A., Curto, M., Gallus, A. S., Johnson, M., Porcari, A., Raskob, G. E., Weitz, J. I., Investigators, Amplify-Ext. Apixaban for extended treatment of venous thromboembolism. N Engl J Med; Feb 21 2013.

2. Agnelli, G., Prandoni, P., Becattini, C., Silingardi, M., Taliani, M. R., Miccio, M., Imberti, D., Poggio, R., Ageno, W., Pogliani, E., Porro, F., Zonzin, P., Warfarin Optimal Duration Italian Trial, Investigators. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med; Jul 1 2003.

3. Agnelli, G., Prandoni, P., Santamaria, M. G., Bagatella, P., Iorio, A., Bazzan, M., Moia, M., Guazzaloca, G., Bertoldi, A., Tomasi, C., Scannapieco, G., Ageno, W., Warfarin Optimal Duration Italian Trial, Investigators. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med; Jul 19 2001.

4. Ahmad, A., Sundquist, K., Zoller, B., Dahlback, B., Svensson, P. J., Sundquist, J., Memon, A. A.. Identification of polymorphisms in Apolipoprotein M gene and their relationship with risk of recurrent venous thromboembolism. Thromb Haemost; Aug 30 2016.

5. Asim, M., Al-Thani, H., El-Menyar, A.. Recurrent Deep Vein Thrombosis After the First Venous Thromboembolism Event: A Single-Institution Experience. Med Sci Monit; May 20 2017.

6. Baarslag, H. J., Koopman, M. M., Hutten, B. A., Linthorst Homan, M. W., Buller, H. R., Reekers, J. A., van Beek, E. J.. Long-term follow-up of patients with suspected deep vein thrombosis of the upper extremity: survival, risk factors and post-thrombotic syndrome. Eur J Intern Med; Dec 2004.

7. Baglin, T., Luddington, R., Brown, K., Baglin, C.. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet; Aug 16 2003.

8. Bezemer, I. D., van der Meer, F. J., Eikenboom, J. C., Rosendaal, F. R., Doggen, C. J.. The value of family history as a risk indicator for venous thrombosis. Archives of Internal Medicine; Mar 23 2009.

9. Brouwer, J. L., Lijfering, W. M., Ten Kate, M. K., Kluin-Nelemans, H. C., Veeger, N. J., van der Meer, J.. High long-term absolute risk of recurrent venous thromboembolism in patients with hereditary deficiencies of protein S, protein C or antithrombin. Thromb Haemost; Jan 2009.

10. Bruwer, G., Limperger, V., Kenet, G., Klostermeier, U. C., Shneyder, M., Degenhardt, F., Finckh, U., Heller, C., Holzhauer, S., Trappe, R., Kentouche, K., Knoefler, R., Kurnik, K., Krumpel, A., Lauten, M., Manner, D., Mesters, R., Junker, R., Nowak-Gottl, U.. Impact of high risk thrombophilia status on recurrence among children and adults with VTE: An observational multicenter cohort study. Blood Cells Mol Dis; Nov 2016.

11. Cebi, N., Tanriverdi, S.. Aetiology of deep vein thrombosis in 63 turkish patients. Turkish Journal of Medical Sciences; April 2009.

12. Christiansen, S. C., Cannegieter, S. C., Koster, T., Vandenbroucke, J. P., Rosendaal, F. R.. Thrombophilia, clinical factors, and recurrent venous thrombotic events. Jama; May 18 2005.

13. Couturaud, F., Sanchez, O., Pernod, G., Mismetti, P., Jego, P., Duhamel, E., Provost, K., dit Sollier, C. B., Presles, E., Castellant, P., Parent, F., Salaun, P. Y., Bressollette, L., Nonent, M., Lorillon, P., Girard, P., Lacut, K., Guegan, M., Bosson, J. L., Laporte, S., Leroyer, C., Decousus, H., Meyer, G., Mottier, D., Investigators, Padis-Pe. Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism: The PADIS-PE Randomized Clinical Trial. Jama; Jul 7 2015.

14. De Stefano, V., Martinelli, I., Mannucci, P. M., Paciaroni, K., Chiusolo, P., Casorelli, I., Rossi, E., Leone, G.. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med; Sep 9 1999.

15. De Stefano, V., Simioni, P., Rossi, E., Tormene, D., Za, T., Pagnan, A., Leone, G.. The risk of recurrent venous thromboembolism in patients with inherited deficiency of natural anticoagulants antithrombin, protein C and protein S. Haematologica; May 2006.

16. Di Minno, M. N., Dentali, F., Lupoli, R., Ageno, W.. Mild antithrombin deficiency and risk of recurrent venous thromboembolism: a prospective cohort study. Circulation; Jan 28 2014.

17. Eichinger, S., Minar, E., Hirschl, M., Bialonczyk, C., Stain, M., Mannhalter, C., Stumpflen, A., Schneider, B., Lechner, K., Kyrle, P. A.. The risk of early recurrent venous thromboembolism after oral anticoagulant therapy in patients with the G20210A transition in the prothrombin gene. Thromb Haemost; Jan 1999.

18. Eichinger, S., Weltermann, A., Mannhalter, C., Minar, E., Bialonczyk, C., Hirschl, M., Schonauer, V., Lechner, K., Kyrle, P. A.. The risk of recurrent venous thromboembolism in heterozygous carriers of factor V Leiden and a first spontaneous venous thromboembolism. Archives of Internal Medicine; Nov 11 2002.

19. Eischer, L., Gartner, V., Schulman, S., Kyrle, P. A., Eichinger, S., investigators, Aurec-Fviii. 6 versus 30 months anticoagulation for recurrent venous thrombosis in patients with high factor VIII. Ann Hematol; May 2009.

20. Eischer, L., Kammer, M., Traby, L., Kyrle, P. A., Eichinger, S.. Risk of cancer after anticoagulation in patients with unprovoked venous thromboembolism: an observational cohort study. Journal of Thrombosis and Haemostasis; July 2017.

21. Garcia-Fuster, M. J., Forner, M. J., Fernandez, C., Gil, J., Vaya, A., Maldonado, L.. Long-term prospective study of recurrent venous thromboembolism in patients younger than 50 years. Pathophysiol Haemost Thromb; 2005.

22. Gonzalez-Porras, J. R., Garcia-Sanz, R., Alberca, I., Lopez, M. L., Balanzategui, A., Gutierrez, O., Lozano, F., San Miguel, J.. Risk of recurrent venous thrombosis in patients with G20210A mutation in the prothrombin gene or factor V Leiden mutation. Blood Coagul Fibrinolysis; Jan 2006.

23. Group, The,Procare. Is recurrent venous thromboembolism more frequent in homozygous patients for the factor V Leiden mutation than in heterozygous patients?. Blood Coagulation and Fibrinolysis; September 2003.

24. Heijboer, H., Brandjes, D. P., Buller, H. R., Sturk, A., ten Cate, J. W.. Deficiencies of coagulation-inhibiting and fibrinolytic proteins in outpatients with deep-vein thrombosis. N Engl J Med; Nov 29 1990.

25. Heit, J. A., Beckman, M. G., Bockenstedt, P. L., Grant, A. M., Key, N. S., Kulkarni, R., Manco-Johnson, M. J., Moll, S., Ortel, T. L., Philipp, C. S., Thrombosis, C.,D.,C., Hemostasis Centers, Research, Prevention, Network. Comparison of characteristics from White- and Black-Americans with venous thromboembolism: a cross-sectional study. Am J Hematol; Jul 2010.

26. Hirmerova, J., Seidlerova, J., Subrt, I.. The association of factor V Leiden with various clinical patterns of venous thromboembolism-the factor V Leiden paradox. Qjm; Sep 2014.

27. Hoibraaten, E., Qvigstad, E., Arnesen, H., Larsen, S., Wickstrom, E., Sandset, P. M.. Increased risk of recurrent venous thromboembolism during hormone replacement therapy--results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). Thromb Haemost; Dec 2000.

28. Investigators, Einstein, Bauersachs, R., Berkowitz, S. D., Brenner, B., Buller, H. R., Decousus, H., Gallus, A. S., Lensing, A. W., Misselwitz, F., Prins, M. H., Raskob, G. E., Segers, A., Verhamme, P., Wells, P., Agnelli, G., Bounameaux, H., Cohen, A., Davidson, B. L., Piovella, F., Schellong, S.. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med; Dec 23 2010.

29. Iorio, A., Kearon, C., Filippucci, E., Marcucci, M., Macura, A., Pengo, V., Siragusa, S., Palareti, G.. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. Archives of Internal Medicine; Oct 25 2010.

30. Kearon, C., Gent, M., Hirsh, J., Weitz, J., Kovacs, M. J., Anderson, D. R., Turpie, A. G., Green, D., Ginsberg, J. S., Wells, P., MacKinnon, B., Julian, J. A.. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med; Mar 25 1999.

31. Kearon, C., Julian, J. A., Kovacs, M. J., Anderson, D. R., Wells, P., Mackinnon, B., Weitz, J. I., Crowther, M. A., Dolan, S., Turpie, A. G., Geerts, W., Solymoss, S., van Nguyen, P., Demers, C., Kahn, S. R., Kassis, J., Rodger, M., Hambleton, J., Gent, M., Ginsberg, J. S., Investigators, Elate. Influence of thrombophilia on risk of recurrent venous thromboembolism while on warfarin: results from a randomized trial. Blood; Dec 1 2008.

32. Kearon, C., Parpia, S., Spencer, F. A., Baglin, T., Stevens, S. M., Bauer, K. A., Lentz, S. R., Kessler, C. M., Douketis, J. D., Moll, S., Kaatz, S., Schulman, S., Connors, J. M., Ginsberg, J. S., Spadafora, L., Bhagirath, V., Liaw, P. C., Weitz, J. I., Julian, J. A.. Antiphospholipid antibodies and recurrent thrombosis after a first unprovoked venous thromboembolism. Blood; May 10 2018.

33. Laczkovics, C., Grafenhofer, H., Kaider, A., Quehenberger, P., Simanek, R., Mannhalter, C., Lechner, K., Pabinger, I.. Risk of recurrence after a first venous thromboembolic event in young women. Haematologica; Sep 2007.

34. Lee, S. Y., Kim, E. K., Kim, M. S., Shin, S. H., Chang, H., Jang, S. Y., Kim, H. J., Kim, D. K.. The prevalence and clinical manifestation of hereditary thrombophilia in Korean patients with unprovoked venous thromboembolisms. PLoS ONE [Electronic Resource]; 2017.

35. Lijfering, W. M., Middeldorp, S., Veeger, N. J., Hamulyak, K., Prins, M. H., Buller, H. R., van der Meer, J.. Risk of recurrent venous thrombosis in homozygous carriers and double heterozygous carriers of factor V Leiden and prothrombin G20210A. Circulation; Apr 20 2010.

36. Lim, H. Y., Chua, C. C., Tacey, M., Sleeman, M., Donnan, G., Nandurkar, H., Ho, P.. Venous thromboembolism management in Northeast Melbourne: how does it compare to international guidelines and data?. Intern Med J; Sep 2017.

37. Lindmarker, P., Schulman, S., Sten-Linder, M., Wiman, B., Egberg, N., Johnsson, H.. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. DURAC Trial Study Group. Duration of Anticoagulation. Thromb Haemost; May 1999.

38. Marcucci, R., Liotta, A. A., Cellai, A. P., Rogolino, A., Gori, A. M., Giusti, B., Poli, D., Fedi, S., Abbate, R., Prisco, D.. Increased plasma levels of lipoprotein(a) and the risk of idiopathic and recurrent venous thromboembolism. Am J Med; Dec 1 2003.

39. Mateo, J., Oliver, A., Borrell, M., Sala, N., Fontcuberta, J.. Laboratory evaluation and clinical characteristics of 2,132 consecutive unselected patients with venous thromboembolism--results of the Spanish Multicentric Study on Thrombophilia (EMET-Study). Thromb Haemost; Mar 1997.

40. Mello, T. B., Orsi, F. L., Montalvao, S. A., Ozelo, M. C., de Paula, E. V., Annichinno-Bizzachi, J. M.. Long-term prospective study of recurrent venous thromboembolism in a Hispanic population. Blood Coagul Fibrinolysis; Oct 2010.

41. Meyer, M. R., Witt, D. M., Delate, T., Johnson, S. G., Fang, M., Go, A., Clark, N. P.. Thrombophilia testing patterns amongst patients with acute venous thromboembolism. Thromb Res; Dec 2015.

42. Miles, J. S., Miletich, J. P., Goldhaber, S. Z., Hennekens, C. H., Ridker, P. M.. G20210A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. J Am Coll Cardiol; Jan 2001.

43. Olie, V., Plu-Bureau, G., Conard, J., Horellou, M. H., Canonico, M., Scarabin, P. Y.. Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. Menopause; May 2011.

44. Palareti, G., Cosmi, B., Legnani, C., Tosetto, A., Brusi, C., Iorio, A., Pengo, V., Ghirarduzzi, A., Pattacini, C., Testa, S., Lensing, A. W., Tripodi, A., Investigators, Prolong. D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med; Oct 26 2006.

45. Palareti, G., Legnani, C., Cosmi, B., Valdre, L., Lunghi, B., Bernardi, F., Coccheri, S.. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation; Jul 22 2003.

46. Prandoni, P., Noventa, F., Ghirarduzzi, A., Pengo, V., Bernardi, E., Pesavento, R., Iotti, M., Tormene, D., Simioni, P., Pagnan, A.. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica; Feb 2007.

47. Ridker, P. M., Miletich, J. P., Stampfer, M. J., Goldhaber, S. Z., Lindpaintner, K., Hennekens, C. H.. Factor V Leiden and risks of recurrent idiopathic venous thromboembolism. Circulation; Nov 15 1995.

48. Rodger, M. A., Kahn, S. R., Wells, P. S., Anderson, D. A., Chagnon, I., Le Gal, G., Solymoss, S., Crowther, M., Perrier, A., White, R., Vickars, L., Ramsay, T., Betancourt, M. T., Kovacs, M. J.. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. Cmaj; Aug 26 2008.

49. Roldan, V., Lecumberri, R., Munoz-Torrero, J. F., Vicente, V., Rocha, E., Brenner, B., Monreal, M., Investigators, Riete. Thrombophilia testing in patients with venous thromboembolism. Findings from the RIETE registry. Thromb Res; Jun 2009.

50. Rossi, E., Za, T., Ciminello, A., Leone, G., De Stefano, V.. The risk of symptomatic pulmonary embolism due to proximal deep venous thrombosis differs in patients with different types of inherited thrombophilia. Thromb Haemost; Jun 2008.

51. Roupie, A. L., Dossier, A., Goulenok, T., Perozziello, A., Papo, T., Sacre, K.. First venous thromboembolism in admitted patients younger than 50years old. Eur J Intern Med; Oct 2016.

52. Rupa-Matysek, J., Gil, L., Wojtasinska, E., Ciepluch, K., Lewandowska, M., Komarnicki, M.. The relationship between mean platelet volume and thrombosis recurrence in patients diagnosed with antiphospholipid syndrome. Rheumatol Int; Nov 2014.

53. Santamaria, M. G., Agnelli, G., Taliani, M. R., Prandoni, P., Moia, M., Bazzan, M., Guazzaloca, G., Ageno, W., Bertoldi, A., Silingardi, M., Tomasi, C., Ambrosio, G. B., Warfarin Optimal Duration Italian Trial, Investigators. Thrombophilic abnormalities and recurrence of venous thromboembolism in patients treated with standardized anticoagulant treatment. Thromb Res; 2005.

54. Schattner, A., Kasher, I., Berrebi, A.. Causes and outcome of deep-vein thrombosis in otherwise-healthy patients under 50 years. Qjm; Apr 1997.

55. Schulman, S., Kearon, C., Kakkar, A. K., Schellong, S., Eriksson, H., Baanstra, D., Kvamme, A. M., Friedman, J., Mismetti, P., Goldhaber, S. Z., Investigators, Re-Medy,Trial, Investigators, Re-Sonate,Trial. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med; Feb 21 2013.

56. Schulman, S., Lindmarker, P., Holmstrom, M., Larfars, G., Carlsson, A., Nicol, P., Svensson, E., Ljungberg, B., Viering, S., Nordlander, S., Leijd, B., Jahed, K., Hjorth, M., Linder, O., Beckman, M.. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. Journal of Thrombosis & Haemostasis; Apr 2006.

57. Schulman, S., Wahlander, K., Lundstrom, T., Clason, S. B., Eriksson, H., Investigators, Thrive,Iii. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. N Engl J Med; Oct 30 2003.

58. Simioni, P., Prandoni, P., Lensing, A. W., Manfrin, D., Tormene, D., Gavasso, S., Girolami, B., Sardella, C., Prins, M., Girolami, A.. Risk for subsequent venous thromboembolic complications in carriers of the prothrombin or the factor V gene mutation with a first episode of deep-vein thrombosis. Blood; Nov 15 2000.

59. Sonnevi, K., Tchaikovski, S. N., Holmstrom, M., Antovic, J. P., Bremme, K., Rosing, J., Larfars, G.. Obesity and thrombin-generation profiles in women with venous thromboembolism. Blood Coagul Fibrinolysis; Jul 2013.

60. Strandberg, K., Svensson, P. J., Ohlin, A. K.. Venous thromboembolism in carriers of the Factor V Leiden mutation and in patients without known thrombophilic risk factor; prediction of recurrence and APC-PCI complex concentration and/or soluble thrombomodulin antigen and activity. Thromb Res; 2007.

61. Sundquist, K., Sundquist, J., Svensson, P. J., Zoller, B., Memon, A. A.. Role of family history of venous thromboembolism and thrombophilia as predictors of recurrence: a prospective follow-up study. Journal of Thrombosis & Haemostasis; Dec 2015.

62. Sveinsdottir, S. V., Saemundsson, Y., Isma, N., Gottsater, A., Svensson, P. J.. Evaluation of recurrent venous thromboembolism in patients with Factor V Leiden mutation in heterozygous form. Thromb Res; Sep 2012.

63. Vitovec, M., Golan, L., Roztocil, K., Linhart, A.. The development of persistent thrombotic masses in patients with deep venous thrombosis randomized to long-term anticoagulation treatment. Vasa; Aug 2009.

64. Wahlander, K., Eriksson, H., Lundstrom, T., Billing Clason, S., Wall, U., Nystrom, P., Wessman, P., Schulman, S., Investigators, Thrive,Iii. Risk of recurrent venous thromboembolism or bleeding in relation to thrombophilic risk factors in patients receiving ximelagatran or placebo for long-term secondary prevention of venous thromboembolism. Br J Haematol; Apr 2006.

65. Weingarz, L., Schindewolf, M., Schwonberg, J., Hecking, C., Wolf, Z., Erbe, M., Lindhoff-Last, E., Linnemann, B.. Thrombophilia and risk of VTE recurrence according to the age at the time of first VTE manifestation. Vasa; Jul 2015.

QUESTION

Should thrombophilia testing and subsequent indefinite anticoagulant treatment in women positive for thrombophilia and stopping anticoagulant treatment in women negative for thrombophilia vs. no thrombophilia testing and stopping anticoagulant treatment in all be used for women with VTE associated with use of combined oral contraceptives who completed primary treatment?

POPULATION:	women with VTE associated with use of combined oral contraceptives who completed primary treatment
INTERVENTION:	thrombophilia testing and subsequent indefinite anticoagulant treatment in women positive for thrombophilia and stopping anticoagulant treatment in women negative for thrombophilia
COMPARISON:	no thrombophilia testing and stopping anticoagulant treatment in all
MAIN OUTCOMES:	Recurrent VTE; Major bleeding - Low risk (0.5% per year); Major bleeding - High risk (1.5% per year);
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Thrombophilia, either acquired or inherited, can be identified in many patients presenting with venous thromboembolism (VTE). The currently most commonly tested inherited thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. The current guideline aims to assess whether identifying patients positive for one or more of these defects allows management options which reduce patient important outcomes. Usually, 3 months of anticoagulant treatment is considered sufficient in the setting of VTE associated with combined oral contraceptives, due to the low risk of VTE recurrence. In this setting, thrombophilia testing might be considered to identify patients at higher risk of VTE recurrence, particularly in young patients, those with recurrent episodes of provoked thrombosis, or having a positive family history for VTE or thrombophilia. Although testing patients with provoked VTE may have a moderate chance of finding a positive test result, the true question is whether a positive test result should alter anticoagulant management. This question addresses whether thrombophilia testing and subsequent indefinite duration of anticoagulant treatment in patients positive for thrombophilia improves patient important outcomes in patients with VTE associated with combined oral contraceptives as compared with no thrombophilia testing and treating all patients with definite duration anticoagulant treatment. Since no randomized controlled trials have addressed this question, we used a modeling approach based on observational evidence for baseline risk of patient-important outcomes, prevalence of thrombophilia and increase in the risk of associated events with thrombophilia, and RCTs based evidence for the effect of extended anticoagulation on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies		

○ Don't know		

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Evidence Profile.	Desirable effect = preventing VTE recurrence. VTE recurrences would be avoided in patients who are positive for thrombophilia by extending their anticoagulation treatment. As for patients with VTE provoked by a non-surgical major non-transient risk factors, the panel considered a reduction in VTE recurrence of 5% to be the threshold to consider the effect Large, and a 2% reduction to be Small in the overall population of interest. However, the panel also discussed that a 2% reduction may be considered Large in subgroups that are at lower risk, such as young women.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	See Evidence Profile.	Undesirable effect = causing major bleeding. Major bleedings would be caused in patients who are positive for thrombophilia by extending their anticoagulation treatment. The panel considered the increase in major bleeding to be Trivial in most women who are at low risk of bleeding, but Small in those at high risk.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows using a scale from 0 (worst possible scenario, usually death), to 1 (best possible scenario, usually perfect health):** **Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(1, 2, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3) **Gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off)(2, 3) **Minor intracranial bleeding event:** 0.75 (standard gamble)(2)	The panel considered that clinicians may value avoiding major bleeding more (they do not want to cause harm), while patients may value avoiding VTE events more (they may prefer avoiding a recurrence of blood clots).

	Major intracranial bleeding event: 0.15 (standard gamble)(2) **Anticoagulant therapy** Patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome.(3) Patients would favor efficacy and safety over convenience of route of administration.(6) Also, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events.(6, 7, 8)	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		No studies assessed extended anticoagulation as life-long treatment. The panel observed that the appraisal of the comparison of the two interventions (testing and treating positives vs treating none) was limited by the absence of studies comparing extended anticoagulation as life-long treatment versus no anticoagulation, which the panel had to extrapolate. The panel assumed that women would discontinue combined oral contraceptives prior to discontinuation of anticoagulation.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		**The panel considered the following cost ranges:** - Cost for testing: $400 -$2,000 per patient - Cost for treatment: $1,000-$ 4,500 per patient per year In assessing the resources required the panel considered that the intervention (testing and treating only patients positive for thrombophilia) added the cost for testing all patients but "saved" the cost of treatment avoided in the patients negative for thrombophilia. The panel did not consider the costs for recurrent clots or for bleeding

	Intervention Costs: <table><tr><th>Test (source)</th><th>Approximate Cost (2005)</th><th>Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016)</th><th>(14/12/2016) £1 = $1,27</th></tr><tr><td>Full Blood Count</td><td>£2.55</td><td>£3.29</td><td>$4,18</td></tr><tr><td>Protein C</td><td>£11.67</td><td>£15.5</td><td>$19,12</td></tr><tr><td>Free Protein S</td><td>£11.67</td><td>£15.5</td><td>$19,12</td></tr><tr><td>Antithrombin</td><td>£11.67</td><td>£15.5</td><td>$19,12</td></tr><tr><td>APCR</td><td>£10.73</td><td>£13.84</td><td>$17,58</td></tr><tr><td>Factor V Leiden</td><td>£85.00</td><td>£109.65</td><td>$141,45</td></tr><tr><td>Prothrombin gene mutation</td><td>£85.00</td><td>£109.65</td><td>$141,45</td></tr><tr><td>Lupus Anticoagulant</td><td>£10.73</td><td>£13.84</td><td>$17,58</td></tr><tr><td>Antiphospholipid antibodies</td><td>£12.30</td><td>£15.87</td><td>$20,15</td></tr><tr><td>Anti Beta-2 GP1 antibody</td><td>£9.50</td><td>£12.25</td><td>$15,81</td></tr><tr><td>The potential cost of a full thrombophilia screen</td><td>£250.82,</td><td>£323.56</td><td>$410,92</td></tr></table> Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx **Cost of the health outcomes:**(9) - **Recurrent VTE:** 11,000 to 15,000 USD - **Major bleeding:** 11,000 to 22,000 USD **Cost of interventions:**(10) - **Dabigatran:** Cost per month: $300.44–$600.88 USD - **Rivaroxaban:** Cost per month: $300.42–$600.84 USD - **Apixaban:** Cost per month: $300.44–$600.88	events.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	One cost-utility study compared the costs and utilities associated with different practices of genetic screening for 15-45 year old women at high risk of VTE (scenario 1) or with a previous VTE event (scenario 2), who visit a gynecologist for a prescription for the oral contraceptive pill (OCP). In women with previous VTE, screening (genetic and biochemical) was not cost-effective and led to an overall loss of QALY. However, it is not clear from the reporting if the VTE was attributed to the use of hormonal contraceptives.(11)	The panel considered the study to be too indirect to make a judgment for cost-effectiveness.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(12)	The panel considered that the health system/service coverage/access to care will be the main aspect affecting health equity. USA is an example where promotion of testing that is not covered by insurance would generate inequities. I.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies. Also, the additional cost for indefinite anticoagulant treatment of the women positive for thrombophilia may or may not be covered.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Research studies suggested the following regarding acceptability and barriers associated with testing and treatment: **Patients**: A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(13) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(14) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives.	The panel considered testing acceptable for many doctors, although maybe not for all. Patients are in general willing to undergo thrombophilia testing. The acceptability of indefinite anticoagulant treatment could also be influenced by the option to remain on combined oral contraceptives.

	Health care providers: A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(15) **Payers**: At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies showed the following regarding feasibility and barriers to utilizing or not utilizing testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed. (Shen 2016) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending. (Aljabry 2012) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombobin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin. (Cunninghma 2011) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering. (Smith 2014) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1. (Somma 2006)	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation. External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

After completion of primary treatment for women with a symptomatic VTE associated with use of combined oral contraceptives, the ASH guideline panel suggests testing for thrombophilia and indefinite anticoagulant treatment in positive women over no testing for thrombophilia and stopping anticoagulant treatment in all women (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:

- A strategy with testing for thrombophilia would mean that positive women would receive indefinite anticoagulant treatment, and negative women would stop anticoagulant treatment.

- This recommendation refers to testing for inherited and acquired types of thrombophilia.

Justification

The panel considered that thrombophilia testing and extending anticoagulant treatment in thrombophilia positives likely has some benefit in terms of prevention of VTE recurrence that outweighs the risk of major bleeding in patients at low risk, and may justify the costs of extended anticoagulant treatment.

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation. Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

Considering the limited specific data in women with VTE associated with use of combined oral contraceptives, research is needed to provide reliable estimates for the prevalence of thrombophilia, risk of VTE recurrence, and cost-effectiveness of testing.

Randomized controlled trials comparing testing vs no testing would be ideal but have shown to be difficult to perform.(Cohn 2008; Cohn Cochrane review 2012) The second best option would be a pragmatic non-randomized controlled study comparing tested and non-tested patients with VTE.(Coppens 2008)

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
7. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
8. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
9. Grosse, S. D., Nelson, R. E., Nyarko, K. A., Richardson, L. C., Raskob, G. E.. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res; Jan 2016.
10. Biskupiak, J., Ghate, S. R., Jiao, T., Brixner, D.. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. J Manag Care Pharm; Nov-Dec 2013.
11. Compagni, A., Melegaro, A., Tarricone, R.. Genetic screening for the predisposition to venous thromboembolism: a cost-utility analysis of clinical practice in the Italian health care system. Value Health; Sep-Oct 2013.
12. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
13. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
14. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
15. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.

Question: In women with VTE associated with use of combined oral contraceptives who completed primary treatment, should thrombophilia testing and subsequent indefinite anticoagulant treatment in women positive for thrombophilia and stopping anticoagulant treatment in women negative for thrombophilia compared to no thrombophilia testing and stopping anticoagulant treatment in all be used?

Setting:

Bibliography: See reference list and footnotes. [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Recurrent VTE (assessed with: any DVT or PE)									
25 [a,b,c,d,e,f,g]	observational studies	not serious	not serious	very serious [h]	serious [i]	none	When testing 1,000 women who completed primary treatment of VTE associated with combined oral contraceptives for any type of thrombophilia, and treating the 380 positives with indefinite anticoagulation (ranging from 216 to 595), 29 VTE recurrences will occur per year (ranging from 15 to 40). When not testing 1,000 women for thrombophilia,and stopping treatment in all of them, 50 VTE recurrences will occur per year. Therefore, a thrombophilia testing strategy is associated with 380 more women treated with indefinite anticoagulation (ranging from 216 to 595) and **21 fewer VTE recurrences (ranging from 10 to 35)** per 1,000 patients per year compared with a no testing strategy. [j]	⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding - Low risk (0.5% per year)[k]									
32 [c,d,l,m,n]	observational studies	not serious	not serious	serious [o]	not serious	none	When testing 1,000 women who completed primary treatment of VTE associated with combined oral contraceptives, and who are at low risk of major bleeding, for any type of thrombophilia, and treating the 380 positives with indefinite anticoagulation (ranging from 216 to 595), 7 major bleedings will occur per year (ranging from 5 to 12). When not testing 1,000 women for thrombophilia and stopping treatment in all of them, 5 major bleedings will occur per year. Therefore, a thrombophilia testing strategy is associated with 380 more women treated indefinite anticoagulation (ranging from 216 to 595) and **2 more major bleedings (ranging from 0 to 7)** per 1,000 patients per year compared with a no testing strategy. [p]	⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding - High risk (1.5% per year)[q]									
32 [c,d,l,m,r]	observational studies	not serious	not serious	serious [o]	serious [i]	none	When testing 1,000 women who completed primary treatment of VTE associated with combined oral contraceptives, and who are at high risk of major bleeding, for any type of thrombophilia, and treating the 380 positives with indefinite anticoagulation (ranging from 216 to 595), 22 major bleedings will occur per year (ranging from 16 to 36). When not testing 1,000 women for thrombophilia and stopping treatment in all of them, 15 major bleedings will occur per year. Therefore, a thrombophilia testing strategy is associated with 380 more women treated with indefinite anticoagulation (ranging from 216 to 595) and **7 more major bleedings (ranging from 1 to 21)** per 1,000 patients per year compared with a no testing strategy. [s]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE recurrence, 1 systematic review; Prevalence, 20 studies; Risk association for thrombophilia positive versus negative, 6 studies (all also reported Prevalence); Extended anticoagulation effect, 4 RCTs

b. Overall risk for VTE recurrence: Iorio 2010

c. Thrombophilia prevalence, used for calculation: Bezemer 2009, Cebi 2009, Di Minno 2014, Garcia-Fuster 2005, Heit 2010, Kearon 1999, Kearon 2018, Lim 2017, Mello 2010, Meyer 2015, Olie 2011, Palareti 2003, Prandoni 2007, Roldan 2009, Rossi 2008, Santamaria 2005, Schattner 1997, Schulman 2006, Sundquist 2015, Weingarz 2015

d. Prevalence of specific thrombophilia types, used to verify calculation estimate: Ahmad 2016, Ahmad 2016, Ahmad 2017, Asim 2017, Baarslag 2004, Baglin 2003, Brouwer 2009, Bruwer 2016, Christiansen 2005, De Stefano 1999, De Stefano 2006, Eichinger 1999, Eichinger 2002, Eischer 2017, Gonzalez-Porras 2006, Heijboer 1990, Hirmerova 2014, Hoibraaten 2000, Kearon 2008, Laczkovics 2007, Lee 2017, Lijfering 2010, Lindmarker 1999, Marcucci 2003, Mateo 1997, Miles 2001, Ridker 1995, Rodger 2008, Roupie 2016, Rupa-Matysek 2014, Simioni 2000, Sonnevi 2013, Strandberg 2007, Sveinsdottir 2012, The Procare group 2003, Wahlander 2006

e. Thrombophilia positive vs negative risk association, used for calculation: Kearon, 1999, Kearon 2018, Mello 2010, Santamaria 2005, Schulman 2006, Weingarz 2015

f. Risk association for specific thrombophilia types, used to verify calculation estimate: Baglin 2003, Brouwer 2009, Christiansen 2005, De Stefano 1999, De Stefano 2006, Di Minno 2014, Eichinger 2002, Gonzalez-Porras 2006, Hoibraaten 2000, Lijfering 2010, Lindmarker 1999, Marcucci 2003, Miles 2001, Palareti 2003, Prandoni 2007, Ridker 1995, Rodger 2008, Schattner 1997, Simioni 2000, Strandberg 2007, Wahlander 2006

g. Effect of extended anticoagulation treatment, used in calculation: Agnelli 2013, Bauersachs 2010, Schulman 2003, Schulman 2013

h. The effect was indirectly calculated using evidence from an indirect population (patients with a symptomatic VTE provoked by a non-surgical major transient risk factor), and using separate studies for thrombophilia prevalence, relative risk of thrombophilia positives vs negatives, and the effect of treatment

i. There is a clinically important difference between the smallest and largest possible effect of the testing strategy

j. Based on the following estimates: Overall risk for VTE recurrence, 50 per 1,000; Prevalence of any thrombophilia, 38.0% (min 21.6 - max 59.5); Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 1.65 (95%CI: 1.28-2.47); Relative risk of VTE recurrence with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.15 (0.10-0.23). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, upper CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

k. Among RCTs assessing the effect of extended treatment against limited treatment, the lowest observed rate of major bleeding with limited treatment was 0.5% (Agnelli 2001)

l. Number of studies used in calculations: Overall risk, 1 RCT; Prevalence, 20 studies; Extended anticoagulation effect, 11 RCTs

m. Effect of extended anticoagulation treatment, used in calculation: Agnelli 2001, Agnelli 2003, Agnelli 2013, Bauersachs 2010, Couturaud 2015, Eischer 2009, Kearon 1999, Palareti 2006, Ridker 2003, Schulman 2003, Schulman 2013

n. Overall risk for Major bleeding: Agnelli 2001

o. The effect was indirectly calculated using separate studies for thrombophilia prevalence and the effect of treatment

p. Based on the following estimates: Overall risk for Major bleeding of 5 per 1,000; Prevalence of any thrombophilia, 38.0% (21.6-59.5); Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 2.17 (1.40-3.35). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the smallest treatment effect (lower CI).

q. Among RCTs assessing the effect of extended treatment against limited treatment, the highest observed rate of major bleeding with limited treatment was 1.5% (Agnelli 2013)

r. Overall risk for Major bleeding: Agnelli 2013

s. Based on the following estimates: Overall risk for Major bleeding of 15 per 1,000; Prevalence of any thrombophilia, 38.0% (21.6-59.5); Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 2.17 (1.40-3.35). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the smallest treatment effect (lower CI).

References

1. Agnelli, G., Buller, H. R., Cohen, A., Curto, M., Gallus, A. S., Johnson, M., Porcari, A., Raskob, G. E., Weitz, J. I., Investigators, Amplify-Ext. Apixaban for extended treatment of venous thromboembolism. N Engl J Med; Feb 21 2013.

2. Agnelli, G., Prandoni, P., Becattini, C., Silingardi, M., Taliani, M. R., Miccio, M., Imberti, D., Poggio, R., Ageno, W., Pogliani, E., Porro, F., Zonzin, P., Warfarin Optimal Duration Italian Trial, Investigators. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med; Jul 1 2003.

3. Agnelli, G., Prandoni, P., Santamaria, M. G., Bagatella, P., Iorio, A., Bazzan, M., Moia, M., Guazzaloca, G., Bertoldi, A., Tomasi, C., Scannapieco, G., Ageno, W., Warfarin Optimal Duration Italian Trial, Investigators. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med; Jul 19 2001.

4. Ahmad, A., Sundquist, K., Zoller, B., Dahlback, B., Svensson, P. J., Sundquist, J., Memon, A. A.. Identification of polymorphisms in Apolipoprotein M gene and their relationship with risk of recurrent venous thromboembolism. Thromb Haemost; Aug 30 2016.

5. Asim, M., Al-Thani, H., El-Menyar, A.. Recurrent Deep Vein Thrombosis After the First Venous Thromboembolism Event: A Single-Institution Experience. Med Sci Monit; May 20 2017.

6. Baarslag, H. J., Koopman, M. M., Hutten, B. A., Linthorst Homan, M. W., Buller, H. R., Reekers, J. A., van Beek, E. J.. Long-term follow-up of patients with suspected deep vein thrombosis of the upper extremity: survival, risk factors and post-thrombotic syndrome. Eur J Intern Med; Dec 2004.

7. Baglin, T., Luddington, R., Brown, K., Baglin, C.. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet; Aug 16 2003.

8. Bezemer, I. D., van der Meer, F. J., Eikenboom, J. C., Rosendaal, F. R., Doggen, C. J.. The value of family history as a risk indicator for venous thrombosis. Archives of Internal Medicine; Mar 23 2009.

9. Brouwer, J. L., Lijfering, W. M., Ten Kate, M. K., Kluin-Nelemans, H. C., Veeger, N. J., van der Meer, J.. High long-term absolute risk of recurrent venous thromboembolism in patients with hereditary deficiencies of protein S, protein C or antithrombin. Thromb Haemost; Jan 2009.

10. Bruwer, G., Limperger, V., Kenet, G., Klostermeier, U. C., Shneyder, M., Degenhardt, F., Finckh, U., Heller, C., Holzhauer, S., Trappe, R., Kentouche, K., Knoefler, R., Kurnik, K., Krumpel, A., Lauten, M., Manner, D., Mesters, R., Junker, R., Nowak-Gottl, U.. Impact of high risk thrombophilia status on recurrence among children and adults with VTE: An observational multicenter cohort study. Blood Cells Mol Dis; Nov 2016.

11. Cebi, N., Tanriverdi, S.. Aetiology of deep vein thrombosis in 63 turkish patients. Turkish Journal of Medical Sciences; April 2009.

12. Christiansen, S. C., Cannegieter, S. C., Koster, T., Vandenbroucke, J. P., Rosendaal, F. R.. Thrombophilia, clinical factors, and recurrent venous thrombotic events. Jama; May 18 2005.

13. Couturaud, F., Sanchez, O., Pernod, G., Mismetti, P., Jego, P., Duhamel, E., Provost, K., dit Sollier, C. B., Presles, E., Castellant, P., Parent, F., Salaun, P. Y., Bressollette, L., Nonent, M., Lorillon, P., Girard, P., Lacut, K., Guegan, M., Bosson, J. L., Laporte, S., Leroyer, C., Decousus, H., Meyer, G., Mottier, D., Investigators, Padis-Pe. Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism: The PADIS-PE Randomized Clinical Trial. Jama; Jul 7 2015.

14. De Stefano, V., Martinelli, I., Mannucci, P. M., Paciaroni, K., Chiusolo, P., Casorelli, I., Rossi, E., Leone, G.. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med; Sep 9 1999.

15. De Stefano, V., Simioni, P., Rossi, E., Tormene, D., Za, T., Pagnan, A., Leone, G.. The risk of recurrent venous thromboembolism in patients with inherited deficiency of natural anticoagulants antithrombin, protein C and protein S. Haematologica; May 2006.

16. Di Minno, M. N., Dentali, F., Lupoli, R., Ageno, W.. Mild antithrombin deficiency and risk of recurrent venous thromboembolism: a prospective cohort study. Circulation; Jan 28 2014.

17. Eichinger, S., Minar, E., Hirschl, M., Bialonczyk, C., Stain, M., Mannhalter, C., Stumpflen, A., Schneider, B., Lechner, K., Kyrle, P. A.. The risk of early recurrent venous thromboembolism after oral anticoagulant therapy in patients with the G20210A transition in the prothrombin gene. Thromb Haemost; Jan 1999.

18. Eichinger, S., Weltermann, A., Mannhalter, C., Minar, E., Bialonczyk, C., Hirschl, M., Schonauer, V., Lechner, K., Kyrle, P. A.. The risk of recurrent venous thromboembolism in heterozygous carriers of factor V Leiden and a first spontaneous venous thromboembolism. Archives of Internal Medicine; Nov 11 2002.

19. Eischer, L., Gartner, V., Schulman, S., Kyrle, P. A., Eichinger, S., investigators, Aurec-Fviii. 6 versus 30 months anticoagulation for recurrent venous thrombosis in patients with high factor VIII. Ann Hematol; May 2009.

20. Eischer, L., Kammer, M., Traby, L., Kyrle, P. A., Eichinger, S.. Risk of cancer after anticoagulation in patients with unprovoked venous thromboembolism: an observational cohort study. Journal of Thrombosis and Haemostasis; July 2017.

21. Garcia-Fuster, M. J., Forner, M. J., Fernandez, C., Gil, J., Vaya, A., Maldonado, L.. Long-term prospective study of recurrent venous thromboembolism in patients younger than 50 years. Pathophysiol Haemost Thromb; 2005.

22. Gonzalez-Porras, J. R., Garcia-Sanz, R., Alberca, I., Lopez, M. L., Balanzategui, A., Gutierrez, O., Lozano, F., San Miguel, J.. Risk of recurrent venous thrombosis in patients with G20210A mutation in the prothrombin gene or factor V Leiden mutation. Blood Coagul Fibrinolysis; Jan 2006.

23. Group, The,Procare. Is recurrent venous thromboembolism more frequent in homozygous patients for the factor V Leiden mutation than in heterozygous patients?. Blood Coagulation and Fibrinolysis; September 2003.

24. Heijboer, H., Brandjes, D. P., Buller, H. R., Sturk, A., ten Cate, J. W.. Deficiencies of coagulation-inhibiting and fibrinolytic proteins in outpatients with deep-vein thrombosis. N Engl J Med; Nov 29 1990.

25. Heit, J. A., Beckman, M. G., Bockenstedt, P. L., Grant, A. M., Key, N. S., Kulkarni, R., Manco-Johnson, M. J., Moll, S., Ortel, T. L., Philipp, C. S., Thrombosis, C.,D.,C., Hemostasis Centers, Research, Prevention, Network. Comparison of characteristics from White- and Black-Americans with venous thromboembolism: a cross-sectional study. Am J Hematol; Jul 2010.

26. Hirmerova, J., Seidlerova, J., Subrt, I.. The association of factor V Leiden with various clinical patterns of venous thromboembolism-the factor V Leiden paradox. Qjm; Sep 2014.

27. Hoibraaten, E., Qvigstad, E., Arnesen, H., Larsen, S., Wickstrom, E., Sandset, P. M.. Increased risk of recurrent venous thromboembolism during hormone replacement therapy--results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). Thromb Haemost; Dec 2000.

28. Investigators, Einstein, Bauersachs, R., Berkowitz, S. D., Brenner, B., Buller, H. R., Decousus, H., Gallus, A. S., Lensing, A. W., Misselwitz, F., Prins, M. H., Raskob, G. E., Segers, A., Verhamme, P., Wells, P., Agnelli, G., Bounameaux, H., Cohen, A., Davidson, B. L., Piovella, F., Schellong, S.. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med; Dec 23 2010.

29. Iorio, A., Kearon, C., Filippucci, E., Marcucci, M., Macura, A., Pengo, V., Siragusa, S., Palareti, G.. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. Archives of Internal Medicine; Oct 25 2010.

30. Kearon, C., Gent, M., Hirsh, J., Weitz, J., Kovacs, M. J., Anderson, D. R., Turpie, A. G., Green, D., Ginsberg, J. S., Wells, P., MacKinnon, B., Julian, J. A.. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med; Mar 25 1999.

31. Kearon, C., Julian, J. A., Kovacs, M. J., Anderson, D. R., Wells, P., Mackinnon, B., Weitz, J. I., Crowther, M. A., Dolan, S., Turpie, A. G., Geerts, W., Solymoss, S., van Nguyen, P., Demers, C., Kahn, S. R., Kassis, J., Rodger, M., Hambleton, J., Gent, M., Ginsberg, J. S., Investigators, Elate. Influence of thrombophilia on risk of recurrent venous thromboembolism while on warfarin: results from a randomized trial. Blood; Dec 1 2008.

32. Kearon, C., Parpia, S., Spencer, F. A., Baglin, T., Stevens, S. M., Bauer, K. A., Lentz, S. R., Kessler, C. M., Douketis, J. D., Moll, S., Kaatz, S., Schulman, S., Connors, J. M., Ginsberg, J. S., Spadafora, L., Bhagirath, V., Liaw, P. C., Weitz, J. I., Julian, J. A.. Antiphospholipid antibodies and recurrent thrombosis after a first unprovoked venous thromboembolism. Blood; May 10 2018.

33. Laczkovics, C., Grafenhofer, H., Kaider, A., Quehenberger, P., Simanek, R., Mannhalter, C., Lechner, K., Pabinger, I.. Risk of recurrence after a first venous thromboembolic event in young women. Haematologica; Sep 2007.

34. Lee, S. Y., Kim, E. K., Kim, M. S., Shin, S. H., Chang, H., Jang, S. Y., Kim, H. J., Kim, D. K.. The prevalence and clinical manifestation of hereditary thrombophilia in Korean patients with unprovoked venous thromboembolisms. PLoS ONE [Electronic Resource]; 2017.

35. Lijfering, W. M., Middeldorp, S., Veeger, N. J., Hamulyak, K., Prins, M. H., Buller, H. R., van der Meer, J.. Risk of recurrent venous thrombosis in homozygous carriers and double heterozygous carriers of factor V Leiden and prothrombin G20210A. Circulation; Apr 20 2010.

36. Lim, H. Y., Chua, C. C., Tacey, M., Sleeman, M., Donnan, G., Nandurkar, H., Ho, P.. Venous thromboembolism management in Northeast Melbourne: how does it compare to international guidelines and data?. Intern Med J; Sep 2017.

37. Lindmarker, P., Schulman, S., Sten-Linder, M., Wiman, B., Egberg, N., Johnsson, H.. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. DURAC Trial Study Group. Duration of Anticoagulation. Thromb Haemost; May 1999.

38. Marcucci, R., Liotta, A. A., Cellai, A. P., Rogolino, A., Gori, A. M., Giusti, B., Poli, D., Fedi, S., Abbate, R., Prisco, D.. Increased plasma levels of lipoprotein(a) and the risk of idiopathic and recurrent venous thromboembolism. Am J Med; Dec 1 2003.

39. Mateo, J., Oliver, A., Borrell, M., Sala, N., Fontcuberta, J.. Laboratory evaluation and clinical characteristics of 2,132 consecutive unselected patients with venous thromboembolism--results of the Spanish Multicentric Study on Thrombophilia (EMET-Study). Thromb Haemost; Mar 1997.

40. Mello, T. B., Orsi, F. L., Montalvao, S. A., Ozelo, M. C., de Paula, E. V., Annichinno-Bizzachi, J. M.. Long-term prospective study of recurrent venous thromboembolism in a Hispanic population. Blood Coagul Fibrinolysis; Oct 2010.

41. Meyer, M. R., Witt, D. M., Delate, T., Johnson, S. G., Fang, M., Go, A., Clark, N. P.. Thrombophilia testing patterns amongst patients with acute venous thromboembolism. Thromb Res; Dec 2015.

42. Miles, J. S., Miletich, J. P., Goldhaber, S. Z., Hennekens, C. H., Ridker, P. M.. G20210A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. J Am Coll Cardiol; Jan 2001.

43. Olie, V., Plu-Bureau, G., Conard, J., Horellou, M. H., Canonico, M., Scarabin, P. Y.. Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. Menopause; May 2011.

44. Palareti, G., Cosmi, B., Legnani, C., Tosetto, A., Brusi, C., Iorio, A., Pengo, V., Ghirarduzzi, A., Pattacini, C., Testa, S., Lensing, A. W., Tripodi, A., Investigators, Prolong. D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med; Oct 26 2006.

45. Palareti, G., Legnani, C., Cosmi, B., Valdre, L., Lunghi, B., Bernardi, F., Coccheri, S.. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation; Jul 22 2003.

46. Prandoni, P., Noventa, F., Ghirarduzzi, A., Pengo, V., Bernardi, E., Pesavento, R., Iotti, M., Tormene, D., Simioni, P., Pagnan, A.. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica; Feb 2007.

47. Ridker, P. M., Miletich, J. P., Stampfer, M. J., Goldhaber, S. Z., Lindpaintner, K., Hennekens, C. H.. Factor V Leiden and risks of recurrent idiopathic venous thromboembolism. Circulation; Nov 15 1995.

48. Rodger, M. A., Kahn, S. R., Wells, P. S., Anderson, D. A., Chagnon, I., Le Gal, G., Solymoss, S., Crowther, M., Perrier, A., White, R., Vickars, L., Ramsay, T., Betancourt, M. T., Kovacs, M. J.. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. Cmaj; Aug 26 2008.

49. Roldan, V., Lecumberri, R., Munoz-Torrero, J. F., Vicente, V., Rocha, E., Brenner, B., Monreal, M., Investigators, Riete. Thrombophilia testing in patients with venous thromboembolism. Findings from the RIETE registry. Thromb Res; Jun 2009.

50. Rossi, E., Za, T., Ciminello, A., Leone, G., De Stefano, V.. The risk of symptomatic pulmonary embolism due to proximal deep venous thrombosis differs in patients with different types of inherited thrombophilia. Thromb Haemost; Jun 2008.

51. Roupie, A. L., Dossier, A., Goulenok, T., Perozziello, A., Papo, T., Sacre, K.. First venous thromboembolism in admitted patients younger than 50years old. Eur J Intern Med; Oct 2016.

52. Rupa-Matysek, J., Gil, L., Wojtasinska, E., Ciepluch, K., Lewandowska, M., Komarnicki, M.. The relationship between mean platelet volume and thrombosis recurrence in patients diagnosed with antiphospholipid syndrome. Rheumatol Int; Nov 2014.

53. Santamaria, M. G., Agnelli, G., Taliani, M. R., Prandoni, P., Moia, M., Bazzan, M., Guazzaloca, G., Ageno, W., Bertoldi, A., Silingardi, M., Tomasi, C., Ambrosio, G. B., Warfarin Optimal Duration Italian Trial, Investigators. Thrombophilic abnormalities and recurrence of venous thromboembolism in patients treated with standardized anticoagulant treatment. Thromb Res; 2005.

54. Schattner, A., Kasher, I., Berrebi, A.. Causes and outcome of deep-vein thrombosis in otherwise-healthy patients under 50 years. Qjm; Apr 1997.

55. Schulman, S., Kearon, C., Kakkar, A. K., Schellong, S., Eriksson, H., Baanstra, D., Kvamme, A. M., Friedman, J., Mismetti, P., Goldhaber, S. Z., Investigators, Re-Medy,Trial, Investigators, Re-Sonate,Trial. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med; Feb 21 2013.

56. Schulman, S., Lindmarker, P., Holmstrom, M., Larfars, G., Carlsson, A., Nicol, P., Svensson, E., Ljungberg, B., Viering, S., Nordlander, S., Leijd, B., Jahed, K., Hjorth, M., Linder, O., Beckman, M.. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. Journal of Thrombosis & Haemostasis; Apr 2006.

57. Schulman, S., Wahlander, K., Lundstrom, T., Clason, S. B., Eriksson, H., Investigators, Thrive,Iii. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. N Engl J Med; Oct 30 2003.

58. Simioni, P., Prandoni, P., Lensing, A. W., Manfrin, D., Tormene, D., Gavasso, S., Girolami, B., Sardella, C., Prins, M., Girolami, A.. Risk for subsequent venous thromboembolic complications in carriers of the prothrombin or the factor V gene mutation with a first episode of deep-vein thrombosis. Blood; Nov 15 2000.

59. Sonnevi, K., Tchaikovski, S. N., Holmstrom, M., Antovic, J. P., Bremme, K., Rosing, J., Larfars, G.. Obesity and thrombin-generation profiles in women with venous thromboembolism. Blood Coagul Fibrinolysis; Jul 2013.

60. Strandberg, K., Svensson, P. J., Ohlin, A. K.. Venous thromboembolism in carriers of the Factor V Leiden mutation and in patients without known thrombophilic risk factor; prediction of recurrence and APC-PCI complex concentration and/or soluble thrombomodulin antigen and activity. Thromb Res; 2007.

61. Sundquist, K., Sundquist, J., Svensson, P. J., Zoller, B., Memon, A. A.. Role of family history of venous thromboembolism and thrombophilia as predictors of recurrence: a prospective follow-up study. Journal of Thrombosis & Haemostasis; Dec 2015.

62. Sveinsdottir, S. V., Saemundsson, Y., Isma, N., Gottsater, A., Svensson, P. J.. Evaluation of recurrent venous thromboembolism in patients with Factor V Leiden mutation in heterozygous form. Thromb Res; Sep 2012.

63. Vitovec, M., Golan, L., Roztocil, K., Linhart, A.. The development of persistent thrombotic masses in patients with deep venous thrombosis randomized to long-term anticoagulation treatment. Vasa; Aug 2009.

64. Wahlander, K., Eriksson, H., Lundstrom, T., Billing Clason, S., Wall, U., Nystrom, P., Wessman, P., Schulman, S., Investigators, Thrive,Iii. Risk of recurrent venous thromboembolism or bleeding in relation to thrombophilic risk factors in patients receiving ximelagatran or placebo for long-term secondary prevention of venous thromboembolism. Br J Haematol; Apr 2006.

65. Weingarz, L., Schindewolf, M., Schwonberg, J., Hecking, C., Wolf, Z., Erbe, M., Lindhoff-Last, E., Linnemann, B.. Thrombophilia and risk of VTE recurrence according to the age at the time of first VTE manifestation. Vasa; Jul 2015.

QUESTION

Should thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia vs. no thrombophilia testing and stopping anticoagulant treatment in all be used for patients with cerebral venous thrombosis who completed primary treatment?

POPULATION:	patients with cerebral venous thrombosis who completed primary treatment
INTERVENTION:	thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia
COMPARISON:	no thrombophilia testing and stopping anticoagulant treatment in all
MAIN OUTCOMES:	Recurrent VTE; Major bleeding - Low risk (0.5% per year); Major bleeding - High risk (1.5% per year);
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Thrombophilia, either acquired or inherited, can be identified in many patients presenting with venous thromboembolism (VTE). The currently most commonly tested inherited thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. Cerebral venous thrombosis can be unprovoked, or provoked by hormones, surgery or medical conditions. It is not clear what the standard of care is for these patients regarding duration of anticoagulant treatment, different guidelines recommend providing extended or limited anticoagulation. Therefore, the ASH guideline panel addressed the value of a strategy with testing for thrombophilia and treating only patients positive with indefinite anticoagulation, as compared to providing definite anticoagulation to everyone (this question) or providing indefinite treatment to everyone (separate question in these ASH guidelines). This question addresses whether thrombophilia testing and subsequent indefinite duration of anticoagulant treatment in patients positive for thrombophilia improves patient-important outcomes in patients with cerebral venous thrombosis, as compared with no thrombophilia testing and treating all patients with definite anticoagulant treatment. Since no randomized controlled trials have addressed this question, we used a modeling approach based on observational evidence for baseline risk of patient-important outcomes, prevalence of thrombophilia and associated risk of recurrent events with thrombophilia, and RCTs based evidence for the effect of indefinite anticoagulation on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		This question is important for cerebral venous thrombosis types (mainly provoked) that would usually be treated with definite anticoagulation.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Evidence Profile.	Desirable effect = preventing VTE recurrence. VTE recurrences would be avoided in patients who are positive for thrombophilia by extending their anticoagulation treatment.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	See Evidence Profile.	Undesirable effect = causing major bleeding. Major bleedings would be caused in patients who are positive for thrombophilia by extending their anticoagulation treatment. The panel considered the increase in major bleeding to be Trivial in most patients who are at low risk of bleeding, but Small in those at high risk.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows using a scale from 0 (worst possible scenario, usually death), to 1 (best possible scenario, usually perfect health):** **Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(1, 2, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3) **Gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off)(2, 3) **Minor intracranial bleeding event:** 0.75 (standard gamble)(2) **Major intracranial bleeding event:** 0.15 (standard gamble)(2) **Anticoagulant therapy** Patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome.(3) Patients would favor efficacy and safety over convenience of route of administration.(6) Also, patients would like to avoid adverse events but most of them are “not afraid of” the adverse events.(6, 7, 8)	The panel considered that clinicians may value avoiding major bleeding more (they do not want to cause harm), while patients may value avoiding VTE events more (they may prefer avoiding a recurrence of blood clots).

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		No studies assessed indefinite anticoagulation as life-long treatment. The panel observed that the appraisal of the comparison of the two interventions (testing and treating positives vs treating none) was limited by the absence of studies comparing extended anticoagulation as life-long treatment versus no anticoagulation, which the panel had to extrapolate.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Intervention Costs: **Test (source)** / Approximate Cost (2005) / Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016) / **(14/12/2016) £1 = $1,27** **Full Blood Count** £2.55 £3.29 **$4,18** **Protein C** £11.67 £15.5 **$19,12** **Free Protein S** £11.67 £15.5 **$19,12** **Antithrombin** £11.67 £15.5 **$19,12** **APCR** £10.73 £13.84 **$17,58** **Factor V Leiden** £85.00 £109.65 **$141,45** **Prothrombin gene mutation** £85.00 £109.65 **$141,45** **Lupus Anticoagulant** £10.73 £13.84 **$17,58** **Antiphospholipid antibodies** £12.30 £15.87 **$20,15** **Anti Beta-2 GP1 antibody** £9.50 £12.25 **$15,81** **The potential cost of a full thrombophilia screen** £250,82, £323,56 **$410,92** Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx **Cost of the health outcomes:**(9)	**The panel considered the following cost ranges:** - Cost for testing: $400 -$2,000 per patient - Cost for treatment: $1,000-$ 4,500 per patient per year In assessing the resources required the panel considered that the intervention (testing and treating only patients positive for thrombophilia) added the cost for testing all patients but "saved" the cost of treatment avoided in the patients negative for thrombophilia. The panel did not consider the costs for recurrent clots or for bleeding events.

	- **Recurrent VTE:** 11,000 to 15,000 USD - **Major bleeding:** 11,000 to 22,000 USD **Cost of interventions:**(10) - **Dabigatran:** Cost per month: $300.44–$600.88 USD - **Rivaroxaban:** Cost per month: $300.42–$600.84 USD - **Apixaban:** Cost per month: $300.44–$600.88	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence was identified for the cost-effectiveness of thrombophilia testing in patients with cerebral venous thrombosis. For patients with any symptomatic VTE: Three studies evaluated the cost-effectiveness of thrombophilia testing and different management strategies in patients with a first venous thromboembolism.(11, 12, 13) All three studies found thrombophilia testing cost-effective, although the uncertainty was high in general due to prevalence of mutation and the variability in the recurrence rate (which depends on the type of thrombophilia), risk of adverse events such as major haemorrhage, age or efficacy of the anticoagulant therapy, among others. Cost per quality-adjusted life year (QALY) for the testing and treatment strategies varied between the 3 studies and in sensitivity analyses (Simpson 2009: approximately £20,000/QALY for patients with PE or DVT; Marchetti 2001: $13,624/QALY for any VTE, Eckman 2002: $16,823/QALY for any VTE) One study evaluated thrombophilia testing using a panel of thrombophilia tests that included Factor V Leiden, Prothrombin G20210A, APC resistance, Protein C, Protein S, antithrombin levels, antiphospholipid antibodies and homocysteine levels, dysfibrinogenaemia, and levels of factor VIII, factor IX and factor XI.(13) Another cost-effectiveness study included only screening for FVL and G20210A prothrombin mutations,(11) and the third study included testing for FVL mutation.(12)	Identified studies assessed cost-effectiveness in patients with any type of VTE, not cerebral venous thrombosis specifically.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test	The panel considered that the health system/Service coverage will be the main aspect affecting the health equity. The US is an example where promotion of testing that is not covered by insurance would generate inequities, i.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies.

	result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(14)	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Research studies suggested the following regarding acceptability and barriers associated with testing and treatment: Patients: A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(15) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(16) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. Health care providers: A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(17) Payers: At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	The panel considered testing acceptable for many doctors, although maybe not for all. Patients are in general willing to undergo thrombophilia testing when testing is proposed by their doctor.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(18) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending.(19) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(20) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(21) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(22)	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation. External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

After completion of primary treatment for patients with cerebral venous thrombosis, the ASH guideline panel suggests testing for thrombophilia and indefinite anticoagulant treatment in positive patients over no testing for thrombophilia and stopping anticoagulant treatment in all patients (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:

- A strategy with testing for thrombophilia would mean that positive patients would receive indefinite anticoagulant treatment, and negative patients would stop anticoagulant treatment.

- This recommendation refers to testing for inherited and acquired types of thrombophilia.

- This recommendation addresses settings where the standard of care for cerebral venous thrombosis patients is stopping anticoagulant treatment; the ASH guideline panel provides a separate recommendation for settings where the standard of care is indefinite anticoagulant treatment (Q7.A.1).

Justification

The panel considered that thrombophilia testing and extending anticoagulant treatment in thrombophilia positives likely has some benefit in terms of prevention of VTE recurrence that outweighs the risk of major bleeding in patients at low risk, and may justify the costs of extended anticoagulant treatment.

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation. Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

Randomized controlled trials comparing testing vs no testing would be ideal but have shown to be difficult to perform.(Cohn 2008; Cohn Cochrane review 2012) The second best option would be a pragmatic non-randomized controlled study comparing tested and non-tested patients with VTE.(Coppens 2008)

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
7. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
8. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
9. Grosse, S. D., Nelson, R. E., Nyarko, K. A., Richardson, L. C., Raskob, G. E.. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res; Jan 2016.
10. Biskupiak, J., Ghate, S. R., Jiao, T., Brixner, D.. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. J Manag Care Pharm; Nov-Dec 2013.
11. Marchetti, M., Quaglini, S., Barosi, G.. Cost-effectiveness of screening and extended anticoagulation for carriers of both factor V Leiden and prothrombin G20210A. Qjm; Jul 2001.
12. Eckman, M. H., Singh, S. K., Erban, J. K., Kao, G.. Testing for factor V Leiden in patients with pulmonary or venous thromboembolism: a cost-effectiveness analysis. Med Decis Making; Mar-Apr 2002.
13. Simpson, E. L., Stevenson, M. D., Rawdin, A., Papaioannou, D.. Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis. Health Technol Assess; Jan 2009.
14. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
15. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
16. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
17. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
18. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
19. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
20. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
21. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
22. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In patients with cerebral venous thrombosis who completed primary treatment, should thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia compared to no thrombophilia testing and stopping anticoagulant treatment in all be used?

Setting:

Bibliography: See reference list and footnotes. [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Recurrent VTE (assessed with: any DVT or PE)									
32 [a,b,c,d,e,f,g]	observational studies	not serious	not serious	serious [h]	not serious	none	When testing 1,000 patients who completed primary treatment for cerebral venous thrombosis for any type of thrombophilia and treating the 436 positives with indefinite anticoagulation (ranging from 419 to 452), 20 VTE recurrences will occur per year (ranging from 15 to 24). When not testing 1,000 patients for thrombophilia and stopping treatment in all of them, 38 VTE recurrences will occur per year. Therefore, a thrombophilia testing strategy is associated with 436 more patients treated with indefinite anticoagulation (ranging from 419 to 452) and **18 fewer VTE recurrences (ranging from 14 to 23)** per 1,000 patients per year compared with a no testing strategy. [i]	⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding - Low risk (0.5% per year)[j]									
30 [c,d,k,l,m]	observational studies	not serious	not serious	serious [n]	not serious	none	When testing 1,000 patients who completed primary treatment for cerebral venous thrombosis, and who are at low risk of major bleeding, for any type of thrombophilia and treating the 436 positives with indefinite anticoagulation (ranging from 419 to 452), 8 major bleedings will occur per year (ranging from 6 to 10). When not testing 1,000 patients for thrombophilia and stopping treatment in all of them, 5 major bleedings will occur per year. Therefore, a thrombophilia testing strategy is associated with 436 more patients treated with indefinite anticoagulation (ranging from 419 to 452) and **3 more major bleedings (ranging from 1 to 5)** per 1,000 patients per year compared with a no testing strategy. [o]	⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding - High risk (1.5% per year)[p]									
30 [c,d,l,q]	observational studies	not serious	not serious	serious [n]	serious [r]	none	When testing 1,000 patients with cerebral venous thrombosis who are at high risk of major bleeding for any type of thrombophilia and treating the 436 positives with indefinite anticoagulation (ranging from 419 to 452), 23 major bleedings will occur per year (ranging from 18 to 31). When not testing 1,000 patients for thrombophilia and stopping treatment in all of them, 15 major bleedings will occur per year. Therefore, a thrombophilia testing strategy is associated with 436 more patients treated with indefinite anticoagulation (ranging from 419 to 452) and **8 more major bleedings (ranging from 3 to 16)** per 1,000 patients per year compared with a no testing strategy. [s]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE recurrence, 4 studies; Prevalence, 18 studies; Risk association for thrombophilia positive versus negative, 6 studies; Extended anticoagulation effect, 4 RCTs

b. Overall risk for VTE recurrence: Martinelli 2010, Miranda 2010, Dentali 2012, Palazzo 2017

c. Thrombophilia prevalence, used for calculation: Algahtani 2011, Camargo 2005, de Veber 2001

d. Prevalence of specific thrombophilia types, used to verify calculation estimate: Bellucci 2008, Coutinho 2009, De Stefano 2007, Duman 2017, Eryildiz 2017, Gunes 2016, Khealani 2008, Krajickova 2016, Lee 2016, Narayan 2012, Passamonti 2012, Sidhom 2014, Terazzi 2005, Uzar 2012, Wasay 2008

e. Thrombophilia positive vs negative risk association, used for calculation: Kearon, 1999, Kearon 2018, Mello 2010, Santamaria 2005, Schulman 2006, Weingarz 2015

f. Effect of extended anticoagulation treatment, used in calculation: Agnelli 2013, Bauersachs 2010, Schulman 2003, Schulman 2013

g. Risk association for specific thrombophilia types, used to verify calculation estimate: Baglin 2003, Brouwer 2009, Christiansen 2005, De Stefano 1999, De Stefano 2006, Di Minno 2014, Eichinger 2002, Gonzalez-Porras 2006, Hoibraaten 2000, Lijfering 2010, Lindmarker 1999, Marcucci 2003, Miles 2001, Palareti 2003, Prandoni 2007, Ridker 1995, Rodger 2008, Schattner 1997, Simioni 2000, Strandberg 2007, Wahlander 2006

h. The effect was indirectly calculated using separate studies for thrombophilia prevalence, relative risk of thrombophilia positives vs negatives, and the effect of treatment. The estimates for the relative risk of thrombophilia positives vs negatives, and the effect of treatment, came from studies including patients with any type of VTE (not CVT).

i. Based on the following estimates: Overall risk for VTE recurrence, 38 per 1,000; Prevalence of any thrombophilia, 43.6% (min 41.9 - max 45.2); Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 1.65 (95%CI: 1.28-2.47); Relative risk of VTE recurrence with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.15 (0.10-0.23). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

j. Among RCTs assessing the effect of extended treatment against limited treatment, the lowest observed rate of major bleeding with limited treatment was 0.5% (Agnelli 2001)

k. Number of studies used in calculations: Overall risk, 1 systematic review; Prevalence, 18 studies; Extended anticoagulation effect, 11 RCTs (see Appendix)

l. Number of studies used in calculations: Overall risk, 1 systematic review; Prevalence, 18 studies; Extended anticoagulation effect, 11 RCTs

m. Overall risk for Major bleeding: Agnelli 2001

n. The effect was indirectly calculated using separate studies for thrombophilia prevalence and the effect of treatment. The estimates for the effect of treatment came from studies including patients with any type of VTE (not CVT).

o. Based on the following estimates: Overall risk for Major bleeding of 5 per 1,000; Prevalence of any thrombophilia, 43.6% (41.9-45.2); Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 2.17 (1.40-3.35). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the smallest treatment effect (lower CI).

p. Among RCTs assessing the effect of extended treatment against limited treatment, the highest observed rate of major bleeding with limited treatment was 1.5% (Agnelli 2013)

q. Overall risk for Major bleeding: Agnelli 2013

r. There is a clinically important difference between the smallest and largest possible effect of the testing strategy

s. Based on the following estimates: Overall risk for Major bleeding of 15 per 1,000; Prevalence of any thrombophilia, 43.6% (41.9-45.2); Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 2.17 (1.40-3.35). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the smallest treatment effect (lower CI).

References

1. Agnelli, G., Buller, H. R., Cohen, A., Curto, M., Gallus, A. S., Johnson, M., Porcari, A., Raskob, G. E., Weitz, J. I., Investigators, Amplify-Ext. Apixaban for extended treatment of venous thromboembolism. N Engl J Med; Feb 21 2013.

2. Agnelli, G., Prandoni, P., Becattini, C., Silingardi, M., Taliani, M. R., Miccio, M., Imberti, D., Poggio, R., Ageno, W., Pogliani, E., Porro, F., Zonzin, P., Warfarin Optimal Duration Italian Trial, Investigators. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med; Jul 1 2003.

3. Agnelli, G., Prandoni, P., Santamaria, M. G., Bagatella, P., Iorio, A., Bazzan, M., Moia, M., Guazzaloca, G., Bertoldi, A., Tomasi, C., Scannapieco, G., Ageno, W., Warfarin Optimal Duration Italian Trial, Investigators. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med; Jul 19 2001.

4. Algahtani, H. A., Abdu, A. P., Shami, A. M., Hassan, A. E., Madkour, M. A., Al-Ghamdi, S. M., Malhotra, R. M., Al-Khathami, A. M.. Cerebral venous sinus thrombosis in Saudi Arabia. Neurosciences (Riyadh); Oct 2011.

5. Bellucci, S., Cassinat, B., Bonnin, N., Marzac, C., Crassard, I.. The V617F JAK 2 mutation is not a frequent event in patients with cerebral venous thrombosis without overt chronic myeloproliferative disorder. Thromb Haemost; Jun 2008.

6. Camargo, E. C., Massaro, A. R., Bacheschi, L. A., D'Amico, E. A., Villaca, P. R., Bassitt, R. P., Gualandro, S. F., Bendit, I., Scaff, M.. Ethnic differences in cerebral venous thrombosis. Cerebrovasc Dis; 2005.

7. Coutinho, J. M., Ferro, J. M., Canhao, P., Barinagarrementeria, F., Cantu, C., Bousser, M. G., Stam, J.. Cerebral venous and sinus thrombosis in women. Stroke; Jul 2009.

8. Couturaud, F., Sanchez, O., Pernod, G., Mismetti, P., Jego, P., Duhamel, E., Provost, K., dit Sollier, C. B., Presles, E., Castellant, P., Parent, F., Salaun, P. Y., Bressollette, L., Nonent, M., Lorillon, P., Girard, P., Lacut, K., Guegan, M., Bosson, J. L., Laporte, S., Leroyer, C., Decousus, H., Meyer, G., Mottier, D., Investigators, Padis-Pe. Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism: The PADIS-PE Randomized Clinical Trial. Jama; Jul 7 2015.

9. De Stefano, V., Fiorini, A., Rossi, E., Za, T., Farina, G., Chiusolo, P., Sica, S., Leone, G.. Incidence of the JAK2 V617F mutation among patients with splanchnic or cerebral venous thrombosis and without overt chronic myeloproliferative disorders. Journal of Thrombosis & Haemostasis; Apr 2007.

10. Dentali, F., Poli, D., Scoditti, U., Di Minno, M. N., De Stefano, V., Siragusa, S., Kostal, M., Palareti, G., Sartori, M. T., Grandone, E., Vedovati, M. C., Ageno, W., Investigators, C.,Erebral,VEin,Thrombosis,International,Study, Falanga, A., Lerede, T., Bianchi, M., Testa, S., Witt, D., McCool, K., Bucherini, E., Grifoni, E., Coalizzo, D., Benedetti, R., Marietta, M., Sessa, M., Guaschino, C., di Minno, G., Tufano, A., Barbar, S., Malato, A., Pini, M., Castellini, P., Barco, S., Barone, M., Paciaroni, M., Alberti, A., Agnelli, G., Giorgi Pierfranceschi, M., Dulicek, P., Silingardi, M., Federica, L., Ghirarduzzi, A., Tiraferri, E., di Lazzaro, V., Rossi, E., Ciminello, A., Pasca, S., Barillari, G., Rezoagli, E., Galli, M., Squizzato, A., Tosetto, A.. Long-term outcomes of patients with cerebral vein thrombosis: a multicenter study. Journal of Thrombosis & Haemostasis; Jul 2012.

11. deVeber, G., Andrew, M., Adams, C., Bjornson, B., Booth, F., Buckley, D. J., Camfield, C. S., David, M., Humphreys, P., Langevin, P., MacDonald, E. A., Gillett, J., Meaney, B., Shevell, M., Sinclair, D. B., Yager, J., Canadian Pediatric Ischemic Stroke Study, Group. Cerebral sinovenous thrombosis in children. N Engl J Med; Aug 9 2001.

12. Duman, T., Uluduz, D., Midi, I., Bektas, H., Kablan, Y., Goksel, B. K., Milanlioglu, A., Necioglu Orken, D., Aluclu, U., Group, Venost,Study. A Multicenter Study of 1144 Patients with Cerebral Venous Thrombosis: The VENOST Study. J Stroke Cerebrovasc Dis; Aug 2017.

13. Eischer, L., Gartner, V., Schulman, S., Kyrle, P. A., Eichinger, S., investigators, Aurec-Fviii. 6 versus 30 months anticoagulation for recurrent venous thrombosis in patients with high factor VIII. Ann Hematol; May 2009.

14. Eryildiz, E. S., Ozdemir, A. O.. Clinical features of cerebral venous sinus thrombosis. Turk Noroloji Dergisi; 2017.

15. Gunes, H. N., Cokal, B. G., Guler, S. K., Yoldas, T. K., Malkan, U. Y., Demircan, C. S., Yon, M. I., Yoldas, Z., Gunes, G., Haznedaroglu, I. C.. Clinical associations, biological risk factors and outcomes of cerebral venous sinus thrombosis. Journal of International Medical Research; 2016.

16. Investigators, Einstein, Bauersachs, R., Berkowitz, S. D., Brenner, B., Buller, H. R., Decousus, H., Gallus, A. S., Lensing, A. W., Misselwitz, F., Prins, M. H., Raskob, G. E., Segers, A., Verhamme, P., Wells, P., Agnelli, G., Bounameaux, H., Cohen, A., Davidson, B. L., Piovella, F., Schellong, S.. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med; Dec 23 2010.

17. Kearon, C., Gent, M., Hirsh, J., Weitz, J., Kovacs, M. J., Anderson, D. R., Turpie, A. G., Green, D., Ginsberg, J. S., Wells, P., MacKinnon, B., Julian, J. A.. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med; Mar 25 1999.

18. Khealani, B. A., Wasay, M., Saadah, M., Sultana, E., Mustafa, S., Khan, F. S., Kamal, A. K.. Cerebral venous thrombosis: a descriptive multicenter study of patients in Pakistan and Middle East. Stroke; Oct 2008.

19. Krajickova, D., Klzo, L., Krajina, A., Vysata, O., Herzig, R., Valis, M.. Cerebral Venous Sinus Thrombosis: Clinical Characteristics and Factors Influencing Clinical Outcome. Clin Appl Thromb Hemost; Oct 2016.

20. Lee, E. J., Noh, S. M., Kang, D. W., Kim, J. S., Kwon, S. U.. Impact of Provoking Risk Factors on the Prognosis of Cerebral Venous Thrombosis in Korean Patients. J Stroke; May 2016.

21. Martinelli, I., Bucciarelli, P., Passamonti, S. M., Battaglioli, T., Previtali, E., Mannucci, P. M.. Long-term evaluation of the risk of recurrence after cerebral sinus-venous thrombosis. Circulation; Jun 29 2010.

22. Miranda, B., Ferro, J. M., Canhao, P., Stam, J., Bousser, M. G., Barinagarrementeria, F., Scoditti, U., Investigators, Iscvt. Venous thromboembolic events after cerebral vein thrombosis. Stroke; Sep 2010.

23. Narayan, D., Kaul, S., Ravishankar, K., Suryaprabha, T., Bandaru, V. C., Mridula, K. R., Jabeen, S. A., Alladi, S., Meena, A. K., Borgohain, R.. Risk factors, clinical profile, and long-term outcome of 428 patients of cerebral sinus venous thrombosis: insights from Nizam's Institute Venous Stroke Registry, Hyderabad (India). Neurol India; Mar-Apr 2012.

24. Palareti, G., Cosmi, B., Legnani, C., Tosetto, A., Brusi, C., Iorio, A., Pengo, V., Ghirarduzzi, A., Pattacini, C., Testa, S., Lensing, A. W., Tripodi, A., Investigators, Prolong. D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med; Oct 26 2006.

25. Palazzo, P., Agius, P., Ingrand, P., Ciron, J., Lamy, M., Berthomet, A., Cantagrel, P., Neau, J. P.. Venous Thrombotic Recurrence After Cerebral Venous Thrombosis: A Long-Term Follow-Up Study. Stroke; Feb 2017.

26. Passamonti, S. M., Biguzzi, E., Cazzola, M., Franchi, F., Gianniello, F., Bucciarelli, P., Pietra, D., Mannucci, P. M., Martinelli, I.. The JAK2 V617F mutation in patients with cerebral venous thrombosis. Journal of Thrombosis & Haemostasis; Jun 2012.

27. Ridker, P. M., Goldhaber, S. Z., Danielson, E., Rosenberg, Y., Eby, C. S., Deitcher, S. R., Cushman, M., Moll, S., Kessler, C. M., Elliott, C. G., Paulson, R., Wong, T., Bauer, K. A., Schwartz, B. A., Miletich, J. P., Bounameaux, H., Glynn, R. J., Investigators, Prevent. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med; Apr 10 2003.

28. Schulman, S., Kearon, C., Kakkar, A. K., Schellong, S., Eriksson, H., Baanstra, D., Kvamme, A. M., Friedman, J., Mismetti, P., Goldhaber, S. Z., Investigators, Re-Medy,Trial, Investigators, Re-Sonate,Trial. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med; Feb 21 2013.

29. Schulman, S., Wahlander, K., Lundstrom, T., Clason, S. B., Eriksson, H., Investigators, Thrive,Iii. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. N Engl J Med; Oct 30 2003.

30. Sidhom, Y., Mansour, M., Messelmani, M., Derbali, H., Fekih-Mrissa, N., Zaouali, J., Mrissa, R.. Cerebral venous thrombosis: clinical features, risk factors, and long-term outcome in a Tunisian cohort. J Stroke Cerebrovasc Dis; Jul 2014.

31. Terazzi, E., Mittino, D., Ruda, R., Cerrato, P., Monaco, F., Sciolla, R., Grasso, E., Leone, M. A., Cerebral Venous Thrombosis, Group. Cerebral venous thrombosis: a retrospective multicentre study of 48 patients. Neurological Sciences; Feb 2005.

32. Uzar, E., Ekici, F., Acar, A., Yucel, Y., Bakir, S., Tekbas, G., Oncel, O., Tasdemir, N.. Cerebral venous sinus thrombosis: an analyses of 47 patients. Eur Rev Med Pharmacol Sci; Oct 2012.

33. Wasay, M., Bakshi, R., Bobustuc, G., Kojan, S., Sheikh, Z., Dai, A., Cheema, Z.. Cerebral venous thrombosis: analysis of a multicenter cohort from the United States. J Stroke Cerebrovasc Dis; Mar-Apr 2008.

QUESTION

Should thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia vs. no thrombophilia testing and indefinite anticoagulant treatment in all be used for patients with cerebral venous thrombosis who completed primary treatment?

POPULATION:	patients with cerebral venous thrombosis who completed primary treatment
INTERVENTION:	thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia
COMPARISON:	no thrombophilia testing and indefinite anticoagulant treatment in all
MAIN OUTCOMES:	Recurrent VTE; Major bleeding - Low risk (0.5% per year); Major bleeding - High risk (1.5% per year);
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Thrombophilia, either acquired or inherited, can be identified in many patients presenting with venous thromboembolism (VTE). The currently most commonly tested inherited thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. Cerebral venous thrombosis can be unprovoked, or provoked by hormones, surgery or medical conditions. It is not clear what the standard of care is for these patients regarding duration of anticoagulant treatment, different guidelines recommend providing extended or limited anticoagulation. Therefore, the ASH guideline panel addressed the value of a strategy with testing for thrombophilia and treating only patients positive with indefinite anticoagulation, as compared to providing indefinite anticoagulation to everyone (this question) or providing definite treatment to everyone (separate question in these ASH guidelines). This question addresses whether thrombophilia testing and subsequent definite duration of anticoagulant treatment in patients negative for thrombophilia improves patient-important outcomes in patients with cerebral venous thrombosis, as compared with no thrombophilia testing and treating all patients with indefinite anticoagulant treatment. Since no randomized controlled trials have addressed this question, we used a modeling approach based on observational evidence for baseline risk of patient-important outcomes, prevalence of thrombophilia and associated risk of recurrent events with thrombophilia, and RCTs based evidence for the effect of indefinite anticoagulation on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		This question is important for cerebral venous thrombosis types (mainly unprovoked) that would usually be treated with extended anticoagulation.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Evidence Profile.	Desirable effect = avoiding major bleeding Major bleedings would be avoided in patients who are negative for thrombophilia by not extending their anticoagulation treatment. The panel considered the effect on major bleeding Trivial in the majority of patients who are at low risk of bleeding, and Small in patients who are at high risk of bleeding.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	See Evidence Profile.	Undesirable effect = allowing VTE recurrence. VTE recurrences would be allowed to happen in patients who are negative for thrombophilia by not extending their anticoagulation treatment.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows using a scale from 0 (worst possible scenario, usually death), to 1 (best possible scenario, usually perfect health):** **Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(1, 2, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3) **Gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off)(2, 3) **Minor intracranial bleeding event:** 0.75 (standard gamble)(2)	The panel considered that clinicians may value avoiding major bleeding more (they do not want to cause harm), while patients may value avoiding VTE events more (they may prefer avoiding a recurrence of blood clots).

	Major intracranial bleeding event: 0.15 (standard gamble)(2) **Anticoagulant therapy** Patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome.(3) Patients would favor efficacy and safety over convenience of route of administration.(6) Also, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events.(6, 7, 8)	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel considered that in the majority of patients who are at low risk of bleeding the balance Probably favors the comparison, while in patients at high risk of bleeding the balance Does not favor either the intervention or the comparison. No studies assessed indefinite anticoagulation as life-long treatment. The panel observed that the appraisal of the comparison of the two interventions (testing and treating positives vs treating none) was limited by the absence of studies comparing extended anticoagulation as life-long treatment versus no anticoagulation, which the panel had to extrapolate.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	Intervention Costs: **Test (source)** / Approximate Cost (2005) / Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016) / **(14/12/2016) £1 = $1,27** **Full Blood Count** / £2.55 / £3.29 / **$4,18** **Protein C** / £11.67 / £15.5 / **$19,12** **Free Protein S** / £11.67 / £15.5 / **$19,12** **Antithrombin** / £11.67 / £15.5 / **$19,12** **APCR** / £10.73 / £13.84 / **$17,58** **Factor V Leiden** / £85.00 / £109.65 / **$141,45** **Prothrombin gene mutation** / £85.00 / £109.65 / **$141,45** **Lupus Anticoagulant** / £10.73 / £13.84 / **$17,58** **Antiphospholipid antibodies** / £12.30 / £15.87 / **$20,15** **Anti Beta-2 GP1 antibody** / £9.50 / £12.25 / **$15,81** **The potential cost of a full thrombophilia screen** / £250.82, / £323.56 / **$410,92** Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx **Cost of the health outcomes:**(9) - **Recurrent VTE:** 11,000 to 15,000 USD - **Major bleeding:** 11,000 to 22,000 USD **Cost of interventions:**(10) - **Dabigatran:** Cost per month: $300.44–$600.88 USD - **Rivaroxaban:** Cost per month: $300.42–$600.84 USD - **Apixaban:** Cost per month: $300.44–$600.88	**The panel considered the following cost ranges:** - Cost for testing: $400 -$2,000 per patient - Cost for treatment: $1,000-$ 4,500 per patient per year In assessing the resources required the panel considered that the intervention (testing and treating only patients positive for thrombophilia) added the cost for testing all patients but "saved" the cost of treatment avoided in the patients negative for thrombophilia. The panel did not consider the costs for recurrent clots or for bleeding events.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence was identified for the cost-effectiveness of thrombophilia testing in patients with cerebral venous thrombosis. For patients with any symptomatic VTE: Three studies evaluated the cost-effectiveness of thrombophilia testing and different management strategies in patients with a first venous thromboembolism.(11, 12, 13) All three studies found thrombophilia testing cost-effective, although the uncertainty was high in general due to prevalence of mutation and the variability in the recurrence rate (which depends on the type of thrombophilia), risk of adverse events such as major haemorrhage, age or efficacy of the anticoagulant therapy, among others. Cost per quality-adjusted life year (QALY) for the testing and treatment strategies varied between the 3 studies and in sensitivity analyses (Simpson 2009: approximately £20,000/QALY for patients with PE or DVT; Marchetti 2001: $13,624/QALY for any VTE, Eckman 2002: $16,823/QALY for any VTE) One study evaluated thrombophilia testing using a panel of thrombophilia tests that included Factor V Leiden, Prothrombin G20210A, APC resistance, Protein C, Protein S, antithrombin levels, antiphospholipid antibodies and homocysteine levels, dysfibrinogenaemia, and levels of factor VIII, factor IX and factor XI.(13) Another cost-effectiveness study included only screening for FVL and G20210A prothrombin mutations,(11) and the third study included testing for FVL mutation.(12)	Identified studies assessed cost-effectiveness in patients with any type of VTE, not cerebral venous thrombosis specifically.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(14)	The panel considered that the health system/Service coverage will be the main aspect affecting the health equity. The US is an example where promotion of testing that is not covered by insurance would generate inequities, i.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no	Research studies suggested the following regarding acceptability and barriers associated with testing and	The panel considered testing acceptable for many doctors,

○ Probably yes ● Yes ○ Varies ○ Don't know	treatment: **Patients**: A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(15) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(16) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers**: A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(17) **Payers**: At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	although maybe not for all. Patients are in general willing to undergo thrombophilia testing when testing is proposed by their doctor.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major

	testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(18) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending.(19) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(20) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(21) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(22)	potential problems or barriers for implementation. External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know

	JUDGEMENT						
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

After completion of primary treatment for patients with cerebral venous thrombosis, the ASH guideline panel suggests not testing for thrombophilia to guide the duration of anticoagulant treatment, and using indefinite anticoagulant treatment in all patients (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:

- A strategy with testing for thrombophilia would mean that positive patients would receive indefinite anticoagulant treatment, and negative patients would stop anticoagulant treatment.

- This recommendation refers to testing for inherited and acquired types of thrombophilia.

- This recommendation addresses settings where the standard of care for cerebral venous thrombosis patients is indefinite anticoagulant treatment; the ASH guideline panel provides a separate recommendation for settings where the standard of care is stopping anticoagulant treatment (Q7.A.2).

Justification

The panel's main consideration in supporting this recommendation is that the increase in the risk of VTE recurrence in patients negative for thrombophilia outweighs the decrease in the risk of major bleeding and does not justify testing and limiting anticoagulant treatment duration.

Subgroup considerations

Subjects at high hemorrhagic risk.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation. Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

Randomized controlled trials comparing testing vs no testing would be ideal but have shown to be difficult to perform.(Cohn 2008; Cohn Cochrane review 2012) The second best option would be a pragmatic non-randomized controlled study comparing tested and non-tested patients with cerebral venous thrombosis.(Coppens 2008)

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
7. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
8. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
9. Grosse, S. D., Nelson, R. E., Nyarko, K. A., Richardson, L. C., Raskob, G. E.. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res; Jan 2016.
10. Biskupiak, J., Ghate, S. R., Jiao, T., Brixner, D.. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. J Manag Care Pharm; Nov-Dec 2013.
11. Marchetti, M., Quaglini, S., Barosi, G.. Cost-effectiveness of screening and extended anticoagulation for carriers of both factor V Leiden and prothrombin G20210A. Qjm; Jul 2001.
12. Eckman, M. H., Singh, S. K., Erban, J. K., Kao, G.. Testing for factor V Leiden in patients with pulmonary or venous thromboembolism: a cost-effectiveness analysis. Med Decis Making; Mar-Apr 2002.
13. Simpson, E. L., Stevenson, M. D., Rawdin, A., Papaioannou, D.. Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis. Health Technol Assess; Jan 2009.
14. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
15. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
16. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
17. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
18. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
19. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
20. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
21. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
22. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In patients with cerebral venous thrombosis who completed primary treatment, should thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia compared to no thrombophilia testing and indefinite anticoagulant treatment in all be used?

Setting:

Bibliography: See reference list and footnotes. [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Recurrent VTE (assessed with: any DVT or PE)									
17 [a,b,c,d,e,f,g]	observational studies	not serious	not serious	serious [h]	not serious	none	When testing 1,000 patients who completed primary treatment of cerebral venous thrombosis for any type of thrombophilia and only treating the 436 positives with indefinite anticoagulation (ranging from 419 to 452), 20 VTE recurrences will occur per year (ranging from 18 to 22). When not testing 1,000 patients for thrombophilia and treating all of them with indefinite anticoagulation, 6 VTE recurrences will occur per year (95% CI: 4 to 9). Therefore, a thrombophilia testing strategy is associated with 564 fewer patients treated with indefinite anticoagulation (ranging from 548 to 581) and **14 more VTE recurrences (ranging from 10 to 18)** per 1,000 patients per year compared with a no testing strategy. [i]	⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding - Low risk (0.5% per year)[j]									
15 [c,d,k,l,m]	observational studies	not serious	not serious	serious [n]	not serious	none	When testing 1,000 patients who completed primary treatment of cerebral venous thrombosis, and who are at low risk of major bleeding, for any type of thrombophilia and only treating the 436 positives with indefinite anticoagulation (ranging from 419 to 452), 8 major bleedings will occur per year (ranging from 6 to 10). When not testing 1,000 patients for thrombophilia and treating all of them with indefinite anticoagulation, 11 major bleedings will occur per year (95% CI: 7-17). Therefore, a thrombophilia testing strategy is associated with 564 fewer patients treated with indefinite anticoagulation (ranging from 548 to 581) and **3 fewer major bleedings (ranging from 1 to 7)** per 1,000 patients per year compared with a no testing strategy. [o]	⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding - High risk (1.5% per year)[p]									
15 [c,d,k,l,q]	observational studies	not serious	not serious	serious [n]	serious [r]	none	When testing 1,000 patients who completed primary treatment of cerebral venous thrombosis, and who are at high risk of major bleeding, for any type of thrombophilia and only treating the 436 positives with indefinite anticoagulation (ranging from 419 to 452), 23 major bleedings will occur per year (ranging from 18 to 30). When not testing 1,000 patients for thrombophilia and treating all of them with indefinite anticoagulation, 33 major bleedings will occur per year (95% CI: 21-50). Therefore, a thrombophilia testing strategy is associated with 564 fewer patients treated with indefinite anticoagulation (ranging from 548 to 581) and **10 fewer major bleedings (ranging from 3 to 20)** per 1,000 patients per year compared with a no testing strategy. [s]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE recurrence, 4 studies; Prevalence, 3 studies; Risk association for thrombophilia positive versus negative, 6 studies; Extended anticoagulation effect, 4 RCTs

b. Overall risk for VTE recurrence: Martinelli 2010, Miranda 2010, Dentali 2012, Palazzo 2017

c. Thrombophilia prevalence, used for calculation: Algahtani 2011, Camargo 2005, de Veber 2001

d. Prevalence of specific thrombophilia types, used to verify calculation estimate: Bellucci 2008, Coutinho 2009, De Stefano 2007, Duman 2017, Eryildiz 2017, Gunes 2016, Khealani 2008, Krajickova 2016, Lee 2016, Narayan 2012, Passamonti 2012, Sidhom 2014, Terazzi 2005, Uzar 2012, Wasay 2008

e. Thrombophilia positive vs negative risk association, used for calculation: Kearon, 1999, Kearon 2018, Mello 2010, Santamaria 2005, Schulman 2006, Weingarz 2015

f. Effect of extended anticoagulation treatment, used in calculation: Agnelli 2013, Bauersachs 2010, Schulman 2003, Schulman 2013

g. Risk association for specific thrombophilia types, used to verify calculation estimate: Baglin 2003, Brouwer 2009, Christiansen 2005, De Stefano 1999, De Stefano 2006, Di Minno 2014, Eichinger 2002, Gonzalez-Porras 2006, Hoibraaten 2000, Lijfering 2010, Lindmarker 1999, Marcucci 2003, Miles 2001, Palareti 2003, Prandoni 2007, Ridker 1995, Rodger 2008, Schattner 1997, Simioni 2000, Strandberg 2007, Wahlander 2006

h. The effect was indirectly calculated using separate studies for thrombophilia prevalence, relative risk of thrombophilia positives vs negatives, and the effect of treatment. The estimates for the relative risk of thrombophilia positives vs negatives, and the effect of treatment, came from studies including patients with any type of VTE (not CVT).

i. Based on the following estimates: Overall risk for VTE recurrence, 38 per 1,000; Prevalence of any thrombophilia, 43.6% (min 41.9 - max 45.2); Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 1.65 (95%CI: 1.28-2.47); Relative risk of VTE recurrence with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.15 (0.10-0.23). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

j. Among RCTs assessing the effect of extended treatment against limited treatment, the lowest observed rate of major bleeding with limited treatment was 0.5% (Agnelli 2001)

k. Number of studies used in calculations: Overall risk, 1 systematic review; Prevalence, 3 studies; Extended anticoagulation effect, 11 RCTs

l. Effect of extended anticoagulation treatment, used in calculation: Agnelli 2001, Agnelli 2003, Agnelli 2013, Bauersachs 2010, Couturaud 2015, Eischer 2009, Kearon 1999, Palareti 2006, Ridker 2003, Schulman 2003, Schulman 2013

m. Overall risk for Major bleeding: Agnelli 2001

n. The effect was indirectly calculated using separate studies for thrombophilia prevalence and the effect of treatment. The estimates for the effect of treatment came from studies including patients with any type of VTE (not CVT).

o. Based on the following estimates: Overall risk for Major bleeding of 5 per 1,000; Prevalence of any thrombophilia, 43.6% (41.9-45.2); Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 2.17 (1.40-3.35). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the smallest treatment effect (lower CI).

p. Among RCTs assessing the effect of extended treatment against limited treatment, the highest observed rate of major bleeding with limited treatment was 1.5% (Agnelli 2013)

q. Overall risk for Major bleeding: Agnelli 2013

r. There is a clinically important difference between the smallest and largest possible effect of the testing strategy

s. Based on the following estimates: Overall risk for Major bleeding of 15 per 1,000; Prevalence of any thrombophilia, 43.6% (41.9-45.2); Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 2.17 (1.40-3.35). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the smallest treatment effect (lower CI).

References

1. Agnelli, G., Buller, H. R., Cohen, A., Curto, M., Gallus, A. S., Johnson, M., Porcari, A., Raskob, G. E., Weitz, J. I., Investigators, Amplify-Ext. Apixaban for extended treatment of venous thromboembolism. N Engl J Med; Feb 21 2013.

2. Agnelli, G., Prandoni, P., Becattini, C., Silingardi, M., Taliani, M. R., Miccio, M., Imberti, D., Poggio, R., Ageno, W., Pogliani, E., Porro, F., Zonzin, P., Warfarin Optimal Duration Italian Trial, Investigators. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med; Jul 1 2003.

3. Agnelli, G., Prandoni, P., Santamaria, M. G., Bagatella, P., Iorio, A., Bazzan, M., Moia, M., Guazzaloca, G., Bertoldi, A., Tomasi, C., Scannapieco, G., Ageno, W., Warfarin Optimal Duration Italian Trial, Investigators. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med; Jul 19 2001.

4. Algahtani, H. A., Abdu, A. P., Shami, A. M., Hassan, A. E., Madkour, M. A., Al-Ghamdi, S. M., Malhotra, R. M., Al-Khathami, A. M.. Cerebral venous sinus thrombosis in Saudi Arabia. Neurosciences (Riyadh); Oct 2011.

5. Bellucci, S., Cassinat, B., Bonnin, N., Marzac, C., Crassard, I.. The V617F JAK 2 mutation is not a frequent event in patients with cerebral venous thrombosis without overt chronic myeloproliferative disorder. Thromb Haemost; Jun 2008.

6. Camargo, E. C., Massaro, A. R., Bacheschi, L. A., D'Amico, E. A., Villaca, P. R., Bassitt, R. P., Gualandro, S. F., Bendit, I., Scaff, M.. Ethnic differences in cerebral venous thrombosis. Cerebrovasc Dis; 2005.

7. Coutinho, J. M., Ferro, J. M., Canhao, P., Barinagarrementeria, F., Cantu, C., Bousser, M. G., Stam, J.. Cerebral venous and sinus thrombosis in women. Stroke; Jul 2009.

8. Couturaud, F., Sanchez, O., Pernod, G., Mismetti, P., Jego, P., Duhamel, E., Provost, K., dit Sollier, C. B., Presles, E., Castellant, P., Parent, F., Salaun, P. Y., Bressollette, L., Nonent, M., Lorillon, P., Girard, P., Lacut, K., Guegan, M., Bosson, J. L., Laporte, S., Leroyer, C., Decousus, H., Meyer, G., Mottier, D., Investigators, Padis-Pe. Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism: The PADIS-PE Randomized Clinical Trial. Jama; Jul 7 2015.

9. De Stefano, V., Fiorini, A., Rossi, E., Za, T., Farina, G., Chiusolo, P., Sica, S., Leone, G.. Incidence of the JAK2 V617F mutation among patients with splanchnic or cerebral venous thrombosis and without overt chronic myeloproliferative disorders. Journal of Thrombosis & Haemostasis; Apr 2007.

10. Dentali, F., Poli, D., Scoditti, U., Di Minno, M. N., De Stefano, V., Siragusa, S., Kostal, M., Palareti, G., Sartori, M. T., Grandone, E., Vedovati, M. C., Ageno, W., Investigators, C.,Erebral,VEin,Thrombosis,International,Study, Falanga, A., Lerede, T., Bianchi, M., Testa, S., Witt, D., McCool, K., Bucherini, E., Grifoni, E., Coalizzo, D., Benedetti, R., Marietta, M., Sessa, M., Guaschino, C., di Minno, G., Tufano, A., Barbar, S., Malato, A., Pini, M., Castellini, P., Barco, S., Barone, M., Paciaroni, M., Alberti, A., Agnelli, G., Giorgi Pierfranceschi, M., Dulicek, P., Silingardi, M., Federica, L., Ghirarduzzi, A., Tiraferri, E., di Lazzaro, V., Rossi, E., Ciminello, A., Pasca, S., Barillari, G., Rezoagli, E., Galli, M., Squizzato, A., Tosetto, A.. Long-term outcomes of patients with cerebral vein thrombosis: a multicenter study. Journal of Thrombosis & Haemostasis; Jul 2012.

11. deVeber, G., Andrew, M., Adams, C., Bjornson, B., Booth, F., Buckley, D. J., Camfield, C. S., David, M., Humphreys, P., Langevin, P., MacDonald, E. A., Gillett, J., Meaney, B., Shevell, M., Sinclair, D. B., Yager, J., Canadian Pediatric Ischemic Stroke Study, Group. Cerebral sinovenous thrombosis in children. N Engl J Med; Aug 9 2001.

12. Duman, T., Uluduz, D., Midi, I., Bektas, H., Kablan, Y., Goksel, B. K., Milanlioglu, A., Necioglu Orken, D., Aluclu, U., Group, Venost,Study. A Multicenter Study of 1144 Patients with Cerebral Venous Thrombosis: The VENOST Study. J Stroke Cerebrovasc Dis; Aug 2017.

13. Eischer, L., Gartner, V., Schulman, S., Kyrle, P. A., Eichinger, S., investigators, Aurec-Fviii. 6 versus 30 months anticoagulation for recurrent venous thrombosis in patients with high factor VIII. Ann Hematol; May 2009.

14. Eryildiz, E. S., Ozdemir, A. O.. Clinical features of cerebral venous sinus thrombosis. Turk Noroloji Dergisi; 2017.

15. Gunes, H. N., Cokal, B. G., Guler, S. K., Yoldas, T. K., Malkan, U. Y., Demircan, C. S., Yon, M. I., Yoldas, Z., Gunes, G., Haznedaroglu, I. C.. Clinical associations, biological risk factors and outcomes of cerebral venous sinus thrombosis. Journal of International Medical Research; 2016.

16. Investigators, Einstein, Bauersachs, R., Berkowitz, S. D., Brenner, B., Buller, H. R., Decousus, H., Gallus, A. S., Lensing, A. W., Misselwitz, F., Prins, M. H., Raskob, G. E., Segers, A., Verhamme, P., Wells, P., Agnelli, G., Bounameaux, H., Cohen, A., Davidson, B. L., Piovella, F., Schellong, S.. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med; Dec 23 2010.

17. Kearon, C., Gent, M., Hirsh, J., Weitz, J., Kovacs, M. J., Anderson, D. R., Turpie, A. G., Green, D., Ginsberg, J. S., Wells, P., MacKinnon, B., Julian, J. A.. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med; Mar 25 1999.

18. Khealani, B. A., Wasay, M., Saadah, M., Sultana, E., Mustafa, S., Khan, F. S., Kamal, A. K.. Cerebral venous thrombosis: a descriptive multicenter study of patients in Pakistan and Middle East. Stroke; Oct 2008.

19. Krajickova, D., Klzo, L., Krajina, A., Vysata, O., Herzig, R., Valis, M.. Cerebral Venous Sinus Thrombosis: Clinical Characteristics and Factors Influencing Clinical Outcome. Clin Appl Thromb Hemost; Oct 2016.

20. Lee, E. J., Noh, S. M., Kang, D. W., Kim, J. S., Kwon, S. U.. Impact of Provoking Risk Factors on the Prognosis of Cerebral Venous Thrombosis in Korean Patients. J Stroke; May 2016.

21. Martinelli, I., Bucciarelli, P., Passamonti, S. M., Battaglioli, T., Previtali, E., Mannucci, P. M.. Long-term evaluation of the risk of recurrence after cerebral sinus-venous thrombosis. Circulation; Jun 29 2010.

22. Miranda, B., Ferro, J. M., Canhao, P., Stam, J., Bousser, M. G., Barinagarrementeria, F., Scoditti, U., Investigators, Iscvt. Venous thromboembolic events after cerebral vein thrombosis. Stroke; Sep 2010.

23. Narayan, D., Kaul, S., Ravishankar, K., Suryaprabha, T., Bandaru, V. C., Mridula, K. R., Jabeen, S. A., Alladi, S., Meena, A. K., Borgohain, R.. Risk factors, clinical profile, and long-term outcome of 428 patients of cerebral sinus venous thrombosis: insights from Nizam's Institute Venous Stroke Registry, Hyderabad (India). Neurol India; Mar-Apr 2012.

24. Palareti, G., Cosmi, B., Legnani, C., Tosetto, A., Brusi, C., Iorio, A., Pengo, V., Ghirarduzzi, A., Pattacini, C., Testa, S., Lensing, A. W., Tripodi, A., Investigators, Prolong. D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med; Oct 26 2006.

25. Palazzo, P., Agius, P., Ingrand, P., Ciron, J., Lamy, M., Berthomet, A., Cantagrel, P., Neau, J. P.. Venous Thrombotic Recurrence After Cerebral Venous Thrombosis: A Long-Term Follow-Up Study. Stroke; Feb 2017.

26. Passamonti, S. M., Biguzzi, E., Cazzola, M., Franchi, F., Gianniello, F., Bucciarelli, P., Pietra, D., Mannucci, P. M., Martinelli, I.. The JAK2 V617F mutation in patients with cerebral venous thrombosis. Journal of Thrombosis & Haemostasis; Jun 2012.

27. Ridker, P. M., Goldhaber, S. Z., Danielson, E., Rosenberg, Y., Eby, C. S., Deitcher, S. R., Cushman, M., Moll, S., Kessler, C. M., Elliott, C. G., Paulson, R., Wong, T., Bauer, K. A., Schwartz, B. A., Miletich, J. P., Bounameaux, H., Glynn, R. J., Investigators, Prevent. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med; Apr 10 2003.

28. Schulman, S., Kearon, C., Kakkar, A. K., Schellong, S., Eriksson, H., Baanstra, D., Kvamme, A. M., Friedman, J., Mismetti, P., Goldhaber, S. Z., Investigators, Re-Medy,Trial, Investigators, Re-Sonate,Trial. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med; Feb 21 2013.

29. Schulman, S., Wahlander, K., Lundstrom, T., Clason, S. B., Eriksson, H., Investigators, Thrive,Iii. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. N Engl J Med; Oct 30 2003.

30. Sidhom, Y., Mansour, M., Messelmani, M., Derbali, H., Fekih-Mrissa, N., Zaouali, J., Mrissa, R.. Cerebral venous thrombosis: clinical features, risk factors, and long-term outcome in a Tunisian cohort. J Stroke Cerebrovasc Dis; Jul 2014.

31. Terazzi, E., Mittino, D., Ruda, R., Cerrato, P., Monaco, F., Sciolla, R., Grasso, E., Leone, M. A., Cerebral Venous Thrombosis, Group. Cerebral venous thrombosis: a retrospective multicentre study of 48 patients. Neurological Sciences; Feb 2005.

32. Uzar, E., Ekici, F., Acar, A., Yucel, Y., Bakir, S., Tekbas, G., Oncel, O., Tasdemir, N.. Cerebral venous sinus thrombosis: an analyses of 47 patients. Eur Rev Med Pharmacol Sci; Oct 2012.

33. Wasay, M., Bakshi, R., Bobustuc, G., Kojan, S., Sheikh, Z., Dai, A., Cheema, Z.. Cerebral venous thrombosis: analysis of a multicenter cohort from the United States. J Stroke Cerebrovasc Dis; Mar-Apr 2008.

QUESTION

Should thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia vs. no thrombophilia testing and stopping anticoagulant treatment in all be used for patients with splanchnic venous thrombosis who completed primary treatment?

POPULATION:	patients with splanchnic venous thrombosis who completed primary treatment
INTERVENTION:	thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia
COMPARISON:	no thrombophilia testing and stopping anticoagulant treatment in all
MAIN OUTCOMES:	Recurrent (any) VTE; Major bleeding - Low risk (0.5% per year); Major bleeding - High risk (1.5% per year);
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Thrombophilia, either acquired or inherited, can be identified in many patients presenting with venous thromboembolism (VTE). The currently most commonly tested inherited thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. Splanchnic thrombosis can be unprovoked, or provoked by hormones, surgery or medical conditions. It is not clear what the standard of care is for these patients regarding duration of anticoagulant treatment, different guidelines recommend providing extended or limited anticoagulation. Therefore, the ASH guideline panel addressed the value of a strategy with testing for thrombophilia and treating only patients positive with indefinite anticoagulation, as compared to providing definite anticoagulation to everyone (this question) or providing indefinite treatment to everyone (separate question in these ASH guidelines). This question addresses whether thrombophilia testing and subsequent indefinite duration of anticoagulant treatment in patients positive for thrombophilia improves patient-important outcomes in patients with splanchnic thrombosis, as compared with no thrombophilia testing and treating all patients with definite anticoagulant treatment. Since no randomized controlled trials have addressed this question, we used a modeling approach based on observational evidence for baseline risk of patient-important outcomes, prevalence of thrombophilia and associated risk of recurrent events with thrombophilia, and RCTs based evidence for the effect of indefinite anticoagulation on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		This question is important for splanchnic venous thrombosis types (mainly provoked) that would usually be treated with definite anticoagulation.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Evidence Profile.	Desirable effect = preventing VTE recurrence. VTE recurrences would be avoided in patients who are positive for thrombophilia by extending their anticoagulation treatment.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	See Evidence Profile.	Undesirable effect = causing major bleeding. Major bleedings would be caused in patients who are positive for thrombophilia by extending their anticoagulation treatment. The panel considered the increase in major bleeding to be Trivial in most patients who are at low risk of bleeding, but Small in those at high risk.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows using a scale from 0 (worst possible scenario, usually death), to 1 (best possible scenario, usually perfect health): Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(1, 2, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3) **Gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off)(2, 3) **Minor intracranial bleeding event:** 0.75 (standard gamble)(2) **Major intracranial bleeding event:** 0.15 (standard gamble)(2) **Anticoagulant therapy** Patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome.(3) Patients would favor efficacy and safety over convenience of route of administration.(6) Also, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events.(6, 7, 8)	The panel considered that clinicians may value avoiding major bleeding more (they do not want to cause harm), while patients may value avoiding VTE events more (they may prefer avoiding a recurrence of blood clots).

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Intervention Costs: **Test (source)** / Approximate Cost (2005) / Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016) / **(14/12/2016) £1 = $1,27** **Full Blood Count** £2.55 £3.29 **$4,18** **Protein C** £11.67 £15.5 **$19,12** **Free Protein S** £11.67 £15.5 **$19,12** **Antithrombin** £11.67 £15.5 **$19,12** **APCR** £10.73 £13.84 **$17,58** **Factor V Leiden** £85.00 £109.65 **$141,45** **Prothrombin gene mutation** £85.00 £109.65 **$141,45** **Lupus Anticoagulant** £10.73 £13.84 **$17,58** **Antiphospholipid antibodies** £12.30 £15.87 **$20,15** **Anti Beta-2 GP1 antibody** £9.50 £12.25 **$15,81** **The potential cost of a full thrombophilia screen** £250.82, £323.56 **$410,92** Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx **Cost of the health outcomes:**(9) - **Recurrent VTE:** 11,000 to 15,000 USD - **Major bleeding:** 11,000 to 22,000 USD **Cost of interventions:**(10) - **Dabigatran:** Cost per month: $300.44–$600.88 USD - **Rivaroxaban:** Cost per month: $300.42–$600.84 USD - **Apixaban:** Cost per month: $300.44–$600.88	**The panel considered the following cost ranges:** - Cost for testing: $400 -$2,000 per patient - Cost for treatment: $1,000-$ 4,500 per patient per year In assessing the resources required the panel considered that the intervention (testing and treating only patients positive for thrombophilia) added the cost for testing all patients but "saved" the cost of treatment avoided in the patients negative for thrombophilia. The panel did not consider the costs for recurrent clots or for bleeding events.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence was identified for the cost-effectiveness of thrombophilia testing in patients with splanchnic venous thrombosis. For patients with any symptomatic VTE: Three studies evaluated the cost-effectiveness of thrombophilia testing and different management strategies in patients with a first venous thromboembolism.(11, 12, 13) All three studies found thrombophilia testing cost-effective, although the uncertainty was high in general due to prevalence of mutation and the variability in the recurrence rate (which depends on the type of thrombophilia), risk of adverse events such as major haemorrhage, age or efficacy of the anticoagulant therapy, among others. Cost per quality-adjusted life year (QALY) for the testing and treatment strategies varied between the 3 studies and in sensitivity analyses (Simpson 2009: approximately £20,000/QALY for patients with PE or DVT; Marchetti 2001: $13,624/QALY for any VTE, Eckman 2002: $16,823/QALY for any VTE) One study evaluated thrombophilia testing using a panel of thrombophilia tests that included Factor V Leiden, Prothrombin G20210A, APC resistance, Protein C, Protein S, antithrombin levels, antiphospholipid antibodies and homocysteine levels, dysfibrinogenaemia, and levels of factor VIII, factor IX and factor XI.(13) Another cost-effectiveness study included only screening for FVL and G20210A prothrombin mutations,(11) and the third study included testing for FVL mutation.(12)	Identified studies assessed cost-effectiveness in patients with any type of VTE, not cerebral venous thrombosis specifically.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(14)	The panel considered that the health system/Service coverage will be the main aspect affecting the health equity. The US is an example where promotion of testing that is not covered by insurance would generate inequities, i.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies suggested the following regarding acceptability and barriers associated with testing and treatment: **Patients:** A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(15) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(16) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers:** A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(17) **Payers:** At present, thrombophilia testing	The panel considered testing acceptable for many doctors, although maybe not for all. Patients are in general willing to undergo thrombophilia testing when testing is proposed by their doctor.

	is discouraged and in some health care settings not reimbursed.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(18) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending.(19) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(20) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(21) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(22)	Provider "lack of awareness" of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation. External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know

	JUDGEMENT						
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

After completion of primary treatment for patients with splanchnic venous thrombosis, the ASH guideline panel suggests testing for thrombophilia and indefinite anticoagulant treatment in positive patients over no testing for thrombophilia and stopping anticoagulant treatment in all patients (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:

- A strategy with testing for thrombophilia would mean that positive patients would receive indefinite anticoagulant treatment, and negative patients would stop anticoagulant treatment.

- This recommendation refers to testing for inherited and acquired types of thrombophilia.

- This recommendation addresses settings where the standard of care for splanchnic venous thrombosis patients is stopping anticoagulant treatment; the ASH guideline panel provides a separate recommendation for settings where the standard of care is indefinite anticoagulant treatment (Q7.B.1).

Justification

The panel considered that thrombophilia testing and extending anticoagulant treatment in thrombophilia positives likely has some benefit in terms of prevention of VTE recurrence that outweighs the risk of major bleeding in patients at low risk, and may justify the costs of extended anticoagulant treatment.

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation. Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

Randomized controlled trials comparing testing vs no testing would be ideal but have shown to be difficult to perform.(Cohn 2008; Cohn Cochrane review 2012) The second best option would be a pragmatic non-randomized controlled study comparing tested and non-tested patients with VTE.(Coppens 2008)

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
7. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
8. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
9. Grosse, S. D., Nelson, R. E., Nyarko, K. A., Richardson, L. C., Raskob, G. E.. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res; Jan 2016.
10. Biskupiak, J., Ghate, S. R., Jiao, T., Brixner, D.. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. J Manag Care Pharm; Nov-Dec 2013.
11. Marchetti, M., Quaglini, S., Barosi, G.. Cost-effectiveness of screening and extended anticoagulation for carriers of both factor V Leiden and prothrombin G20210A. Qjm; Jul 2001.
12. Eckman, M. H., Singh, S. K., Erban, J. K., Kao, G.. Testing for factor V Leiden in patients with pulmonary or venous thromboembolism: a cost-effectiveness analysis. Med Decis Making; Mar-Apr 2002.
13. Simpson, E. L., Stevenson, M. D., Rawdin, A., Papaioannou, D.. Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis. Health Technol Assess; Jan 2009.
14. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
15. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
16. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
17. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
18. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
19. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
20. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
21. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
22. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In patients with splanchnic venous thrombosis who completed primary treatment, should thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia compared to no thrombophilia testing and stopping anticoagulant treatment in all be used?

Setting:

Bibliography: See reference list and footnotes. [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Recurrent (any) VTE (assessed with: any DVT or PE)									
18 [a,b,c,d,e,f,g]	observational studies	not serious	not serious	serious [h]	not serious	none	When testing 1,000 patients who completed primary treatment for splanchnic venous thrombosis for any type of thrombophilia and treating the 416 positives with indefinite anticoagulation (ranging from 310 to 613), 27 VTE recurrences will occur per year (ranging from 14 to 36). When not testing 1,000 patientsfor thrombophilia and stopping treatment in all of them, 50 VTE recurrences will occur per year. Therefore, a thrombophilia testing strategy is associated with 416 more patients treated with indefinite anticoagulation (ranging from 310 to 613) and **23 fewer VTE recurrences (ranging from 14 to 36)** per 1,000 patients per year compared with a no testing strategy. [i]	⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding - Low risk (0.5% per year)[j]									
18 [c,d,k,l,m]	observational studies	not serious	not serious	serious [n]	not serious	none	When testing 1,000 patients who completed primary treatment for splanchnic venous thrombosis, and who are at low risk of major bleeding, for any type of thrombophilia and treating the 416 positives with indefinite anticoagulation (ranging from 310 to 613), 7 major bleedings will occur per year (ranging from 6 to 12). When not testing 1,000 patients for thrombophilia and stopping treatment in all of them, 5 major bleedings will occur per year. Therefore, a thrombophilia testing strategy is associated with 416 more patients treated with indefinite anticoagulation (ranging from 310 to 613) and **2 more major bleedings (ranging from 1 to 7)** per 1,000 patients per year compared with a no testing strategy. [o]	⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding - High risk (1.5% per year)[p]									
18 [c,d,k,l,q]	observational studies	not serious	not serious	serious [n]	serious [r]	none	When testing 1,000 patients who completed primary treatment for splanchnic venous thrombosis, and who are at high risk of major bleeding, for any type of thrombophilia and treating the 416 positives with indefinite anticoagulation (ranging from 310 to 613), 22 major bleedings will occur per year (ranging from 17 to 37). When not testing 1,000 patients for thrombophilia and stopping treatment in all of them, 15 major bleedings will occur per year. Therefore, a thrombophilia testing strategy is associated with 416 more patients treated with indefinite anticoagultion (ranging from 310 to 613) and **7 more major bleedings (ranging from 2 to 22)** per 1,000 patients per year compared with a no testing strategy. [s]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE recurrence, 2 studies; Prevalence, 6 studies; Risk association for thrombophilia positive versus negative, 6 studies; Extended anticoagulation effect, 4 RCTs

b. Overall risk for VTE recurrence: Condat 2001, Dentali 2009

c. Thrombophilia prevalence, used for calculation: Algahtani 2011, Camargo 2005, Darwish Murad 2009, Mutreja 2013, Sutkowska 2013, Zarrouk 2017. In the absence of specific evidence for splanchnic venous thrombosis, two studies including cerebral venous thrombosis patients (Algahtani and Camargo) were used for prevalence of antiphospholipid antibodies

d. Prevalence of specific thrombophilia types, used to verify calculation estimate: Acosta 2008, Al-Thani 2015, Algahtani 2011, Al Hashmi 2017, Ali 2014, Alvi 2009, Amarapurkar 2007, Camargo 2005, Condat 2001, Denninger 2000, Dentali 2009, Elkrief 2014, Klute 2016, Ma 2016, Plessier 2010, Primignani 2006, Starakis 2010, Sutkowska 2013, Yang 2014, Zarrouk 2017. In the absence of specific evidence for splanchnic venous thrombosis, two studies including cerebral venous thrombosis patients (Algahtani and Camargo) were used for prevalence of antiphospholipid antibodies

e. Thrombophilia positive vs negative risk association, used for calculation: Kearon, 1999, Kearon 2018, Mello 2010, Santamaria 2005, Schulman 2006, Weingarz 2015

f. Risk association for specific thrombophilia types, used to verify calculation estimate: Baglin 2003, Brouwer 2009, Christiansen 2005, De Stefano 1999, De Stefano 2006, Di Minno 2014, Eichinger 2002, Gonzalez-Porras 2006, Hoibraaten 2000, Lijfering 2010, Lindmarker 1999, Marcucci 2003, Miles 2001, Palareti 2003, Prandoni 2007, Ridker 1995, Rodger 2008, Schattner 1997, Simioni 2000, Strandberg 2007, Wahlander 2006

g. Effect of extended anticoagulation treatment, used in calculation: Agnelli 2013, Bauersachs 2010, Schulman 2003, Schulman 2013

h. The effect was indirectly calculated using separate studies for thrombophilia prevalence, relative risk of thrombophilia positives vs negatives, and the effect of treatment. The estimates for the relative risk of thrombophilia positives vs negatives, and the effect of treatment, came from studies including patients with any type of VTE (not splanchnic venous thrombosis).

i. Based on the following estimates: Overall risk for VTE recurrence, 50 per 1,000; Prevalence of any thrombophilia, 41.6% (min 31.0 - max 61.3); Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 1.65 (95%CI: 1.28-2.47); Relative risk of VTE recurrence with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.15 (0.10-0.23). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

j. Among RCTs assessing the effect of extended treatment against limited treatment, the lowest observed rate of major bleeding with limited treatment was 0.5% (Agnelli 2001)

k. Number of studies used in calculations: Overall risk, 1 systematic review; Prevalence, 6 studies; Extended anticoagulation effect, 11 RCTs

l. Effect of extended anticoagulation treatment, used in calculation: Agnelli 2001, Agnelli 2003, Agnelli 2013, Bauersachs 2010, Couturaud 2015, Eischer 2009, Kearon 1999, Palareti 2006, Ridker 2003, Schulman 2003, Schulman 2013

m. Overall risk for Major bleeding: Agnelli 2001

n. The effect was indirectly calculated using separate studies for thrombophilia prevalence and the effect of treatment. The estimates for the effect of treatment came from studies including patients with any type of VTE (not splanchnic venous thrombosis).

o. Based on the following estimates: Overall risk for Major bleeding of 5 per 1,000; Prevalence of any thrombophilia, 41.6% (31.0-61.3); Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 2.17 (1.40-3.35). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the smallest treatment effect (lower CI).

p. Among RCTs assessing the effect of extended treatment against limited treatment, the highest observed rate of major bleeding with limited treatment was 1.5% (Agnelli 2013)

q. Overall risk for Major bleeding: Agnelli 2013

r. There is a clinically important difference between the smallest and largest possible effect of the testing strategy

s. Based on the following estimates: Overall risk for Major bleeding of 15 per 1,000; Prevalence of any thrombophilia, 41.6% (31.0-61.3); Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 2.17 (1.40-3.35). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the smallest treatment effect (lower CI)

References

1. Mutreja, D., Kotru, M., Sazawal, S., Ranjan, R., Sharma, A., Acharya, S. K., Saxena, R.. Hereditary and Acquired Thrombophilia in Splanchnic Vein Thrombosis: A Single-Center Experience. Clin Appl Thromb Hemost; Sep 2015.

2. Al Hashmi, K., Al Aamri, L., Al Lamki, S., Pathare, A.. Portal vein thrombosis in adult Omani patients: A retrospective cohort study. Oman Medical Journal; November 2017.

3. Acosta, S., Alhadad, A., Svensson, P., Ekberg, O.. Epidemiology, risk and prognostic factors in mesenteric venous thrombosis. Br J Surg; Oct 2008.

4. Agnelli, G., Buller, H. R., Cohen, A., Curto, M., Gallus, A. S., Johnson, M., Porcari, A., Raskob, G. E., Weitz, J. I., Investigators, Amplify-Ext. Apixaban for extended treatment of venous thromboembolism. N Engl J Med; Feb 21 2013.

5. Agnelli, G., Prandoni, P., Becattini, C., Silingardi, M., Taliani, M. R., Miccio, M., Imberti, D., Poggio, R., Ageno, W., Pogliani, E., Porro, F., Zonzin, P., Warfarin Optimal Duration Italian Trial, Investigators. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med; Jul 1 2003.

6. Agnelli, G., Prandoni, P., Santamaria, M. G., Bagatella, P., Iorio, A., Bazzan, M., Moia, M., Guazzaloca, G., Bertoldi, A., Tomasi, C., Scannapieco, G., Ageno, W., Warfarin Optimal Duration Italian Trial, Investigators. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med; Jul 19 2001.

7. Algahtani, H. A., Abdu, A. P., Shami, A. M., Hassan, A. E., Madkour, M. A., Al-Ghamdi, S. M., Malhotra, R. M., Al-Khathami, A. M.. Cerebral venous sinus thrombosis in Saudi Arabia. Neurosciences (Riyadh); Oct 2011.

8. Ali, N., Ayyub, M., Khan, S. A.. High prevalence of protein C, protein S, antithrombin deficiency, and Factor V Leiden mutation as a cause of hereditary thrombophilia in patients of venous thromboembolism and cerebrovascular accident. Pak J Med Sci; Nov-Dec 2014.

9. Al-Thani, H., El-Mabrok, J., El-Menyar, A., Al-Sulaiti, M., Tabeb, A. H., Hajaji, K., Elgohary, H., Asim, M., Latifi, R.. Clinical presentation and outcome of mesenteric vein thrombosis: a single-center experience. Angiology; Mar 2015.

10. Alvi, A. R., Khan, S., Niazi, S. K., Ghulam, M., Bibi, S.. Acute mesenteric venous thrombosis: improved outcome with early diagnosis and prompt anticoagulation therapy. Int J Surg; Jun 2009.

11. Amarapurkar, D. N., Patel, N. D., Jatania, J.. Primary mesenteric venous thrombosis: a study from western India. Indian J Gastroenterol; May-Jun 2007.

12. Baglin, T., Luddington, R., Brown, K., Baglin, C.. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet; Aug 16 2003.

13. Brouwer, J. L., Lijfering, W. M., Ten Kate, M. K., Kluin-Nelemans, H. C., Veeger, N. J., van der Meer, J.. High long-term absolute risk of recurrent venous thromboembolism in patients with hereditary deficiencies of protein S, protein C or antithrombin. Thromb Haemost; Jan 2009.

14. Camargo, E. C., Massaro, A. R., Bacheschi, L. A., D'Amico, E. A., Villaca, P. R., Bassitt, R. P., Gualandro, S. F., Bendit, I., Scaff, M.. Ethnic differences in cerebral venous thrombosis. Cerebrovasc Dis; 2005.

15. Christiansen, S. C., Cannegieter, S. C., Koster, T., Vandenbroucke, J. P., Rosendaal, F. R.. Thrombophilia, clinical factors, and recurrent venous thrombotic events. Jama; May 18 2005.

16. Condat, B., Pessione, F., Hillaire, S., Denninger, M. H., Guillin, M. C., Poliquin, M., Hadengue, A., Erlinger, S., Valla, D.. Current outcome of portal vein thrombosis in adults: risk and benefit of anticoagulant therapy. Gastroenterology; Feb 2001.

17. Couturaud, F., Sanchez, O., Pernod, G., Mismetti, P., Jego, P., Duhamel, E., Provost, K., dit Sollier, C. B., Presles, E., Castellant, P., Parent, F., Salaun, P. Y., Bressollette, L., Nonent, M., Lorillon, P., Girard, P., Lacut, K., Guegan, M., Bosson, J. L., Laporte, S., Leroyer, C., Decousus, H., Meyer, G., Mottier, D., Investigators, Padis-Pe. Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism: The PADIS-PE Randomized Clinical Trial. Jama; Jul 7 2015.

18. Darwish Murad, S., Plessier, A., Hernandez-Guerra, M., Fabris, F., Eapen, C. E., Bahr, M. J., Trebicka, J., Morard, I., Lasser, L., Heller, J., Hadengue, A., Langlet, P., Miranda, H., Primignani, M., Elias, E., Leebeek, F. W., Rosendaal, F. R., Garcia-Pagan, J. C., Valla, D. C., Janssen, H. L., Vie, E.,N.. Etiology, management, and outcome of the Budd-Chiari syndrome. Ann Intern Med; Aug 4 2009.

19. De Stefano, V., Martinelli, I., Mannucci, P. M., Paciaroni, K., Chiusolo, P., Casorelli, I., Rossi, E., Leone, G.. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med; Sep 9 1999.

20. De Stefano, V., Simioni, P., Rossi, E., Tormene, D., Za, T., Pagnan, A., Leone, G.. The risk of recurrent venous thromboembolism in patients with inherited deficiency of natural anticoagulants antithrombin, protein C and protein S. Haematologica; May 2006.

21. Denninger, M. H., Chait, Y., Casadevall, N., Hillaire, S., Guillin, M. C., Bezeaud, A., Erlinger, S., Briere, J., Valla, D.. Cause of portal or hepatic venous thrombosis in adults: the role of multiple concurrent factors. Hepatology; Mar 2000.

22. Dentali, F., Ageno, W., Witt, D., Malato, A., Clark, N., Garcia, D., McCool, K., Siragusa, S., Dyke, S., Crowther, M., consortium, Warped. Natural history of mesenteric venous thrombosis in patients treated with vitamin K antagonists: a multi-centre, retrospective cohort study. Thromb Haemost; Sep 2009.

23. Di Minno, M. N., Dentali, F., Lupoli, R., Ageno, W.. Mild antithrombin deficiency and risk of recurrent venous thromboembolism: a prospective cohort study. Circulation; Jan 28 2014.

24. Eichinger, S., Weltermann, A., Mannhalter, C., Minar, E., Bialonczyk, C., Hirschl, M., Schonauer, V., Lechner, K., Kyrle, P. A.. The risk of recurrent venous thromboembolism in heterozygous carriers of factor V Leiden and a first spontaneous venous thromboembolism. Archives of Internal Medicine; Nov 11 2002.

25. Eischer, L., Gartner, V., Schulman, S., Kyrle, P. A., Eichinger, S., investigators, Aurec-Fviii. 6 versus 30 months anticoagulation for recurrent venous thrombosis in patients with high factor VIII. Ann Hematol; May 2009.

26. Elkrief, L., Corcos, O., Bruno, O., Larroque, B., Rautou, P. E., Zekrini, K., Bretagnol, F., Joly, F., Francoz, C., Bondjemah, V., Cazals-Hatem, D., Boudaoud, L., De Raucourt, E., Panis, Y., Goria, O., Hillaire, S., Valla, D., Plessier, A.. Type 2 diabetes mellitus as a risk factor for intestinal resection in patients with superior mesenteric vein thrombosis. Liver Int; Oct 2014.

27. Gonzalez-Porras, J. R., Garcia-Sanz, R., Alberca, I., Lopez, M. L., Balanzategui, A., Gutierrez, O., Lozano, F., San Miguel, J.. Risk of recurrent venous thrombosis in patients with G20210A mutation in the prothrombin gene or factor V Leiden mutation. Blood Coagul Fibrinolysis; Jan 2006.

28. Hoibraaten, E., Qvigstad, E., Arnesen, H., Larsen, S., Wickstrom, E., Sandset, P. M.. Increased risk of recurrent venous thromboembolism during hormone replacement therapy--results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). Thromb Haemost; Dec 2000.

29. Investigators, Einstein, Bauersachs, R., Berkowitz, S. D., Brenner, B., Buller, H. R., Decousus, H., Gallus, A. S., Lensing, A. W., Misselwitz, F., Prins, M. H., Raskob, G. E., Segers, A., Verhamme, P., Wells, P., Agnelli, G., Bounameaux, H., Cohen, A., Davidson, B. L., Piovella, F., Schellong, S.. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med; Dec 23 2010.

30. Kearon, C., Gent, M., Hirsh, J., Weitz, J., Kovacs, M. J., Anderson, D. R., Turpie, A. G., Green, D., Ginsberg, J. S., Wells, P., MacKinnon, B., Julian, J. A.. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med; Mar 25 1999.

31. Kearon, C., Parpia, S., Spencer, F. A., Baglin, T., Stevens, S. M., Bauer, K. A., Lentz, S. R., Kessler, C. M., Douketis, J. D., Moll, S., Kaatz, S., Schulman, S., Connors, J. M., Ginsberg, J. S., Spadafora, L., Bhagirath, V., Liaw, P. C., Weitz, J. I., Julian, J. A.. Antiphospholipid antibodies and recurrent thrombosis after a first unprovoked venous thromboembolism. Blood; May 10 2018.

32. Klute, K., DeFilippis, E. M., Shillingford, K., Chapin, J., DeSancho, M. T.. Clinical presentations, risk factors, treatment and outcomes in patients with splanchnic vein thrombosis: a single-center experience. J Thromb Thrombolysis; Aug 2016.

33. Lijfering, W. M., Middeldorp, S., Veeger, N. J., Hamulyak, K., Prins, M. H., Buller, H. R., van der Meer, J.. Risk of recurrent venous thrombosis in homozygous carriers and double heterozygous carriers of factor V Leiden and prothrombin G20210A. Circulation; Apr 20 2010.

34. Lindmarker, P., Schulman, S., Sten-Linder, M., Wiman, B., Egberg, N., Johnsson, H.. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. DURAC Trial Study Group. Duration of Anticoagulation. Thromb Haemost; May 1999.

35. Ma, K., Wells, P., Guzman, C., Anderson, D., Blostein, M., Hirsch, A., Lazo-Langner, A., Kovacs, M. J., Rodger, M., Tagalakis, V., Kahn, S. R.. A multicenter prospective study of risk factors and treatment of unusual site thrombosis. Thromb Res; Aug 2016.

36. Marcucci, R., Liotta, A. A., Cellai, A. P., Rogolino, A., Gori, A. M., Giusti, B., Poli, D., Fedi, S., Abbate, R., Prisco, D.. Increased plasma levels of lipoprotein(a) and the risk of idiopathic and recurrent venous thromboembolism. Am J Med; Dec 1 2003.

37. Mello, T. B., Orsi, F. L., Montalvao, S. A., Ozelo, M. C., de Paula, E. V., Annichinno-Bizzachi, J. M.. Long-term prospective study of recurrent venous thromboembolism in a Hispanic population. Blood Coagul Fibrinolysis; Oct 2010.

38. Miles, J. S., Miletich, J. P., Goldhaber, S. Z., Hennekens, C. H., Ridker, P. M.. G20210A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. J Am Coll Cardiol; Jan 2001.

39. Palareti, G., Cosmi, B., Legnani, C., Tosetto, A., Brusi, C., Iorio, A., Pengo, V., Ghirarduzzi, A., Pattacini, C., Testa, S., Lensing, A. W., Tripodi, A., Investigators, Prolong. D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med; Oct 26 2006.

40. Palareti, G., Legnani, C., Cosmi, B., Valdre, L., Lunghi, B., Bernardi, F., Coccheri, S.. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation; Jul 22 2003.

41. Plessier, A., Darwish-Murad, S., Hernandez-Guerra, M., Consigny, Y., Fabris, F., Trebicka, J., Heller, J., Morard, I., Lasser, L., Langlet, P., Denninger, M. H., Vidaud, D., Condat, B., Hadengue, A., Primignani, M., Garcia-Pagan, J. C., Janssen, H. L., Valla, D., European Network for Vascular Disorders of the, Liver. Acute portal vein thrombosis unrelated to cirrhosis: a prospective multicenter follow-up study. Hepatology; Jan 2010.

42. Prandoni, P., Noventa, F., Ghirarduzzi, A., Pengo, V., Bernardi, E., Pesavento, R., Iotti, M., Tormene, D., Simioni, P., Pagnan, A.. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica; Feb 2007.

43. Primignani, M., Barosi, G., Bergamaschi, G., Gianelli, U., Fabris, F., Reati, R., Dell'Era, A., Bucciarelli, P., Mannucci, P. M.. Role of the JAK2 mutation in the diagnosis of chronic myeloproliferative disorders in splanchnic vein thrombosis. Hepatology; Dec 2006.

44. Ridker, P. M., Goldhaber, S. Z., Danielson, E., Rosenberg, Y., Eby, C. S., Deitcher, S. R., Cushman, M., Moll, S., Kessler, C. M., Elliott, C. G., Paulson, R., Wong, T., Bauer, K. A., Schwartz, B. A., Miletich, J. P., Bounameaux, H., Glynn, R. J., Investigators, Prevent. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med; Apr 10 2003.

45. Ridker, P. M., Miletich, J. P., Stampfer, M. J., Goldhaber, S. Z., Lindpaintner, K., Hennekens, C. H.. Factor V Leiden and risks of recurrent idiopathic venous thromboembolism. Circulation; Nov 15 1995.

46. Rodger, M. A., Kahn, S. R., Wells, P. S., Anderson, D. A., Chagnon, I., Le Gal, G., Solymoss, S., Crowther, M., Perrier, A., White, R., Vickars, L., Ramsay, T., Betancourt, M. T., Kovacs, M. J.. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. Cmaj; Aug 26 2008.

47. Santamaria, M. G., Agnelli, G., Taliani, M. R., Prandoni, P., Moia, M., Bazzan, M., Guazzaloca, G., Ageno, W., Bertoldi, A., Silingardi, M., Tomasi, C., Ambrosio, G. B., Warfarin Optimal Duration Italian Trial, Investigators. Thrombophilic abnormalities and recurrence of venous thromboembolism in patients treated with standardized anticoagulant treatment. Thromb Res; 2005.

48. Schattner, A., Kasher, I., Berrebi, A.. Causes and outcome of deep-vein thrombosis in otherwise-healthy patients under 50 years. Qjm; Apr 1997.

49. Schulman, S., Kearon, C., Kakkar, A. K., Schellong, S., Eriksson, H., Baanstra, D., Kvamme, A. M., Friedman, J., Mismetti, P., Goldhaber, S. Z., Investigators, Re-Medy,Trial, Investigators, Re-Sonate,Trial. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med; Feb 21 2013.

50. Schulman, S., Lindmarker, P., Holmstrom, M., Larfars, G., Carlsson, A., Nicol, P., Svensson, E., Ljungberg, B., Viering, S., Nordlander, S., Leijd, B., Jahed, K., Hjorth, M., Linder, O., Beckman, M.. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. Journal of Thrombosis & Haemostasis; Apr 2006.

51. Schulman, S., Wahlander, K., Lundstrom, T., Clason, S. B., Eriksson, H., Investigators, Thrive,Iii. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. N Engl J Med; Oct 30 2003.

52. Simioni, P., Prandoni, P., Lensing, A. W., Manfrin, D., Tormene, D., Gavasso, S., Girolami, B., Sardella, C., Prins, M., Girolami, A.. Risk for subsequent venous thromboembolic complications in carriers of the prothrombin or the factor V gene mutation with a first episode of deep-vein thrombosis. Blood; Nov 15 2000.

53. Starakis, I., Mazokopakis, E., Mougiou, A., Koutras, A., Gogos, C. A.. Thrombophilia and abdominal vessel thrombosis in a Greek University hospital: A five-year experience. Gastroenterology Insights; 2010.

54. Strandberg, K., Svensson, P. J., Ohlin, A. K.. Venous thromboembolism in carriers of the Factor V Leiden mutation and in patients without known thrombophilic risk factor; prediction of recurrence and APC-PCI complex concentration and/or soluble thrombomodulin antigen and activity. Thromb Res; 2007.

55. Sutkowska, E., McBane, R. D., Tafur, A. J., Sutkowski, K., Grill, D. E., Slusser, J. P., Wysokinski, W. E.. Thrombophilia differences in splanchnic vein thrombosis and lower extremity deep venous thrombosis in North America. J Gastroenterol; Oct 2013.

56. Wahlander, K., Eriksson, H., Lundstrom, T., Billing Clason, S., Wall, U., Nystrom, P., Wessman, P., Schulman, S., Investigators, Thrive,Iii. Risk of recurrent venous thromboembolism or bleeding in relation to thrombophilic risk factors in patients receiving ximelagatran or placebo for long-term secondary prevention of venous thromboembolism. Br J Haematol; Apr 2006.

57. Weingarz, L., Schindewolf, M., Schwonberg, J., Hecking, C., Wolf, Z., Erbe, M., Lindhoff-Last, E., Linnemann, B.. Thrombophilia and risk of VTE recurrence according to the age at the time of first VTE manifestation. Vasa; Jul 2015.

58. Yang, S., Fan, X., Ding, W., Liu, B., Meng, J., Wang, K., Wu, X., Li, J.. D-dimer as an early marker of severity in patients with acute superior mesenteric venous thrombosis. Medicine (Baltimore); Dec 2014.

59. Zarrouk, M., Salim, S., Elf, J., Gottsater, A., Acosta, S.. Testing for thrombophilia in mesenteric venous thrombosis - Retrospective original study and systematic review. Best Pract Res Clin Gastroenterol; Feb 2017.

QUESTION

Should thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia vs. no thrombophilia testing and indefinite anticoagulant treatment in all be used for patients with splanchnic venous thrombosis who completed primary treatment?

POPULATION:	patients with splanchnic venous thrombosis who completed primary treatment
INTERVENTION:	thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia
COMPARISON:	no thrombophilia testing and indefinite anticoagulant treatment in all
MAIN OUTCOMES:	Recurrent VTE; Major bleeding - Low risk (0.5% per year); Major bleeding - High risk (1.5% per year);
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Thrombophilia, either acquired or inherited, can be identified in many patients presenting with venous thromboembolism (VTE). The currently most commonly tested inherited thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. Splanchnic thrombosis can be unprovoked, or provoked by hormones, surgery or medical conditions. It is not clear what the standard of care is for these patients regarding duration of anticoagulant treatment, different guidelines recommend providing extended or limited anticoagulation. Therefore, the ASH guideline panel addressed the value of a strategy with testing for thrombophilia and treating only patients positive with indefinite anticoagulation, as compared to providing definite anticoagulation to everyone (this question) or providing indefinite treatment to everyone (separate question in these ASH guidelines). This question addresses whether thrombophilia testing and subsequent definite duration of anticoagulant treatment in patients negative for thrombophilia improves patient-important outcomes in patients with splanchnic thrombosis, as compared with no thrombophilia testing and treating all patients with indefinite anticoagulant treatment. Since no randomized controlled trials have addressed this question, we used a modeling approach based on observational evidence for baseline risk of patient-important outcomes, prevalence of thrombophilia and associated risk of recurrent events with thrombophilia, and RCTs based evidence for the effect of indefinite anticoagulation on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		This question is important for splanchnic venous thrombosis types (mainly unprovoked) that would usually be treated with extended anticoagulation.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Evidence Profile.	Major bleedings would be avoided in patients who are negative for thrombophilia by not extending their anticoagulation treatment. The panel considered the effect on major bleeding Small in the of patients who are at high risk of bleeding and Trivial in patients who are at low risk of bleeding.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	See Evidence Profile.	Undesirable effect = allowing VTE recurrence. VTE recurrences would be allowed to happen in patients who are negative for thrombophilia by not extending their anticoagulation treatment.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows using a scale from 0 (worst possible scenario, usually death), to 1 (best possible scenario, usually perfect health): Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(1, 2, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3) **Gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off)(2, 3) **Minor intracranial bleeding event:** 0.75 (standard gamble)(2) **Major intracranial bleeding event:** 0.15 (standard gamble)(2) **Anticoagulant therapy** Patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome.(3) Patients would favor efficacy and safety over convenience of route of administration.(6) Also, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events.(6, 7, 8)	The panel considered that clinicians may value avoiding major bleeding more (they do not want to cause harm), while patients may value avoiding VTE events more (they may prefer avoiding a recurrence of blood clots).

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel considered that clinicians may value avoiding major bleeding more (they do not want to cause harm), while patients may value avoiding VTE events more (they prefer avoiding a recurrence of clots).

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know		**The panel considered the following cost ranges:** - Cost for testing: $400 -$2,000 per patient - Cost for treatment: $1,000-$ 4,500 per patient per year In assessing the resources required the panel considered that the intervention (testing and treating only patients positive for thrombophilia) added the cost for testing all patients but "saved" the cost of treatment avoided in the patients negative for thrombophilia. The panel did not

	Intervention Costs: **Test (source)** / Approximate Cost (2005) / Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016) / **(14/12/2016) £1 = $1,27** **Full Blood Count** — £2.55 — £3.29 — **$4,18** **Protein C** — £11.67 — £15.5 — **$19,12** **Free Protein S** — £11.67 — £15.5 — **$19,12** **Antithrombin** — £11.67 — £15.5 — **$19,12** **APCR** — £10.73 — £13.84 — **$17,58** **Factor V Leiden** — £85.00 — £109.65 — **$141,45** **Prothrombin gene mutation** — £85.00 — £109.65 — **$141,45** **Lupus Anticoagulant** — £10.73 — £13.84 — **$17,58** **Antiphospholipid antibodies** — £12.30 — £15.87 — **$20,15** **Anti Beta-2 GP1 antibody** — £9.50 — £12.25 — **$15,81** **The potential cost of a full thrombophilia screen** — £250.82, — £323.56 — **$410,92** Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx **Cost of the health outcomes:**(9) - **Recurrent VTE:** 11,000 to 15,000 USD - **Major bleeding:** 11,000 to 22,000 USD **Cost of interventions:**(10) - **Dabigatran:** Cost per month: $300.44–$600.88 USD - **Rivaroxaban:** Cost per month: $300.42–$600.84 USD - **Apixaban:** Cost per month: $300.44–$600.88	consider the costs for recurrent clots or for bleeding events.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence was identified for the cost-effectiveness of thrombophilia testing in patients with splanchnic venous thrombosis. For patients with any symptomatic VTE: Three studies evaluated the cost-effectiveness of thrombophilia testing and different management strategies in patients with a first venous thromboembolism.(11, 12, 13) All three studies found thrombophilia testing cost-effective, although the uncertainty was high in general due to prevalence of mutation and the variability in the recurrence rate (which depends on the type of thrombophilia), risk of adverse events such as major haemorrhage, age or efficacy of the anticoagulant therapy, among others. Cost per quality-adjusted life year (QALY) for the testing and treatment strategies varied between the 3 studies and in sensitivity analyses (Simpson 2009: approximately £20,000/QALY for patients with PE or DVT; Marchetti 2001: $13,624/QALY for any VTE, Eckman 2002: $16,823/QALY for any VTE) One study evaluated thrombophilia testing using a panel of thrombophilia tests that included Factor V Leiden, Prothrombin G20210A, APC resistance, Protein C, Protein S, antithrombin levels, antiphospholipid antibodies and homocysteine levels, dysfibrinogenaemia, and levels of factor VIII, factor IX and factor XI.(13) Another cost-effectiveness study included only screening for FVL and G20210A prothrombin mutations,(11) and the third study included testing for FVL mutation.(12)	Identified studies assessed cost-effectiveness in patients with any type of VTE, not splanchnic venous thrombosis specifically.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(14)	The panel considered that the health system/Service coverage will be the main aspect affecting the health equity. The US is an example where promotion of testing that is not covered by insurance would generate inequities, i.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Research studies suggested the following regarding acceptability and barriers associated with testing and treatment: **Patients:** A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(15) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(16) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers:** A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial	The panel considered testing acceptable for many doctors, although maybe not for all. Patients are in general willing to undergo thrombophilia testing when testing is proposed by their doctor.

	infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(17) **Payers:** At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(18) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending.(19) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(20) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(21) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(22)	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation. External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know

	JUDGEMENT						
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

After completion of primary treatment for patients with splanchnic venous thrombosis, the ASH guideline panel suggests not testing for thrombophilia to guide the duration of anticoagulant treatment, and using indefinite anticoagulant treatment in all patients (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:

- A strategy with testing for thrombophilia would mean that positive patients would receive indefinite anticoagulant treatment, and negative patients would stop anticoagulant treatment.

- This recommendation refers to testing for inherited and acquired types of thrombophilia.

- This recommendation addresses settings where the standard of care for splanchnic venous thrombosis patients is indefinite anticoagulant treatment; the ASH guideline panel provides a separate recommendation for settings where the standard of care is stopping anticoagulant treatment (Q7.B.2).

Justification

The panel's main consideration in supporting this recommendation is that the increase in the risk of VTE recurrence in patients negative for thrombophilia outweighs the decrease in the risk of major bleeding and does not justify testing and limiting anticoagulant treatment duration.

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation. Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

Randomized controlled trials comparing testing vs no testing would be ideal but have shown to be difficult to perform.(Cohn 2008; Cohn Cochrane review 2012) The second best option would be a pragmatic non-randomized controlled study comparing tested and non-tested patients with VTE.(Coppens 2008)

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
7. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
8. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
9. Grosse, S. D., Nelson, R. E., Nyarko, K. A., Richardson, L. C., Raskob, G. E.. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res; Jan 2016.
10. Biskupiak, J., Ghate, S. R., Jiao, T., Brixner, D.. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. J Manag Care Pharm; Nov-Dec 2013.
11. Marchetti, M., Quaglini, S., Barosi, G.. Cost-effectiveness of screening and extended anticoagulation for carriers of both factor V Leiden and prothrombin G20210A. Qjm; Jul 2001.
12. Eckman, M. H., Singh, S. K., Erban, J. K., Kao, G.. Testing for factor V Leiden in patients with pulmonary or venous thromboembolism: a cost-effectiveness analysis. Med Decis Making; Mar-Apr 2002.
13. Simpson, E. L., Stevenson, M. D., Rawdin, A., Papaioannou, D.. Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis. Health Technol Assess; Jan 2009.
14. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
15. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
16. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
17. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
18. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
19. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
20. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
21. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
22. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In patients with splanchnic venous thrombosis who completed primary treatment, should thrombophilia testing and subsequent indefinite anticoagulant treatment in patients positive for thrombophilia and stopping anticoagulant treatment in patients negative for thrombophilia compared to no thrombophilia testing and indefinite anticoagulant treatment in all be used?

Setting:

Bibliography: See reference list and footnotes. [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Recurrent VTE (assessed with: any DVT or PE)									
18 [a,b,c,d,e,f,g]	observational studies	not serious	not serious	serious [h]	not serious	none	When testing 1,000 patients who completed primary treatment for splanchnic venous thrombosis for any type of thrombophilia and only treating the 416 positives with indefinite anticoagulation (ranging from 310 to 613), 27 VTE recurrences will occur per year (ranging from 19 to 34). When not testing 1,000 patients for thrombophilia and treating all of them with indefinite anticoagulation, 8 VTE recurrences will occur per year (95% CI: 5 to 12). Therefore, a thrombophilia testing strategy is associated with 584 fewer patients treated with indefinite anticoagulation (ranging from 387 to 690) and **20 more VTE recurrences (ranging from 8 to 29)** per 1,000 patients per year compared with a no testing strategy. [i]	⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding - Low risk (0.5% per year)[j]									
18 [c,d,k,l,m]	observational studies	not serious	not serious	serious [n]	not serious	none	When testing 1,000 patients who completed primary treatment for splanchnic venous thrombosis, and who are at low risk of major bleeding, for any type of thrombophilia and only treating the 416 positives with indefinite anticoagulation (ranging from 310 to 613), 7 major bleedings will occur per year (ranging from 6 to 9). When not testing 1,000 patients for thrombophilia and treating all of them with indefinite anticoagulation, 11 major bleedings will occur per year (95% CI: 7-17). Therefore, a thrombophilia testing strategy is associated with 584 fewer patients treated with indefinite anticoagulation (ranging from 387 to 690) and **3 fewer major bleedings (ranging from 1 to 8)** per 1,000 patients per year compared with a no testing strategy. [o]	⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding - High risk (1.5% per year)[p]									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
18 [c,d,l,q,r]	observational studies	not serious	not serious	serious [n]	serious [s]	none	When testing 1,000 patients with splanchnic venous thrombosis who are at high risk of major bleeding for any type of thrombophilia and only treating the 416 positives with indefinite anticoagulation (ranging from 310 to 613), 22 major bleedings will occur per year (ranging from 19 to 26). When not testing 1,000 patients for thrombophilia and treating all of them with indefinite anticoagulation, 33 major bleedings will occur per year (95% CI: 21-50). Therefore, a thrombophilia testing strategy is associated with 584 fewer patients treated with indefinite anticoagulation (ranging from 387 to 690) and **10 fewer major bleedings (ranging from 2 to 24)** per 1,000 patients per year compared with a no testing strategy. [t]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE recurrence, 2 studies; Prevalence, 6 studies; Risk association for thrombophilia positive versus negative, 6 studies; Extended anticoagulation effect, 4 RCTs

b. Overall risk for VTE recurrence: Condat 2001, Dentali 2009

c. Thrombophilia prevalence, used for calculation: Algahtani 2011, Camargo 2005, Darwish Murad 2009, Mutreja 2013, Sutkowska 2013, Zarrouk 2017. In the absence of specific evidence for splanchnic venous thrombosis, two studies including cerebral venous thrombosis patients (Algahtani and Camargo) were used for prevalence of antiphospholipid antibodies

d. Prevalence of specific thrombophilia types, used to verify calculation estimate: Acosta 2008, Al-Thani 2015, Algahtani 2011, Al Hashmi 2017, Ali 2014, Alvi 2009, Amarapurkar 2007, Camargo 2005, Condat 2001, Denninger 2000, Dentali 2009, Elkrief 2014, Klute 2016, Ma 2016, Plessier 2010, Primignani 2006, Starakis 2010, Sutkowska 2013, Yang 2014, Zarrouk 2017. In the absence of specific evidence for splanchnic venous thrombosis, two studies including cerebral venous thrombosis patients (Algahtani and Camargo) were used for prevalence of antiphospholipid antibodies

e. Thrombophilia positive vs negative risk association, used for calculation: Kearon, 1999, Kearon 2018, Mello 2010, Santamaria 2005, Schulman 2006, Weingarz 2015

f. Effect of extended anticoagulation treatment, used in calculation: Agnelli 2013, Bauersachs 2010, Schulman 2003, Schulman 2013

g. Risk association for specific thrombophilia types, used to verify calculation estimate: Baglin 2003, Brouwer 2009, Christiansen 2005, De Stefano 1999, De Stefano 2006, Di Minno 2014, Eichinger 2002, Gonzalez-Porras 2006, Hoibraaten 2000, Lijfering 2010, Lindmarker 1999, Marcucci 2003, Miles 2001, Palareti 2003, Prandoni 2007, Ridker 1995, Rodger 2008, Schattner 1997, Simioni 2000, Strandberg 2007, Wahlander 2006

h. The effect was indirectly calculated using separate studies for thrombophilia prevalence, relative risk of thrombophilia positives vs negatives, and the effect of treatment. The estimates for the relative risk of thrombophilia positives vs negatives, and the effect of treatment, came from studies including patients with any type of VTE (not splanchnic venous thrombosis).

i. Based on the following estimates: Overall risk for VTE recurrence, 50 per 1,000; Prevalence of any thrombophilia, 41.6% (min 31.0 - max 61.3); Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 1.65 (95%CI: 1.28-2.47); Relative risk of VTE recurrence with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.15 (0.10-0.23). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

j. Among RCTs assessing the effect of extended treatment against limited treatment, the lowest observed rate of major bleeding with limited treatment was 0.5% (Agnelli 2001)

k. Number of studies used in calculations: Overall risk, 1 systematic review; Prevalence, 6 studies; Extended anticoagulation effect, 11 RCTs

l. Effect of extended anticoagulation treatment, used in calculation: Agnelli 2001, Agnelli 2003, Agnelli 2013, Bauersachs 2010, Couturaud 2015, Eischer 2009, Kearon 1999, Palareti 2006, Ridker 2003, Schulman 2003, Schulman 2013

m. Overall risk for Major bleeding: Agnelli 2001

n. The effect was indirectly calculated using separate studies for thrombophilia prevalence and the effect of treatment. The estimates for the effect of treatment came from studies including patients with any type of VTE (not splanchnic venous thrombosis).

o. Based on the following estimates: Overall risk for Major bleeding of 5 per 1,000; Prevalence of any thrombophilia, 41.6% (31.0-61.3); Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 2.17 (1.40-3.35). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the smallest treatment effect (lower CI).

p. Among RCTs assessing the effect of extended treatment against limited treatment, the highest observed rate of major bleeding with limited treatment was 1.5% (Agnelli 2013)

q. Number of studies used in calculations: Overall risk, 1 systematic review; Prevalence, 5 studies; Extended anticoagulation effect, 11 RCTs (see Appendix)

r. Overall risk for Major bleeding: Agnelli 2013

s. There is a clinically important difference between the smallest and largest possible effect of the testing strategy

t. Based on the following estimates: Overall risk for Major bleeding of 15 per 1,000; Prevalence of any thrombophilia, 41.6% (31.0-61.3); Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 2.17 (1.40-3.35). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the smallest treatment effect (lower CI)

References

1. Mutreja, D., Kotru, M., Sazawal, S., Ranjan, R., Sharma, A., Acharya, S. K., Saxena, R.. Hereditary and Acquired Thrombophilia in Splanchnic Vein Thrombosis: A Single-Center Experience. Clin Appl Thromb Hemost; Sep 2015.

2. Al Hashmi, K., Al Aamri, L., Al Lamki, S., Pathare, A.. Portal vein thrombosis in adult Omani patients: A retrospective cohort study. Oman Medical Journal; November 2017.

3. Acosta, S., Alhadad, A., Svensson, P., Ekberg, O.. Epidemiology, risk and prognostic factors in mesenteric venous thrombosis. Br J Surg; Oct 2008.

4. Agnelli, G., Buller, H. R., Cohen, A., Curto, M., Gallus, A. S., Johnson, M., Porcari, A., Raskob, G. E., Weitz, J. I., Investigators, Amplify-Ext. Apixaban for extended treatment of venous thromboembolism. N Engl J Med; Feb 21 2013.

5. Agnelli, G., Prandoni, P., Becattini, C., Silingardi, M., Taliani, M. R., Miccio, M., Imberti, D., Poggio, R., Ageno, W., Pogliani, E., Porro, F., Zonzin, P., Warfarin Optimal Duration Italian Trial, Investigators. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med; Jul 1 2003.

6. Agnelli, G., Prandoni, P., Santamaria, M. G., Bagatella, P., Iorio, A., Bazzan, M., Moia, M., Guazzaloca, G., Bertoldi, A., Tomasi, C., Scannapieco, G., Ageno, W., Warfarin Optimal Duration Italian Trial, Investigators. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med; Jul 19 2001.

7. Algahtani, H. A., Abdu, A. P., Shami, A. M., Hassan, A. E., Madkour, M. A., Al-Ghamdi, S. M., Malhotra, R. M., Al-Khathami, A. M.. Cerebral venous sinus thrombosis in Saudi Arabia. Neurosciences (Riyadh); Oct 2011.

8. Ali, N., Ayyub, M., Khan, S. A.. High prevalence of protein C, protein S, antithrombin deficiency, and Factor V Leiden mutation as a cause of hereditary thrombophilia in patients of venous thromboembolism and cerebrovascular accident. Pak J Med Sci; Nov-Dec 2014.

9. Al-Thani, H., El-Mabrok, J., El-Menyar, A., Al-Sulaiti, M., Tabeb, A. H., Hajaji, K., Elgohary, H., Asim, M., Latifi, R.. Clinical presentation and outcome of mesenteric vein thrombosis: a single-center experience. Angiology; Mar 2015.

10. Alvi, A. R., Khan, S., Niazi, S. K., Ghulam, M., Bibi, S.. Acute mesenteric venous thrombosis: improved outcome with early diagnosis and prompt anticoagulation therapy. Int J Surg; Jun 2009.

11. Amarapurkar, D. N., Patel, N. D., Jatania, J.. Primary mesenteric venous thrombosis: a study from western India. Indian J Gastroenterol; May-Jun 2007.

12. Baglin, T., Luddington, R., Brown, K., Baglin, C.. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet; Aug 16 2003.

13. Brouwer, J. L., Lijfering, W. M., Ten Kate, M. K., Kluin-Nelemans, H. C., Veeger, N. J., van der Meer, J.. High long-term absolute risk of recurrent venous thromboembolism in patients with hereditary deficiencies of protein S, protein C or antithrombin. Thromb Haemost; Jan 2009.

14. Camargo, E. C., Massaro, A. R., Bacheschi, L. A., D'Amico, E. A., Villaca, P. R., Bassitt, R. P., Gualandro, S. F., Bendit, I., Scaff, M.. Ethnic differences in cerebral venous thrombosis. Cerebrovasc Dis; 2005.

15. Christiansen, S. C., Cannegieter, S. C., Koster, T., Vandenbroucke, J. P., Rosendaal, F. R.. Thrombophilia, clinical factors, and recurrent venous thrombotic events. Jama; May 18 2005.

16. Condat, B., Pessione, F., Hillaire, S., Denninger, M. H., Guillin, M. C., Poliquin, M., Hadengue, A., Erlinger, S., Valla, D.. Current outcome of portal vein thrombosis in adults: risk and benefit of anticoagulant therapy. Gastroenterology; Feb 2001.

17. Couturaud, F., Sanchez, O., Pernod, G., Mismetti, P., Jego, P., Duhamel, E., Provost, K., dit Sollier, C. B., Presles, E., Castellant, P., Parent, F., Salaun, P. Y., Bressollette, L., Nonent, M., Lorillon, P., Girard, P., Lacut, K., Guegan, M., Bosson, J. L., Laporte, S., Leroyer, C., Decousus, H., Meyer, G., Mottier, D., Investigators, Padis-Pe. Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism: The PADIS-PE Randomized Clinical Trial. Jama; Jul 7 2015.

18. Darwish Murad, S., Plessier, A., Hernandez-Guerra, M., Fabris, F., Eapen, C. E., Bahr, M. J., Trebicka, J., Morard, I., Lasser, L., Heller, J., Hadengue, A., Langlet, P., Miranda, H., Primignani, M., Elias, E., Leebeek, F. W., Rosendaal, F. R., Garcia-Pagan, J. C., Valla, D. C., Janssen, H. L., Vie, E.,N.. Etiology, management, and outcome of the Budd-Chiari syndrome. Ann Intern Med; Aug 4 2009.

19. De Stefano, V., Martinelli, I., Mannucci, P. M., Paciaroni, K., Chiusolo, P., Casorelli, I., Rossi, E., Leone, G.. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med; Sep 9 1999.

20. De Stefano, V., Simioni, P., Rossi, E., Tormene, D., Za, T., Pagnan, A., Leone, G.. The risk of recurrent venous thromboembolism in patients with inherited deficiency of natural anticoagulants antithrombin, protein C and protein S. Haematologica; May 2006.

21. Denninger, M. H., Chait, Y., Casadevall, N., Hillaire, S., Guillin, M. C., Bezeaud, A., Erlinger, S., Briere, J., Valla, D.. Cause of portal or hepatic venous thrombosis in adults: the role of multiple concurrent factors. Hepatology; Mar 2000.

22. Dentali, F., Ageno, W., Witt, D., Malato, A., Clark, N., Garcia, D., McCool, K., Siragusa, S., Dyke, S., Crowther, M., consortium, Warped. Natural history of mesenteric venous thrombosis in patients treated with vitamin K antagonists: a multi-centre, retrospective cohort study. Thromb Haemost; Sep 2009.

23. Di Minno, M. N., Dentali, F., Lupoli, R., Ageno, W.. Mild antithrombin deficiency and risk of recurrent venous thromboembolism: a prospective cohort study. Circulation; Jan 28 2014.

24. Eichinger, S., Weltermann, A., Mannhalter, C., Minar, E., Bialonczyk, C., Hirschl, M., Schonauer, V., Lechner, K., Kyrle, P. A.. The risk of recurrent venous thromboembolism in heterozygous carriers of factor V Leiden and a first spontaneous venous thromboembolism. Archives of Internal Medicine; Nov 11 2002.

25. Eischer, L., Gartner, V., Schulman, S., Kyrle, P. A., Eichinger, S., investigators, Aurec-Fviii. 6 versus 30 months anticoagulation for recurrent venous thrombosis in patients with high factor VIII. Ann Hematol; May 2009.

26. Elkrief, L., Corcos, O., Bruno, O., Larroque, B., Rautou, P. E., Zekrini, K., Bretagnol, F., Joly, F., Francoz, C., Bondjemah, V., Cazals-Hatem, D., Boudaoud, L., De Raucourt, E., Panis, Y., Goria, O., Hillaire, S., Valla, D., Plessier, A.. Type 2 diabetes mellitus as a risk factor for intestinal resection in patients with superior mesenteric vein thrombosis. Liver Int; Oct 2014.

27. Gonzalez-Porras, J. R., Garcia-Sanz, R., Alberca, I., Lopez, M. L., Balanzategui, A., Gutierrez, O., Lozano, F., San Miguel, J.. Risk of recurrent venous thrombosis in patients with G20210A mutation in the prothrombin gene or factor V Leiden mutation. Blood Coagul Fibrinolysis; Jan 2006.

28. Hoibraaten, E., Qvigstad, E., Arnesen, H., Larsen, S., Wickstrom, E., Sandset, P. M.. Increased risk of recurrent venous thromboembolism during hormone replacement therapy--results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). Thromb Haemost; Dec 2000.

29. Investigators, Einstein, Bauersachs, R., Berkowitz, S. D., Brenner, B., Buller, H. R., Decousus, H., Gallus, A. S., Lensing, A. W., Misselwitz, F., Prins, M. H., Raskob, G. E., Segers, A., Verhamme, P., Wells, P., Agnelli, G., Bounameaux, H., Cohen, A., Davidson, B. L., Piovella, F., Schellong, S.. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med; Dec 23 2010.

30. Kearon, C., Gent, M., Hirsh, J., Weitz, J., Kovacs, M. J., Anderson, D. R., Turpie, A. G., Green, D., Ginsberg, J. S., Wells, P., MacKinnon, B., Julian, J. A.. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med; Mar 25 1999.

31. Kearon, C., Parpia, S., Spencer, F. A., Baglin, T., Stevens, S. M., Bauer, K. A., Lentz, S. R., Kessler, C. M., Douketis, J. D., Moll, S., Kaatz, S., Schulman, S., Connors, J. M., Ginsberg, J. S., Spadafora, L., Bhagirath, V., Liaw, P. C., Weitz, J. I., Julian, J. A.. Antiphospholipid antibodies and recurrent thrombosis after a first unprovoked venous thromboembolism. Blood; May 10 2018.

32. Klute, K., DeFilippis, E. M., Shillingford, K., Chapin, J., DeSancho, M. T.. Clinical presentations, risk factors, treatment and outcomes in patients with splanchnic vein thrombosis: a single-center experience. J Thromb Thrombolysis; Aug 2016.

33. Lijfering, W. M., Middeldorp, S., Veeger, N. J., Hamulyak, K., Prins, M. H., Buller, H. R., van der Meer, J.. Risk of recurrent venous thrombosis in homozygous carriers and double heterozygous carriers of factor V Leiden and prothrombin G20210A. Circulation; Apr 20 2010.

34. Lindmarker, P., Schulman, S., Sten-Linder, M., Wiman, B., Egberg, N., Johnsson, H.. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. DURAC Trial Study Group. Duration of Anticoagulation. Thromb Haemost; May 1999.

35. Ma, K., Wells, P., Guzman, C., Anderson, D., Blostein, M., Hirsch, A., Lazo-Langner, A., Kovacs, M. J., Rodger, M., Tagalakis, V., Kahn, S. R.. A multicenter prospective study of risk factors and treatment of unusual site thrombosis. Thromb Res; Aug 2016.

36. Marcucci, R., Liotta, A. A., Cellai, A. P., Rogolino, A., Gori, A. M., Giusti, B., Poli, D., Fedi, S., Abbate, R., Prisco, D.. Increased plasma levels of lipoprotein(a) and the risk of idiopathic and recurrent venous thromboembolism. Am J Med; Dec 1 2003.

37. Mello, T. B., Orsi, F. L., Montalvao, S. A., Ozelo, M. C., de Paula, E. V., Annichinno-Bizzachi, J. M.. Long-term prospective study of recurrent venous thromboembolism in a Hispanic population. Blood Coagul Fibrinolysis; Oct 2010.

38. Miles, J. S., Miletich, J. P., Goldhaber, S. Z., Hennekens, C. H., Ridker, P. M.. G20210A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. J Am Coll Cardiol; Jan 2001.

39. Palareti, G., Cosmi, B., Legnani, C., Tosetto, A., Brusi, C., Iorio, A., Pengo, V., Ghirarduzzi, A., Pattacini, C., Testa, S., Lensing, A. W., Tripodi, A., Investigators, Prolong. D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med; Oct 26 2006.

40. Palareti, G., Legnani, C., Cosmi, B., Valdre, L., Lunghi, B., Bernardi, F., Coccheri, S.. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation; Jul 22 2003.

41. Plessier, A., Darwish-Murad, S., Hernandez-Guerra, M., Consigny, Y., Fabris, F., Trebicka, J., Heller, J., Morard, I., Lasser, L., Langlet, P., Denninger, M. H., Vidaud, D., Condat, B., Hadengue, A., Primignani, M., Garcia-Pagan, J. C., Janssen, H. L., Valla, D., European Network for Vascular Disorders of the, Liver. Acute portal vein thrombosis unrelated to cirrhosis: a prospective multicenter follow-up study. Hepatology; Jan 2010.

42. Prandoni, P., Noventa, F., Ghirarduzzi, A., Pengo, V., Bernardi, E., Pesavento, R., Iotti, M., Tormene, D., Simioni, P., Pagnan, A.. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica; Feb 2007.

43. Primignani, M., Barosi, G., Bergamaschi, G., Gianelli, U., Fabris, F., Reati, R., Dell'Era, A., Bucciarelli, P., Mannucci, P. M.. Role of the JAK2 mutation in the diagnosis of chronic myeloproliferative disorders in splanchnic vein thrombosis. Hepatology; Dec 2006.

44. Ridker, P. M., Goldhaber, S. Z., Danielson, E., Rosenberg, Y., Eby, C. S., Deitcher, S. R., Cushman, M., Moll, S., Kessler, C. M., Elliott, C. G., Paulson, R., Wong, T., Bauer, K. A., Schwartz, B. A., Miletich, J. P., Bounameaux, H., Glynn, R. J., Investigators, Prevent. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med; Apr 10 2003.

45. Ridker, P. M., Miletich, J. P., Stampfer, M. J., Goldhaber, S. Z., Lindpaintner, K., Hennekens, C. H.. Factor V Leiden and risks of recurrent idiopathic venous thromboembolism. Circulation; Nov 15 1995.

46. Rodger, M. A., Kahn, S. R., Wells, P. S., Anderson, D. A., Chagnon, I., Le Gal, G., Solymoss, S., Crowther, M., Perrier, A., White, R., Vickars, L., Ramsay, T., Betancourt, M. T., Kovacs, M. J.. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. Cmaj; Aug 26 2008.

47. Santamaria, M. G., Agnelli, G., Taliani, M. R., Prandoni, P., Moia, M., Bazzan, M., Guazzaloca, G., Ageno, W., Bertoldi, A., Silingardi, M., Tomasi, C., Ambrosio, G. B., Warfarin Optimal Duration Italian Trial, Investigators. Thrombophilic abnormalities and recurrence of venous thromboembolism in patients treated with standardized anticoagulant treatment. Thromb Res; 2005.

48. Schattner, A., Kasher, I., Berrebi, A.. Causes and outcome of deep-vein thrombosis in otherwise-healthy patients under 50 years. Qjm; Apr 1997.

49. Schulman, S., Kearon, C., Kakkar, A. K., Schellong, S., Eriksson, H., Baanstra, D., Kvamme, A. M., Friedman, J., Mismetti, P., Goldhaber, S. Z., Investigators, Re-Medy,Trial, Investigators, Re-Sonate,Trial. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med; Feb 21 2013.

50. Schulman, S., Lindmarker, P., Holmstrom, M., Larfars, G., Carlsson, A., Nicol, P., Svensson, E., Ljungberg, B., Viering, S., Nordlander, S., Leijd, B., Jahed, K., Hjorth, M., Linder, O., Beckman, M.. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. Journal of Thrombosis & Haemostasis; Apr 2006.

51. Schulman, S., Wahlander, K., Lundstrom, T., Clason, S. B., Eriksson, H., Investigators, Thrive,Iii. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. N Engl J Med; Oct 30 2003.

52. Simioni, P., Prandoni, P., Lensing, A. W., Manfrin, D., Tormene, D., Gavasso, S., Girolami, B., Sardella, C., Prins, M., Girolami, A.. Risk for subsequent venous thromboembolic complications in carriers of the prothrombin or the factor V gene mutation with a first episode of deep-vein thrombosis. Blood; Nov 15 2000.

53. Starakis, I., Mazokopakis, E., Mougiou, A., Koutras, A., Gogos, C. A.. Thrombophilia and abdominal vessel thrombosis in a Greek University hospital: A five-year experience. Gastroenterology Insights; 2010.

54. Strandberg, K., Svensson, P. J., Ohlin, A. K.. Venous thromboembolism in carriers of the Factor V Leiden mutation and in patients without known thrombophilic risk factor; prediction of recurrence and APC-PCI complex concentration and/or soluble thrombomodulin antigen and activity. Thromb Res; 2007.

55. Sutkowska, E., McBane, R. D., Tafur, A. J., Sutkowski, K., Grill, D. E., Slusser, J. P., Wysokinski, W. E.. Thrombophilia differences in splanchnic vein thrombosis and lower extremity deep venous thrombosis in North America. J Gastroenterol; Oct 2013.

56. Wahlander, K., Eriksson, H., Lundstrom, T., Billing Clason, S., Wall, U., Nystrom, P., Wessman, P., Schulman, S., Investigators, Thrive,Iii. Risk of recurrent venous thromboembolism or bleeding in relation to thrombophilic risk factors in patients receiving ximelagatran or placebo for long-term secondary prevention of venous thromboembolism. Br J Haematol; Apr 2006.

57. Weingarz, L., Schindewolf, M., Schwonberg, J., Hecking, C., Wolf, Z., Erbe, M., Lindhoff-Last, E., Linnemann, B.. Thrombophilia and risk of VTE recurrence according to the age at the time of first VTE manifestation. Vasa; Jul 2015.

58. Yang, S., Fan, X., Ding, W., Liu, B., Meng, J., Wang, K., Wu, X., Li, J.. D-dimer as an early marker of severity in patients with acute superior mesenteric venous thrombosis. Medicine (Baltimore); Dec 2014.

59. Zarrouk, M., Salim, S., Elf, J., Gottsater, A., Acosta, S.. Testing for thrombophilia in mesenteric venous thrombosis - Retrospective original study and systematic review. Best Pract Res Clin Gastroenterol; Feb 2017.

QUESTION

Should thrombophilia testing and subsequent thromboprophylaxis in relatives positive for thrombophilia and no thromboprophylaxis in relatives negative for thrombophilia vs. no thrombophilia testing and no thromboprophylaxis in all be used for first- and second-degree relatives of patients with VTE and a known hereditary thrombophilia who have a minor provoking risk factor for VTE?	
POPULATION:	first- and second-degree relatives of patients with VTE and a known hereditary thrombophilia who have a minor provoking risk factor for VTE
INTERVENTION:	thrombophilia testing and subsequent thromboprophylaxis in relatives positive for thrombophilia and no thromboprophylaxis in relatives negative for thrombophilia
COMPARISON:	no thrombophilia testing and no thromboprophylaxis in all
MAIN OUTCOMES:	First-time VTE; Major bleeding
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Inherited thrombophilia can be identified in many patients with a venous thromboembolism (VTE). Consequently, relatives of these patients are also at increased risk to have inherited thrombophilia. The currently most commonly tested inherited thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. Thrombophilia testing is often performed in relatives of patients with VTE and inherited thrombophilia, particularly if they are in a high risk episode such as immobilization. Although testing relatives of patients with a VTE and inherited thrombophilia has a high chance of finding a positive test result, primarily the same thrombophilia type as the proband but also others, the relevant question and aim of the current guideline is to assess whether thrombophilia testing and tailoring management to the test result would improve patient important outcomes. This question addresses whether testing for any inherited thrombophilia and subsequent thromboprophylaxis in patients positive for thrombophilia improves patient important outcomes in relatives of patients with VTE and a known familial thrombophilia who have a minor provoking risk factor for VTE (e.g. immobility, minor injury, illness, infection), as compared with no thrombophilia testing and no thromboprophylaxis in all. Since no randomized controlled trials have addressed this question, we used a modeling exercise based on observational evidence for baseline risk, prevalence of thrombophilia and associated risk of events with thrombophilia, and RCTs with evidence for the effect of thromboprophylaxis on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies		A separate question in this guideline addresses selective testing in relatives, i.e. only testing for the inherited thrombophilia type that was identified in the patient with VTE. The current question addresses whether testing for all inherited thrombophilia types has any additional benefit

○ Don't know		compared with selective testing.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Evidence Profile.	Desirable effect = preventing VTE. VTE would be avoided in relatives who are positive for thrombophilia by using thromboprophylaxis. The panel considered a reduction in first-time VTE of 5 per 1,000 or lower to be Trivial. The panel considered the following thresholds: Trivial: ≤5 per 1000; Small: 5-20 per 1,000; Moderate: 20-50 per 1,000 Trivial for FVL and prothrombin. Small for antithrombin, protein C, and protein S. These effects were considered Small to Moderate by the panel. The overall judgment was Trivial as FVL and prothrombin mutations are more prevalent than antithrombin, protein C, and protein S deficiencies.

		Second-degree relatives: For modeling the effect in second-degree relatives we assumed a prevalence of 25% of the same thrombophilia type as the proband. Effect estimates for VTE in second-degree relatives: FVL: 2.82 fewer per 1,000 (from 0.47 to 4.83 fewer) PT: 2.82 fewer per 1,000 (from 0.43 to 5.12 fewer) AT: 12.10 fewer per 1,000 (from 1.96 to 19.80 fewer) PC: 11.67 fewer per 1,000 (from 1.66 to 20.40 fewer) PS: 11.40 fewer per 1,000 (from 1.53 to 20.23 fewer)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	See Evidence Profile.	Undesirable effect = causing major bleeding. Major bleedings would be caused in patients who are positive for thrombophilia by using thromboprophylaxis. Second-degree relatives: For modeling the effect in second-degree relatives we assumed a prevalence of 25% of the same thrombophilia type as the proband. Effect estimates for Major bleeding in second-degree

		relatives: FVL: 1.17 more per 1,000 (from 0.35 to 2.44 more) PT: 1.25 more per 1,000 (from 0.38 to 2.60 more) AT: 1.31 more per 1,000 (from 0.40 to 2.72 more) PC: 1.31 more per 1,000 (from 0.40 to 2.72 more) PS: 1.31 more per 1,000 (from 0.40 to 2.73 more)

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows using a scale from 0 (worst possible scenario, usually death), to 1 (best possible scenario, usually perfect health): Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(1, 2, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3) **Gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off)(2, 3) **Minor intracranial bleeding event:** 0.75 (standard gamble)(2) **Major intracranial bleeding event:** 0.15 (standard gamble)(2) **Anticoagulant therapy** Patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome.(3) Patients would favor efficacy and safety over convenience of route of administration.(6) Also, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events.(7, 6, 8)	The panel considered clinicians may value avoiding major bleedings more (they do not want to cause harm), while patients may value avoiding VTE events more (they prefer avoiding a recurrence of clots).

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know		FVL and prothrombin: Does not favor either the intervention or comparison, in first- and second-degree relatives Antithrombin, protein C, and protein S: Probably favors the intervention, for first- and second-degree relatives

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Intervention Costs: **Test (source)** / Approximate Cost (2005) / Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016) / **(14/12/2016) £1 = $1,27** **Full Blood Count** £2.55 £3.29 **$4,18** **Protein C** £11.67 £15.5 **$19,12** **Free Protein S** £11.67 £15.5 **$19,12** **Antithrombin** £11.67 £15.5 **$19,12** **APCR** £10.73 £13.84 **$17,58** **Factor V Leiden** £85.00 £109.65 **$141,45** **Prothrombin gene mutation** £85.00 £109.65 **$141,45** **Lupus Anticoagulant** £10.73 £13.84 **$17,58** **Antiphospholipid antibodies** £12.30 £15.87 **$20,15** **Anti Beta-2 GP1 antibody** £9.50 £12.25 **$15,81** **The potential cost of a full thrombophilia screen** £250.82, £323.56 **$410,92** Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx **Cost of the health outcomes:**(9) - **Recurrent VTE:** 11,000 to 15,000 USD - **Major bleeding:** 11,000 to 22,000 USD **Cost of interventions:**(10) - **Dabigatran:** Cost per month: $300.44–$600.88 USD - **Rivaroxaban:** Cost per month:	**The panel considered the following cost ranges:** - Cost for testing: $400 -$2,000 per patient - Cost for treatment: $1,000-$ 4,500 per patient per year Costs for testing all hereditary thrombophilia types and short course of thromboprophylaxis, as compared to no testing and no thromboprophylaxis.

	$300.42–$600.84 USD - **Apixaban:** Cost per month: $300.44–$600.88	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(11)	The panel considered that the health system/service coverage will be the main aspect affecting health equity. USA is an example where promotion of testing that is not covered by insurance would generate inequities. I.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Research studies suggested the following regarding acceptability and barriers associated with testing and treatment: **Patients:** A survey was conducted in members of a large family with heritable protein C deficiency. For those who had not been tested before, using a 7-point scale (1 - not at all interested; 7 extremely interested), the mean score for interest in testing interest was 4.6 (standard deviation 2.4). Patients in general were willing to take the test for thrombophilia.(12) A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(13) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(14) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers:** A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(15) **Payers:** At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	The panel considered testing acceptable for many doctors, although maybe not for all. Patients are in general willing to undergo thrombophilia testing when testing is proposed by their doctor.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(16) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending.(17) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(18) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(19) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(20)	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation. External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories.

SUMMARY OF JUDGEMENTS

JUDGEMENT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

Factor V Leiden or prothrombin mutation

In first- and second-degree relatives of patients with VTE and known factor V Leiden or prothrombin mutation (low risk thrombophilia types), and who have a minor provoking risk factor for VTE, the ASH guideline panel suggests not testing for any hereditary thrombophilia to guide thromboprophylaxis, and not using thromboprophylaxis in all relatives (conditional recommendation based on very low certainty in the evidence about effects)

Antithrombin, protein C, or protein S deficiency

In first- and second-degree relatives of patients with VTE and known antithrombin, protein C, or protein S deficiency (high risk thrombophilia types), and who have a minor provoking risk factor for VTE, the ASH guideline panel suggests testing for any hereditary thrombophilia and thromboprophylaxis in relatives positive for thrombophilia over no testing for thrombophilia and no thromboprophylaxis in all relatives (conditional recommendation based on very low certainty in the evidence about effects)

Remarks:

- A strategy with testing for any hereditary thrombophilia would mean that positive relatives receive thromboprophylaxis, and negative relatives would receive no thromboprophylaxis.

- These recommendations do not address homozygous defects, or combinations of thrombophilia types.

- These recommendations refer to testing for any inherited type of thrombophilia. A separate question in this guideline addressed selective testing only for the known familial thrombophilia type in this population, and the resulting recommendations are the same.

Justification

The panel considered that testing for any inherited thrombophilia and thromboprophylaxis in relatives who are positive likely has some benefit in terms of prevention of VTE that outweighs the risk of major bleeding in first- and second-degree relatives of patients with VTE and high risk thrombophilias (antithrombin, protein C, protein S), but not low risk thrombophilias (factor V Leiden, prothrombin).

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation.

Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

The difference in patient important outcomes between testing for all inherited thrombophilia, as addressed here, and selective testing only for the thrombophilia type of the proband, as addressed in a separate guideline question, was negligible. Therefore we advise to focus future research on selective testing.

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
7. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
8. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
9. Grosse, S. D., Nelson, R. E., Nyarko, K. A., Richardson, L. C., Raskob, G. E.. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res; Jan 2016.
10. Biskupiak, J., Ghate, S. R., Jiao, T., Brixner, D.. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. J Manag Care Pharm; Nov-Dec 2013.
11. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
12. van Korlaar, I. M., Vossen, C. Y., Rosendaal, F. R., Bovill, E. G., Naud, S., Cameron, L. D., Kaptein, A. A.. Attitudes toward genetic testing for thrombophilia in asymptomatic members of a large family with heritable protein C deficiency. Journal of Thrombosis & Haemostasis; Nov 2005.
13. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
14. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
15. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
16. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
17. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
18. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
19. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
20. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In first- and second-degree relatives of patients with VTE and a known hereditary thrombophilia who have a minor provoking risk factor for VTE (e.g. immobility, minor injury, illness, infection), should testing for any hereditary thrombophilia and subsequent thromboprophylaxis in relatives positive for thrombophilia and no thromboprophylaxis in relatives negative for thrombophilia compared to no thrombophilia testing and no thromboprophylaxis in all be used?

Setting:

Bibliography: See reference list and footnotes. [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
VTE - Factor V Leiden - First-degree relatives (follow up: minor provoking risk factor episode; assessed with: any first-time DVT or PE)									
23 [a,b,c,d,e]	observational studies	not serious	not serious	serious [f]	not serious	none	When testing first-degree relatives of patients with VTE and factor V Leiden (FVL) who have a minor provoking VTE risk factor for any hereditary thrombophilia, and treating the 512 positives with thromboprophylaxis, 9.84 VTE events will occur per 1,000 risk episodes (ranging from 6.84 to 14.07). When not testing first-degree relatives for thrombophilia and treating none of them with thromboprophylaxis, 15 VTE events will occur per 1,000 risk episodes. Therefore, a thrombophilia testing strategy is associated with 512 more relatives treated with thromboprophylaxis and **5.16 fewer VTE events (ranging from 0.93 to 8.16)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [g]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Prothrombin mutation - First-degree relatives (follow up: minor provoking risk factor episode; assessed with: any first-time DVT or PE)									
23 [a,b,c,d,e]	observational studies	not serious	not serious	serious [f]	not serious	none	When testing first-degree relatives of patients with VTE and prothrombin mutation (PT) who have a minor provoking VTE risk factor for any hereditary thrombophilia, and treating the 524 positives with thromboprophylaxis, 9.91 VTE events will occur per 1,000 risk episodes (ranging from 6.65 to 14.14). When not testing first-degree relatives for thrombophilia and treating none of them with thromboprophylaxis, 15 VTE events will occur per 1,000 risk episodes. Therefore, a thrombophilia testing strategy is associated with 524 more relatives treated with thromboprophylaxis and **5.09 fewer VTE events (ranging from 0.86 to 8.35)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [h]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Antithrombin deficiency - First-degree relatives (follow up: minor provoking risk factor episode; assessed with: any first-time DVT or PE)									
23 [a,b,c,d,e]	observational studies	not serious	not serious	serious [f]	serious [i]	none	When testing first-degree relatives of patients with VTE and antithrombin deficiency (AT) who have a minor provoking VTE risk factor for any hereditary thrombophilia, and treating the 533 positives with thromboprophylaxis, 28.59 VTE events will occur per 1,000 risk episodes (ranging from 17.11 to 46.13). When not testing first-degree relatives for thrombophilia and treating none of them with thromboprophylaxis, 50 VTE events will occur per 1,000 risk episodes. Therefore, a thrombophilia testing strategy is associated with 533 more relatives treated with thromboprophylaxis and **21.41 fewer VTE events (ranging from 3.87 to 32.89)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [j]	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
VTE - Protein C deficiency - First-degree relatives (follow up: minor provoking risk factor episode; assessed with: any first-time DVT or PE)									
23 [a,b,c,d,e]	observational studies	not serious	not serious	serious [f]	serious [i]	none	When testing first-degree relatives of patients with VTE and protein C deficiency (PC) who have a minor provoking VTE risk factor for any hereditary thrombophilia, and treating the 533 positives with thromboprophylaxis, 29.44 VTE events will occur per 1,000 risk episodes (ranging from 17.49 to 46.55). When not testing first-degree relatives for thrombophilia and treating none of them with thromboprophylaxis, 50 VTE events will occur per 1,000 risk episodes. Therefore, a thrombophilia testing strategy is associated with 533 more relatives treated with thromboprophylaxis and **20.56 fewer VTE events (ranging from 3.45 to 32.51)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [k]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Protein S deficiency - First-degree relatives (follow up: minor provoking risk factor episode; assessed with: any first-time DVT or PE)									
23 [a,b,c,d,e]	observational studies	not serious	not serious	serious [f]	serious [i]	none	When testing first-degree relatives of patients with VTE and protein S deficiency (PS) who have a minor provoking VTE risk factor for any hereditary thrombophilia, and treating the 534 positives with thromboprophylaxis, 29.93 VTE events will occur per 1,000 risk episodes (ranging from 17.96 to 46.71). When not testing first-degree relatives for thrombophilia and treating none of them with thromboprophylaxis, 50 VTE events will occur per 1,000 risk episodes. Therefore, a thrombophilia testing strategy is associated with 534 more relatives treated with thromboprophylaxis and **20.07 fewer VTE events (ranging from 3.29 to 32.04)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [l]	⨁◯◯◯ VERY LOW	CRITICAL
Major Bleeding - Factor V Leiden - First-degree relatives (follow up: minor provoking risk factor episode)									
9 [c,e,m,n]	observational studies	not serious	not serious	serious [o]	not serious	none	When testing first-degree relatives of patients with VTE and factor V Leiden (FVL) who have a minor provoking VTE risk factor for any hereditary thrombophilia, and treating the 512 positives with thromboprophylaxis, 6.23 major bleedings will occur per 1,000 risk episodes (ranging from 4.68 to 8.65). When not testing first-degree relatives for thrombophilia and treating none of them with thromboprophylaxis, 4 major bleedings will occur per 1,000 risk episodes. Therefore, a thrombophilia testing strategy is associated with 512 more relatives treated with thromboprophylaxis and **2.23 more major bleedings (ranging from 0.68 to 4.65)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [p]	⨁◯◯◯ VERY LOW	CRITICAL
Major Bleeding - Prothrombin mutation - First-degree relatives (follow up: minor provoking risk factor episode)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
9 [c,e,m,n]	observational studies	not serious	not serious	serious [o]	not serious	none	When testing first-degree relatives of patients with VTE and prothrombin mutation (PT) who have a minor provoking VTE risk factor for any hereditary thrombophilia, and treating the 524 positives with thromboprophylaxis, 6.29 major bleedings will occur per 1,000 risk episodes (ranging from 4.69 to 8.76). When not testing first-degree relatives for thrombophilia and treating none of them with thromboprophylaxis, 4 major bleedings will occur per 1,000 risk episodes. Therefore, a thrombophilia testing strategy is associated with 524 more relatives treated with thromboprophylaxis and **2.29 more major bleedings (ranging from 0.69 to 4.76)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [p]	⨁◯◯◯ VERY LOW	CRITICAL

Major Bleeding - Antithrombin deficiency - First-degree relatives (follow up: minor provoking risk factor episode)

9 [c,e,m,n]	observational studies	not serious	not serious	serious [o]	not serious	none	When testing first-degree relatives of patients with VTE and antithrombin deficiency (AT) who have a minor provoking VTE risk factor for any hereditary thrombophilia, and treating the 533 positives with thromboprophylaxis, 6.33 major bleedings will occur per 1,000 risk episodes (ranging from 4.70 to 8.84). When not testing first-degree relatives for thrombophilia and treating none of them with thromboprophylaxis, 4 major bleedings will occur per 1,000 risk episodes. Therefore, a thrombophilia testing strategy is associated with 533 more relatives treated with thromboprophylaxis and **2.33 more major bleedings (ranging from 0.70 to 4.84)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [p]	⨁◯◯◯ VERY LOW	CRITICAL

Major Bleeding - Protein C deficiency - First-degree relatives (follow up: minor provoking risk factor episode)

9 [c,e,m,n]	observational studies	not serious	not serious	serious [o]	not serious	none	When testing first-degree relatives of patients with VTE and protein C deficiency (PC) who have a minor provoking VTE risk factor for any hereditary thrombophilia, and treating the 533 positives with thromboprophylaxis, 6.32 major bleedings will occur per 1,000 risk episodes (ranging from 4.70 to 8.84). When not testing first-degree relatives for thrombophilia and treating none of them with thromboprophylaxis, 4 major bleedings will occur per 1,000 risk episodes. Therefore, a thrombophilia testing strategy is associated with 533 more relatives treated with thromboprophylaxis and **2.32 more major bleedings (ranging from 0.70 to 4.84)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [p]	⨁◯◯◯ VERY LOW	CRITICAL

Major Bleeding - Protein S deficiency - First-degree relatives (follow up: minor provoking risk factor episode)

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
9 [c,e,m,n]	observational studies	not serious	not serious	serious [o]	not serious	none	When testing first-degree relatives of patients with VTE and protein S deficiency (PS) who have a minor provoking VTE risk factor for any hereditary thrombophilia, and treating the 534 positives with thromboprophylaxis, 6.33 major bleedings will occur per 1,000 risk episodes (ranging from 4.70 to 8.85). When not testing first-degree relatives for thrombophilia and treating none of them with thromboprophylaxis, 4 major bleedings will occur per 1,000 risk episodes. Therefore, a thrombophilia testing strategy is associated with 534 more relatives treated with thromboprophylaxis and **2.33 more major bleedings (ranging from 0.70 to 4.85)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [p]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE, 6 studies; Prevalence of thrombophilia types in the general population, 5 studies; Risk association for thrombophilia positive versus negative, 14 studies (6 also reported overall risk for VTE); Thromboprophylaxis effect, 4 RCTs

b. Overall risk for VTE: estimated from Bank 2004, Coppens 2006, Mahmoodi 2010, Middeldorp 1998, Simioni 1999, Simioni 2002

c. Prevalence of thrombophilia in the general population: Dykes 2001, Rees 1995, Rosendaal 1998, Tait 1994, Tait 1995

d. Thrombophilia positive vs negative risk association, used for calculation: Bank 2004, Brouwer 2005, Brouwer 2006, Cohen 2012, Coppens 2006, Couturaud 2006, Faioni 1999, Lensen 2001, Mahmoodi 2010, Martinelli 1998, Martinelli 2000, Middeldorp 1998, Simioni 1999, Simioni 2002

e. Effect of thromboprophylaxis: Cohen 2013, Cohen 2016, Goldhaber 2011, Hull 2010

f. The effect was indirectly calculated using separate studies for overall risk of VTE, thrombophilia prevalence in the general population, relative risk of thrombophilia positives vs negatives, and the effect of thromboprophylaxis

g. Based on the following estimates: Overall risk for VTE, 15 per 1,000; Prevalence of thrombophilia in first-degree relatives, 50% for FVL plus general population prevalence of other thrombophilia types in those who are FVL negative; Relative risk for VTE in thrombophilia positives versus negatives, RR 2.82 (95%CI: 2.10-3.81); Relative risk of VTE with thromboprophylaxis versus no thromboprophylaxis, RR 0.54 (0.32-0.91). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the upper CI of the Relative risk for VTE, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE, and the smallest treatment effect (upper CI).

h. Based on the following estimates: Overall risk for VTE, 15 per 1,000; Prevalence of thrombophilia in first-degree relatives, 50% for PT plus general population prevalence of other thrombophilia types in those who are PT negative; Relative risk for VTE in thrombophilia positives versus negatives, RR 2.55 (95%CI: 1.60-4.09); Relative risk of VTE with thromboprophylaxis versus no thromboprophylaxis, RR 0.54 (0.32-0.91). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the upper CI of the Relative risk for VTE, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE, and the smallest treatment effect (upper CI).

i. There is a clinically important difference between the smallest and largest possible effect of the testing strategy

j. Based on the following estimates: Overall risk for VTE, 50 per 1,000; Prevalence of thrombophilia in first-degree relatives, 50% for AT plus general population prevalence of other thrombophilia types in those who are AT negative; Relative risk for VTE in thrombophilia positives versus negatives, RR 11.76 (95%CI: 5.35-26.00); Relative risk of VTE with thromboprophylaxis versus no thromboprophylaxis, RR 0.54 (0.32-0.91). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the upper CI of the Relative risk for VTE, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE, and the smallest treatment effect (upper CI).

k. Based on the following estimates: Overall risk for VTE, 50 per 1,000; Prevalence of thrombophilia in first-degree relatives, 50% for PC plus general population prevalence of other thrombophilia types in those who are PC negative; Relative risk for VTE in thrombophilia positives versus negatives, RR 7.36 (95%CI: 2.88-19.12); Relative risk of VTE with thromboprophylaxis versus no thromboprophylaxis, RR 0.54 (0.32-0.91). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the upper CI of the Relative risk for VTE, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE, and the smallest treatment effect (upper CI).

l. Based on the following estimates: Overall risk for VTE, 50 per 1,000; Prevalence of thrombophilia in first-degree relatives, 50% for PS plus general population prevalence of other thrombophilia types in those who are PS negative; Relative risk for VTE in thrombophilia positives versus negatives, RR 5.98 (95%CI: 2.38-14.24); Relative risk of VTE with thromboprophylaxis versus no thromboprophylaxis, RR 0.54 (0.32-0.91). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the upper CI of the Relative risk for VTE, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE, and the smallest treatment effect (upper CI).

m. Number of studies used in calculations: Overall risk for major bleeding and effect of thromboprophylaxis, 4 RCTs; Prevalence of thrombophilia types in the general population, 5 studies

n. Overall risk of major bleeding: Cohen 2013, Cohen 2016, Goldhaber 2011, Hull 2010

o. The effect was indirectly calculated using separate studies for overall risk of major bleeding, thrombophilia prevalence in the general population, and the effect of thromboprophylaxis

p. Based on the following estimates: Overall risk for Major Bleeding, 4 per 1,000; Prevalence of thrombophilia in first-degree relatives, 50% for the same type plus general population prevalence of other thrombophilia types in those who were FVL negative; Relative risk of Major Bleeding with thromboprophylaxis versus no thromboprophylaxis, RR 2.09 (1.33-3.27). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the smallest treatment effect (lower CI).

References

1. Bank, I., Libourel, E. J., Middeldorp, S., Van Pampus, E. C., Koopman, M. M., Hamulyak, K., Prins, M. H., Van Der Meer, J. , Buller, H. R.. Prothrombin 20210A mutation: a mild risk factor for venous thromboembolism but not for arterial thrombotic disease and pregnancy-related complications in a family study. Archives of Internal Medicine; Sep 27 2004.

2. Brouwer, J. L., Veeger, N. J., Kluin-Nelemans, H. C., van der Meer, J.. The pathogenesis of venous thromboembolism: evidence for multiple interrelated causes. Ann Intern Med; Dec 5 2006.

3. Brouwer, J. L., Veeger, N. J., van der Schaaf, W., Kluin-Nelemans, H. C., van der Meer, J.. Difference in absolute risk of venous and arterial thrombosis between familial protein S deficiency type I and type III. Results from a family cohort study to assess the clinical impact of a laboratory test-based classification. Br J Haematol; Mar 2005.

4. Cohen, A. T., Harrington, R. A., Goldhaber, S. Z., Hull, R. D., Wiens, B. L., Gold, A., Hernandez, A. F., Gibson, C. M., Investigators, Apex. Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients. N Engl J Med; Aug 11 2016.

5. Cohen, A. T., Spiro, T. E., Buller, H. R., Haskell, L., Hu, D., Hull, R., Mebazaa, A., Merli, G., Schellong, S., Spyropoulos, A. C., Tapson, V., Investigators, Magellan. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. N Engl J Med; Feb 7 2013.

6. Cohen, W., Castelli, C., Alessi, M. C., Aillaud, M. F., Bouvet, S., Saut, N., Brunet, D., Barthet, M. C., Tregouet, D. A., Lavigne, G., Morange, P. E.. ABO blood group and von Willebrand factor levels partially explained the incomplete penetrance of congenital thrombophilia. Arterioscler Thromb Vasc Biol; Aug 2012.

7. Coppens, M., van de Poel, M. H., Bank, I., Hamulyak, K., van der Meer, J., Veeger, N. J., Prins, M. H., Buller, H. R., Middeldorp, S.. A prospective cohort study on the absolute incidence of venous thromboembolism and arterial cardiovascular disease in asymptomatic carriers of the prothrombin 20210A mutation. Blood; Oct 15 2006.

8. Couturaud, F., Kearon, C., Leroyer, C., Mercier, B., Abgrall, J. F., Le Gal, G., Lacut, K., Oger, E., Bressollette, L., Ferec, C., Lamure, M., Mottier, D., Groupe d'Etude de la Thrombose de Bretagne, Occidentale. Incidence of venous thromboembolism in first-degree relatives of patients with venous thromboembolism who have factor V Leiden. Thromb Haemost; Dec 2006.

9. Dykes, A. C., Walker, I. D., McMahon, A. D., Islam, S. I., Tait, R. C.. A study of Protein S antigen levels in 3788 healthy volunteers: influence of age, sex and hormone use, and estimate for prevalence of deficiency state. Br J Haematol; Jun 2001.

10. Faioni, E. M., Franchi, F., Bucciarelli, P., Margaglione, M., De Stefano, V., Castaman, G., Finazzi, G., Mannucci, P. M.. Coinheritance of the HR2 haplotype in the factor V gene confers an increased risk of venous thromboembolism to carriers of factor V R506Q (factor V Leiden). Blood; Nov 1 1999.

11. Goldhaber, S. Z., Leizorovicz, A., Kakkar, A. K., Haas, S. K., Merli, G., Knabb, R. M., Weitz, J. I., Investigators, Adopt,Trial. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. N Engl J Med; Dec 8 2011.

12. Hull, R. D., Schellong, S. M., Tapson, V. F., Monreal, M., Samama, M. M., Nicol, P., Vicaut, E., Turpie, A. G., Yusen, R. D., study, Exclaim. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. Ann Intern Med; Jul 6 2010.

13. Lensen, R., Bertina, R. M., Vandenbroucke, J. P., Rosendaal, F. R.. High factor VIII levels contribute to the thrombotic risk in families with factor V Leiden. Br J Haematol; Aug 2001.

14. Mahmoodi, B. K., Brouwer, J. L., Ten Kate, M. K., Lijfering, W. M., Veeger, N. J., Mulder, A. B., Kluin-Nelemans, H. C., Van Der Meer, J.. A prospective cohort study on the absolute risks of venous thromboembolism and predictive value of screening asymptomatic relatives of patients with hereditary deficiencies of protein S, protein C or antithrombin. Journal of Thrombosis & Haemostasis; Jun 2010.

15. Martinelli, I., Bucciarelli, P., Margaglione, M., De Stefano, V., Castaman, G., Mannucci, P. M.. The risk of venous thromboembolism in family members with mutations in the genes of factor V or prothrombin or both. Br J Haematol; Dec 2000.

16. Martinelli, I., Mannucci, P. M., De Stefano, V., Taioli, E., Rossi, V., Crosti, F., Paciaroni, K., Leone, G., Faioni, E. M.. Different risks of thrombosis in four coagulation defects associated with inherited thrombophilia: a study of 150 families. Blood; Oct 1 1998.

17. Middeldorp, S., Henkens, C. M., Koopman, M. M., van Pampus, E. C., Hamulyak, K., van der Meer, J., Prins, M. H., Buller, H. R.. The incidence of venous thromboembolism in family members of patients with factor V Leiden mutation and venous thrombosis. Ann Intern Med; Jan 1 1998.

18. Rees, D. C., Cox, M., Clegg, J. B.. World distribution of factor V Leiden. Lancet; Oct 28 1995.

19. Rosendaal, F. R., Doggen, C. J., Zivelin, A., Arruda, V. R., Aiach, M., Siscovick, D. S., Hillarp, A., Watzke, H. H., Bernardi, F., Cumming, A. M., Preston, F. E., Reitsma, P. H.. Geographic distribution of the 20210 G to A prothrombin variant. Thromb Haemost; Apr 1998.

20. Simioni, P., Sanson, B. J., Prandoni, P., Tormene, D., Friederich, P. W., Girolami, B., Gavasso, S., Huisman, M. V., Buller, H. R., Wouter ten Cate, J., Girolami, A., Prins, M. H.. Incidence of venous thromboembolism in families with inherited thrombophilia. Thromb Haemost; Feb 1999.

21. Simioni, P., Tormene, D., Prandoni, P., Zerbinati, P., Gavasso, S., Cefalo, P., Girolami, A.. Incidence of venous thromboembolism in asymptomatic family members who are carriers of factor V Leiden: a prospective cohort study. Blood; Mar 15 2002.

22. Tait, R. C., Walker, I. D., Perry, D. J., Islam, S. I., Daly, M. E., McCall, F., Conkie, J. A., Carrell, R. W.. Prevalence of antithrombin deficiency in the healthy population. Br J Haematol; May 1994.

23. Tait, R. C., Walker, I. D., Reitsma, P. H., Islam, S. I., McCall, F., Poort, S. R., Conkie, J. A., Bertina, R. M.. Prevalence of protein C deficiency in the healthy population. Thromb Haemost; Jan 1995.

QUESTION

Should selective thrombophilia testing and subsequent thromboprophylaxis in relatives positive for thrombophilia and no thromboprophylaxis in relatives negative for thrombophilia vs. no thrombophilia testing and no thromboprophylaxis in all be used for first- and second-degree relatives of patients with VTE and a known thrombophilia who have a minor provoking risk factor for VTE?

POPULATION:	first- and second-degree relatives of patients with VTE and a known thrombophilia who have a minor provoking risk factor for VTE
INTERVENTION:	selective thrombophilia testing and subsequent thromboprophylaxis in relatives positive for thrombophilia and no thromboprophylaxis in relatives negative for thrombophilia
COMPARISON:	no thrombophilia testing and no thromboprophylaxis in all
MAIN OUTCOMES:	VTE - Factor V Leiden - First-degree relatives; VTE - Prothrombin mutation - First-degree relatives; VTE - Antithrombin deficiency - First-degree relatives; VTE - Protein C deficiency - First-degree relatives; VTE - Protein S deficiency - First-degree relatives; Major Bleeding - First-degree relatives;
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Inherited thrombophilia can be identified in many patients with a venous thromboembolism (VTE). Consequently, relatives of these patients are also at increased risk to have inherited thrombophilia. The currently most commonly tested inherited thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. Thrombophilia testing is often performed in relatives of patients with VTE and inherited thrombophilia, particularly if they are in a high risk episode such as immobilization. Although testing relatives of patients with a VTE and inherited thrombophilia has a high chance of finding a positive test result, the relevant question and aim of the current guideline is to assess whether thrombophilia testing and tailoring management to the test result would improve patient important outcomes. This question addresses whether selective testing for the same inherited thrombophilia and subsequent thromboprophylaxis in patients positive for the same thrombophilia improves patient important outcomes in relatives of patients with VTE and a known familial thrombophilia who have a minor provoking risk factor for VTE (e.g. immobility, minor injury, illness, infection), as compared with no thrombophilia testing and no thromboprophylaxis in all. Since no randomized controlled trials have addressed this question, we used a modeling exercise based on observational evidence for baseline risk, prevalence of thrombophilia and associated risk of events with thrombophilia, and RCTs with evidence for the effect of thromboprophylaxis on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies		A separate question in this guideline addresses testing for any inherited thrombophilia type, i.e. not only the one that was found in the proband. The current question addresses whether only selectively testing for the thrombophilia type

○ Don't know		that was found in the proband has benefit.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		Desirable effect = preventing VTE. VTE would be avoided in relatives who are positive for thrombophilia by using thromboprophylaxis. The panel considered a reduction in first-time VTE of 5 per 1,000 or lower to be Trivial. The panel considered the following thresholds: Trivial: ≤5 per 1000; Small: 5-20 per 1,000; Moderate: 20-50 per 1,000 Trivial for FVL and prothrombin. Small for antithrombin, protein C, and protein S. These effects were considered Small to Moderate by the panel. The overall judgment was Trivial as FVL and prothrombin mutations are more prevalent than antithrombin, protein C, and protein S deficiencies. <u>Second-degree relatives:</u> For modeling the effect in second-degree relatives we assumed a prevalence of 25% of the same thrombophilia

		type as the proband. Effect estimates for VTE in second-degree relatives: FVL: 2.62 fewer per 1,000 (from 0.44 to 4.43 fewer) PT: 2.42 fewer per 1,000 (from 0.35 to 4.55 fewer) AT: 10.70 fewer per 1,000 (from 1.68 to 17.76 fewer) PC: 10.17 fewer per 1,000 (from 1.35 to 18.31 fewer) PS: 9.80 fewer per 1,000 (from 1.29 to 18.04 fewer)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		Undesirable effect = causing major bleeding. Major bleedings would be caused in patients who are positive for thrombophilia by using thromboprophylaxis. <u>Second-degree relatives:</u> For modeling the effect in second-degree relatives we assumed a prevalence of 25% of the same thrombophilia type as the proband. Effect estimates for Major bleeding in second-degree relatives: All types: 1.09 more per 1,000 (from 0.33 to 2.27 more)

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows using a scale from 0 (worst possible scenario, usually death), to 1 (best possible scenario, usually perfect health): Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(1, 2, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3) **Gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off)(2, 3) **Minor intracranial bleeding event:** 0.75 (standard gamble)(2) **Major intracranial bleeding event:** 0.15 (standard gamble)(2) **Anticoagulant therapy** Patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome.(3) Patients would favor efficacy and safety over convenience of route of administration.(6) Also, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events.(7, 6, 8)	The panel considered clinicians may value avoiding major bleedings more (they do not want to cause harm), while patients may value avoiding VTE events more (they prefer avoiding a recurrence of clots).

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know		FVL and prothrombin: Does not favor either the intervention or comparison, for first- and second-degree relatives. Antithrombin, protein C, and protein S: Probably favors the intervention, for first- and second-degree relatives.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Intervention Costs: **Test (source)** / Approximate Cost (2005) / Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016) / **(14/12/2016) £1 = $1,27** **Full Blood Count** £2.55 £3.29 **$4,18** **Protein C** £11.67 £15.5 **$19,12** **Free Protein S** £11.67 £15.5 **$19,12** **Antithrombin** £11.67 £15.5 **$19,12** **APCR** £10.73 £13.84 **$17,58** **Factor V Leiden** £85.00 £109.65 **$141,45** **Prothrombin gene mutation** £85.00 £109.65 **$141,45** **Lupus Anticoagulant** £10.73 £13.84 **$17,58** **Antiphospholipid antibodies** £12.30 £15.87 **$20,15** **Anti Beta-2 GP1 antibody** £9.50 £12.25 **$15,81** **The potential cost of a full thrombophilia screen** £250.82, £323.56 **$410,92** Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx **Cost of the health outcomes:**(9) - **Recurrent VTE:** 11,000 to 15,000 USD - **Major bleeding:** 11,000 to 22,000 USD **Cost of interventions:**(10) - **Dabigatran:** Cost per month: $300.44–$600.88 USD - **Rivaroxaban:** Cost per month: $300.42–$600.84 USD - **Apixaban:** Cost per month: $300.44–$600.88	**The panel considered the following cost ranges:** - Cost for testing: $400 -$2,000 per patient - Cost for treatment: $1,000-$ 4,500 per patient per year Costs for testing all inherited thrombophilia types and short course of prophylaxis, as compared to no testing and no prophylaxis. Costs for selective testing would be less than running full thrombophilia panels.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(11)	The panel considered that the health system/service coverage will be the main aspect affecting health equity. USA is an example where promotion of testing that is not covered by insurance would generate inequities. I.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Research studies suggested the following regarding acceptability and barriers associated with testing and treatment: **Patients:** A survey was conducted in members of a large family with heritable protein C deficiency. For those who had not been tested before, using a 7-point scale (1 - not at all interested; 7 extremely interested), the mean score for interest in testing interest was 4.6 (standard deviation 2.4). Patients in general were willing to take the test for thrombophilia.(12) A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(13) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(14) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers:** A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(15) **Payers:** At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	The panel considered testing acceptable for many doctors, although maybe not for all. Patients are in general willing to undergo thrombophilia testing when testing is proposed by their doctor.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(16) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending.(17) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(18) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(19) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(20)	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation. External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**

	JUDGEMENT						
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

Factor V Leiden or prothrombin mutation

In first- and second-degree relatives of patients with VTE and known factor V Leiden or prothrombin mutation (low risk thrombophilia), and who have a minor provoking risk factor for VTE, the ASH guideline panel suggests not testing for the known familial thrombophilia to guide thromboprophylaxis, and not using thromboprophylaxis in all relatives (conditional recommendation based on very low certainty in the evidence about effects)

Antithrombin, protein C, or protein S deficiency

In first- and second-degree relatives of patients with VTE and known antithrombin, protein C, or protein S deficiency (high risk thrombophilia), and who have a minor provoking risk factor for VTE, the ASH guideline panel suggests testing for the known familial thrombophilia and thromboprophylaxis in relatives positive for thrombophilia over no testing for thrombophilia and no thromboprophylaxis in all relatives (conditional recommendation based on very low certainty in the evidence about effects)

Remarks:

- A strategy with selective testing for the known familial thrombophilia type would mean that positive relatives would receive thromboprophylaxis, and negative relatives would receive no thromboprophylaxis.

- These recommendations do not address homozygous defects, or combinations of thrombophilia types.

- These recommendations refer to selective testing for the known familial thrombophilia type. A separate question in this guideline addressed testing for any hereditary thrombophilia type in this population, and the resulting recommendations are the same.

Justification

The panel considered that selective testing for the same thrombophilia type and thromboprophylaxis in relatives who are positive likely has some benefit in terms of prevention of VTE that outweighs the risk of major bleeding in first- and second-degree relatives of patients with VTE and high risk thrombophilias (antithrombin, protein C, protein S), but not low risk thrombophilias (factor V Leiden, prothrombin).

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation.

Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

The difference in patient important outcomes between selective testing for only the thrombophilia type of the proband, as addressed here, and testing for all inherited thrombophilia, as addressed in a separate guideline question, was negligible. Therefore we advise to focus future research on selective testing.

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
7. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
8. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
9. Grosse, S. D., Nelson, R. E., Nyarko, K. A., Richardson, L. C., Raskob, G. E.. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res; Jan 2016.
10. Biskupiak, J., Ghate, S. R., Jiao, T., Brixner, D.. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. J Manag Care Pharm; Nov-Dec 2013.
11. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
12. van Korlaar, I. M., Vossen, C. Y., Rosendaal, F. R., Bovill, E. G., Naud, S., Cameron, L. D., Kaptein, A. A.. Attitudes toward genetic testing for thrombophilia in asymptomatic members of a large family with heritable protein C deficiency. Journal of Thrombosis & Haemostasis; Nov 2005.
13. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
14. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
15. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
16. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
17. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
18. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
19. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
20. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In first- and second-degree relatives of patients with VTE and a known thrombophilia who have a minor provoking risk factor for VTE (e.g. immobility, minor injury, illness, infection), should selective testing for the known familial thrombophilia and subsequent thromboprophylaxis in relatives positive for thrombophilia and no thromboprophylaxis in relatives negative for thrombophilia compared to no thrombophilia testing and no thromboprophylaxis in all be used?

Setting:

Bibliography: See reference list and footnotes. [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
VTE - Factor V Leiden - First-degree relatives (follow up: minor provoking risk factor episode; assessed with: any first-time DVT or PE)									
16 [a,b,c,d]	observational studies	not serious	not serious	serious [e]	not serious	none	When testing first-degree relatives of patients with VTE and factor V Leiden (FVL) who have a minor provoking VTE risk factor for FVL, and treating the 500 positives with thromboprophylaxis, 9.96 VTE events will occur per 1,000 risk episodes (ranging from 7.04 to 14.09). When not testing first-degree relatives and treating none of them with thromboprophylaxis, 15 VTE events will occur per 1,000 risk episodes. Therefore, a selective thrombophilia testing strategy is associated with 500 more relatives treated with thromboprophylaxis and **5.04 fewer VTE events (ranging from 0.91 to 7.96)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [f]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Prothrombin mutation - First-degree relatives (follow up: minor provoking risk factor episode; assessed with: any first-time DVT or PE)									
12 [b,d,g,h]	observational studies	not serious	not serious	serious [e]	not serious	none	When testing first-degree relatives of patients with VTE and prothrombin mutation (PT) who have a minor provoking VTE risk factor for PT, and treating the 500 positives with thromboprophylaxis, 10.16 VTE events will occur per 1,000 high-risk episodes (ranging from 6.93 to 14.20). When not testing first-degree relatives and treating none of them with thromboprophylaxis, 15 VTE events will occur per 1,000 risk episodes. Therefore, a selective thrombophilia testing strategy is associated with 500 more relatives treated with thromboprophylaxis and **4.84 fewer VTE events (ranging from 0.80 to 8.07)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [i]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Antithrombin deficiency - First-degree relatives (follow up: minor provoking risk factor episode; assessed with: any first-time DVT or PE)									
14 [b,d,j,k]	observational studies	not serious	not serious	serious [e]	serious [l]	none	When testing first-degree relatives of patients with VTE and antithrombin deficiency (AT) who have a minor provoking VTE risk factor for AT, and only treating the 500 positives with thromboprophylaxis, 28.75 VTE events will occur per 1,000 risk episodes (ranging from 17.21 to 46.20). When not testing first-degree relatives and treating none of them with thromboprophylaxis, 50 VTE events will occur per 1,000 risk episodes. Therefore, a selective thrombophilia testing strategy is associated with 500 more relatives treated with thromboprophylaxis and **21.25 fewer VTE events (ranging from 3.80 to 32.79)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [m]	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
VTE - Protein C deficiency - First-degree relatives (follow up: minor provoking risk factor episode; assessed with: any first-time DVT or PE)									
14 [b,d,n,o]	observational studies	not serious	not serious	serious [e]	serious [l]	none	When testing first-degree relatives of patients with VTE and protein C deficiency (PC) who have a minor provoking VTE risk factor for PC, and only treating the 500 positives with thromboprophylaxis, 29.72 VTE events will occur per 1,000 risk episodes (ranging from 17.63 to 46.68). When not testing first-degree relatives and treating none of them with thromboprophylaxis, 50 VTE events will occur per 1,000 risk episodes. Therefore, a selective thrombophilia testing strategy is associated with 500 more relatives treated with thromboprophylaxis and 20.28 fewer VTE events (ranging from 3.32 to 32.37) per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [p]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Protein S deficiency - First-degree relatives (follow up: minor provoking risk factor episode; assessed with: any first-time DVT or PE)									
15 [b,d,q,r]	observational studies	not serious	not serious	serious [e]	serious [l]	none	When testing first-degree relatives of patients with VTE and protein S deficiency (PS) who have a minor provoking VTE risk factor for PS, and only treating the 500 positives with thromboprophylaxis, 30.30 VTE events will occur per 1,000 risk episodes (ranging from 18.18 to 46.80). When not testing first-degree relatives and treating none of them with thromboprophylaxis, 50 VTE events will occur per 1,000 risk episodes. Therefore, a selective thrombophilia testing strategy is associated with 500 more relatives treated with thromboprophylaxis and **19.70 fewer VTE events (ranging from 3.20 to 31.82)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [s]	⨁◯◯◯ VERY LOW	CRITICAL
Major Bleeding - First-degree relatives (follow up: minor provoking risk factor episode)									
4 [t,u]	observational studies	not serious	not serious	serious [v]	not serious	none	When testing first-degree relatives of patients with VTE and an inherited thrombophilia who have a minor provoking VTE risk factor for the same thrombophilia type, and only treating the 500 positives with thromboprophylaxis, 6.18 major bleedings will occur per 1,000 risk episodes (ranging from 4.66 to 8.54). When not testing first-degree relatives and treating none of them with thromboprophylaxis, 4 major bleedings will occur per 1,000 risk episodes. Therefore, a selective thrombophilia testing strategy is associated with **2.18 more major bleedings (ranging from 0.66 to 4.54)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [w]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE, 6 studies; Risk association for thrombophilia positive versus negative, 9 studies (3 also reported overall risk for VTE); Thromboprophylaxis effect, 4 RCTs

b. Overall risk for VTE: estimated from Bank 2004, Coppens 2006, Mahmoodi 2010, Middeldorp 1998, Simioni 1999, Simioni 2002

c. Factor V Leiden positive vs negative risk association: Cohen 2012, Couturaud 2006, Faioni 1999, Lensen 2001, Martinelli 1998, Martinelli 2000, Middeldorp 1998, Simioni 1999, Simioni 2002

d. Effect of thromboprophylaxis: Cohen 2013, Cohen 2016, Goldhaber 2011, Hull 2010

e. The effect was indirectly calculated using separate studies for overall risk of VTE, relative risk of thrombophilia positives vs negatives, and the effect of thromboprophylaxis

f. Based on the following estimates: Overall risk for VTE, 15 per 1,000; Prevalence of FVL in first-degree relatives, 50%; Relative risk for VTE in FVL positives versus negatives, RR 2.71 (95%CI: 2.06-3.56); Relative risk of VTE with thromboprophylaxis versus no thromboprophylaxis, RR 0.54 (0.32-0.91). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the upper CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

g. Prothrombin positive vs negative risk association: Bank 2004, Coppens 2006, Faioni 1999, Martinelli 2000

h. Number of studies used in calculations: Overall risk for VTE, 6 studies; Risk association for thrombophilia positive versus negative, 4 studies (2 also reported overall risk for VTE); Thromboprophylaxis effect, 4 RCTs

i. Based on the following estimates: Overall risk for VTE, 15 per 1,000; Prevalence of PT in first-degree relatives, 50%; Relative risk for VTE in PT positives versus negatives, RR 2.35 (95%CI: 1.46-3.78); Relative risk of VTE with thromboprophylaxis versus no thromboprophylaxis, RR 0.54 (0.32-0.91). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the upper CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

j. Number of studies used in calculations: Overall risk for VTE, 6 studies; Risk association for thrombophilia positive versus negative, 5 studies (1 also reported overall risk for VTE); Thromboprophylaxis effect, 4 RCTs

k. Antithrombin positive vs negative risk association: Brouwer 2006, Cohen 2012, Faioni 1999, Mahmoodi 2010, Martinelli 1998

l. There is a clinically important difference between the smallest and largest possible effect of the testing strategy

m. Based on the following estimates: Overall risk for VTE, 50 per 1,000; Prevalence of antiithrombin in first-degree relatives, 50%; Relative risk for VTE in thrombophilia positives versus negatives, RR 12.17 (95%CI: 5.45-27.17); Relative risk of VTE with thromboprophylaxis versus no thromboprophylaxis, RR 0.54 (0.32-0.91). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the upper CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

n. Protein C positive vs negative risk association: Brouwer 2006, Cohen 2012, Faioni 1999, Mahmoodi 2010, Martinelli 1998

o. Number of studies used in calculations: Overall risk for VTE, 6 studies; Risk association for thrombophilia positive versus negative, 5 studies (1 also reported overall risk for VTE); Thromboprophylaxis effect, 4 RCTs

p. Based on the following estimates: Overall risk for VTE, 50 per 1,000; Prevalence of FVL in first-degree relatives, 50%; Relative risk for VTE in thrombophilia positives versus negatives, RR 7.47 (95%CI: 2.81-19.81); Relative risk of VTE with thromboprophylaxis versus no thromboprophylaxis, RR 0.54 (0.32-0.91). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the upper CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

q. Number of studies used in calculations: Overall risk for VTE, 6 studies; Risk association for thrombophilia positive versus negative, 6 studies (1 also reported overall risk for VTE); Thromboprophylaxis effect, 4 RCTs

r. Protein S positive vs negative risk association: Brouwer 2005, Brouwer 2006, Cohen 2012, Faioni 1999, Mahmoodi 2010, Martinelli 1998

s. Based on the following estimates: Overall risk for VTE, 50 per 1,000; Prevalence of FVL in first-degree relatives, 50%; Relative risk for VTE in thrombophilia positives versus negatives, RR 5.98 (95%CI: 2.45-14.57); Relative risk of VTE with thromboprophylaxis versus no thromboprophylaxis, RR 0.54 (0.32-0.91). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the upper CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

t. Number of studies used in calculations: Overall risk for major bleeding and thromboprophylaxis effect, 4 RCTs

u. Overall risk of bleeding and effect of thromboprophylaxis: Cohen 2013, Cohen 2016, Goldhaber 2011, Hull 2010

v. The effect was indirectly calculated using separate studies for overall risk and the effect of thromboprophylaxis

w. Based on the following estimates: Overall risk for Major Bleeding, 4 per 1,000; Prevalence of inheritable thrombophilia in first-degree relatives, 50%; Relative risk of Major Bleeding with thromboprophylaxis versus no thromboprophylaxis, RR 2.09 (1.33-3.27). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the smallest treatment effect (lower CI).

References

1. Bank, I., Libourel, E. J., Middeldorp, S., Van Pampus, E. C., Koopman, M. M., Hamulyak, K., Prins, M. H., Van Der Meer, J. , Buller, H. R.. Prothrombin 20210A mutation: a mild risk factor for venous thromboembolism but not for arterial thrombotic disease and pregnancy-related complications in a family study. Archives of Internal Medicine; Sep 27 2004.

2. Brouwer, J. L., Veeger, N. J., Kluin-Nelemans, H. C., van der Meer, J.. The pathogenesis of venous thromboembolism: evidence for multiple interrelated causes. Ann Intern Med; Dec 5 2006.

3. Brouwer, J. L., Veeger, N. J., van der Schaaf, W., Kluin-Nelemans, H. C., van der Meer, J.. Difference in absolute risk of venous and arterial thrombosis between familial protein S deficiency type I and type III. Results from a family cohort study to assess the clinical impact of a laboratory test-based classification. Br J Haematol; Mar 2005.

4. Cohen, A. T., Harrington, R. A., Goldhaber, S. Z., Hull, R. D., Wiens, B. L., Gold, A., Hernandez, A. F., Gibson, C. M., Investigators, Apex. Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients. N Engl J Med; Aug 11 2016.

5. Cohen, A. T., Spiro, T. E., Buller, H. R., Haskell, L., Hu, D., Hull, R., Mebazaa, A., Merli, G., Schellong, S., Spyropoulos, A. C., Tapson, V., Investigators, Magellan. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. N Engl J Med; Feb 7 2013.

6. Coppens, M., van de Poel, M. H., Bank, I., Hamulyak, K., van der Meer, J., Veeger, N. J., Prins, M. H., Buller, H. R., Middeldorp, S.. A prospective cohort study on the absolute incidence of venous thromboembolism and arterial cardiovascular disease in asymptomatic carriers of the prothrombin 20210A mutation. Blood; Oct 15 2006.

7. Couturaud, F., Kearon, C., Leroyer, C., Mercier, B., Abgrall, J. F., Le Gal, G., Lacut, K., Oger, E., Bressollette, L., Ferec, C., Lamure, M., Mottier, D., Groupe d'Etude de la Thrombose de Bretagne, Occidentale. Incidence of venous thromboembolism in first-degree relatives of patients with venous thromboembolism who have factor V Leiden. Thromb Haemost; Dec 2006.

8. Faioni, E. M., Franchi, F., Bucciarelli, P., Margaglione, M., De Stefano, V., Castaman, G., Finazzi, G., Mannucci, P. M.. Coinheritance of the HR2 haplotype in the factor V gene confers an increased risk of venous thromboembolism to carriers of factor V R506Q (factor V Leiden). Blood; Nov 1 1999.

9. Goldhaber, S. Z., Leizorovicz, A., Kakkar, A. K., Haas, S. K., Merli, G., Knabb, R. M., Weitz, J. I., Investigators, Adopt,Trial. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. N Engl J Med; Dec 8 2011.

10. Hull, R. D., Schellong, S. M., Tapson, V. F., Monreal, M., Samama, M. M., Nicol, P., Vicaut, E., Turpie, A. G., Yusen, R. D., study, Exclaim. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. Ann Intern Med; Jul 6 2010.

11. Lensen, R., Bertina, R. M., Vandenbroucke, J. P., Rosendaal, F. R.. High factor VIII levels contribute to the thrombotic risk in families with factor V Leiden. Br J Haematol; Aug 2001.

12. Mahmoodi, B. K., Brouwer, J. L., Ten Kate, M. K., Lijfering, W. M., Veeger, N. J., Mulder, A. B., Kluin-Nelemans, H. C., Van Der Meer, J.. A prospective cohort study on the absolute risks of venous thromboembolism and predictive value of screening asymptomatic relatives of patients with hereditary deficiencies of protein S, protein C or antithrombin. Journal of Thrombosis & Haemostasis; Jun 2010.

13. Martinelli, I., Bucciarelli, P., Margaglione, M., De Stefano, V., Castaman, G., Mannucci, P. M.. The risk of venous thromboembolism in family members with mutations in the genes of factor V or prothrombin or both. Br J Haematol; Dec 2000.

14. Martinelli, I., Mannucci, P. M., De Stefano, V., Taioli, E., Rossi, V., Crosti, F., Paciaroni, K., Leone, G., Faioni, E. M.. Different risks of thrombosis in four coagulation defects associated with inherited thrombophilia: a study of 150 families. Blood; Oct 1 1998.

15. Middeldorp, S., Henkens, C. M., Koopman, M. M., van Pampus, E. C., Hamulyak, K., van der Meer, J., Prins, M. H., Buller, H. R.. The incidence of venous thromboembolism in family members of patients with factor V Leiden mutation and venous thrombosis. Ann Intern Med; Jan 1 1998.

16. Simioni, P., Sanson, B. J., Prandoni, P., Tormene, D., Friederich, P. W., Girolami, B., Gavasso, S., Huisman, M. V., Buller, H. R., Wouter ten Cate, J., Girolami, A., Prins, M. H.. Incidence of venous thromboembolism in families with inherited thrombophilia. Thromb Haemost; Feb 1999.

17. Simioni, P., Tormene, D., Prandoni, P., Zerbinati, P., Gavasso, S., Cefalo, P., Girolami, A.. Incidence of venous thromboembolism in asymptomatic family members who are carriers of factor V Leiden: a prospective cohort study. Blood; Mar 15 2002.

QUESTION

Should testing for any hereditary thrombophilia and subsequent thromboprophylaxis in relatives positive for thrombophilia and no thromboprophylaxis in relatives negative for thrombophilia vs. no thrombophilia testing and no thromboprophylaxis in all be used for first- and second-degree relatives of patients with VTE and unknown thrombophilia status who have a minor provoking risk factor for VTE?

POPULATION:	first- and second-degree relatives of patients with VTE and unknown thrombophilia status who have a minor provoking risk factor for VTE
INTERVENTION:	testing for any hereditary thrombophilia and subsequent thromboprophylaxis in relatives positive for thrombophilia and no thromboprophylaxis in relatives negative for thrombophilia
COMPARISON:	no thrombophilia testing and no thromboprophylaxis in all
MAIN OUTCOMES:	VTE - First-degree relatives; Major Bleeding - First-degree relatives;
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Inherited thrombophilia can be identified in many patients with a venous thromboembolism (VTE). Consequently, relatives of these patients are also at increased risk to have inherited thrombophilia. The currently most commonly tested inherited thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. Thrombophilia testing is often performed in relatives of patients with VTE, particularly if they are in a risk episode such as immobilization. Although testing relatives of patients with a VTE has a high chance of finding a positive test result, the relevant question and aim of the current guideline is to assess whether thrombophilia testing and tailoring management to the test result would improve patient important outcomes. This question addresses whether testing for any inherited thrombophilia and subsequent thromboprophylaxis in positive relatives improves important outcomes in relatives of patients with VTE and unknown thrombophilia status who have a minor provoking risk factor for VTE (e.g. immobility, minor injury, illness, infection), as compared with no thrombophilia testing and no thromboprophylaxis in all. Since no randomized controlled trials have addressed this question, we used a modeling exercise based on observational evidence for baseline risk, prevalence of thrombophilia and associated risk of events with thrombophilia, and RCTs with evidence for the effect of thromboprophylaxis on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Evidence Profile.	Desirable effect = preventing VTE. VTE would be avoided in relatives who are positive for thrombophilia by using thromboprophylaxis. <u>Second-degree relatives:</u> For modeling the effect in second-degree relatives we assumed a prevalence of 25% of the prevalence among probands. Effect estimates for VTE in second-degree relatives: 1.16 fewer per 1,000 (from 0.00 to 3.75 fewer)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	See Evidence Profile.	Undesirable effect = causing major bleeding. Major bleedings would be caused in patients who are positive for thrombophilia by using thromboprophylaxis. <u>Second-degree relatives:</u> For modeling the effect in second-degree relatives we assumed a prevalence of 25% of prevalence among probands.

		Effect estimates for Major bleeding in second-degree relatives: Major bleeding: 0.31 more per 1,000 (from 0.07 to 0.91 more)

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows using a scale from 0 (worst possible scenario, usually death), to 1 (best possible scenario, usually perfect health): Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(1, 2, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3) **Gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off)(2, 3) **Minor intracranial bleeding event:** 0.75 (standard gamble)(2) **Major intracranial bleeding event:** 0.15 (standard gamble)(2) **Anticoagulant therapy** Patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome.(3) Patients would favor efficacy and safety over convenience of route of administration.(6) Also, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events.(7, 6, 8)	The panel considered clinicians may value avoiding major bleedings more (they do not want to cause harm), while patients may value avoiding VTE events more (they prefer avoiding a recurrence of clots).

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Intervention Costs: **Test (source)** | Approximate Cost (2005) | Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016) | **(14/12/2016) £1 = $1,27** **Full Blood Count** | £2.55 | £3.29 | **$4,18** **Protein C** | £11.67 | £15.5 | **$19,12** **Free Protein S** | £11.67 | £15.5 | **$19,12** **Antithrombin** | £11.67 | £15.5 | **$19,12** **APCR** | £10.73 | £13.84 | **$17,58** **Factor V Leiden** | £85.00 | £109.65 | **$141,45** **Prothrombin gene mutation** | £85.00 | £109.65 | **$141,45** **Lupus Anticoagulant** | £10.73 | £13.84 | **$17,58** **Antiphospholipid antibodies** | £12.30 | £15.87 | **$20,15** **Anti Beta-2 GP1 antibody** | £9.50 | £12.25 | **$15,81** **The potential cost of a full thrombophilia screen** | £250,82, | £323,56 | **$410,92** Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx **Cost of the health outcomes:**(9) - **Recurrent VTE:** 11,000 to 15,000 USD - **Major bleeding:** 11,000 to 22,000 USD **Cost of interventions:**(10) - **Dabigatran:** Cost per month: $300.44–$600.88 USD - **Rivaroxaban:** Cost per month:	**The panel considered the following cost ranges:** - Cost for testing: $400 -$2,000 per patient - Cost for treatment: $1,000-$ 4,500 per patient per year Costs for testing all hereditary thrombophilia types and short course of thromboprophylaxis, as compared to no testing and no thromboprophylaxis.

	$300.42–$600.84 USD - **Apixaban:** Cost per month: $300.44–$600.88	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(11)	The panel considered that the health system/service coverage/access to care will be the main aspect affecting health equity. USA is an example where promotion of testing that is not covered by insurance would generate inequities. I.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Research studies suggested the following regarding acceptability and barriers associated with testing and treatment: **Patients:** A survey was conducted in members of a large family with heritable protein C deficiency. For those who had not been tested before, using a 7-point scale (1 - not at all interested; 7 extremely interested), the mean score for interest in testing interest was 4.6 (standard deviation 2.4). Patients in general were willing to take the test for thrombophilia.(12) A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(13) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(14) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers:** A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(15) **Payers:** At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	The panel considered testing acceptable for many doctors, although maybe not for all. Patients are in general willing to undergo thrombophilia testing when testing is proposed by their doctor.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(16) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending.(17) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(18) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(19) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(20)	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation. External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories.

SUMMARY OF JUDGEMENTS

JUDGEMENT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

In first- and second-degree relatives of patients with VTE and unknown thrombophilia status, and who have a minor provoking risk factor for VTE, the ASH guideline panel suggests not testing for any hereditary thrombophilia to guide thromboprophylaxis, and not using thromboprophylaxis in all relatives (conditional recommendation based on very low certainty in the evidence about effects)

Remarks:

- Thrombophilia testing may be considered if relatives had multiple family members with a VTE, if the family member with VTE was of young age, with patient preference, and in settings where testing incurs a low cost.

- A strategy with testing for any hereditary thrombophilia would mean that positive relatives receive thromboprophylaxis, and negative relatives would receive no thromboprophylaxis.

- These recommendations do not address homozygous defects, or combinations of thrombophilia types.

Justification

The panel considered that testing for any hereditary thrombophilia and thromboprophylaxis in relatives who are positive likely has no benefit in terms of prevention of VTE that outweighs the risk of major bleeding in first- and second-degree relatives.

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation.

Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

No research priorities.

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
7. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
8. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
9. Grosse, S. D., Nelson, R. E., Nyarko, K. A., Richardson, L. C., Raskob, G. E.. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res; Jan 2016.
10. Biskupiak, J., Ghate, S. R., Jiao, T., Brixner, D.. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. J Manag Care Pharm; Nov-Dec 2013.
11. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
12. van Korlaar, I. M., Vossen, C. Y., Rosendaal, F. R., Bovill, E. G., Naud, S., Cameron, L. D., Kaptein, A. A.. Attitudes toward genetic testing for thrombophilia in asymptomatic members of a large family with heritable protein C deficiency. Journal of Thrombosis & Haemostasis; Nov 2005.
13. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
14. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
15. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
16. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
17. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
18. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
19. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
20. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In first- and second-degree relatives of patients with VTE and unknown thrombophilia status who have a minor provoking risk factor for VTE (e.g. immobility, minor injury, illness, infection), should testing for any hereditary thrombophilia and subsequent thromboprophylaxis in relatives positive for thrombophilia and no thromboprophylaxis in relatives negative for thrombophilia compared to no thrombophilia testing and no thromboprophylaxis in all be used?

Setting:

Bibliography: See reference list and footnotes. [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
VTE - First-degree relatives (follow up: minor provoking risk factor episode; assessed with: any first-time DVT or PE)									
29 [a,b,c,d,e,f,g]	observational studies	not serious	not serious	serious [h]	not serious	none	When testing first-degree relatives of patients with VTE and unknown thrombophilia status for any hereditary thrombophilia, and treating the 142 positives with thromboprophylaxis (ranging from 99 to 201), 9.84 VTE events will occur per 1,000 risk episodes (ranging from 6.34 to 11.98). When not testing first-degree relatives for thrombophilia and treating none of them with thromboprophylaxis, 12 VTE events will occur per 1,000 risk episodes. Therefore, a thrombophilia testing strategy is associated with 142 more relatives treated with thromboprophylaxis (ranging from 99 to 201) and **2.16 fewer VTE events (ranging from 0.02 to 5.66)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [i]	⨁◯◯◯ VERY LOW	CRITICAL
Major Bleeding - First-degree relatives (follow up: minor provoking risk factor episode)									
24 [c,d,g,j,k]	observational studies	not serious	not serious	serious [l]	not serious	none	When testing first-degree relatives of patients with VTE and unknown thrombophilia status for any type of thrombophilia, and treating the 142 positives with thromboprophylaxis (ranging from 99 to 201), 4.62 major bleedings will occur per 1,000 high-risk episodes (ranging from 4.13 to 5.82). When not testing first-degree relatives for thrombophilia and treating none of them with extended anticoagulation, 4 major bleedings will occur per 1,000 high-risk episodes. Therefore, a thrombophilia testing strategy is associated with 142 more relatives treated with thromboprophylaxis (ranging from 99 to 201) and **0.62 more major bleedings (ranging from 0.13 to 1.82)** per 1,000 high-risk episodes in first-degree relatives compared with a no testing strategy. [m]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE, 6 studies; Prevalence of thrombophilia, 20 studies (1 also providing overall risk); Risk association for thrombophilia positive versus negative, 4 studies; Thromboprophylaxis effect, 4 RCTs (all also providing overall risk for VTE)

b. Overall risk for VTE: Bezemer 2009, Cohen 2013, Cohen 2016, Goldhaber 2011, Hull 2010, Karasu 2016

c. Thrombophilia prevalence, used for calculation: Bezemer 2009, Cebi 2009, Di Minno 2014, Garcia-Fuster 2005, Heit 2010, Kearon 1999, Kearon 2018, Lim 2017, Mello 2010, Meyer 2015, Olie 2011, Palareti 2003, Prandoni 2007, Roldan 2009, Rossi 2008, Santamaria 2005, Schattner 1997, Schulman 2006, Sundquist 2015, Weingarz 2015

d. Prevalence of specific thrombophilia types, used to verify calculation estimate: Ahmad 2016, Ahmad 2016, Ahmad 2017, Asim 2017, Baarslag 2004, Baglin 2003, Brouwer 2009, Bruwer 2016, Christiansen 2005, De Stefano 1999, De Stefano 2006, Eichinger 1999, Eichinger 2002, Eischer 2017, Gonzalez-Porras 2006, Heijboer 1990, Hirmerova 2014, Hoibraaten 2000, Kearon 2008, Laczkovics 2007, Lee 2017, Lijfering 2010, Lindmarker 1999, Marcucci 2003, Mateo 1997, Miles 2001, Ridker 1995, Rodger 2008, Roupie 2016, Rupa-Matysek 2014, Simioni 2000, Sonnevi 2013, Strandberg 2007, Sveinsdottir 2012, The Procare group 2003, Wahlander 2006

e. Thrombophilia positive vs negative risk association, used for calculation: Cohen 2012, Faioni 1999, Rossi 2011, Simioni 1999

f. Risk association for specific thrombophilia types, used to verify calculation estimate: Bank 2004, Brouwer 2005, Brouwer 2006, Cohen2012, Coppens 2006, Couturaud 2006, Faioni 1999, Lensen 2001, Mahmoodi 2010, Martinelli 1998, Martinelli 2000, Middeldorp 1998, Simioni 1999, Simioni 2002

g. Effect of thromboprophylaxis: Cohen 2013, Cohen 2016, Goldhaber 2011, Hull 2010

h. The effect was indirectly calculated using separate studies for overall risk, thrombophilia prevalence, relative risk of thrombophilia positives vs negatives, and the effect of thromboprophylaxis

i. Based on the following estimates: Overall risk for VTE, 12 per 1,000; Prevalence of any inherited thrombophilia, 14.2% (min 9.9 - max 20.1); Relative risk for VTE in thrombophilia positives versus negatives, RR 3.89 (95%CI: 2.15-9.01); Relative risk for VTE in patients with family history of VTE versus not family history, RR 2.0; Relative risk of VTE with thromboprophylaxis versus no thromboprophylaxis, RR 0.54 (0.32-0.91). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, upper CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

j. Number of studies used in calculations: Overall risk for VTE, 4 RCTs; Prevalence of thrombophilia, 20 studies; Thromboprophylaxis effect, 4 RCTs (also providing overall risk for Major bleeding)

k. Overall risk for VTE: Cohen 2013, Cohen 2016, Goldhaber 2011, Hull 2010

l. The effect was indirectly calculated using separate studies for overall risk, thrombophilia prevalence and the effect of thromboprophylaxis

m. Based on the following estimates: Overall risk for Major bleeding of 4 per 1,000; Prevalence of any inherited thrombophilia, 14.2% (min 9.9 - max 20.1); Relative risk of Major bleeding with thromboprophylaxis versus no thromboprophylaxis, RR 2.09 (1.33-3.27). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the smallest treatment effect (lower CI).

References

1. Ahmad, A., Sundquist, K., Zoller, B., Dahlback, B., Svensson, P. J., Sundquist, J., Memon, A. A.. Identification of polymorphisms in Apolipoprotein M gene and their relationship with risk of recurrent venous thromboembolism. Thromb Haemost; Aug 30 2016.

2. Asim, M., Al-Thani, H., El-Menyar, A.. Recurrent Deep Vein Thrombosis After the First Venous Thromboembolism Event: A Single-Institution Experience. Med Sci Monit; May 20 2017.

3. Baarslag, H. J., Koopman, M. M., Hutten, B. A., Linthorst Homan, M. W., Buller, H. R., Reekers, J. A., van Beek, E. J.. Long-term follow-up of patients with suspected deep vein thrombosis of the upper extremity: survival, risk factors and post-thrombotic syndrome. Eur J Intern Med; Dec 2004.

4. Baglin, T., Luddington, R., Brown, K., Baglin, C.. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet; Aug 16 2003.

5. Bank, I., Libourel, E. J., Middeldorp, S., Van Pampus, E. C., Koopman, M. M., Hamulyak, K., Prins, M. H., Van Der Meer, J., Buller, H. R.. Prothrombin 20210A mutation: a mild risk factor for venous thromboembolism but not for arterial thrombotic disease and pregnancy-related complications in a family study. Archives of Internal Medicine; Sep 27 2004.

6. Bezemer, I. D., van der Meer, F. J., Eikenboom, J. C., Rosendaal, F. R., Doggen, C. J.. The value of family history as a risk indicator for venous thrombosis. Archives of Internal Medicine; Mar 23 2009.

7. Brouwer, J. L., Lijfering, W. M., Ten Kate, M. K., Kluin-Nelemans, H. C., Veeger, N. J., van der Meer, J.. High long-term absolute risk of recurrent venous thromboembolism in patients with hereditary deficiencies of protein S, protein C or antithrombin. Thromb Haemost; Jan 2009.

8. Brouwer, J. L., Veeger, N. J., Kluin-Nelemans, H. C., van der Meer, J.. The pathogenesis of venous thromboembolism: evidence for multiple interrelated causes. Ann Intern Med; Dec 5 2006.

9. Brouwer, J. L., Veeger, N. J., van der Schaaf, W., Kluin-Nelemans, H. C., van der Meer, J.. Difference in absolute risk of venous and arterial thrombosis between familial protein S deficiency type I and type III. Results from a family cohort study to assess the clinical impact of a laboratory test-based classification. Br J Haematol; Mar 2005.

10. Bruwer, G., Limperger, V., Kenet, G., Klostermeier, U. C., Shneyder, M., Degenhardt, F., Finckh, U., Heller, C., Holzhauer, S., Trappe, R., Kentouche, K., Knoefler, R., Kurnik, K., Krumpel, A., Lauten, M., Manner, D., Mesters, R., Junker, R., Nowak-Gottl, U.. Impact of high risk thrombophilia status on recurrence among children and adults with VTE: An observational multicenter cohort study. Blood Cells Mol Dis; Nov 2016.

11. Cebi, N., Tanriverdi, S.. Aetiology of deep vein thrombosis in 63 turkish patients. Turkish Journal of Medical Sciences; April 2009.

12. Christiansen, S. C., Cannegieter, S. C., Koster, T., Vandenbroucke, J. P., Rosendaal, F. R.. Thrombophilia, clinical factors, and recurrent venous thrombotic events. Jama; May 18 2005.

13. Cohen, A. T., Harrington, R. A., Goldhaber, S. Z., Hull, R. D., Wiens, B. L., Gold, A., Hernandez, A. F., Gibson, C. M., Investigators, Apex. Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients. N Engl J Med; Aug 11 2016.

14. Cohen, A. T., Spiro, T. E., Buller, H. R., Haskell, L., Hu, D., Hull, R., Mebazaa, A., Merli, G., Schellong, S., Spyropoulos, A. C., Tapson, V., Investigators, Magellan. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. N Engl J Med; Feb 7 2013.

15. Cohen, W., Castelli, C., Alessi, M. C., Aillaud, M. F., Bouvet, S., Saut, N., Brunet, D., Barthet, M. C., Tregouet, D. A., Lavigne, G., Morange, P. E.. ABO blood group and von Willebrand factor levels partially explained the incomplete penetrance of congenital thrombophilia. Arterioscler Thromb Vasc Biol; Aug 2012.

16. Coppens, M., van de Poel, M. H., Bank, I., Hamulyak, K., van der Meer, J., Veeger, N. J., Prins, M. H., Buller, H. R., Middeldorp, S.. A prospective cohort study on the absolute incidence of venous thromboembolism and arterial cardiovascular disease in asymptomatic carriers of the prothrombin 20210A mutation. Blood; Oct 15 2006.

17. Couturaud, F., Kearon, C., Leroyer, C., Mercier, B., Abgrall, J. F., Le Gal, G., Lacut, K., Oger, E., Bressollette, L., Ferec, C., Lamure, M., Mottier, D., Groupe d'Etude de la Thrombose de Bretagne, Occidentale. Incidence of venous thromboembolism in first-degree relatives of patients with venous thromboembolism who have factor V Leiden. Thromb Haemost; Dec 2006.

18. De Stefano, V., Martinelli, I., Mannucci, P. M., Paciaroni, K., Chiusolo, P., Casorelli, I., Rossi, E., Leone, G.. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med; Sep 9 1999.

19. De Stefano, V., Simioni, P., Rossi, E., Tormene, D., Za, T., Pagnan, A., Leone, G.. The risk of recurrent venous thromboembolism in patients with inherited deficiency of natural anticoagulants antithrombin, protein C and protein S. Haematologica; May 2006.

20. Di Minno, M. N., Dentali, F., Lupoli, R., Ageno, W.. Mild antithrombin deficiency and risk of recurrent venous thromboembolism: a prospective cohort study. Circulation; Jan 28 2014.

21. Eichinger, S., Minar, E., Hirschl, M., Bialonczyk, C., Stain, M., Mannhalter, C., Stumpflen, A., Schneider, B., Lechner, K., Kyrle, P. A.. The risk of early recurrent venous thromboembolism after oral anticoagulant therapy in patients with the G20210A transition in the prothrombin gene. Thromb Haemost; Jan 1999.

22. Eichinger, S., Weltermann, A., Mannhalter, C., Minar, E., Bialonczyk, C., Hirschl, M., Schonauer, V., Lechner, K., Kyrle, P. A.. The risk of recurrent venous thromboembolism in heterozygous carriers of factor V Leiden and a first spontaneous venous thromboembolism. Archives of Internal Medicine; Nov 11 2002.

23. Eischer, L., Kammer, M., Traby, L., Kyrle, P. A., Eichinger, S.. Risk of cancer after anticoagulation in patients with unprovoked venous thromboembolism: an observational cohort study. Journal of Thrombosis and Haemostasis; July 2017.

24. Faioni, E. M., Franchi, F., Bucciarelli, P., Margaglione, M., De Stefano, V., Castaman, G., Finazzi, G., Mannucci, P. M.. Coinheritance of the HR2 haplotype in the factor V gene confers an increased risk of venous thromboembolism to carriers of factor V R506Q (factor V Leiden). Blood; Nov 1 1999.

25. Garcia-Fuster, M. J., Forner, M. J., Fernandez, C., Gil, J., Vaya, A., Maldonado, L.. Long-term prospective study of recurrent venous thromboembolism in patients younger than 50 years. Pathophysiol Haemost Thromb; 2005.

26. Goldhaber, S. Z., Leizorovicz, A., Kakkar, A. K., Haas, S. K., Merli, G., Knabb, R. M., Weitz, J. I., Investigators, Adopt,Trial. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. N Engl J Med; Dec 8 2011.

27. Gonzalez-Porras, J. R., Garcia-Sanz, R., Alberca, I., Lopez, M. L., Balanzategui, A., Gutierrez, O., Lozano, F., San Miguel, J.. Risk of recurrent venous thrombosis in patients with G20210A mutation in the prothrombin gene or factor V Leiden mutation. Blood Coagul Fibrinolysis; Jan 2006.

28. Group, The,Procare. Is recurrent venous thromboembolism more frequent in homozygous patients for the factor V Leiden mutation than in heterozygous patients?. Blood Coagulation and Fibrinolysis; September 2003.

29. Heijboer, H., Brandjes, D. P., Buller, H. R., Sturk, A., ten Cate, J. W.. Deficiencies of coagulation-inhibiting and fibrinolytic proteins in outpatients with deep-vein thrombosis. N Engl J Med; Nov 29 1990.

30. Heit, J. A., Beckman, M. G., Bockenstedt, P. L., Grant, A. M., Key, N. S., Kulkarni, R., Manco-Johnson, M. J., Moll, S., Ortel, T. L., Philipp, C. S., Thrombosis, C.,D.,C., Hemostasis Centers, Research, Prevention, Network. Comparison of characteristics from White- and Black-Americans with venous thromboembolism: a cross-sectional study. Am J Hematol; Jul 2010.

31. Hirmerova, J., Seidlerova, J., Subrt, I.. The association of factor V Leiden with various clinical patterns of venous thromboembolism-the factor V Leiden paradox. Qjm; Sep 2014.

32. Hoibraaten, E., Qvigstad, E., Arnesen, H., Larsen, S., Wickstrom, E., Sandset, P. M.. Increased risk of recurrent venous thromboembolism during hormone replacement therapy--results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). Thromb Haemost; Dec 2000.

33. Hull, R. D., Pineo, G. F., Stein, P. D., Mah, A. F., MacIsaac, S. M., Dahl, O. E., Butcher, M., Brant, R. F., Ghali, W. A., Bergqvist, D., Raskob, G. E.. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. Ann Intern Med; Nov 20 2001.

34. Karasu, A., Engbers, M. J., Cushman, M., Rosendaal, F. R., van Hylckama Vlieg, A.. Genetic risk factors for venous thrombosis in the elderly in a case-control study. Journal of Thrombosis & Haemostasis; Sep 2016.

35. Kearon, C., Gent, M., Hirsh, J., Weitz, J., Kovacs, M. J., Anderson, D. R., Turpie, A. G., Green, D., Ginsberg, J. S., Wells, P., MacKinnon, B., Julian, J. A.. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med; Mar 25 1999.

36. Kearon, C., Julian, J. A., Kovacs, M. J., Anderson, D. R., Wells, P., Mackinnon, B., Weitz, J. I., Crowther, M. A., Dolan, S., Turpie, A. G., Geerts, W., Solymoss, S., van Nguyen, P., Demers, C., Kahn, S. R., Kassis, J., Rodger, M., Hambleton, J., Gent, M., Ginsberg, J. S., Investigators, Elate. Influence of thrombophilia on risk of recurrent venous thromboembolism while on warfarin: results from a randomized trial. Blood; Dec 1 2008.

37. Kearon, C., Parpia, S., Spencer, F. A., Baglin, T., Stevens, S. M., Bauer, K. A., Lentz, S. R., Kessler, C. M., Douketis, J. D., Moll, S., Kaatz, S., Schulman, S., Connors, J. M., Ginsberg, J. S., Spadafora, L., Bhagirath, V., Liaw, P. C., Weitz, J. I., Julian, J. A.. Antiphospholipid antibodies and recurrent thrombosis after a first unprovoked venous thromboembolism. Blood; May 10 2018.

38. Laczkovics, C., Grafenhofer, H., Kaider, A., Quehenberger, P., Simanek, R., Mannhalter, C., Lechner, K., Pabinger, I.. Risk of recurrence after a first venous thromboembolic event in young women. Haematologica; Sep 2007.

39. Lee, S. Y., Kim, E. K., Kim, M. S., Shin, S. H., Chang, H., Jang, S. Y., Kim, H. J., Kim, D. K.. The prevalence and clinical manifestation of hereditary thrombophilia in Korean patients with unprovoked venous thromboembolisms. PLoS ONE [Electronic Resource]; 2017.

40. Lensen, R., Bertina, R. M., Vandenbroucke, J. P., Rosendaal, F. R.. High factor VIII levels contribute to the thrombotic risk in families with factor V Leiden. Br J Haematol; Aug 2001.

41. Lijfering, W. M., Middeldorp, S., Veeger, N. J., Hamulyak, K., Prins, M. H., Buller, H. R., van der Meer, J.. Risk of recurrent venous thrombosis in homozygous carriers and double heterozygous carriers of factor V Leiden and prothrombin G20210A. Circulation; Apr 20 2010.

42. Lim, H. Y., Chua, C. C., Tacey, M., Sleeman, M., Donnan, G., Nandurkar, H., Ho, P.. Venous thromboembolism management in Northeast Melbourne: how does it compare to international guidelines and data?. Intern Med J; Sep 2017.

43. Lindmarker, P., Schulman, S., Sten-Linder, M., Wiman, B., Egberg, N., Johnsson, H.. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. DURAC Trial Study Group. Duration of Anticoagulation. Thromb Haemost; May 1999.

44. Mahmoodi, B. K., Brouwer, J. L., Ten Kate, M. K., Lijfering, W. M., Veeger, N. J., Mulder, A. B., Kluin-Nelemans, H. C., Van Der Meer, J.. A prospective cohort study on the absolute risks of venous thromboembolism and predictive value of screening asymptomatic relatives of patients with hereditary deficiencies of protein S, protein C or antithrombin. Journal of Thrombosis & Haemostasis; Jun 2010.

45. Marcucci, R., Liotta, A. A., Cellai, A. P., Rogolino, A., Gori, A. M., Giusti, B., Poli, D., Fedi, S., Abbate, R., Prisco, D.. Increased plasma levels of lipoprotein(a) and the risk of idiopathic and recurrent venous thromboembolism. Am J Med; Dec 1 2003.

46. Martinelli, I., Bucciarelli, P., Margaglione, M., De Stefano, V., Castaman, G., Mannucci, P. M.. The risk of venous thromboembolism in family members with mutations in the genes of factor V or prothrombin or both. Br J Haematol; Dec 2000.

47. Martinelli, I., Mannucci, P. M., De Stefano, V., Taioli, E., Rossi, V., Crosti, F., Paciaroni, K., Leone, G., Faioni, E. M.. Different risks of thrombosis in four coagulation defects associated with inherited thrombophilia: a study of 150 families. Blood; Oct 1 1998.

48. Mateo, J., Oliver, A., Borrell, M., Sala, N., Fontcuberta, J.. Laboratory evaluation and clinical characteristics of 2,132 consecutive unselected patients with venous thromboembolism--results of the Spanish Multicentric Study on Thrombophilia (EMET-Study). Thromb Haemost; Mar 1997.

49. Mello, T. B., Orsi, F. L., Montalvao, S. A., Ozelo, M. C., de Paula, E. V., Annichinno-Bizzachi, J. M.. Long-term prospective study of recurrent venous thromboembolism in a Hispanic population. Blood Coagul Fibrinolysis; Oct 2010.

50. Meyer, M. R., Witt, D. M., Delate, T., Johnson, S. G., Fang, M., Go, A., Clark, N. P.. Thrombophilia testing patterns amongst patients with acute venous thromboembolism. Thromb Res; Dec 2015.

51. Middeldorp, S., Henkens, C. M., Koopman, M. M., van Pampus, E. C., Hamulyak, K., van der Meer, J., Prins, M. H., Buller, H. R.. The incidence of venous thromboembolism in family members of patients with factor V Leiden mutation and venous thrombosis. Ann Intern Med; Jan 1 1998.

52. Miles, J. S., Miletich, J. P., Goldhaber, S. Z., Hennekens, C. H., Ridker, P. M.. G20210A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. J Am Coll Cardiol; Jan 2001.

53. Olie, V., Plu-Bureau, G., Conard, J., Horellou, M. H., Canonico, M., Scarabin, P. Y.. Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. Menopause; May 2011.

54. Palareti, G., Legnani, C., Cosmi, B., Valdre, L., Lunghi, B., Bernardi, F., Coccheri, S.. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation; Jul 22 2003.

55. Prandoni, P., Noventa, F., Ghirarduzzi, A., Pengo, V., Bernardi, E., Pesavento, R., Iotti, M., Tormene, D., Simioni, P., Pagnan, A.. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica; Feb 2007.

56. Ridker, P. M., Miletich, J. P., Stampfer, M. J., Goldhaber, S. Z., Lindpaintner, K., Hennekens, C. H.. Factor V Leiden and risks of recurrent idiopathic venous thromboembolism. Circulation; Nov 15 1995.

57. Rodger, M. A., Kahn, S. R., Wells, P. S., Anderson, D. A., Chagnon, I., Le Gal, G., Solymoss, S., Crowther, M., Perrier, A., White, R., Vickars, L., Ramsay, T., Betancourt, M. T., Kovacs, M. J.. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. Cmaj; Aug 26 2008.

58. Roldan, V., Lecumberri, R., Munoz-Torrero, J. F., Vicente, V., Rocha, E., Brenner, B., Monreal, M., Investigators, Riete. Thrombophilia testing in patients with venous thromboembolism. Findings from the RIETE registry. Thromb Res; Jun 2009.

59. Rossi, E., Za, T., Ciminello, A., Leone, G., De Stefano, V.. The risk of symptomatic pulmonary embolism due to proximal deep venous thrombosis differs in patients with different types of inherited thrombophilia. Thromb Haemost; Jun 2008.

60. Roupie, A. L., Dossier, A., Goulenok, T., Perozziello, A., Papo, T., Sacre, K.. First venous thromboembolism in admitted patients younger than 50years old. Eur J Intern Med; Oct 2016.

61. Rupa-Matysek, J., Gil, L., Wojtasinska, E., Ciepluch, K., Lewandowska, M., Komarnicki, M.. The relationship between mean platelet volume and thrombosis recurrence in patients diagnosed with antiphospholipid syndrome. Rheumatol Int; Nov 2014.

62. Santamaria, M. G., Agnelli, G., Taliani, M. R., Prandoni, P., Moia, M., Bazzan, M., Guazzaloca, G., Ageno, W., Bertoldi, A., Silingardi, M., Tomasi, C., Ambrosio, G. B., Warfarin Optimal Duration Italian Trial, Investigators. Thrombophilic abnormalities and recurrence of venous thromboembolism in patients treated with standardized anticoagulant treatment. Thromb Res; 2005.

63. Schattner, A., Kasher, I., Berrebi, A.. Causes and outcome of deep-vein thrombosis in otherwise-healthy patients under 50 years. Qjm; Apr 1997.

64. Schulman, S., Lindmarker, P., Holmstrom, M., Larfars, G., Carlsson, A., Nicol, P., Svensson, E., Ljungberg, B., Viering, S., Nordlander, S., Leijd, B., Jahed, K., Hjorth, M., Linder, O., Beckman, M.. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. Journal of Thrombosis & Haemostasis; Apr 2006.

65. Simioni, P., Prandoni, P., Lensing, A. W., Manfrin, D., Tormene, D., Gavasso, S., Girolami, B., Sardella, C., Prins, M., Girolami, A.. Risk for subsequent venous thromboembolic complications in carriers of the prothrombin or the factor V gene mutation with a first episode of deep-vein thrombosis. Blood; Nov 15 2000.

66. Simioni, P., Sanson, B. J., Prandoni, P., Tormene, D., Friederich, P. W., Girolami, B., Gavasso, S., Huisman, M. V., Buller, H. R., Wouter ten Cate, J., Girolami, A., Prins, M. H.. Incidence of venous thromboembolism in families with inherited thrombophilia. Thromb Haemost; Feb 1999.

67. Simioni, P., Tormene, D., Prandoni, P., Zerbinati, P., Gavasso, S., Cefalo, P., Girolami, A.. Incidence of venous thromboembolism in asymptomatic family members who are carriers of factor V Leiden: a prospective cohort study. Blood; Mar 15 2002.

68. Sonnevi, K., Tchaikovski, S. N., Holmstrom, M., Antovic, J. P., Bremme, K., Rosing, J., Larfars, G.. Obesity and thrombin-generation profiles in women with venous thromboembolism. Blood Coagul Fibrinolysis; Jul 2013.

69. Strandberg, K., Svensson, P. J., Ohlin, A. K.. Venous thromboembolism in carriers of the Factor V Leiden mutation and in patients without known thrombophilic risk factor; prediction of recurrence and APC-PCI complex concentration and/or soluble thrombomodulin antigen and activity. Thromb Res; 2007.

70. Sundquist, K., Sundquist, J., Svensson, P. J., Zoller, B., Memon, A. A.. Role of family history of venous thromboembolism and thrombophilia as predictors of recurrence: a prospective follow-up study. Journal of Thrombosis & Haemostasis; Dec 2015.

71. Sveinsdottir, S. V., Saemundsson, Y., Isma, N., Gottsater, A., Svensson, P. J.. Evaluation of recurrent venous thromboembolism in patients with Factor V Leiden mutation in heterozygous form. Thromb Res; Sep 2012.

72. Wahlander, K., Eriksson, H., Lundstrom, T., Billing Clason, S., Wall, U., Nystrom, P., Wessman, P., Schulman, S., Investigators, Thrive,Iii. Risk of recurrent venous thromboembolism or bleeding in relation to thrombophilic risk factors in patients receiving ximelagatran or placebo for long-term secondary prevention of venous thromboembolism. Br J Haematol; Apr 2006.

73. Weingarz, L., Schindewolf, M., Schwonberg, J., Hecking, C., Wolf, Z., Erbe, M., Lindhoff-Last, E., Linnemann, B.. Thrombophilia and risk of VTE recurrence according to the age at the time of first VTE manifestation. Vasa; Jul 2015.

QUESTION

Should selective thrombophilia testing and subsequent thromboprophylaxis in relatives positive for thrombophilia and no thromboprophylaxis in relatives negative for thrombophilia vs. no thrombophilia testing and no thromboprophylaxis in all be used for first- and second-degree relatives of patients with a known thrombophilia but no history of VTE who have a minor provoking risk factor for VTE?

POPULATION:	first- and second-degree relatives of patients with a known thrombophilia but no history of VTE who have a minor provoking risk factor for VTE
INTERVENTION:	selective thrombophilia testing and subsequent thromboprophylaxis in relatives positive for thrombophilia and no thromboprophylaxis in relatives negative for thrombophilia
COMPARISON:	no thrombophilia testing and no thromboprophylaxis in all
MAIN OUTCOMES:	VTE - Factor V Leiden - First-degree relatives; VTE - Prothrombin mutation - First-degree relatives; VTE - Antithrombin deficiency - First-degree relatives; VTE - Protein C deficiency - First-degree relatives; VTE - Protein S deficiency - First-degree relatives; Major Bleeding - First-degree relatives;
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Inherited thrombophilia can be identified in many patients with a venous thromboembolism (VTE). Consequently, relatives of these patients are also at increased risk to have inherited thrombophilia. The currently most commonly tested inherited thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. Thrombophilia testing is often performed in relatives of patients with an inherited thrombophilia but no history of VTE, particularly if they are in a high risk episode such as immobilization. Although testing relatives of patients with an inherited thrombophilia but no history of VTE has a high chance of finding a positive test result, the relevant question and aim of the current guideline is to assess whether thrombophilia testing and tailoring management to the test result would improve patient important outcomes. This question addresses whether selective testing for the same inherited thrombophilia and subsequent thromboprophylaxis in patients positive for the same thrombophilia improves patient important outcomes in relatives of patients with a known familial thrombophilia but no history of VTE who have a minor provoking risk factor for VTE (e.g. immobility, minor injury, illness, infection), as compared with no thrombophilia testing and no thromboprophylaxis in all. Since no randomized controlled trials have addressed this question, we used a modeling exercise based on observational evidence for baseline risk, prevalence of thrombophilia and associated risk of events with thrombophilia, and RCTs with evidence for the effect of thromboprophylaxis on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies		A separate question in this guideline addresses selective testing for thrombophilia in relatives of patients who also had a VTE in addition to a known inherited thrombophilia. The current question addresses whether selective testing for the thrombophilia type that was found in the proband

○ Don't know		has benefit, if the proband did not have a VTE.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know		Desirable effect = preventing VTE. VTE would be avoided in relatives who are positive for thrombophilia by using thromboprophylaxis. The panel considered a reduction in first-time VTE of 5 per 1,000 or lower to be Trivial. The panel considered the following thresholds: Trivial: ≤5 per 1000; Small: 5-20 per 1,000; Moderate: 20-50 per 1,000 Trivial for FVL and prothrombin. Small for antithrombin, protein C, and protein S. These effects were considered Small to Moderate by the panel. <u>Second-degree relatives:</u> For modeling the effect in second-degree relatives we assumed a prevalence of 25% of the same thrombophilia type as the proband.

		Effect estimates for VTE in second-degree relatives: FVL: 1.31 fewer per 1,000 (from 0.22 to 2.21 fewer) PT: 1.21 fewer per 1,000 (from 0.18 to 2.27 fewer) AT: 5.54 fewer per 1,000 (from 0.87 to 9.19 fewer) PC: 4.92 fewer per 1,000 (from 0.65 to 8.86 fewer) PS: 4.59 fewer per 1,000 (from 0.61 to 8.46 fewer)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		Undesirable effect = causing major bleeding. Major bleedings would be caused in patients who are positive for thrombophilia by using thromboprophylaxis. <u>Second-degree relatives:</u> For modeling the effect in second-degree relatives we assumed a prevalence of 25% of the same thrombophilia type as the proband. Effect estimates for Major bleeding in second-degree relatives: All types: 1.09 more per 1,000 (from 0.33 to 2.27 more)

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows using a scale from 0 (worst possible scenario, usually death), to 1 (best possible scenario, usually perfect health): Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(1, 2, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3) **Gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off)(2, 3) **Minor intracranial bleeding event:** 0.75 (standard gamble)(2) **Major intracranial bleeding event:** 0.15 (standard gamble)(2) **Anticoagulant therapy** Patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome.(3) Patients would favor efficacy and safety over convenience of route of administration.(6) Also, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events.(7, 6, 8)	The panel considered clinicians may value avoiding major bleedings more (they do not want to cause harm), while patients may value avoiding VTE events more (they prefer avoiding a recurrence of clots).

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know		FVL and prothrombin: Does not favor either the intervention or comparison, for first- and second-degree relatives. Antithrombin, protein C, and protein S: Probably favors the intervention, for first- and second-degree relatives.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Intervention Costs: **Test (source)** / Approximate Cost (2005) / Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016) / **(14/12/2016) £1 = $1,27** **Full Blood Count** £2.55 £3.29 **$4,18** **Protein C** £11.67 £15.5 **$19,12** **Free Protein S** £11.67 £15.5 **$19,12** **Antithrombin** £11.67 £15.5 **$19,12** **APCR** £10.73 £13.84 **$17,58** **Factor V Leiden** £85.00 £109.65 **$141,45** **Prothrombin gene mutation** £85.00 £109.65 **$141,45** **Lupus Anticoagulant** £10.73 £13.84 **$17,58** **Antiphospholipid antibodies** £12.30 £15.87 **$20,15** **Anti Beta-2 GP1 antibody** £9.50 £12.25 **$15,81** **The potential cost of a full thrombophilia screen** £250.82, £323.56 **$410,92** Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx **Cost of the health outcomes:**(9) - **Recurrent VTE:** 11,000 to 15,000 USD - **Major bleeding:** 11,000 to 22,000 USD **Cost of interventions:**(10) - **Dabigatran:** Cost per month: $300.44–$600.88 USD - **Rivaroxaban:** Cost per month: $300.42–$600.84 USD - **Apixaban:** Cost per month: $300.44–$600.88	**The panel considered the following cost ranges:** - Cost for testing: $400 -$2,000 per patient - Cost for treatment: $1,000-$ 4,500 per patient per year Costs for testing all inherited thrombophilia types and short course of prophylaxis, as compared to no testing and no prophylaxis. Costs for selective testing would be less than running full thrombophilia panels.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(11)	The panel considered that the health system/service coverage will be the main aspect affecting health equity. USA is an example where promotion of testing that is not covered by insurance would generate inequities. I.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Research studies suggested the following regarding acceptability and barriers associated with testing and treatment: **Patients:** A survey was conducted in members of a large family with heritable protein C deficiency. For those who had not been tested before, using a 7-point scale (1 - not at all interested; 7 extremely interested), the mean score for interest in testing interest was 4.6 (standard deviation 2.4). Patients in general were willing to take the test for thrombophilia.(12) A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(13) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(14) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers:** A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(15) **Payers:** At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	The panel considered testing acceptable for many doctors, although maybe not for all. Patients are in general willing to undergo thrombophilia testing when testing is proposed by their doctor. Due to the high number of second-degree relatives that would be tested in this population, many will be labeled as having thrombophilia.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(16) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending.(17) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(18) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(19) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(20)	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation. External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**

	JUDGEMENT						
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

Factor V Leiden or prothrombin mutation in first- and second-degree relatives

In first- and second-degree relatives of patients with known factor V Leiden or prothrombin mutation (low risk thrombophilia) but no history of VTE, and who have a minor provoking risk factor for VTE, the ASH guideline panel suggests not testing for the known familial thrombophilia to guide thromboprophylaxis, and not using thromboprophylaxis in all relatives (conditional recommendation based on very low certainty in the evidence about effects)

Antithrombin, protein C, or protein S deficiency in first-degree relatives

In first-degree relatives of patients with known antithrombin, protein C, or protein S deficiency (high risk thrombophilia) but no history of VTE, and who have a minor provoking risk factor for VTE, the ASH guideline panel suggests testing for the known familial thrombophilia and thromboprophylaxis in relatives positive for thrombophilia over not testing for thrombophilia and no thromboprophylaxis in all relatives (conditional recommendation based on very low certainty in the evidence about effects)

Antithrombin, protein C, or protein S deficiency in second-degree relatives

In second-degree relatives of patients with known antithrombin, protein C, or protein S deficiency (high risk thrombophilia) but no history of VTE, and who have a minor provoking risk factor for VTE, the ASH guideline panel suggests either testing for the known familial thrombophilia and thromboprophylaxis in relatives positive for thrombophilia or not testing for thrombophilia and not using thromboprophylaxis in all relatives (conditional recommendation based on very low certainty in the evidence about effects)

Remarks:

- A strategy with selective testing for the known familial thrombophilia type would mean that positive relatives would receive thromboprophylaxis, and negative relatives would receive no thromboprophylaxis.

- These recommendations do not address homozygous defects, or combinations of thrombophilia types.

Justification

The panel considered that thrombophilia testing and prophylaxis in thrombophilia positives likely has some benefit in terms of prevention of VTE that outweighs the risk of major bleeding in first-degree relatives of patients with high risk thrombophilias (antithrombin, protein C, protein S), but not in second-degree relatives of patients with high risk thrombophilias and first- and second-degree relatives of patients with low risk thrombophilias (factor V Leiden, prothrombin).

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation.

Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

No research priorities.

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
7. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
8. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
9. Grosse, S. D., Nelson, R. E., Nyarko, K. A., Richardson, L. C., Raskob, G. E.. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res; Jan 2016.
10. Biskupiak, J., Ghate, S. R., Jiao, T., Brixner, D.. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. J Manag Care Pharm; Nov-Dec 2013.
11. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
12. van Korlaar, I. M., Vossen, C. Y., Rosendaal, F. R., Bovill, E. G., Naud, S., Cameron, L. D., Kaptein, A. A.. Attitudes toward genetic testing for thrombophilia in asymptomatic members of a large family with heritable protein C deficiency. Journal of Thrombosis & Haemostasis; Nov 2005.
13. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
14. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
15. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
16. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
17. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
18. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
19. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
20. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In first- and second-degree relatives of patients with a known thrombophilia but no history of VTE who have a minor provoking risk factor for VTE (e.g. immobility, minor injury, illness, infection), should selective testing for the known familial thrombophilia and subsequent thromboprophylaxis in relatives positive for thrombophilia and no thromboprophylaxis in relatives negative for thrombophilia compared to no thrombophilia testing and no thromboprophylaxis in all be used?

Setting:

Bibliography: See reference list and footnotes. [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
VTE - Factor V Leiden - First-degree relatives (follow up: minor provoking risk factor episode; assessed with: any first-time DVT or PE)									
16 [a,b,c,d]	observational studies	not serious	not serious	serious [e]	not serious	none	When testing first-degree relatives of patients with factor V Leiden (FVL) but no history of VTE who have a minor provoking VTE risk factor for FVL, and treating the 500 positives with thromboprophylaxis, 4.98 VTE events will occur per 1,000 risk episodes (ranging from 3.52 to 7.05). When not testing first-degree relatives and treating none of them with thromboprophylaxis, 7.5 VTE events will occur per 1,000 risk episodes. Therefore, a selective thrombophilia testing strategy is associated with 500 more relatives treated with thromboprophylaxis and **2.52 fewer VTE events (ranging from 0.45 to 3.98)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [f]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Prothrombin mutation - First-degree relatives (follow up: minor provoking risk factor episode; assessed with: any first-time DVT or PE)									
12 [b,d,g,h]	observational studies	not serious	not serious	serious [e]	not serious	none	When testing first-degree relatives of patients with prothrombin mutation (PT) but no history of VTE who have a minor provoking VTE risk factor for PT, and treating the 500 positives with thromboprophylaxis, 5.08 VTE events will occur per 1,000 risk episodes (ranging from 3.47 to 7.10). When not testing first-degree relatives and treating none of them with thromboprophylaxis, 7.5 VTE events will occur per 1,000 risk episodes. Therefore, a selective thrombophilia testing strategy is associated with 500 more relatives treated with thromboprophylaxis and **2.42 fewer VTE events (ranging from 0.40 to 4.03)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [i]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Antithrombin deficiency - First-degree relatives (follow up: minor provoking risk factor episode; assessed with: any first-time DVT or PE)									
14 [b,d,j,k]	observational studies	not serious	not serious	serious [e]	serious [l]	none	When testing first-degree relatives of patients with antithrombin deficiency (AT) but no history of VTE who have a minor provoking VTE risk factor for AT, and treating the 500 positives with thromboprophylaxis, 14.37 VTE events will occur per 1,000 risk episodes (ranging from 8.60 to 23.10). When not testing first-degree relatives and treating none of them with thromboprophylaxis, 25 VTE events will occur per 1,000 risk episodes. Therefore, a selective thrombophilia testing strategy is associated with 500 more relatives treated with thromboprophylaxis and **10.63 fewer VTE events (ranging from 1.90 to 16.40)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [m]	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
VTE - Protein C deficiency - First-degree relatives (follow up: minor provoking risk factor episode; assessed with: any first-time DVT or PE)									
14 [b,d,n,o]	observational studies	not serious	not serious	serious [e]	serious [l]	none	When testing first-degree relatives of patients with protein C deficiency (PC) but no history of VTE for PC, and treating the 500 positives with thromboprophylaxis, 14.86 VTE events will occur per 1,000 risk episodes (ranging from 8.82 to 23.34). When not testing first-degree relatives and treating none of them with thromboprophylaxis, 25 VTE events will occur per 1,000 risk episodes. Therefore, a selective thrombophilia testing strategy is associated with 500 more relatives treated with thromboprophylaxis and **10.14 fewer VTE events (ranging from 1.66 to 16.18)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [p]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Protein S deficiency - First-degree relatives (follow up: minor provoking risk factor episode; assessed with: any first-time DVT or PE)									
15 [b,d,q,r]	observational studies	not serious	not serious	serious [e]	serious [l]	none	When testing first-degree relatives of patients with protein S deficiency (PS) but no history of VTE for PS, and treating the 500 positives with thromboprophylaxis, 15.15 VTE events will occur per 1,000 risk episodes (ranging from 9.09 to 23.40). When not testing first-degree relatives and treating none of them with thromboprophylaxis, 25 VTE events will occur per 1,000 risk episodes. Therefore, a selective thrombophilia testing strategy is associated with 500 more relatives treated with thromboprophylaxis and **9.85 fewer VTE events (ranging from 1.60 to 15.91)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [s]	⨁◯◯◯ VERY LOW	CRITICAL
Major Bleeding - First-degree relatives (follow up: minor provoking risk factor episode)									
4 [t,u]	observational studies	not serious	not serious	serious [v]	not serious	none	When testing first-degree relatives of patients with an inherited thrombophilia but no history of VTE for the same thrombophilia, and treating the 500 positives with thromboprophylaxis, 6.18 major bleedings will occur per 1,000 high-risk episodes (ranging from 4.66 to 8.54). When not testing first-degree relatives and treating none of them with thromboprophylaxis, 4 major bleedings will occur per 1,000 risk episodes. Therefore, a selective thrombophilia testing strategy is associated with 500 more relatives treated with thromboprophylaxis and **2.18 fewer major bleedings (ranging from 0.66 to 4.54)** per 1,000 risk episodes in first-degree relatives compared with a no testing strategy. [w]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE, 6 studies; Risk association for thrombophilia positive versus negative, 9 studies (3 also reported overall risk for VTE); Thromboprophylaxis effect, 4 RCTs

b. Overall risk for VTE: estimated from Bank 2004, Coppens 2006, Mahmoodi 2010, Middeldorp 1998, Simioni 1999, Simioni 2002

c. Factor V Leiden positive vs negative risk association: Cohen 2012, Couturaud 2006, Faioni 1999, Lensen 2001, Martinelli 1998, Martinelli 2000, Middeldorp 1998, Simioni 1999, Simioni 2002

d. Effect of thromboprophylaxis: Cohen 2013, Cohen 2016, Goldhaber 2011, Hull 2010

e. The effect was indirectly calculated using separate studies for overall risk of VTE, relative risk of thrombophilia positives vs negatives, and the effect of thromboprophylaxis

f. Based on the following estimates: Overall risk for VTE, 7.5 per 1,000; Prevalence of FVL in first-degree relatives, 50%; Relative risk for VTE in FVL positives versus negatives, RR 2.71 (95%CI: 2.06-3.56); Relative risk of VTE with thromboprophylaxis versus no thromboprophylaxis, RR 0.54 (0.32-0.91). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the upper CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

g. Prothrombin positive vs negative risk association: Bank 2004, Coppens 2006, Faioni 1999, Martinelli 2000

h. Number of studies used in calculations: Overall risk for VTE, 6 studies; Risk association for thrombophilia positive versus negative, 4 studies (2 also reported overall risk for VTE); Thromboprophylaxis effect, 4 RCTs

i. Based on the following estimates: Overall risk for VTE, 7.5 per 1,000; Prevalence of PT in first-degree relatives, 50% plus general population prevalence of other thrombophilia types in those who were PT negative; Relative risk for VTE in PT positives versus negatives, RR 2.54 (95%CI: 1.60-4.07); Relative risk of VTE with thromboprophylaxis versus no thromboprophylaxis, RR 0.54 (0.32-0.91). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the upper CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

j. Number of studies used in calculations: Overall risk for VTE, 6 studies; Risk association for thrombophilia positive versus negative, 5 studies (1 also reported overall risk for VTE); Thromboprophylaxis effect, 4 RCTs

k. Antithrombin positive vs negative risk association: Brouwer 2006, Cohen 2012, Faioni 1999, Mahmoodi 2010, Martinelli 1998

l. There is a clinically important difference between the smallest and largest possible effect of the testing strategy

m. Based on the following estimates: Overall risk for VTE, 25 per 1,000; Prevalence of antithrombin in first-degree relatives, 50%; Relative risk for VTE in thrombophilia positives versus negatives, RR 12.17 (95%CI: 5.45-27.17); Relative risk of VTE with thromboprophylaxis versus no thromboprophylaxis, RR 0.54 (0.32-0.91). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the upper CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

n. Protein C positive vs negative risk association: Brouwer 2006, Cohen 2012, Faioni 1999, Mahmoodi 2010, Martinelli 1998

o. Number of studies used in calculations: Overall risk for VTE, 6 studies; Risk association for thrombophilia positive versus negative, 5 studies (1 also reported overall risk for VTE); Thromboprophylaxis effect, 4 RCTs

p. Based on the following estimates: Overall risk for VTE, 25 per 1,000; Prevalence of FVL in first-degree relatives, 50%; Relative risk for VTE in thrombophilia positives versus negatives, RR 7.47 (95%CI: 2.81-19.81); Relative risk of VTE with thromboprophylaxis versus no thromboprophylaxis, RR 0.54 (0.32-0.91). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the upper CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

q. Number of studies used in calculations: Overall risk for VTE, 6 studies; Risk association for thrombophilia positive versus negative, 6 studies (1 also reported overall risk for VTE); Thromboprophylaxis effect, 4 RCTs

r. Protein S positive vs negative risk association: Brouwer 2005, Brouwer 2006, Cohen 2012, Faioni 1999, Mahmoodi 2010, Martinelli 1998

s. Based on the following estimates: Overall risk for VTE, 25 per 1,000; Prevalence of FVL in first-degree relatives, 50%; Relative risk for VTE in thrombophilia positives versus negatives, RR 5.98 (95%CI: 2.45-14.57); Relative risk of VTE with thromboprophylaxis versus no thromboprophylaxis, RR 0.54 (0.32-0.91). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the upper CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

t. Number of studies used in calculations: Overall risk for major bleeding and thromboprophylaxis effect, 4 RCTs

u. Overall risk of bleeding and effect of thromboprophylaxis: Cohen 2013, Cohen 2016, Goldhaber 2011, Hull 2010

v. The effect was indirectly calculated using separate studies for the overall risk and effect of thromboprophylaxis

w. Based on the following estimates: Overall risk for Major Bleeding, 4 per 1,000; Prevalence of inheritable thrombophilia in first-degree relatives, 50%; Relative risk of Major Bleeding with thromboprophylaxis versus no thromboprophylaxis, RR 2.09 (1.33-3.27). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the smallest treatment effect (lower CI).

References

1. Bank, I., Libourel, E. J., Middeldorp, S., Van Pampus, E. C., Koopman, M. M., Hamulyak, K., Prins, M. H., Van Der Meer, J. , Buller, H. R.. Prothrombin 20210A mutation: a mild risk factor for venous thromboembolism but not for arterial thrombotic disease and pregnancy-related complications in a family study. Archives of Internal Medicine; Sep 27 2004.

2. Brouwer, J. L., Veeger, N. J., Kluin-Nelemans, H. C., van der Meer, J.. The pathogenesis of venous thromboembolism: evidence for multiple interrelated causes. Ann Intern Med; Dec 5 2006.

3. Brouwer, J. L., Veeger, N. J., van der Schaaf, W., Kluin-Nelemans, H. C., van der Meer, J.. Difference in absolute risk of venous and arterial thrombosis between familial protein S deficiency type I and type III. Results from a family cohort study to assess the clinical impact of a laboratory test-based classification. Br J Haematol; Mar 2005.

4. Cohen, A. T., Harrington, R. A., Goldhaber, S. Z., Hull, R. D., Wiens, B. L., Gold, A., Hernandez, A. F., Gibson, C. M., Investigators, Apex. Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients. N Engl J Med; Aug 11 2016.

5. Cohen, A. T., Spiro, T. E., Buller, H. R., Haskell, L., Hu, D., Hull, R., Mebazaa, A., Merli, G., Schellong, S., Spyropoulos, A. C., Tapson, V., Investigators, Magellan. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. N Engl J Med; Feb 7 2013.

6. Coppens, M., van de Poel, M. H., Bank, I., Hamulyak, K., van der Meer, J., Veeger, N. J., Prins, M. H., Buller, H. R. , Middeldorp, S.. A prospective cohort study on the absolute incidence of venous thromboembolism and arterial cardiovascular disease in asymptomatic carriers of the prothrombin 20210A mutation. Blood; Oct 15 2006.

7. Couturaud, F., Kearon, C., Leroyer, C., Mercier, B., Abgrall, J. F., Le Gal, G., Lacut, K., Oger, E., Bressollette, L., Ferec, C., Lamure, M., Mottier, D., Groupe d'Etude de la Thrombose de Bretagne, Occidentale. Incidence of venous thromboembolism in first-degree relatives of patients with venous thromboembolism who have factor V Leiden. Thromb Haemost; Dec 2006.

8. Faioni, E. M., Franchi, F., Bucciarelli, P., Margaglione, M., De Stefano, V., Castaman, G., Finazzi, G., Mannucci, P. M.. Coinheritance of the HR2 haplotype in the factor V gene confers an increased risk of venous thromboembolism to carriers of factor V R506Q (factor V Leiden). Blood; Nov 1 1999.

9. Goldhaber, S. Z., Leizorovicz, A., Kakkar, A. K., Haas, S. K., Merli, G., Knabb, R. M., Weitz, J. I., Investigators, Adopt,Trial. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. N Engl J Med; Dec 8 2011.

10. Hull, R. D., Schellong, S. M., Tapson, V. F., Monreal, M., Samama, M. M., Nicol, P., Vicaut, E., Turpie, A. G., Yusen, R. D., study, Exclaim. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. Ann Intern Med; Jul 6 2010.

11. Lensen, R., Bertina, R. M., Vandenbroucke, J. P., Rosendaal, F. R.. High factor VIII levels contribute to the thrombotic risk in families with factor V Leiden. Br J Haematol; Aug 2001.

12. Mahmoodi, B. K., Brouwer, J. L., Ten Kate, M. K., Lijfering, W. M., Veeger, N. J., Mulder, A. B., Kluin-Nelemans, H. C., Van Der Meer, J.. A prospective cohort study on the absolute risks of venous thromboembolism and predictive value of screening asymptomatic relatives of patients with hereditary deficiencies of protein S, protein C or antithrombin. Journal of Thrombosis & Haemostasis; Jun 2010.

13. Martinelli, I., Bucciarelli, P., Margaglione, M., De Stefano, V., Castaman, G., Mannucci, P. M.. The risk of venous thromboembolism in family members with mutations in the genes of factor V or prothrombin or both. Br J Haematol; Dec 2000.

14. Martinelli, I., Mannucci, P. M., De Stefano, V., Taioli, E., Rossi, V., Crosti, F., Paciaroni, K., Leone, G., Faioni, E. M.. Different risks of thrombosis in four coagulation defects associated with inherited thrombophilia: a study of 150 families. Blood; Oct 1 1998.

15. Middeldorp, S., Henkens, C. M., Koopman, M. M., van Pampus, E. C., Hamulyak, K., van der Meer, J., Prins, M. H., Buller, H. R.. The incidence of venous thromboembolism in family members of patients with factor V Leiden mutation and venous thrombosis. Ann Intern Med; Jan 1 1998.

16. Simioni, P., Sanson, B. J., Prandoni, P., Tormene, D., Friederich, P. W., Girolami, B., Gavasso, S., Huisman, M. V., Buller, H. R., Wouter ten Cate, J., Girolami, A., Prins, M. H.. Incidence of venous thromboembolism in families with inherited thrombophilia. Thromb Haemost; Feb 1999.

17. Simioni, P., Tormene, D., Prandoni, P., Zerbinati, P., Gavasso, S., Cefalo, P., Girolami, A.. Incidence of venous thromboembolism in asymptomatic family members who are carriers of factor V Leiden: a prospective cohort study. Blood; Mar 15 2002.

QUESTION

Should testing for any hereditary thrombophilia and subsequent avoidance of combined oral contraceptives (COC) in women positive for thrombophilia and COC in women negative for thrombophilia vs. no thrombophilia testing and COC in all be used for women from the general population?

POPULATION:	women from the general population
INTERVENTION:	testing for any hereditary thrombophilia and subsequent avoidance of combined oral contraceptives (COC) in women positive for thrombophilia and COC in women negative for thrombophilia
COMPARISON:	no thrombophilia testing and COC in all
MAIN OUTCOMES:	VTE;
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Inherited and acquired thrombophilia can put patients at higher risk of venous thromboembolism (VTE). Combined oral contraceptives (COC) may further increase risk in such patients. The currently most commonly tested inherited and acquired thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. Thrombophilia testing is usually not performed in women considering to start or continue COC. Although testing women from the general population has a low chance of finding a positive test result, the relevant question and aim of the current guideline is to assess whether thrombophilia testing and tailoring management to the test result would improve patient important outcomes. This question addresses whether testing for any hereditary thrombophilia and subsequent COC avoidance in positive women improves patient important outcomes in women who are candidates to take COC, as compared with no thrombophilia testing and no COC avoidance in all. Since no randomized controlled trials have addressed this question, we used a modeling exercise based on observational evidence for baseline risk, prevalence of thrombophilia and associated risk of events with thrombophilia, and studies with evidence for the effect of COC avoidance on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		This question is important for health policy makers.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Evidence Profile.	Desirable effect = preventing VTE. VTE would be avoided in women who are positive for thrombophilia by avoiding COC.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	See Evidence Profile.	Undesirable effect = intangible, as they fall into a wider scope than VTE. The panel considered unwanted pregnancies, labeling women as thrombophilia positive, and potential other consequences of testing.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows:** **Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(2, 1, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3)	The values of potential undesirable effects are not included here. The panel considered that there is important variability, as younger women may value a different trade-off than older women who are candidates for COC.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know		The panel selected “Don’t know” as the potential desirable effect on VTE is (very) trivial, and the magnitude of potential undesirable effects is unknown.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Intervention Costs: **Test (source)** / Approximate Cost (2005) / Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016) / **(14/12/2016) £1 = $1,27** **Full Blood Count** £2.55 £3.29 **$4,18** **Protein C** £11.67 £15.5 **$19,12** **Free Protein S** £11.67 £15.5 **$19,12** **Antithrombin** £11.67 £15.5 **$19,12** **APCR** £10.73 £13.84 **$17,58** **Factor V Leiden** £85.00 £109.65 **$141,45** **Prothrombin gene mutation** £85.00 £109.65 **$141,45** **Lupus Anticoagulant** £10.73 £13.84 **$17,58** **Antiphospholipid antibodies** £12.30 £15.87 **$20,15** **Anti Beta-2 GP1 antibody** £9.50 £12.25 **$15,81** **The potential cost of a full thrombophilia screen** £250.82, £323.56 **$410,92** Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx	The panel considered that in the USA around 20% of women of child-bearing age use COC.**(REF Andi)**

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Based on a hypothetical model of 10,000 patients, in the absence of thrombophilia screening, adverse clinical complications would be found in approximately seven women on COC at cost of £119,147. When taking effectiveness of screening into account, universal screening of patients prior to prescribing COC would only prevent three **VTE events** and was the least cost-effective strategy (ICER £200,402).(6) To prevent one fatal VTE attributable to the use of COC in women with factor V Leiden, >92,000 carriers would need to be identified and stopped from using COC. The estimated charge to prevent this one **death** would exceed $300 million. If the price of testing were discounted to 34.5% of current charges, the cost still would be between $105 million and $130 million.(7)	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(8)	The panel considered that the health system/service coverage/access to care will be the main aspect affecting health equity. USA is an example where promotion of testing that is not covered by insurance would generate inequities. I.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Research studies suggested the following regarding acceptability and barriers associated with testing and treatment: **Patients:** A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(9) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited	**Patients:** the panel agreed that acceptability can vary importantly according to patient preference. **Health care providers:** most panel members agree that testing is acceptable to health care providers, although in some thrombophilias multiple tests need to be performed and knowledge about pitfalls and interpretation of thrombophilia testing is required. **Health care payers:** testing all women considered for COC

	to short-term follow-up, or lacked methodological accuracy.(10) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers:** A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(11) **Payers:** At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	would probably not be acceptable due to the high cost.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(12) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending.(13) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(14) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(15) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(16)	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation. External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories. Testing is feasible as it is currently being done, but it may be less feasible if this required rolling out a large program to test all women considered for COC.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know

	JUDGEMENT						
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		**Varies**	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
●	○	○	○	○

CONCLUSIONS

Recommendation

In women from the general population who are considering using combined oral contraceptives (COC), the ASH guideline panel recommends not testing for any hereditary thrombophilia to guide prescription of COC (strong recommendation based on low certainty in the evidence about effects)

Remarks:

Women with risk factors for VTE, such as familial VTE and/or thrombophilia, are at higher risk of VTE. Other recommendations in this guideline address thrombophilia testing in these populations.

Justification

The panel issued a strong recommendation due to the trivial benefit in terms of VTE prevention, unknown harmful effects, and the very large costs involved in testing all women who are considered for COC.

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation.

Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

The panel suggests not to pursue further research on this topic in the general population, but to focus on potential subgroups of women at higher risk of VTE or adverse effects.

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Wu, O., Robertson, L., Twaddle, S., Lowe, G. D., Clark, P., Greaves, M., Walker, I. D., Langhorne, P., Brenkel, I., Regan, L., Greer, I.. Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. Health Technol Assess; Apr 2006.
7. Creinin, M. D., Lisman, R., Strickler, R. C.. Screening for factor V Leiden mutation before prescribing combination oral contraceptives. Fertil Steril; Oct 1999.
8. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
9. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
10. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
11. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
12. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
13. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
14. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
15. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
16. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In women from the general population, should testing for any hereditary thrombophilia and subsequent avoidance of combined oral contraceptives (COC) in women positive for thrombophilia and COC in women negative for thrombophilia compared to no thrombophilia testing and COC in all be used?

Setting:

Bibliography: See reference list and footnotes. [1,2,3,4,5,6,7,8,9,10]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
VTE (follow up: 12 months; assessed with: any first-time DVT or PE)									
10 [a,b,c,d,e]	observational studies	not serious	not serious	serious [f]	not serious	none	When testing 1,000 women from the general population for any hereditary thrombophilia and avoiding combined oral contraceptives (COC) in the 69 positives (ranging from 34 to 137), 0.96 VTE events will occur per year (ranging from 0.85 to 0.93). When not testing 1,000 women from the general population for any hereditary thrombophilia and treating all of them with COC, 1.23 VTE events will occur per year (95% CI: 1.02 to 1.51). Therefore, a thrombophilia testing strategy is associated with 69 fewer women using COC (ranging from 34 to 137) and **0.26 fewer VTE events (ranging from 0.09 to 0.65)** per 1,000 women per year compared with a no testing strategy. [g]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE, 3 studies; Prevalence, 5 studies; Risk association for thrombophilia positive versus negative, 1 systematic review; COC effect on VTE, 1 systematic review

b. Overall risk for VTE: Dinger 2016, Lidegaard 2011, Samuelsson 2004

c. Prevalence of thrombophilia in the general population: Dykes 2001, Rees 1995, Rosendaal 1998, Tait 1994, Tait 1995

d. Thrombophilia positive vs negative risk association: van Vlijmen 2016

e. Effect of COC: de Bastos 2014

f. The effect was indirectly calculated using separate studies for overall risk, thrombophilia prevalence, relative risk of thrombophilia positives vs negatives, and the effect of avoiding COC.

g. Based on the following estimates: Overall risk for VTE, 0.35 per 1,000; Prevalence of any thrombophilia, 6.85% (min 3.43 - max 13.70); Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 5.89 (95%CI: 4.21-8.23); Relative risk of first-time VTE with COC versus no COC, RR 3.5 (2.9-4.3). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

References

1. de Bastos, Marcos, Stegeman Bernardine, H., Rosendaal Frits, R., Van Hylckama Vlieg, Astrid, Helmerhorst Frans, M., Stijnen, Theo, Dekkers Olaf, M.. Combined oral contraceptives: venous thrombosis. Cochrane Database of Systematic Reviews; 2014.

2. Dinger, J., Do Minh, T., Heinemann, K.. Impact of estrogen type on cardiovascular safety of combined oral contraceptives. Contraception; 01 Oct 2016.

3. Dykes, A. C., Walker, I. D., McMahon, A. D., Islam, S. I., Tait, R. C.. A study of Protein S antigen levels in 3788 healthy volunteers: influence of age, sex and hormone use, and estimate for prevalence of deficiency state. Br J Haematol; Jun 2001.

4. Lidegaard, O., Nielsen, L. H., Skovlund, C. W., Skjeldestad, F. E., Lokkegaard, E.. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. Bmj; 2011.

5. Rees, D. C., Cox, M., Clegg, J. B.. World distribution of factor V Leiden. Lancet; Oct 28 1995.

6. Rosendaal, F. R., Doggen, C. J., Zivelin, A., Arruda, V. R., Aiach, M., Siscovick, D. S., Hillarp, A., Watzke, H. H., Bernardi, F., Cumming, A. M., Preston, F. E., Reitsma, P. H.. Geographic distribution of the 20210 G to A prothrombin variant. Thromb Haemost; Apr 1998.

7. Samuelsson, E., Hagg, S.. Incidence of venous thromboembolism in young Swedish women and possibly preventable cases among combined oral contraceptive users. Acta Obstet Gynecol Scand; Jul 2004.

8. Tait, R. C., Walker, I. D., Perry, D. J., Islam, S. I., Daly, M. E., McCall, F., Conkie, J. A., Carrell, R. W.. Prevalence of antithrombin deficiency in the healthy population. Br J Haematol; May 1994.

9. Tait, R. C., Walker, I. D., Reitsma, P. H., Islam, S. I., McCall, F., Poort, S. R., Conkie, J. A., Bertina, R. M.. Prevalence of protein C deficiency in the healthy population. Thromb Haemost; Jan 1995.

10. van Vlijmen, E. F., Wiewel-Verschueren, S., Monster, T. B., Meijer, K.. Combined oral contraceptives, thrombophilia and the risk of venous thromboembolism: a systematic review and meta-analysis. Journal of Thrombosis & Haemostasis; Jul 2016.

QUESTION

Should testing for any hereditary thrombophilia and subsequent avoidance of hormone replacement therapy (HRT) in women positive for thrombophilia and HRT in women negative for thrombophilia vs. no thrombophilia testing and HRT in all be used for women from the general population?

POPULATION:	women from the general population
INTERVENTION:	testing for any hereditary thrombophilia and subsequent avoidance of hormone replacement therapy (HRT) in women positive for thrombophilia and HRT in women negative for thrombophilia
COMPARISON:	no thrombophilia testing and HRT in all
MAIN OUTCOMES:	VTE - Estrogen alone; VTE - Combined HRT;
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Inherited and acquired thrombophilia can put patients at higher risk of venous thromboembolism (VTE). Hormone replacement therapy (HRT) may further increase risk in such patients. The currently most commonly tested inherited and acquired thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. Thrombophilia testing is usually not performed in women considering to start or continue HRT. Although testing women from the general population has a low chance of finding a positive test result, the relevant question and aim of the current guideline is to assess whether thrombophilia testing and tailoring management to the test result would improve patient important outcomes. This question addresses whether testing for any hereditary thrombophilia and subsequent HRT avoidance in positive women improves patient important outcomes in women who are candidates to take HRT, as compared with no thrombophilia testing and no HRT avoidance in all. Since no randomized controlled trials have addressed this question, we used a modeling exercise based on observational evidence for baseline risk, prevalence of thrombophilia and associated risk of events with thrombophilia, and studies with evidence for the effect of HRT avoidance on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		This questions is important for health policy makers.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Evidence Profile.	Desirable effect = preventing VTE. VTE would be avoided in women who are positive for thrombophilia by avoiding HRT.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	See Evidence Profile.	Undesirable effect: = intangible as they fall into a wider scope than VTE. The panel considered labeling as thrombophilia positive, and potential other consequences of testing.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	The effect of treating with estrogen or combined estrogen-progestin HRT came from RCTs comparing with placebo.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows:** **Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(1, 2, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3)	The values of potential undesirable effects are not included here.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know		The panel selected “Don’t know” as the potential desirable effect on VTE is (very) trivial, and the magnitude of potential undesirable effects are unknown.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Intervention Costs: <table><tr><th>Test (source)</th><th>Approximate Cost (2005)</th><th>Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016)</th><th>(14/12/2016) £1 = $1,27</th></tr><tr><td>Full Blood Count</td><td>£2.55</td><td>£3.29</td><td>$4,18</td></tr><tr><td>Protein C</td><td>£11.67</td><td>£15.5</td><td>$19,12</td></tr><tr><td>Free Protein S</td><td>£11.67</td><td>£15.5</td><td>$19,12</td></tr><tr><td>Antithrombin</td><td>£11.67</td><td>£15.5</td><td>$19,12</td></tr><tr><td>APCR</td><td>£10.73</td><td>£13.84</td><td>$17,58</td></tr><tr><td>Factor V Leiden</td><td>£85.00</td><td>£109.65</td><td>$141,45</td></tr><tr><td>Prothrombin gene mutation</td><td>£85.00</td><td>£109.65</td><td>$141,45</td></tr><tr><td>Lupus Anticoagulant</td><td>£10.73</td><td>£13.84</td><td>$17,58</td></tr><tr><td>Antiphospholipid antibodies</td><td>£12.30</td><td>£15.87</td><td>$20,15</td></tr><tr><td>Anti Beta-2 GP1 antibody</td><td>£9.50</td><td>£12.25</td><td>$15,81</td></tr><tr><td>The potential cost of a full thrombophilia screen</td><td>£250.82,</td><td>£323.56</td><td>$410,92</td></tr></table> Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Based on a hypothetical model of 10,000 patients, in the absence of thrombophilia screening, adverse clinical complications would be found in approximately 104 women on HRT at cost of £1,185,428. When taking effectiveness of screening into account, universal screening of patients prior to prescribing HRT and restricting prescription to those tested negative for thrombophilia would prevent 42 VTE events and was the most cost-effective strategy (ICER £6824). Irrespective of patient groups, selective screening based on the presence of previous personal or family history of VTE prevented fewer cases of adverse clinical complications but was more cost effective than universal screening in all four screening scenarios.(6)	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(7)	The panel considered that the health system/service coverage/access to care will be the main aspect affecting health equity. USA is an example where promotion of testing that is not covered by insurance would generate inequities. I.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies suggested the following regarding acceptability and barriers associated with testing and treatment: **Patients**: A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(8) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(9) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers:** A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(10) **Payers:** At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	**Patients:** the panel agreed that acceptability can vary importantly according to patient preference. **Health care providers:** most panel members agree that testing is acceptable to health care providers, although in some thrombophilias multiple tests need to be performed and knowledge about pitfalls and interpretation of thrombophilia testing is required. **Health care payers:** testing all women considered for COC would probably not be acceptable due to the high cost.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(11) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending.(12) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(13) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(14) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(15)	Provider "lack of awareness" of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation. External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories. Testing is feasible as it is currently being done, but it may be less feasible if this required rolling out a large program to test all women considered for HRT.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		**Varies**	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know

	JUDGEMENT						
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

In women from the general population who are considering using hormone replacement therapy (HRT), the ASH guideline panel suggests not testing for any hereditary thrombophilia to guide prescription of HRT (conditional recommendation based on low certainty in the evidence about effects)

Remarks:

Women with risk factors for VTE, such as familial VTE and/or thrombophilia, are at higher risk of VTE. Other recommendations in this guideline address thrombophilia testing in these populations.

Justification

The panel suggested against testing due to the lack of benefit, unknown harmful effects, and the large costs involved in testing all women who are considered for HRT.

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation.

Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

The panel suggests not to pursue further research on this topic in the general population, but to focus on potential subgroups at higher risk of VTE or adverse effects.

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Wu, O., Robertson, L., Twaddle, S., Lowe, G. D., Clark, P., Greaves, M., Walker, I. D., Langhorne, P., Brenkel, I., Regan, L., Greer, I.. Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. Health Technol Assess; Apr 2006.
7. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
8. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
9. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
10. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
11. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
12. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
13. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
14. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
15. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In women from the general population, should testing for any hereditary thrombophilia and subsequent avoidance of hormone replacement therapy (HRT) in women positive for thrombophilia and HRT in women negative for thrombophilia compared to no thrombophilia testing and HRT in all be used?

Setting:

Bibliography: See reference list and footnotes. [1,2,3,4,5,6,7,8,9]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
VTE - Estrogen alone (follow up: 12 months; assessed with: any first-time DVT or PE)									
9 [a,b,c,d,e]	observational studies	not serious	not serious	serious [f]	not serious	none	When testing 1,000 women from the general population for any hereditary thrombophilia and avoiding hormone replacement therapy (HRT) with estrogen alone in the 69 positives (ranging from 34 to 137), 4.15 VTE events will occur per year (ranging from 2.23 to 6.80). When not testing 1,000 women and treating all of them with estrogen only HRT, 4.44 VTE events will occur per year (95% CI: 2.24 to 8.78). Therefore, a thrombophilia testing strategy is associated with 69 fewer women treated with estrogen only HRT (ranging from 34 to 137) and **0.29 fewer VTE events (ranging from 0.01 to 1.98)** per 1,000 women per year compared with a no testing strategy. [g]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Combined HRT (follow up: 12 months; assessed with: any first-time PE or DVT)									
9 [a,b,c,d,e]	observational studies	not serious	not serious	serious [f]	not serious	none	When testing 1,000 women from the general population for any hereditary thrombophilia and avoiding combined hormone replacement therapy (HRT) in the 69 positives (ranging from 34 to 137), 7.79 VTE events will occur per year (ranging from 4.90 to 10.98). When not testing 1,000 women and treating all of them with combined HRT, 8.56 VTE events will occur per year (95% CI: 4.98 to 14.68). Therefore, a thrombophilia testing strategy is associated with 69 fewer women treated with combined HRT (ranging from 34 to 137) and **0.77 fewer VTE events (ranging from 0.08 to 3.70)** per 1,000 women per year compared with a no testing strategy. [h]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE, 1 study; Prevalence of thrombophilia in the general population, 5 studies; Risk association for thrombophilia positive versus negative, 2 studies; HRT effect, 1 SR

b. Overall risk for VTE: Burwen 2017

c. Prevalence of thrombophilia in the general population: Dykes 2001, Rees 1995, Rosendaal 1998, Tait 1994, Tait 1995

d. Thrombophilia positive vs negative risk association: Cushman 2004, Cushman 2018

e. Effect of Estrogen therapy: Marjoribanks 2017

f. The effect was indirectly calculated using separate studies for thrombophilia prevalence, relative risk of thrombophilia positives vs negatives, and the effect of avoiding HRT.

g. Based on the following estimates: Overall risk for VTE recurrence, 2 per 1,000; Prevalence of any thrombophilia, 6.85% (min 3.43 - max 13.70); Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 1.8 (95%CI: 0.8-2.6); Relative risk of VTE recurrence with estrogen only HRT versus no HRT, RR 2.22 (1.12-4.39). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

h. Based on the following estimates: Overall risk for VTE recurrence, 2 per 1,000; Prevalence of any thrombophilia, 6.85% (min 3.43 - max 13.70); Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 1.8 (95%CI: 0.8-2.6); Relative risk of VTE recurrence with combined HRT versus no HRT, RR 4.28 (2.49-7.34). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

References

1. Burwen, D. R., Wu, C., Cirillo, D., Rossouw, J. E., Margolis, K. L., Limacher, M., Wallace, R., Allison, M., Eaton, C. B., Safford, M., Freiberg, M.. Venous thromboembolism incidence, recurrence, and mortality based on Women's Health Initiative data and Medicare claims. Thromb Res; Feb 2017.

2. Cushman, M., Kuller, L. H., Prentice, R., Rodabough, R. J., Psaty, B. M., Stafford, R. S., Sidney, S., Rosendaal, F. R., Women's Health Initiative, Investigators. Estrogen plus progestin and risk of venous thrombosis. Jama; Oct 6 2004.

3. Cushman, M., Larson, J. C., Rosendaal, F. R., Heckbert, S. R., Curb, J. D., Phillips, L. S., Baird, A. E., Eaton, C. B., Stafford, R. S.. Biomarkers, menopausal hormone therapy and risk of venous thrombosis: The Women's Health Initiative. Res Pract Thromb Haemost; Apr 2018.

4. Dykes, A. C., Walker, I. D., McMahon, A. D., Islam, S. I., Tait, R. C.. A study of Protein S antigen levels in 3788 healthy volunteers: influence of age, sex and hormone use, and estimate for prevalence of deficiency state. Br J Haematol; Jun 2001.

5. Marjoribanks, Jane, Farquhar, Cindy, Roberts, Helen, Lethaby, Anne, Lee, Jasmine. Long-term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database of Systematic Reviews; 2017.

6. Rees, D. C., Cox, M., Clegg, J. B.. World distribution of factor V Leiden. Lancet; Oct 28 1995.

7. Rosendaal, F. R., Doggen, C. J., Zivelin, A., Arruda, V. R., Aiach, M., Siscovick, D. S., Hillarp, A., Watzke, H. H., Bernardi, F., Cumming, A. M., Preston, F. E., Reitsma, P. H.. Geographic distribution of the 20210 G to A prothrombin variant. Thromb Haemost; Apr 1998.

8. Tait, R. C., Walker, I. D., Perry, D. J., Islam, S. I., Daly, M. E., McCall, F., Conkie, J. A., Carrell, R. W.. Prevalence of antithrombin deficiency in the healthy population. Br J Haematol; May 1994.

9. Tait, R. C., Walker, I. D., Reitsma, P. H., Islam, S. I., McCall, F., Poort, S. R., Conkie, J. A., Bertina, R. M.. Prevalence of protein C deficiency in the healthy population. Thromb Haemost; Jan 1995.

QUESTION

Should thrombophilia testing and subsequent avoidance of combined oral contraceptives (COC) in women positive for thrombophilia and COC in women negative for thrombophilia vs. no thrombophilia testing and COC in all be used for asymptomatic women with a family history of VTE (first or second degree) and unknown thrombophilia in the family?

POPULATION:	asymptomatic women with a family history of VTE (first or second degree) and unknown thrombophilia in the family
INTERVENTION:	thrombophilia testing and subsequent avoidance of combined oral contraceptives (COC) in women positive for thrombophilia and COC in women negative for thrombophilia
COMPARISON:	no thrombophilia testing and COC in all
MAIN OUTCOMES:	VTE - First-degree relatives;
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Inherited and acquired thrombophilia can put patients at higher risk of venous thromboembolism (VTE), especially if there also is a family history of VTE. Combined oral contraceptives (COC) may further increase risk in such patients. The currently most commonly tested inherited and acquired thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. Thrombophilia testing is sometimes considered in women considering to start or continue COC and who have a family history of VTE. Although testing these women has a reasonable chance of finding a positive test result (in first-degree relatives, 50% of the prevalence of VTE patients), the relevant question and aim of the current guideline is to assess whether thrombophilia testing and tailoring management to the test result would improve patient important outcomes. This question addresses whether testing for thrombophilia and subsequent COC avoidance in positive women improves patient important outcomes in women who are candidates to take COC and who have a family history of VTE, as compared with no thrombophilia testing and no COC avoidance in all. Since no randomized controlled trials have addressed this question, we used a modeling exercise based on observational evidence for baseline risk, prevalence of thrombophilia and associated risk of events with thrombophilia, and studies with evidence for the effect of COC avoidance on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		Considering that this population has two important risk factors for VTE, i.e. family history of VTE and using COC, detecting thrombophilia as a third risk factor may influence management decisions.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Evidence Profile.	Desirable effect = preventing VTE. VTE would be avoided in women who are positive for thrombophilia by avoiding COC.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	See Evidence Profile.	Undesirable effect = intangible as they fall into a wider scope than VTE. The panel considered unwanted pregnancies, delaying COC, labeling as thrombophilia positive, and potential other consequences of testing.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows:** **Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(2, 1, 3, 4, 5) **Deep vein thrombosis patients' own current health**: 0.95 (Time trade off)(3)	The values of potential undesirable effects are not included here. The panel considered that there is important variability, as younger women may value a different trade-off than older women who are candidates for COC.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know		The panel selected “Don’t know” as the potential desirable effect on VTE is (very) trivial, and the magnitude of potential undesirable effects are unknown.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		The panel considered that the costs would be much lower than testing in the general population, but not negligible as many women will have a first- or second-degree relative with a history of VTE.

Intervention Costs:

Test (source)	Approximate Cost (2005)	Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016)	(14/12/2016) £1 = $1,27
Full Blood Count	£2.55	£3.29	$4,18
Protein C	£11.67	£15.5	$19,12
Free Protein S	£11.67	£15.5	$19,12
Antithrombin	£11.67	£15.5	$19,12
APCR	£10.73	£13.84	$17,58
Factor V Leiden	£85.00	£109.65	$141,45
Prothrombin gene mutation	£85.00	£109.65	$141,45
Lupus Anticoagulant	£10.73	£13.84	$17,58
Antiphospholipid antibodies	£12.30	£15.87	$20,15
Anti Beta-2 GP1 antibody	£9.50	£12.25	$15,81
The potential cost of a full thrombophilia screen	£250.82,	£323.56	$410,92

Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Based on a hypothetical model of 10,000 patients, in the absence of thrombophilia screening, adverse clinical complications would be found in approximately seven women on COC at cost of £119,147. When taking effectiveness of screening into account, universal screening of patients prior to prescribing COC would only prevent three VTE events and was the least cost-effective strategy (ICER £200,402). Irrespective of patient groups, selective screening based on the presence of previous personal or family history of VTE prevented fewer cases of adverse clinical complications but was more cost effective than universal screening in all four screening scenarios.(6) Current FVL and PT testing practices for COC in women with a familial history of VTE generate an incremental cost-effectiveness ratio of €72,412/QALY, which is well above the acceptable threshold of cost-effectiveness of €40,000-	

	50,000/QALY.(7)	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(8)	The panel considered that the health system/service coverage/access to care will be the main aspect affecting health equity. USA is an example where promotion of testing that is not covered by insurance would generate inequities. I.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Research studies suggested the following regarding acceptability and barriers associated with testing and treatment: **Patients:** A survey was conducted in members of a large family with heritable protein C deficiency. For those who had not been tested before, using a 7-point scale (1 - not at all interested; 7 extremely interested), the mean score for interest in testing interest was 4.6 (standard deviation 2.4). Patients in general were willing to take the test for thrombophilia.(9) A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(10) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(11) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers:** A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(12) **Payers:** At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	**Patients:** the panel agreed that acceptability can vary importantly according to patient preference. **Health care providers**: most panel members agree that testing is acceptable to health care providers, although in some thrombophilias multiple tests need to be performed and knowledge about pitfalls and interpretation of thrombophilia testing is required. **Health care payers:** testing all women with family history of VTE considered for COC would probably not be acceptable due to the cost.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(13) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending.(14) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(15) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(16) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(17)	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation. External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories. Testing is feasible as it is currently being done, but it may be less feasible if this required rolling out a program to test all women considered for COC who have a family history of VTE.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		**Varies**	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the	Probably favors the intervention	Favors the intervention	Varies	No included studies

	JUDGEMENT						
			comparison				
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

In women with a family history of VTE and unknown thrombophilia in the family who are considering using combined oral contraceptives (COC), the ASH guideline panel suggests not testing for any hereditary thrombophilia to guide prescription of COC (conditional recommendation based on very low certainty in the evidence about effects)

Remarks:

Women with a family history of VTE and a known thrombophilia in the family are at higher risk for testing positive for thrombophilia and are therefore at higher risk for VTE. Another recommendation in this guideline addresses thrombophilia testing in this population.

Justification

The considered the trivial benefit in terms of VTE prevention, unknown harmful effects, and the moderate costs involved in testing women who are considered for COC and who have a family history of VTE.

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation.

Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

No research priorities.

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Wu, O., Robertson, L., Twaddle, S., Lowe, G. D., Clark, P., Greaves, M., Walker, I. D., Langhorne, P., Brenkel, I., Regan, L., Greer, I.. Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. Health Technol Assess; Apr 2006.
7. Compagni, A., Melegaro, A., Tarricone, R.. Genetic screening for the predisposition to venous thromboembolism: a cost-utility analysis of clinical practice in the Italian health care system. Value Health; Sep-Oct 2013.
8. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
9. van Korlaar, I. M., Vossen, C. Y., Rosendaal, F. R., Bovill, E. G., Naud, S., Cameron, L. D., Kaptein, A. A.. Attitudes toward genetic testing for thrombophilia in asymptomatic members of a large family with heritable protein C deficiency. Journal of Thrombosis & Haemostasis; Nov 2005.
10. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
11. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
12. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
13. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
14. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
15. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
16. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
17. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In asymptomatic women with a family history of VTE (first or second degree) and unknown thrombophilia in the family, should testing for any hereditary thrombophilia and subsequent avoidance of combined oral contraceptives (COC) in women positive for thrombophilia and COC in women negative for thrombophilia compared to no thrombophilia testing and COC in all be used?

Setting:

Bibliography: See reference list and footnotes. [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
VTE - First-degree relatives (follow up: 12 months; assessed with: any first-time DVT or PE)									
36 [a,b,c,d,e,f]	observational studies	not serious	not serious	serious [g]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and unknown thrombophilia in the family for any hereditary thrombophilia and avoiding combined oral contraceptives (COC) in the 142 positives (ranging from 99 to 201), 3.03 VTE events will occur per year (ranging from 1.93 to 5.10). When not testing 1,000 women and treating all of them with COC, 4.20 VTE events will occur per year (95% CI: 3.48 to 5.10). Therefore, a thrombophilia testing strategy is associated with 142 fewer women treated with COC (ranging from 99 to 201) and **1.17 fewer VTE events (ranging from 0.06 to 1.55)** per 1,000 women per year compared with a no testing strategy. [h]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE, 1 study; Prevalence, 20 studies; Risk association for thrombophilia positive versus negative, 14 studies; COC effect, 1 systematic review

b. Overall risk for VTE: Couturaud 2014

c. Thrombophilia prevalence, used for calculation: Bezemer 2009, Cebi 2009, Di Minno 2014, Garcia-Fuster 2005, Heit 2010, Kearon 1999, Kearon 2018, Lim 2017, Mello 2010, Meyer 2015, Olie 2011, Palareti 2003, Prandoni 2007, Roldan 2009, Rossi 2008, Santamaria 2005, Schattner 1997, Schulman 2006, Sundquist 2015, Weingarz 2015

d. Prevalence of specific thrombophilia types, used to verify calculation estimate: Ahmad 2016, Ahmad 2016, Ahmad 2017, Asim 2017, Baarslag 2004, Baglin 2003, Brouwer 2009, Bruwer 2016, Christiansen 2005, De Stefano 1999, De Stefano 2006, Eichinger 1999, Eichinger 2002, Eischer 2017, Gonzalez-Porras 2006, Heijboer 1990, Hirmerova 2014, Hoibraaten 2000, Kearon 2008, Laczkovics 2007, Lee 2017, Lijfering 2010, Lindmarker 1999, Marcucci 2003, Mateo 1997, Miles 2001, Ridker 1995, Rodger 2008, Roupie 2016, Rupa-Matysek 2014, Simioni 2000, Sonnevi 2013, Strandberg 2007, Sveinsdottir 2012, The Procare group 2003, Wahlander 2006

e. Thrombophilia positive vs negative risk association: Bank 2004, Brouwer 2005, Brouwer 2006, Cohen 2012, Coppens 2006, Couturaud 2006, Faioni 1999, Lensen 2001, Mahmoodi 2010, Martinelli 1998, Martinelli 2000, Middeldorp 1998, Simioni 1999, Simioni 2002

f. Effect of COC: de Bastos 2014

g. The effect was indirectly calculated using separate studies for overall risk, thrombophilia prevalence, relative risk of thrombophilia positives vs negatives, and the effect of avoiding COC.

h. Based on the following estimates: Overall risk for VTE, 1.2 per 1,000; Prevalence of any thrombophilia, 14.2% (min 9.9 - max 20.1); Relative risk for VTE in thrombophilia positives versus negatives, RR 3.87 (95%CI: 2.18-8.40); Relative risk of VTE with COC treatment versus no COC, RR 3.5 (2.9-4.3). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

References

1. Ahmad, A., Sundquist, K., Zoller, B., Dahlback, B., Svensson, P. J., Sundquist, J., Memon, A. A.. Identification of polymorphisms in Apolipoprotein M gene and their relationship with risk of recurrent venous thromboembolism. Thromb Haemost; Aug 30 2016.

2. Asim, M., Al-Thani, H., El-Menyar, A.. Recurrent Deep Vein Thrombosis After the First Venous Thromboembolism Event: A Single-Institution Experience. Med Sci Monit; May 20 2017.

3. Baarslag, H. J., Koopman, M. M., Hutten, B. A., Linthorst Homan, M. W., Buller, H. R., Reekers, J. A., van Beek, E. J.. Long-term follow-up of patients with suspected deep vein thrombosis of the upper extremity: survival, risk factors and post-thrombotic syndrome. Eur J Intern Med; Dec 2004.

4. Baglin, T., Luddington, R., Brown, K., Baglin, C.. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet; Aug 16 2003.

5. Bank, I., Libourel, E. J., Middeldorp, S., Van Pampus, E. C., Koopman, M. M., Hamulyak, K., Prins, M. H., Van Der Meer, J., Buller, H. R.. Prothrombin 20210A mutation: a mild risk factor for venous thromboembolism but not for arterial thrombotic disease and pregnancy-related complications in a family study. Archives of Internal Medicine; Sep 27 2004.

6. Bezemer, I. D., van der Meer, F. J., Eikenboom, J. C., Rosendaal, F. R., Doggen, C. J.. The value of family history as a risk indicator for venous thrombosis. Archives of Internal Medicine; Mar 23 2009.

7. Brouwer, J. L., Lijfering, W. M., Ten Kate, M. K., Kluin-Nelemans, H. C., Veeger, N. J., van der Meer, J.. High long-term absolute risk of recurrent venous thromboembolism in patients with hereditary deficiencies of protein S, protein C or antithrombin. Thromb Haemost; Jan 2009.

8. Brouwer, J. L., Veeger, N. J., Kluin-Nelemans, H. C., van der Meer, J.. The pathogenesis of venous thromboembolism: evidence for multiple interrelated causes. Ann Intern Med; Dec 5 2006.

9. Brouwer, J. L., Veeger, N. J., van der Schaaf, W., Kluin-Nelemans, H. C., van der Meer, J.. Difference in absolute risk of venous and arterial thrombosis between familial protein S deficiency type I and type III. Results from a family cohort study to assess the clinical impact of a laboratory test-based classification. Br J Haematol; Mar 2005.

10. Bruwer, G., Limperger, V., Kenet, G., Klostermeier, U. C., Shneyder, M., Degenhardt, F., Finckh, U., Heller, C., Holzhauer, S., Trappe, R., Kentouche, K., Knoefler, R., Kurnik, K., Krumpel, A., Lauten, M., Manner, D., Mesters, R., Junker, R., Nowak-Gottl, U.. Impact of high risk thrombophilia status on recurrence among children and adults with VTE: An observational multicenter cohort study. Blood Cells Mol Dis; Nov 2016.

11. Cebi, N., Tanriverdi, S.. Aetiology of deep vein thrombosis in 63 turkish patients. Turkish Journal of Medical Sciences; April 2009.

12. Christiansen, S. C., Cannegieter, S. C., Koster, T., Vandenbroucke, J. P., Rosendaal, F. R.. Thrombophilia, clinical factors, and recurrent venous thrombotic events. Jama; May 18 2005.

13. Cohen, W., Castelli, C., Alessi, M. C., Aillaud, M. F., Bouvet, S., Saut, N., Brunet, D., Barthet, M. C., Tregouet, D. A., Lavigne, G., Morange, P. E.. ABO blood group and von Willebrand factor levels partially explained the incomplete penetrance of congenital thrombophilia. Arterioscler Thromb Vasc Biol; Aug 2012.

14. Coppens, M., van de Poel, M. H., Bank, I., Hamulyak, K., van der Meer, J., Veeger, N. J., Prins, M. H., Buller, H. R., Middeldorp, S.. A prospective cohort study on the absolute incidence of venous thromboembolism and arterial cardiovascular disease in asymptomatic carriers of the prothrombin 20210A mutation. Blood; Oct 15 2006.

15. Couturaud, F., Leroyer, C., Tromeur, C., Julian, J. A., Kahn, S. R., Ginsberg, J. S., Wells, P. S., Douketis, J. D., Mottier, D., Kearon, C.. Factors that predict thrombosis in relatives of patients with venous thromboembolism. Blood; Sep 25 2014.

16. de Bastos, Marcos, Stegeman Bernardine, H., Rosendaal Frits, R., Van Hylckama Vlieg, Astrid, Helmerhorst Frans, M., Stijnen, Theo, Dekkers Olaf, M.. Combined oral contraceptives: venous thrombosis. Cochrane Database of Systematic Reviews; 2014.

17. De Stefano, V., Martinelli, I., Mannucci, P. M., Paciaroni, K., Chiusolo, P., Casorelli, I., Rossi, E., Leone, G.. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med; Sep 9 1999.

18. De Stefano, V., Simioni, P., Rossi, E., Tormene, D., Za, T., Pagnan, A., Leone, G.. The risk of recurrent venous thromboembolism in patients with inherited deficiency of natural anticoagulants antithrombin, protein C and protein S. Haematologica; May 2006.

19. Di Minno, M. N., Dentali, F., Lupoli, R., Ageno, W.. Mild antithrombin deficiency and risk of recurrent venous thromboembolism: a prospective cohort study. Circulation; Jan 28 2014.

20. Eichinger, S., Minar, E., Hirschl, M., Bialonczyk, C., Stain, M., Mannhalter, C., Stumpflen, A., Schneider, B., Lechner, K., Kyrle, P. A.. The risk of early recurrent venous thromboembolism after oral anticoagulant therapy in patients with the G20210A transition in the prothrombin gene. Thromb Haemost; Jan 1999.

21. Eichinger, S., Weltermann, A., Mannhalter, C., Minar, E., Bialonczyk, C., Hirschl, M., Schonauer, V., Lechner, K., Kyrle, P. A.. The risk of recurrent venous thromboembolism in heterozygous carriers of factor V Leiden and a first spontaneous venous thromboembolism. Archives of Internal Medicine; Nov 11 2002.

22. Eischer, L., Kammer, M., Traby, L., Kyrle, P. A., Eichinger, S.. Risk of cancer after anticoagulation in patients with unprovoked venous thromboembolism: an observational cohort study. Journal of Thrombosis and Haemostasis; July 2017.

23. Faioni, E. M., Franchi, F., Bucciarelli, P., Margaglione, M., De Stefano, V., Castaman, G., Finazzi, G., Mannucci, P. M.. Coinheritance of the HR2 haplotype in the factor V gene confers an increased risk of venous thromboembolism to carriers of factor V R506Q (factor V Leiden). Blood; Nov 1 1999.

24. Garcia-Fuster, M. J., Forner, M. J., Fernandez, C., Gil, J., Vaya, A., Maldonado, L.. Long-term prospective study of recurrent venous thromboembolism in patients younger than 50 years. Pathophysiol Haemost Thromb; 2005.

25. Gonzalez-Porras, J. R., Garcia-Sanz, R., Alberca, I., Lopez, M. L., Balanzategui, A., Gutierrez, O., Lozano, F., San Miguel, J.. Risk of recurrent venous thrombosis in patients with G20210A mutation in the prothrombin gene or factor V Leiden mutation. Blood Coagul Fibrinolysis; Jan 2006.

26. Group, The,Procare. Is recurrent venous thromboembolism more frequent in homozygous patients for the factor V Leiden mutation than in heterozygous patients?. Blood Coagulation and Fibrinolysis; September 2003.

27. Heijboer, H., Brandjes, D. P., Buller, H. R., Sturk, A., ten Cate, J. W.. Deficiencies of coagulation-inhibiting and fibrinolytic proteins in outpatients with deep-vein thrombosis. N Engl J Med; Nov 29 1990.

28. Heit, J. A., Beckman, M. G., Bockenstedt, P. L., Grant, A. M., Key, N. S., Kulkarni, R., Manco-Johnson, M. J., Moll, S., Ortel, T. L., Philipp, C. S., Thrombosis, C.,D.,C., Hemostasis Centers, Research, Prevention, Network. Comparison of characteristics from White- and Black-Americans with venous thromboembolism: a cross-sectional study. Am J Hematol; Jul 2010.

29. Hirmerova, J., Seidlerova, J., Subrt, I.. The association of factor V Leiden with various clinical patterns of venous thromboembolism-the factor V Leiden paradox. Qjm; Sep 2014.

30. Hoibraaten, E., Qvigstad, E., Arnesen, H., Larsen, S., Wickstrom, E., Sandset, P. M.. Increased risk of recurrent venous thromboembolism during hormone replacement therapy--results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). Thromb Haemost; Dec 2000.

31. Kearon, C., Gent, M., Hirsh, J., Weitz, J., Kovacs, M. J., Anderson, D. R., Turpie, A. G., Green, D., Ginsberg, J. S., Wells, P., MacKinnon, B., Julian, J. A.. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med; Mar 25 1999.

32. Kearon, C., Julian, J. A., Kovacs, M. J., Anderson, D. R., Wells, P., Mackinnon, B., Weitz, J. I., Crowther, M. A., Dolan, S., Turpie, A. G., Geerts, W., Solymoss, S., van Nguyen, P., Demers, C., Kahn, S. R., Kassis, J., Rodger, M., Hambleton, J., Gent, M., Ginsberg, J. S., Investigators, Elate. Influence of thrombophilia on risk of recurrent venous thromboembolism while on warfarin: results from a randomized trial. Blood; Dec 1 2008.

33. Kearon, C., Parpia, S., Spencer, F. A., Baglin, T., Stevens, S. M., Bauer, K. A., Lentz, S. R., Kessler, C. M., Douketis, J. D., Moll, S., Kaatz, S., Schulman, S., Connors, J. M., Ginsberg, J. S., Spadafora, L., Bhagirath, V., Liaw, P. C., Weitz, J. I., Julian, J. A.. Antiphospholipid antibodies and recurrent thrombosis after a first unprovoked venous thromboembolism. Blood; May 10 2018.

34. Laczkovics, C., Grafenhofer, H., Kaider, A., Quehenberger, P., Simanek, R., Mannhalter, C., Lechner, K., Pabinger, I.. Risk of recurrence after a first venous thromboembolic event in young women. Haematologica; Sep 2007.

35. Lee, S. Y., Kim, E. K., Kim, M. S., Shin, S. H., Chang, H., Jang, S. Y., Kim, H. J., Kim, D. K.. The prevalence and clinical manifestation of hereditary thrombophilia in Korean patients with unprovoked venous thromboembolisms. PLoS ONE [Electronic Resource]; 2017.

36. Lensen, R., Bertina, R. M., Vandenbroucke, J. P., Rosendaal, F. R.. High factor VIII levels contribute to the thrombotic risk in families with factor V Leiden. Br J Haematol; Aug 2001.

37. Lijfering, W. M., Middeldorp, S., Veeger, N. J., Hamulyak, K., Prins, M. H., Buller, H. R., van der Meer, J.. Risk of recurrent venous thrombosis in homozygous carriers and double heterozygous carriers of factor V Leiden and prothrombin G20210A. Circulation; Apr 20 2010.

38. Lim, H. Y., Chua, C. C., Tacey, M., Sleeman, M., Donnan, G., Nandurkar, H., Ho, P.. Venous thromboembolism management in Northeast Melbourne: how does it compare to international guidelines and data?. Intern Med J; Sep 2017.

39. Lindmarker, P., Schulman, S., Sten-Linder, M., Wiman, B., Egberg, N., Johnsson, H.. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. DURAC Trial Study Group. Duration of Anticoagulation. Thromb Haemost; May 1999.

40. Mahmoodi, B. K., Brouwer, J. L., Ten Kate, M. K., Lijfering, W. M., Veeger, N. J., Mulder, A. B., Kluin-Nelemans, H. C., Van Der Meer, J.. A prospective cohort study on the absolute risks of venous thromboembolism and predictive value of screening asymptomatic relatives of patients with hereditary deficiencies of protein S, protein C or antithrombin. Journal of Thrombosis & Haemostasis; Jun 2010.

41. Marcucci, R., Liotta, A. A., Cellai, A. P., Rogolino, A., Gori, A. M., Giusti, B., Poli, D., Fedi, S., Abbate, R., Prisco, D.. Increased plasma levels of lipoprotein(a) and the risk of idiopathic and recurrent venous thromboembolism. Am J Med; Dec 1 2003.

42. Martinelli, I., Bucciarelli, P., Margaglione, M., De Stefano, V., Castaman, G., Mannucci, P. M.. The risk of venous thromboembolism in family members with mutations in the genes of factor V or prothrombin or both. Br J Haematol; Dec 2000.

43. Martinelli, I., Mannucci, P. M., De Stefano, V., Taioli, E., Rossi, V., Crosti, F., Paciaroni, K., Leone, G., Faioni, E. M.. Different risks of thrombosis in four coagulation defects associated with inherited thrombophilia: a study of 150 families. Blood; Oct 1 1998.

44. Mateo, J., Oliver, A., Borrell, M., Sala, N., Fontcuberta, J.. Laboratory evaluation and clinical characteristics of 2,132 consecutive unselected patients with venous thromboembolism--results of the Spanish Multicentric Study on Thrombophilia (EMET-Study). Thromb Haemost; Mar 1997.

45. Mello, T. B., Orsi, F. L., Montalvao, S. A., Ozelo, M. C., de Paula, E. V., Annichinno-Bizzachi, J. M.. Long-term prospective study of recurrent venous thromboembolism in a Hispanic population. Blood Coagul Fibrinolysis; Oct 2010.

46. Meyer, M. R., Witt, D. M., Delate, T., Johnson, S. G., Fang, M., Go, A., Clark, N. P.. Thrombophilia testing patterns amongst patients with acute venous thromboembolism. Thromb Res; Dec 2015.

47. Middeldorp, S., Henkens, C. M., Koopman, M. M., van Pampus, E. C., Hamulyak, K., van der Meer, J., Prins, M. H., Buller, H. R.. The incidence of venous thromboembolism in family members of patients with factor V Leiden mutation and venous thrombosis. Ann Intern Med; Jan 1 1998.

48. Miles, J. S., Miletich, J. P., Goldhaber, S. Z., Hennekens, C. H., Ridker, P. M.. G20210A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. J Am Coll Cardiol; Jan 2001.

49. Olie, V., Plu-Bureau, G., Conard, J., Horellou, M. H., Canonico, M., Scarabin, P. Y.. Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. Menopause; May 2011.

50. Palareti, G., Legnani, C., Cosmi, B., Valdre, L., Lunghi, B., Bernardi, F., Coccheri, S.. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation; Jul 22 2003.

51. Prandoni, P., Noventa, F., Ghirarduzzi, A., Pengo, V., Bernardi, E., Pesavento, R., Iotti, M., Tormene, D., Simioni, P., Pagnan, A.. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica; Feb 2007.

52. Ridker, P. M., Miletich, J. P., Stampfer, M. J., Goldhaber, S. Z., Lindpaintner, K., Hennekens, C. H.. Factor V Leiden and risks of recurrent idiopathic venous thromboembolism. Circulation; Nov 15 1995.

53. Rodger, M. A., Kahn, S. R., Wells, P. S., Anderson, D. A., Chagnon, I., Le Gal, G., Solymoss, S., Crowther, M., Perrier, A., White, R., Vickars, L., Ramsay, T., Betancourt, M. T., Kovacs, M. J.. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. Cmaj; Aug 26 2008.

54. Roldan, V., Lecumberri, R., Munoz-Torrero, J. F., Vicente, V., Rocha, E., Brenner, B., Monreal, M., Investigators, Riete. Thrombophilia testing in patients with venous thromboembolism. Findings from the RIETE registry. Thromb Res; Jun 2009.

55. Rossi, E., Za, T., Ciminello, A., Leone, G., De Stefano, V.. The risk of symptomatic pulmonary embolism due to proximal deep venous thrombosis differs in patients with different types of inherited thrombophilia. Thromb Haemost; Jun 2008.

56. Roupie, A. L., Dossier, A., Goulenok, T., Perozziello, A., Papo, T., Sacre, K.. First venous thromboembolism in admitted patients younger than 50years old. Eur J Intern Med; Oct 2016.

57. Rupa-Matysek, J., Gil, L., Wojtasinska, E., Ciepluch, K., Lewandowska, M., Komarnicki, M.. The relationship between mean platelet volume and thrombosis recurrence in patients diagnosed with antiphospholipid syndrome. Rheumatol Int; Nov 2014.

58. Santamaria, M. G., Agnelli, G., Taliani, M. R., Prandoni, P., Moia, M., Bazzan, M., Guazzaloca, G., Ageno, W., Bertoldi, A., Silingardi, M., Tomasi, C., Ambrosio, G. B., Warfarin Optimal Duration Italian Trial, Investigators. Thrombophilic abnormalities and recurrence of venous thromboembolism in patients treated with standardized anticoagulant treatment. Thromb Res; 2005.

59. Schattner, A., Kasher, I., Berrebi, A.. Causes and outcome of deep-vein thrombosis in otherwise-healthy patients under 50 years. Qjm; Apr 1997.

60. Schulman, S., Lindmarker, P., Holmstrom, M., Larfars, G., Carlsson, A., Nicol, P., Svensson, E., Ljungberg, B., Viering, S., Nordlander, S., Leijd, B., Jahed, K., Hjorth, M., Linder, O., Beckman, M.. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. Journal of Thrombosis & Haemostasis; Apr 2006.

61. Simioni, P., Prandoni, P., Lensing, A. W., Manfrin, D., Tormene, D., Gavasso, S., Girolami, B., Sardella, C., Prins, M., Girolami, A.. Risk for subsequent venous thromboembolic complications in carriers of the prothrombin or the factor V gene mutation with a first episode of deep-vein thrombosis. Blood; Nov 15 2000.

62. Simioni, P., Sanson, B. J., Prandoni, P., Tormene, D., Friederich, P. W., Girolami, B., Gavasso, S., Huisman, M. V., Buller, H. R., Wouter ten Cate, J., Girolami, A., Prins, M. H.. Incidence of venous thromboembolism in families with inherited thrombophilia. Thromb Haemost; Feb 1999.

63. Simioni, P., Tormene, D., Prandoni, P., Zerbinati, P., Gavasso, S., Cefalo, P., Girolami, A.. Incidence of venous thromboembolism in asymptomatic family members who are carriers of factor V Leiden: a prospective cohort study. Blood; Mar 15 2002.

64. Sonnevi, K., Tchaikovski, S. N., Holmstrom, M., Antovic, J. P., Bremme, K., Rosing, J., Larfars, G.. Obesity and thrombin-generation profiles in women with venous thromboembolism. Blood Coagul Fibrinolysis; Jul 2013.

65. Strandberg, K., Svensson, P. J., Ohlin, A. K.. Venous thromboembolism in carriers of the Factor V Leiden mutation and in patients without known thrombophilic risk factor; prediction of recurrence and APC-PCI complex concentration and/or soluble thrombomodulin antigen and activity. Thromb Res; 2007.

66. Sundquist, K., Sundquist, J., Svensson, P. J., Zoller, B., Memon, A. A.. Role of family history of venous thromboembolism and thrombophilia as predictors of recurrence: a prospective follow-up study. Journal of Thrombosis & Haemostasis; Dec 2015.

67. Sveinsdottir, S. V., Saemundsson, Y., Isma, N., Gottsater, A., Svensson, P. J.. Evaluation of recurrent venous thromboembolism in patients with Factor V Leiden mutation in heterozygous form. Thromb Res; Sep 2012.

68. Wahlander, K., Eriksson, H., Lundstrom, T., Billing Clason, S., Wall, U., Nystrom, P., Wessman, P., Schulman, S., Investigators, Thrive,Iii. Risk of recurrent venous thromboembolism or bleeding in relation to thrombophilic risk factors in patients receiving ximelagatran or placebo for long-term secondary prevention of venous thromboembolism. Br J Haematol; Apr 2006.

69. Weingarz, L., Schindewolf, M., Schwonberg, J., Hecking, C., Wolf, Z., Erbe, M., Lindhoff-Last, E., Linnemann, B.. Thrombophilia and risk of VTE recurrence according to the age at the time of first VTE manifestation. Vasa; Jul 2015.

QUESTION

Should testing for any hereditary thrombophilia and subsequent avoidance of hormone replacement therapy (HRT) in women positive for thrombophilia and HRT in women negative for thrombophilia vs. no thrombophilia testing and HRT in all be used for asymptomatic women with a family history of VTE (first or second degree) and unknown thrombophilia in the family?

POPULATION:	asymptomatic women with a family history of VTE (first or second degree) and unknown thrombophilia in the family
INTERVENTION:	testing for any hereditary thrombophilia and subsequent avoidance of hormone replacement therapy (HRT) in women positive for thrombophilia and HRT in women negative for thrombophilia
COMPARISON:	no thrombophilia testing and HRT in all
MAIN OUTCOMES:	VTE - Estrogen alone HRT - First-degree relatives; VTE - Combined HRT - First-degree relatives;
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Inherited and acquired thrombophilia can put patients at higher risk of venous thromboembolism (VTE), especially if there also is a family history of VTE. Hormone replacement therapy may further increase risk in such patients. The currently most commonly tested inherited and acquired thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. Thrombophilia testing is sometimes considered in women considering to start or continue HRT and who have a family history of VTE. Although testing these women has a reasonable chance of finding a positive test result (in first-degree relatives, 50% of the prevalence of VTE patients), the relevant question and aim of the current guideline is to assess whether thrombophilia testing and tailoring management to the test result would improve patient important outcomes. This question addresses whether testing for thrombophilia and subsequent HRT avoidance in positive women improves patient important outcomes in women who are candidates to take HRT and who have a family history of VTE, as compared with no thrombophilia testing and no HRT avoidance in all. Since no randomized controlled trials have addressed this question, we used a modeling exercise based on observational evidence for baseline risk, prevalence of thrombophilia and associated risk of events with thrombophilia, and studies with evidence for the effect of HRT avoidance on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		Considering that this population has two important risk factors for VTE, i.e. family history of VTE and using HRT, detecting thrombophilia as a third risk factor may influence management decisions.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Evidence Profile.	Desirable effect = preventing VTE. VTE would be avoided in women who are positive for thrombophilia by avoiding HRT.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	See Evidence Profile.	Undesirable effect = intangible as they fall into a wider scope than VTE. The panel considered labeling as thrombophilia positive, and potential other consequences of testing.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	The effect of treating with estrogen or combined estrogen-progestin therapy came from RCTs comparing with placebo.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows:** **Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(2, 1, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3)	The values of potential undesirable effects are not included here.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know		The panel selected “Don’t know” as the potential desirable effect on VTE is trivial, and the magnitude of potential undesirable effects are unknown.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		The panel considered that the costs would be much lower than testing in the general population, but not negligible as many women will have a first- or second-degree relative with a history of VTE.

Intervention Costs:

Test (source)	Approximate Cost (2005)	Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016)	(14/12/2016) £1 = $1,27
Full Blood Count	£2.55	£3.29	$4,18
Protein C	£11.67	£15.5	$19,12
Free Protein S	£11.67	£15.5	$19,12
Antithrombin	£11.67	£15.5	$19,12
APCR	£10.73	£13.84	$17,58
Factor V Leiden	£85.00	£109.65	$141,45
Prothrombin gene mutation	£85.00	£109.65	$141,45
Lupus Anticoagulant	£10.73	£13.84	$17,58
Antiphospholipid antibodies	£12.30	£15.87	$20,15
Anti Beta-2 GP1 antibody	£9.50	£12.25	$15,81
The potential cost of a full thrombophilia screen	£250.82,	£323.56	$410,92

Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Based on a hypothetical model of 10,000 patients, in the absence of thrombophilia screening, adverse clinical complications would be found in approximately 104 women on HRT at cost of £1,185,428. When taking effectiveness of screening into account, universal screening of patients prior to prescribing HRT and restricting prescription to those tested negative for thrombophilia would prevent 42 VTE events and was the most cost-effective strategy (ICER £6824). Irrespective of patient groups, selective screening based on the presence of previous personal or family history of VTE prevented fewer cases of adverse clinical complications but was more cost effective than universal screening in all four screening scenarios.(6)	

Equity

What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(7)	The panel considered that the health system/service coverage/access to care will be the main aspect affecting health equity. USA is an example where promotion of testing that is not covered by insurance would generate inequities. I.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Research studies suggested the following regarding acceptability and barriers associated with testing and treatment: **Patients:** A survey was conducted in members of a large family with heritable protein C deficiency. For those who had not been tested before, using a 7-point scale (1 - not at all interested; 7 extremely interested), the mean score for interest in testing interest was 4.6 (standard deviation 2.4). Patients in general were willing to take the test for thrombophilia.(8) A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(9) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(10) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers:** A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(11) **Payers:** At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	**Patients:** the panel agreed that acceptability can vary importantly according to patient preference. **Health care providers:** most panel members agree that testing is acceptable to health care providers, although in some thrombophilias multiple tests need to be performed and knowledge about pitfalls and interpretation of thrombophilia testing is required. **Health care payers:** testing all women with family history of VTE considered for HRT may not be acceptable due to the cost.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(12) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending.(13) In addition, an external quality	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation.

	assurance program among USCAP laboratories showed that 98% of tests for anithrombin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(14) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(15) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(16)	External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		**Varies**	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention

○	●	○	○	○

CONCLUSIONS

Recommendation

In women with a family history of VTE and unknown thrombophilia in the family who are considering using hormone replacement therapy (HRT), the ASH guideline panel suggests not testing for any hereditary thrombophilia to guide prescription of HRT (conditional recommendation based on very low certainty in the evidence about effects)

Remarks:

Women with a family history of VTE and a known thrombophilia in the family are at higher risk for testing positive for thrombophilia and are therefore at higher risk for VTE. Another recommendation in this guideline addresses thrombophilia testing in this population.

Justification

The panel considered the trivial benefit in terms of VTE prevention, unknown harmful effects, and the moderate costs involved in testing women who are considered for HRT and who have a family history of VTE.

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation.

Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

No research priorities.

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Wu, O., Robertson, L., Twaddle, S., Lowe, G. D., Clark, P., Greaves, M., Walker, I. D., Langhorne, P., Brenkel, I., Regan, L., Greer, I.. Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. Health Technol Assess; Apr 2006.
7. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
8. van Korlaar, I. M., Vossen, C. Y., Rosendaal, F. R., Bovill, E. G., Naud, S., Cameron, L. D., Kaptein, A. A.. Attitudes toward genetic testing for thrombophilia in asymptomatic members of a large family with heritable protein C deficiency. Journal of Thrombosis & Haemostasis; Nov 2005.
9. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
10. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
11. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
12. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
13. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
14. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
15. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
16. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In asymptomatic women with a family history of VTE (first or second degree) and unknown thrombophilia in the family, should testing for any hereditary thrombophilia and subsequent avoidance of hormone replacement therapy (HRT) in women positive for thrombophilia and HRT in women negative for thrombophilia compared to no thrombophilia testing and HRT in all be used?

Setting:

Bibliography: See reference list and footnotes. [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
VTE - Estrogen alone HRT - First-degree relatives (follow up: 12 months; assessed with: any first-time DVT or PE)									
24 [a,b,c,d,e,f]	observational studies	not serious	not serious	serious [g]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and unknown thrombophilia in the family for any hereditary thrombophilia and avoiding hormone replacement therapy (HRT) with estrogen alone in the 99 positives (ranging from 142 to 201), 5.72 VTE events will occur per year (ranging from 3.35 to 8.01). When not testing 1,000 women and treating all of them with estrogen only HRT, 6.66 VTE events will occur per year (95% CI: 3.36 to 13.17). Therefore, a thrombophilia testing strategy is associated with 99 fewer women treated with estrogen only HRT (ranging from 142 to 201) and **0.94 fewer VTE events (ranging from 0.01 to 5.16)** per 1,000 women per year compared with a no testing strategy. [h]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Combined HRT - First-degree relatives (follow up: 12 months; assessed with: any first-time DVT or PE)									
24 [a,b,c,d,e,f]	observational studies	not serious	not serious	serious [g]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and unknown thrombophilia in the family for any hereditary thrombophilia and avoiding combined hormone replacement therapy (HRT) in the 99 positives (ranging from 142 to 201), 10.32 VTE events will occur per year (ranging from 7.40 to 12.37). When not testing 1,000 women and treating all of them with combined HRT, 12.84 VTE events will occur per year (95% CI: 7.47 to 22.02). Therefore, a thrombophilia testing strategy is associated with 99 fewer women treated with combination HRT (ranging from 142 to 201) and **2.52 fewer VTE events (ranging from 0.07 to 9.65)** per 1,000 women per year compared with a no testing strategy. [i]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE, 1 study; Prevalence of thrombophilia, 20 studies; Risk association for thrombophilia positive versus negative, 2 studies; HRT effect, 1 SR

b. Overall risk for VTE: Couturaud 2014

c. Effect of Estrogen therapy: Marjoribanks 2017

d. Thrombophilia prevalence, used for calculation: Bezemer 2009, Cebi 2009, Di Minno 2014, Garcia-Fuster 2005, Heit 2010, Kearon 1999, Kearon 2018, Lim 2017, Mello 2010, Meyer 2015, Olie 2011, Palareti 2003, Prandoni 2007, Roldan 2009, Rossi 2008, Santamaria 2005, Schattner 1997, Schulman 2006, Sundquist 2015, Weingarz 2015

e. Prevalence of specific thrombophilia types, used to verify calculation estimate: Ahmad 2016, Ahmad 2016, Ahmad 2017, Asim 2017, Baarslag 2004, Baglin 2003, Brouwer 2009, Bruwer 2016, Christiansen 2005, De Stefano 1999, De Stefano 2006, Eichinger 1999, Eichinger 2002, Eischer 2017, Gonzalez-Porras 2006, Heijboer 1990, Hirmerova 2014, Hoibraaten 2000, Kearon 2008, Laczkovics 2007, Lee 2017, Lijfering 2010, Lindmarker 1999, Marcucci 2003, Mateo 1997, Miles 2001, Ridker 1995, Rodger 2008, Roupie 2016, Rupa-Matysek 2014, Simioni 2000, Sonnevi 2013, Strandberg 2007, Sveinsdottir 2012, The Procare group 2003, Wahlander 2006

f. Thrombophilia positive vs negative risk association: Cushman 2004, Cushman 2018

g. The effect was indirectly calculated using separate studies for overall risk, thrombophilia prevalence, relative risk of thrombophilia positives vs negatives, and the effect of treatment. The estimates for the relative risk of thrombophilia positives vs negatives, and the effect of treatment, came from studies including patients with any type of VTE (not CVT).

h. Based on the following estimates: Overall risk for VTE, 3 per 1,000; Prevalence of any thrombophilia, 14.2% (min 9.9 - max 20.1); Relative risk for VTE in thrombophilia positives versus negatives, RR 2.08 (95%CI: 1.02-4.10); Effect of estrogen only HRT, RR 2.22 (1.12-4.39). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

i. Based on the following estimates: Overall risk for VTE, 3 per 1,000; Prevalence of any thrombophilia, 14.2% (min 9.9 - max 20.1); Relative risk for VTE in thrombophilia positives versus negatives, RR 2.08 (95%CI: 1.02-4.10); Effect of estrogen only HRT, RR 4.28 (2.49-7.34). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

References

1. Ahmad, A., Sundquist, K., Zoller, B., Dahlback, B., Svensson, P. J., Sundquist, J., Memon, A. A.. Identification of polymorphisms in Apolipoprotein M gene and their relationship with risk of recurrent venous thromboembolism. Thromb Haemost; Aug 30 2016.

2. Asim, M., Al-Thani, H., El-Menyar, A.. Recurrent Deep Vein Thrombosis After the First Venous Thromboembolism Event: A Single-Institution Experience. Med Sci Monit; May 20 2017.

3. Baarslag, H. J., Koopman, M. M., Hutten, B. A., Linthorst Homan, M. W., Buller, H. R., Reekers, J. A., van Beek, E. J.. Long-term follow-up of patients with suspected deep vein thrombosis of the upper extremity: survival, risk factors and post-thrombotic syndrome. Eur J Intern Med; Dec 2004.

4. Baglin, T., Luddington, R., Brown, K., Baglin, C.. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet; Aug 16 2003.

5. Bezemer, I. D., van der Meer, F. J., Eikenboom, J. C., Rosendaal, F. R., Doggen, C. J.. The value of family history as a risk indicator for venous thrombosis. Archives of Internal Medicine; Mar 23 2009.

6. Brouwer, J. L., Lijfering, W. M., Ten Kate, M. K., Kluin-Nelemans, H. C., Veeger, N. J., van der Meer, J.. High long-term absolute risk of recurrent venous thromboembolism in patients with hereditary deficiencies of protein S, protein C or antithrombin. Thromb Haemost; Jan 2009.

7. Bruwer, G., Limperger, V., Kenet, G., Klostermeier, U. C., Shneyder, M., Degenhardt, F., Finckh, U., Heller, C., Holzhauer, S., Trappe, R., Kentouche, K., Knoefler, R., Kurnik, K., Krumpel, A., Lauten, M., Manner, D., Mesters, R., Junker, R., Nowak-Gottl, U.. Impact of high risk thrombophilia status on recurrence among children and adults with VTE: An observational multicenter cohort study. Blood Cells Mol Dis; Nov 2016.

8. Cebi, N., Tanriverdi, S.. Aetiology of deep vein thrombosis in 63 turkish patients. Turkish Journal of Medical Sciences; April 2009.

9. Christiansen, S. C., Cannegieter, S. C., Koster, T., Vandenbroucke, J. P., Rosendaal, F. R.. Thrombophilia, clinical factors, and recurrent venous thrombotic events. Jama; May 18 2005.

10. Couturaud, F., Leroyer, C., Tromeur, C., Julian, J. A., Kahn, S. R., Ginsberg, J. S., Wells, P. S., Douketis, J. D., Mottier, D., Kearon, C.. Factors that predict thrombosis in relatives of patients with venous thromboembolism. Blood; Sep 25 2014.

11. Cushman, M., Kuller, L. H., Prentice, R., Rodabough, R. J., Psaty, B. M., Stafford, R. S., Sidney, S., Rosendaal, F. R., Women's Health Initiative, Investigators. Estrogen plus progestin and risk of venous thrombosis. Jama; Oct 6 2004.

12. Cushman, M., Larson, J. C., Rosendaal, F. R., Heckbert, S. R., Curb, J. D., Phillips, L. S., Baird, A. E., Eaton, C. B., Stafford, R. S.. Biomarkers, menopausal hormone therapy and risk of venous thrombosis: The Women's Health Initiative. Res Pract Thromb Haemost; Apr 2018.

13. De Stefano, V., Martinelli, I., Mannucci, P. M., Paciaroni, K., Chiusolo, P., Casorelli, I., Rossi, E., Leone, G.. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med; Sep 9 1999.

14. De Stefano, V., Simioni, P., Rossi, E., Tormene, D., Za, T., Pagnan, A., Leone, G.. The risk of recurrent venous thromboembolism in patients with inherited deficiency of natural anticoagulants antithrombin, protein C and protein S. Haematologica; May 2006.

15. Di Minno, M. N., Dentali, F., Lupoli, R., Ageno, W.. Mild antithrombin deficiency and risk of recurrent venous thromboembolism: a prospective cohort study. Circulation; Jan 28 2014.

16. Eichinger, S., Minar, E., Hirschl, M., Bialonczyk, C., Stain, M., Mannhalter, C., Stumpflen, A., Schneider, B., Lechner, K., Kyrle, P. A.. The risk of early recurrent venous thromboembolism after oral anticoagulant therapy in patients with the G20210A transition in the prothrombin gene. Thromb Haemost; Jan 1999.

17. Eichinger, S., Weltermann, A., Mannhalter, C., Minar, E., Bialonczyk, C., Hirschl, M., Schonauer, V., Lechner, K., Kyrle, P. A.. The risk of recurrent venous thromboembolism in heterozygous carriers of factor V Leiden and a first spontaneous venous thromboembolism. Archives of Internal Medicine; Nov 11 2002.

18. Eischer, L., Kammer, M., Traby, L., Kyrle, P. A., Eichinger, S.. Risk of cancer after anticoagulation in patients with unprovoked venous thromboembolism: an observational cohort study. Journal of Thrombosis and Haemostasis; July 2017.

19. Garcia-Fuster, M. J., Forner, M. J., Fernandez, C., Gil, J., Vaya, A., Maldonado, L.. Long-term prospective study of recurrent venous thromboembolism in patients younger than 50 years. Pathophysiol Haemost Thromb; 2005.

20. Gonzalez-Porras, J. R., Garcia-Sanz, R., Alberca, I., Lopez, M. L., Balanzategui, A., Gutierrez, O., Lozano, F., San Miguel, J.. Risk of recurrent venous thrombosis in patients with G20210A mutation in the prothrombin gene or factor V Leiden mutation. Blood Coagul Fibrinolysis; Jan 2006.

21. Group, The,Procare. Is recurrent venous thromboembolism more frequent in homozygous patients for the factor V Leiden mutation than in heterozygous patients?. Blood Coagulation and Fibrinolysis; September 2003.

22. Heijboer, H., Brandjes, D. P., Buller, H. R., Sturk, A., ten Cate, J. W.. Deficiencies of coagulation-inhibiting and fibrinolytic proteins in outpatients with deep-vein thrombosis. N Engl J Med; Nov 29 1990.

23. Heit, J. A., Beckman, M. G., Bockenstedt, P. L., Grant, A. M., Key, N. S., Kulkarni, R., Manco-Johnson, M. J., Moll, S., Ortel, T. L., Philipp, C. S., Thrombosis, C.,D.,C., Hemostasis Centers, Research, Prevention, Network. Comparison of characteristics from White- and Black-Americans with venous thromboembolism: a cross-sectional study. Am J Hematol; Jul 2010.

24. Hirmerova, J., Seidlerova, J., Subrt, I.. The association of factor V Leiden with various clinical patterns of venous thromboembolism-the factor V Leiden paradox. Qjm; Sep 2014.

25. Hoibraaten, E., Qvigstad, E., Arnesen, H., Larsen, S., Wickstrom, E., Sandset, P. M.. Increased risk of recurrent venous thromboembolism during hormone replacement therapy--results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). Thromb Haemost; Dec 2000.

26. Kearon, C., Gent, M., Hirsh, J., Weitz, J., Kovacs, M. J., Anderson, D. R., Turpie, A. G., Green, D., Ginsberg, J. S., Wells, P., MacKinnon, B., Julian, J. A.. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med; Mar 25 1999.

27. Kearon, C., Julian, J. A., Kovacs, M. J., Anderson, D. R., Wells, P., Mackinnon, B., Weitz, J. I., Crowther, M. A., Dolan, S., Turpie, A. G., Geerts, W., Solymoss, S., van Nguyen, P., Demers, C., Kahn, S. R., Kassis, J., Rodger, M., Hambleton, J., Gent, M., Ginsberg, J. S., Investigators, Elate. Influence of thrombophilia on risk of recurrent venous thromboembolism while on warfarin: results from a randomized trial. Blood; Dec 1 2008.

28. Kearon, C., Parpia, S., Spencer, F. A., Baglin, T., Stevens, S. M., Bauer, K. A., Lentz, S. R., Kessler, C. M., Douketis, J. D., Moll, S., Kaatz, S., Schulman, S., Connors, J. M., Ginsberg, J. S., Spadafora, L., Bhagirath, V., Liaw, P. C., Weitz, J. I., Julian, J. A.. Antiphospholipid antibodies and recurrent thrombosis after a first unprovoked venous thromboembolism. Blood; May 10 2018.

29. Laczkovics, C., Grafenhofer, H., Kaider, A., Quehenberger, P., Simanek, R., Mannhalter, C., Lechner, K., Pabinger, I.. Risk of recurrence after a first venous thromboembolic event in young women. Haematologica; Sep 2007.

30. Lee, S. Y., Kim, E. K., Kim, M. S., Shin, S. H., Chang, H., Jang, S. Y., Kim, H. J., Kim, D. K.. The prevalence and clinical manifestation of hereditary thrombophilia in Korean patients with unprovoked venous thromboembolisms. PLoS ONE [Electronic Resource]; 2017.

31. Lijfering, W. M., Middeldorp, S., Veeger, N. J., Hamulyak, K., Prins, M. H., Buller, H. R., van der Meer, J.. Risk of recurrent venous thrombosis in homozygous carriers and double heterozygous carriers of factor V Leiden and prothrombin G20210A. Circulation; Apr 20 2010.

32. Lim, H. Y., Chua, C. C., Tacey, M., Sleeman, M., Donnan, G., Nandurkar, H., Ho, P.. Venous thromboembolism management in Northeast Melbourne: how does it compare to international guidelines and data?. Intern Med J; Sep 2017.

33. Lindmarker, P., Schulman, S., Sten-Linder, M., Wiman, B., Egberg, N., Johnsson, H.. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. DURAC Trial Study Group. Duration of Anticoagulation. Thromb Haemost; May 1999.

34. Marcucci, R., Liotta, A. A., Cellai, A. P., Rogolino, A., Gori, A. M., Giusti, B., Poli, D., Fedi, S., Abbate, R., Prisco, D.. Increased plasma levels of lipoprotein(a) and the risk of idiopathic and recurrent venous thromboembolism. Am J Med; Dec 1 2003.

35. Marjoribanks, Jane, Farquhar, Cindy, Roberts, Helen, Lethaby, Anne, Lee, Jasmine. Long-term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database of Systematic Reviews; 2017.

36. Mateo, J., Oliver, A., Borrell, M., Sala, N., Fontcuberta, J.. Laboratory evaluation and clinical characteristics of 2,132 consecutive unselected patients with venous thromboembolism--results of the Spanish Multicentric Study on Thrombophilia (EMET-Study). Thromb Haemost; Mar 1997.

37. Mello, T. B., Orsi, F. L., Montalvao, S. A., Ozelo, M. C., de Paula, E. V., Annichinno-Bizzachi, J. M.. Long-term prospective study of recurrent venous thromboembolism in a Hispanic population. Blood Coagul Fibrinolysis; Oct 2010.

38. Meyer, M. R., Witt, D. M., Delate, T., Johnson, S. G., Fang, M., Go, A., Clark, N. P.. Thrombophilia testing patterns amongst patients with acute venous thromboembolism. Thromb Res; Dec 2015.

39. Miles, J. S., Miletich, J. P., Goldhaber, S. Z., Hennekens, C. H., Ridker, P. M.. G20210A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. J Am Coll Cardiol; Jan 2001.

40. Olie, V., Plu-Bureau, G., Conard, J., Horellou, M. H., Canonico, M., Scarabin, P. Y.. Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. Menopause; May 2011.

41. Palareti, G., Legnani, C., Cosmi, B., Valdre, L., Lunghi, B., Bernardi, F., Coccheri, S.. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation; Jul 22 2003.

42. Prandoni, P., Noventa, F., Ghirarduzzi, A., Pengo, V., Bernardi, E., Pesavento, R., Iotti, M., Tormene, D., Simioni, P., Pagnan, A.. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica; Feb 2007.

43. Ridker, P. M., Miletich, J. P., Stampfer, M. J., Goldhaber, S. Z., Lindpaintner, K., Hennekens, C. H.. Factor V Leiden and risks of recurrent idiopathic venous thromboembolism. Circulation; Nov 15 1995.

44. Rodger, M. A., Kahn, S. R., Wells, P. S., Anderson, D. A., Chagnon, I., Le Gal, G., Solymoss, S., Crowther, M., Perrier, A., White, R., Vickars, L., Ramsay, T., Betancourt, M. T., Kovacs, M. J.. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. Cmaj; Aug 26 2008.

45. Roldan, V., Lecumberri, R., Munoz-Torrero, J. F., Vicente, V., Rocha, E., Brenner, B., Monreal, M., Investigators, Riete. Thrombophilia testing in patients with venous thromboembolism. Findings from the RIETE registry. Thromb Res; Jun 2009.

46. Rossi, E., Za, T., Ciminello, A., Leone, G., De Stefano, V.. The risk of symptomatic pulmonary embolism due to proximal deep venous thrombosis differs in patients with different types of inherited thrombophilia. Thromb Haemost; Jun 2008.

47. Roupie, A. L., Dossier, A., Goulenok, T., Perozziello, A., Papo, T., Sacre, K.. First venous thromboembolism in admitted patients younger than 50years old. Eur J Intern Med; Oct 2016.

48. Rupa-Matysek, J., Gil, L., Wojtasinska, E., Ciepluch, K., Lewandowska, M., Komarnicki, M.. The relationship between mean platelet volume and thrombosis recurrence in patients diagnosed with antiphospholipid syndrome. Rheumatol Int; Nov 2014.

49. Santamaria, M. G., Agnelli, G., Taliani, M. R., Prandoni, P., Moia, M., Bazzan, M., Guazzaloca, G., Ageno, W., Bertoldi, A., Silingardi, M., Tomasi, C., Ambrosio, G. B., Warfarin Optimal Duration Italian Trial, Investigators. Thrombophilic abnormalities and recurrence of venous thromboembolism in patients treated with standardized anticoagulant treatment. Thromb Res; 2005.

50. Schattner, A., Kasher, I., Berrebi, A.. Causes and outcome of deep-vein thrombosis in otherwise-healthy patients under 50 years. Qjm; Apr 1997.

51. Schulman, S., Lindmarker, P., Holmstrom, M., Larfars, G., Carlsson, A., Nicol, P., Svensson, E., Ljungberg, B., Viering, S., Nordlander, S., Leijd, B., Jahed, K., Hjorth, M., Linder, O., Beckman, M.. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. Journal of Thrombosis & Haemostasis; Apr 2006.

52. Simioni, P., Prandoni, P., Lensing, A. W., Manfrin, D., Tormene, D., Gavasso, S., Girolami, B., Sardella, C., Prins, M., Girolami, A.. Risk for subsequent venous thromboembolic complications in carriers of the prothrombin or the factor V gene mutation with a first episode of deep-vein thrombosis. Blood; Nov 15 2000.

53. Sonnevi, K., Tchaikovski, S. N., Holmstrom, M., Antovic, J. P., Bremme, K., Rosing, J., Larfars, G.. Obesity and thrombin-generation profiles in women with venous thromboembolism. Blood Coagul Fibrinolysis; Jul 2013.

54. Strandberg, K., Svensson, P. J., Ohlin, A. K.. Venous thromboembolism in carriers of the Factor V Leiden mutation and in patients without known thrombophilic risk factor; prediction of recurrence and APC-PCI complex concentration and/or soluble thrombomodulin antigen and activity. Thromb Res; 2007.

55. Sundquist, K., Sundquist, J., Svensson, P. J., Zoller, B., Memon, A. A.. Role of family history of venous thromboembolism and thrombophilia as predictors of recurrence: a prospective follow-up study. Journal of Thrombosis & Haemostasis; Dec 2015.

56. Sveinsdottir, S. V., Saemundsson, Y., Isma, N., Gottsater, A., Svensson, P. J.. Evaluation of recurrent venous thromboembolism in patients with Factor V Leiden mutation in heterozygous form. Thromb Res; Sep 2012.

57. Wahlander, K., Eriksson, H., Lundstrom, T., Billing Clason, S., Wall, U., Nystrom, P., Wessman, P., Schulman, S., Investigators, Thrive,Iii. Risk of recurrent venous thromboembolism or bleeding in relation to thrombophilic risk factors in patients receiving ximelagatran or placebo for long-term secondary prevention of venous thromboembolism. Br J Haematol; Apr 2006.

58. Weingarz, L., Schindewolf, M., Schwonberg, J., Hecking, C., Wolf, Z., Erbe, M., Lindhoff-Last, E., Linnemann, B.. Thrombophilia and risk of VTE recurrence according to the age at the time of first VTE manifestation. Vasa; Jul 2015.

QUESTION

Should selective testing for the known familial thrombophilia and subsequent avoidance of combined oral contraceptives (COC) in women positive for thrombophilia and COC in women negative for thrombophilia vs. no thrombophilia testing and COC in all be used for asymptomatic women with a family history of VTE (first or second degree) and known thrombophilia in the family?

POPULATION:	asymptomatic women with a family history of VTE (first or second degree) and known thrombophilia in the family
INTERVENTION:	selective testing for the known familial thrombophilia and subsequent avoidance of combined oral contraceptives (COC) in women positive for thrombophilia and COC in women negative for thrombophilia
COMPARISON:	no thrombophilia testing and COC in all
MAIN OUTCOMES:	VTE - Factor V Leiden - First-degree relatives; VTE - Prothrombin mutation - First-degree relatives; VTE - Antithrombin deficiency - First-degree relatives; VTE - Protein C deficiency - First-degree relatives; VTE - Protein S deficiency - First-degree relatives;
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Inherited and acquired thrombophilia can put patients at higher risk of venous thromboembolism (VTE), especially if there also is a family history of VTE and known thrombophilia in the family. Combined oral contraceptives (COC) may further increase risk in such patients. The currently most commonly tested inherited and acquired thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. Thrombophilia testing is sometimes considered in women considering to start or continue COC and who have a family history of VTE and known thrombophilia in the family. Although testing these women has a high chance of finding a positive test result (in first-degree relatives, 50%), the relevant question and aim of the current guideline is to assess whether thrombophilia testing and tailoring management to the test result would improve patient important outcomes. This question addresses whether testing for thrombophilia and subsequent COC avoidance in positive women improves patient important outcomes in women who are candidates to take COC and who have a family history of VTE and known thrombophilia in the family, as compared with no thrombophilia testing and no COC avoidance in all. Since no randomized controlled trials have addressed this question, we used a modeling exercise based on observational evidence for baseline risk, prevalence of thrombophilia and associated risk of events with thrombophilia, and studies with evidence for the effect of COC avoidance on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies		Considering that this population has three important risk factors for VTE, i.e. family history of VTE, known thrombophilia in the family and using COC, detecting thrombophilia as a fourth risk factor may influence

○ Don't know		management decisions.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Evidence Profile.	Desirable effect = preventing VTE. VTE would be avoided in women who are positive for thrombophilia by avoiding COC. Desirable effects may vary depending on the thrombophilia type. <u>Second-degree relatives:</u> For modeling the effect in second-degree relatives we assumed a prevalence of 25% of the same thrombophilia type as the proband. Effect estimates for VTE in second-degree relatives: FVL: 2.25 fewer per 1,000 (from 1.47 to 3.40 fewer) PT: 2.20 fewer per 1,000 (from 1.24 to 3.68 fewer) AT: 9.61 fewer per 1,000 (from 6.16 to 14.03 fewer) PC: 6.89 fewer per 1,000 (from 3.64 to 11.04 fewer) PS: 5.16 fewer per 1,000 (from 2.65 to 8.48 fewer)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	See Evidence Profile.	Undesirable effect = intangible as they fall into a wider scope than VTE. The panel considered unwanted pregnancies, delaying COC, labeling as thrombophilia positive, and potential other consequences of testing.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows:** **Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(2, 1, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3)	The values of potential undesirable effects are not included here. The panel considered that there is important variability, as younger women may value a different trade-off than older women who are candidates for COC.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Factor V Leiden and prothrombin mutation: Does not favor either the intervention or comparison, for first- and second-degree relatives. Antithrombin, protein C, and protein S deficiencies: Probably favors the intervention, for first- and second-degree relatives.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Intervention Costs: **Test (source)** / Approximate Cost (2005) / Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016) / **(14/12/2016) £1 = $1,27** **Full Blood Count** £2.55 £3.29 **$4,18** **Protein C** £11.67 £15.5 **$19,12** **Free Protein S** £11.67 £15.5 **$19,12** **Antithrombin** £11.67 £15.5 **$19,12** **APCR** £10.73 £13.84 **$17,58** **Factor V Leiden** £85.00 £109.65 **$141,45** **Prothrombin gene mutation** £85.00 £109.65 **$141,45** **Lupus Anticoagulant** £10.73 £13.84 **$17,58** **Antiphospholipid antibodies** £12.30 £15.87 **$20,15** **Anti Beta-2 GP1 antibody** £9.50 £12.25 **$15,81** **The potential cost of a full thrombophilia screen** £250,82, £323,56 **$410,92** Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx	The panel considered that the costs would be much lower than testing in the general population, but not negligible as many women will have a first- or second-degree relative with a history of VTE and known thrombophilia in the family.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Based on a hypothetical model of 10,000 patients, in the absence of thrombophilia screening, adverse clinical complications would be found in approximately seven women on COC at cost of £119,147. When taking effectiveness of screening into account, universal screening of patients prior to prescribing COC would only prevent three VTE events and was the least cost-effective strategy (ICER £200,402). Irrespective of patient groups, selective screening based on the presence of previous personal or family history of VTE prevented fewer cases of adverse clinical complications but was more cost effective than universal screening in all four screening scenarios.(6) Current FVL and PT testing practices for COC in women with a familial history of VTE generate an incremental cost-effectiveness ratio of €72,412/QALY, which is well above the acceptable threshold of cost-effectiveness of €40,000-50,000/QALY.(7)	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(8)	The panel considered that the health system/service coverage/access to care will be the main aspect affecting health equity. USA is an example where promotion of testing that is not covered by insurance would generate inequities. I.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Research studies suggested the following regarding acceptability and barriers associated with testing and treatment: **Patients:** A survey was conducted in members of a large family with heritable protein C deficiency. For those who had not been tested before, using a 7-point scale (1 - not at all interested; 7 extremely interested), the mean score for interest in testing interest was 4.6 (standard deviation 2.4). Patients in general were willing to take the test for thrombophilia.(9) A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(10) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(11) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers:** A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(12) **Payers:** At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	**Patients:** the panel agreed that acceptability can vary importantly according to patient preference. **Health care providers**: most panel members agree that testing is acceptable to health care providers, although in some thrombophilias multiple tests need to be performed and knowledge about pitfalls and interpretation of thrombophilia testing is required. **Health care payers:** testing all women with family history of VTE considered for COC would probably not be acceptable due to the cost.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(13) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending.(14) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(15) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(16) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(17)	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation. External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories. Testing is feasible as it is currently being done, but it may be less feasible if this required rolling out a program to test all women considered for COC who have a family history of VTE and a known thrombophilia in the family.

SUMMARY OF JUDGEMENTS

JUDGEMENT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

Factor V Leiden or prothrombin mutation

In first- and second-degree relatives of patients with VTE and known factor V Leiden or prothrombin mutation in the family (low risk thrombophilia), the ASH guideline panel suggests not testing for the known familial thrombophilia to guide prescription of COC (conditional recommendation based on very low certainty in the evidence about effects)

Antithrombin, protein C, or protein S deficiency

In first- and second-degree relatives of patients with VTE and known antithrombin, protein C or protein S deficiency in the family (high risk thrombophilia), the ASH guideline panel suggests testing for the known familial thrombophilia and avoidance of COC in women positive for thrombophilia over no testing for thrombophilia and COC in all women (conditional recommendation based on very low certainty in the evidence about effects)

Remarks:

- A strategy with selective testing for the known familial thrombophilia would mean that positive women would avoid COC, and negative women would use COC.

- These recommendations do not address homozygous defects, or combinations of thrombophilia types.

Justification

The considered the small to moderate benefit in terms of VTE prevention, unknown harmful effects, and the moderate costs involved in testing women who are considered for COC and who have a family history of VTE and known thrombophilia in the family.

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation.

Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

No research priorities.

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Wu, O., Robertson, L., Twaddle, S., Lowe, G. D., Clark, P., Greaves, M., Walker, I. D., Langhorne, P., Brenkel, I., Regan, L., Greer, I.. Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. Health Technol Assess; Apr 2006.
7. Compagni, A., Melegaro, A., Tarricone, R.. Genetic screening for the predisposition to venous thromboembolism: a cost-utility analysis of clinical practice in the Italian health care system. Value Health; Sep-Oct 2013.
8. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
9. van Korlaar, I. M., Vossen, C. Y., Rosendaal, F. R., Bovill, E. G., Naud, S., Cameron, L. D., Kaptein, A. A.. Attitudes toward genetic testing for thrombophilia in asymptomatic members of a large family with heritable protein C deficiency. Journal of Thrombosis & Haemostasis; Nov 2005.
10. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
11. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
12. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
13. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
14. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
15. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
16. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
17. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In asymptomatic women with a family history of VTE (first or second degree) and known thrombophilia in the family, should selective testing for the known familial thrombophilia and subsequent avoidance of combined oral contraceptives (COC) in women positive for thrombophilia and COC in women negative for thrombophilia compared to no thrombophilia testing and COC in all be used?

Setting:

Bibliography: See reference list and footnotes. [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
VTE - Factor V Leiden - First-degree relatives (follow up: 12 months; assessed with: any first-time DVT or PE)									
14 [a,b,c,d]	observational studies	not serious	not serious	serious [e]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and factor V Leiden (FVL) in the family for FVL and avoiding combined oral contraceptives (COC) in the 500 positives, 4.18 VTE events will occur per year (ranging from 3.54 to 5.20). When not testing 1,000 women and treating all of them with COC, 8.75 VTE events will occur per year (95% CI: 7.25 to 10.75). Therefore, a selective thrombophilia testing strategy is associated with 500 fewer women treated with COC and **4.57 fewer VTE events (ranging from 3.71 to 5.55)** per 1,000 women per year compared with a no testing strategy. [f]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Prothrombin mutation - First-degree relatives (follow up: 12 months; assessed with: any first-time DVT or PE)									
10 [b,d,g,h]	observational studies	not serious	not serious	serious [e]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and prothrombin mutation (PT) in the family for PT and avoiding combined oral contraceptives (COC) in the 500 positives, 4.37 VTE events will occur per year (ranging from 3.49 to 5.85). When not testing 1,000 women and treating all of them with COC, 8.75 VTE events will occur per year (95% CI: 7.25 to 10.75). Therefore, a selective thrombophilia testing strategy is associated with 500 fewer women treated with COC and **4.38 fewer VTE events (ranging from 3.76 to 4.90)** per 1,000 women per year compared with a no testing strategy. [i]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Antithrombin deficiency - First-degree relatives (follow up: 12 months; assessed with: any first-time DVT or PE)									
12 [b,d,j,k]	observational studies	not serious	not serious	serious [e]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and antithrombin deficiency (AT) in the family for AT and avoiding combined oral contraceptives (COC) in the 500 positives, 10.01 VTE events will occur per year (ranging from 9.06 to 12.22). When not testing 1,000 women and treating all of them with COC, 29.40 VTE events will occur per year (95% CI: 24.36 to 36.12). Therefore, a selective thrombophilia testing strategy is associated with 500 fewer women treated with COC and **19.39 fewer VTE events (ranging from 15.30 to 23.90)** per 1,000 women per year compared with a no testing strategy. [l]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Protein C deficiency - First-degree relatives (follow up: 12 months; assessed with: any first-time DVT or PE)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
12 [b,d,j,m]	observational studies	not serious	not serious	serious [e]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and protein C deficiency (PC) in the family for PC and avoiding combined oral contraceptives (COC) in the 500 positives, 8.21 VTE events will occur per year (ranging from 6.93 to 11.64). When not testing 1,000 women and treating all of them with COC, 22.05 VTE events will occur per year (95% CI: 18.27 to 27.09). Therefore, a selective thrombophilia testing strategy is associated with 500 fewer women treated with COC and **13.84 fewer VTE events (ranging from 11.34 to 15.45)** per 1,000 women per year compared with a no testing strategy. [n]	⨁◯◯◯ VERY LOW	CRITICAL

VTE - Protein S deficiency - First-degree relatives (follow up: 12 months; assessed with: any first-time DVT or PE)

13 [b,d,o,p]	observational studies	not serious	not serious	serious [e]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and protein S deficiency (PS) in the family for PS and avoiding combined oral contraceptives (COC) in the 500 positives, 6.66 VTE events will occur per year (ranging from 5.50 to 9.59). When not testing 1,000 women and treating all of them with COC, 17.15 VTE events will occur per year (95% CI: 14.21 to 21.07). Therefore, a selective thrombophilia testing strategy is associated with 500 fewer women treated with COC and **10.49 fewer VTE events (ranging from 8.71 to 11.48)** per 1,000 women per year compared with a no testing strategy. [q]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE, 7 studies; Risk association for FVL positive versus negative, 9 studies (3 also provided Overall Risk); COC effect, 1 systematic review

b. Overall risk for VTE: estimated from Bank 2004, Couturaud 2009, Coppens 2006, Mahmoodi 2010, Middeldorp 1998, Simioni 1999, Simioni 2002

c. Factor V Leiden positive vs negative risk association: Cohen 2012, Couturaud 2006, Faioni 1999, Lensen 2001, Martinelli 1998, Martinelli 2000, Middeldorp 1998, Simioni 1999, Simioni 2002

d. Effect of COC: de Bastos 2014

e. The effect was indirectly calculated using separate studies for overall risk for first-time VTE, relative risk of thrombophilia positives vs negatives, and the effect of avoiding COC

f. Based on the following estimates: Overall risk for VTE, 2.5 per 1,000; Prevalence of FVL, 50%; Relative risk for VTE in FVL positives versus negatives, RR 2.71 (95%CI: 2.06-3.56); Relative risk of VTE with COC versus no COC, RR 3.5 (2.9-4.3). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

g. Number of studies used in calculations: Overall risk for VTE, 7 studies; Risk association for prothrombin positive versus negative, 4 studies (2 also provided Overall Risk); COC effect, 1 systematic review

h. Prothrombin positive vs negative risk association: Bank 2004, Coppens 2006, Faioni 1999, Martinelli 2000

i. Based on the following estimates: Overall risk for VTE, 2.5 per 1,000; Prevalence of PT, 50%; Relative risk for VTE in PT positives versus negatives, RR 2.35 (95%CI: 1.46-3.78); Relative risk of VTE with COC versus no COC, RR 3.5 (2.9-4.3). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

j. Number of studies used in calculations: Overall risk for VTE, 7 studies; Risk association for FVL positive versus negative, 5 studies (1 also provided Overall Risk); COC effect, 1 systematic review

k. Antithrombin positive vs negative risk association: Brouwer 2006, Cohen 2012, Faioni 1999, Mahmoodi 2010, Martinelli 1998

l. Based on the following estimates: Overall risk for VTE, 8.4 per 1,000; Prevalence of AT, 50%; Relative risk for VTE in AT positives versus negatives, RR 12.07 (95%CI: 6.25-23.30); Relative risk of VTE with COC versus no COC, RR 3.5 (2.9-4.3). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

m. Protein C positive vs negative risk association: Brouwer 2006, Cohen 2012, Faioni 1999, Mahmoodi 2010, Martinelli 1998

n. Based on the following estimates: Overall risk for VTE, 6.3 per 1,000; Prevalence of PC, 50%; Relative risk for VTE in PC positives versus negatives, RR 7.24 (95%CI: 2.89-18.15); Relative risk of VTE with COC versus no COC, RR 3.5 (2.9-4.3). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

o. Number of studies used in calculations: Overall risk for VTE, 7 studies; Risk association for FVL positive versus negative, 6 studies (1 also provided Overall Risk); COC effect, 1 systematic review

p. Protein S positive vs negative risk association: Brouwer 2005, Brouwer 2006, Cohen 2012, Faioni 1999, Mahmoodi 2010, Martinelli 1998

q. Based on the following estimates: Overall risk for VTE, 4.9 per 1,000; Prevalence of PS, 50%; Relative risk for VTE in PS positives versus negatives, RR 5.98 (95%CI: 2.45-14.57); Relative risk of VTE with COC versus no COC, RR 3.5 (2.9-4.3). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

References

1. Bank, I., Libourel, E. J., Middeldorp, S., Van Pampus, E. C., Koopman, M. M., Hamulyak, K., Prins, M. H., Van Der Meer, J., Buller, H. R.. Prothrombin 20210A mutation: a mild risk factor for venous thromboembolism but not for arterial thrombotic disease and pregnancy-related complications in a family study. Archives of Internal Medicine; Sep 27 2004.

2. Brouwer, J. L., Veeger, N. J., Kluin-Nelemans, H. C., van der Meer, J.. The pathogenesis of venous thromboembolism: evidence for multiple interrelated causes. Ann Intern Med; Dec 5 2006.

3. Brouwer, J. L., Veeger, N. J., van der Schaaf, W., Kluin-Nelemans, H. C., van der Meer, J.. Difference in absolute risk of venous and arterial thrombosis between familial protein S deficiency type I and type III. Results from a family cohort study to assess the clinical impact of a laboratory test-based classification. Br J Haematol; Mar 2005.

4. Cohen, W., Castelli, C., Alessi, M. C., Aillaud, M. F., Bouvet, S., Saut, N., Brunet, D., Barthet, M. C., Tregouet, D. A., Lavigne, G., Morange, P. E.. ABO blood group and von Willebrand factor levels partially explained the incomplete penetrance of congenital thrombophilia. Arterioscler Thromb Vasc Biol; Aug 2012.

5. Coppens, M., van de Poel, M. H., Bank, I., Hamulyak, K., van der Meer, J., Veeger, N. J., Prins, M. H., Buller, H. R., Middeldorp, S.. A prospective cohort study on the absolute incidence of venous thromboembolism and arterial cardiovascular disease in asymptomatic carriers of the prothrombin 20210A mutation. Blood; Oct 15 2006.

6. Couturaud, F., Kearon, C., Leroyer, C., Mercier, B., Abgrall, J. F., Le Gal, G., Lacut, K., Oger, E., Bressollette, L., Ferec, C., Lamure, M., Mottier, D., Groupe d'Etude de la Thrombose de Bretagne, Occidentale. Incidence of venous thromboembolism in first-degree relatives of patients with venous thromboembolism who have factor V Leiden. Thromb Haemost; Dec 2006.

7. Couturaud, F., Leroyer, C., Julian, J. A., Kahn, S. R., Ginsberg, J. S., Wells, P. S., Douketis, J. D., Mottier, D., Kearon, C.. Factors that predict risk of thrombosis in relatives of patients with unprovoked venous thromboembolism. Chest; Dec 2009.

8. de Bastos, Marcos, Stegeman Bernardine, H., Rosendaal Frits, R., Van Hylckama Vlieg, Astrid, Helmerhorst Frans, M., Stijnen, Theo, Dekkers Olaf, M.. Combined oral contraceptives: venous thrombosis. Cochrane Database of Systematic Reviews; 2014.

9. Faioni, E. M., Franchi, F., Bucciarelli, P., Margaglione, M., De Stefano, V., Castaman, G., Finazzi, G., Mannucci, P. M.. Coinheritance of the HR2 haplotype in the factor V gene confers an increased risk of venous thromboembolism to carriers of factor V R506Q (factor V Leiden). Blood; Nov 1 1999.

10. Lensen, R., Bertina, R. M., Vandenbroucke, J. P., Rosendaal, F. R.. High factor VIII levels contribute to the thrombotic risk in families with factor V Leiden. Br J Haematol; Aug 2001.

11. Mahmoodi, B. K., Brouwer, J. L., Ten Kate, M. K., Lijfering, W. M., Veeger, N. J., Mulder, A. B., Kluin-Nelemans, H. C., Van Der Meer, J.. A prospective cohort study on the absolute risks of venous thromboembolism and predictive value of screening asymptomatic relatives of patients with hereditary deficiencies of protein S, protein C or antithrombin. Journal of Thrombosis & Haemostasis; Jun 2010.

12. Martinelli, I., Bucciarelli, P., Margaglione, M., De Stefano, V., Castaman, G., Mannucci, P. M.. The risk of venous thromboembolism in family members with mutations in the genes of factor V or prothrombin or both. Br J Haematol; Dec 2000.

13. Martinelli, I., Mannucci, P. M., De Stefano, V., Taioli, E., Rossi, V., Crosti, F., Paciaroni, K., Leone, G., Faioni, E. M.. Different risks of thrombosis in four coagulation defects associated with inherited thrombophilia: a study of 150 families. Blood; Oct 1 1998.

14. Middeldorp, S., Henkens, C. M., Koopman, M. M., van Pampus, E. C., Hamulyak, K., van der Meer, J., Prins, M. H., Buller, H. R.. The incidence of venous thromboembolism in family members of patients with factor V Leiden mutation and venous thrombosis. Ann Intern Med; Jan 1 1998.

15. Simioni, P., Sanson, B. J., Prandoni, P., Tormene, D., Friederich, P. W., Girolami, B., Gavasso, S., Huisman, M. V., Buller, H. R., Wouter ten Cate, J., Girolami, A., Prins, M. H.. Incidence of venous thromboembolism in families with inherited thrombophilia. Thromb Haemost; Feb 1999.

16. Simioni, P., Tormene, D., Prandoni, P., Zerbinati, P., Gavasso, S., Cefalo, P., Girolami, A.. Incidence of venous thromboembolism in asymptomatic family members who are carriers of factor V Leiden: a prospective cohort study. Blood; Mar 15 2002.

QUESTION

Should selective testing for the known familial thrombophilia and subsequent avoidance of hormone replacement therapy (HRT) in women positive for thrombophilia and HRT in women negative for thrombophilia vs. no thrombophilia testing and HRT in all be used for asymptomatic women with a family history of VTE (first or second degree) and known thrombophilia in the family?

POPULATION:	asymptomatic women with a family history of VTE (first or second degree) and known thrombophilia in the family
INTERVENTION:	selective testing for the known familial thrombophilia and subsequent avoidance of hormone replacement therapy (HRT) in women positive for thrombophilia and HRT in women negative for thrombophilia
COMPARISON:	no thrombophilia testing and HRT in all
MAIN OUTCOMES:	Venous thromboembolism (first-time)
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Inherited and acquired thrombophilia can put patients at higher risk of venous thromboembolism (VTE), especially if there also is a family history of VTE and known thrombophilia in the family. Hormone replacement therapy (HRT) may further increase risk in such patients. The currently most commonly tested inherited and acquired thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. Thrombophilia testing is sometimes considered in women considering to start or continue HRT and who have a family history of VTE and known thrombophilia in the family. Although testing these women has a high chance of finding a positive test result (in first-degree relatives, 50%), the relevant question and aim of the current guideline is to assess whether thrombophilia testing and tailoring management to the test result would improve patient important outcomes. This question addresses whether testing for thrombophilia and subsequent HRT avoidance in positive women improves patient important outcomes in women who are candidates to take HRT and who have a family history of VTE and known thrombophilia in the family, as compared with no thrombophilia testing and no HRT avoidance in all. Since no randomized controlled trials have addressed this question, we used a modeling exercise based on observational evidence for baseline risk, prevalence of thrombophilia and associated risk of events with thrombophilia, and studies with evidence for the effect of COC avoidance on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		Considering that this population has several important risk factors for VTE, i.e. family history of VTE, known thrombophilia in the family, advanced age, and using HRT, detecting thrombophilia as an additional risk factor may influence management decisions.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Evidence Profile.	Desirable effect = preventing VTE. VTE would be avoided in women who are positive for thrombophilia by avoiding HRT. Desirable effects may vary depending on the thrombophilia type. <u>Second-degree relatives:</u> For modeling the effect in second-degree relatives we assumed a prevalence of 25% of the same thrombophilia type as the proband. Effect estimates for VTE in second-degree relatives – Estrogen alone HRT: FVL: 1.08 fewer per 1,000 (from 0.07 to 4.08 fewer) PT: 0.67 fewer per 1,000 (from 0.03 to 3.73 fewer) AT: 3.22 fewer per 1,000 (from 0.20 to 12.77 fewer) PC: 2.47 fewer per 1,000 (from 0.15 to 10.23 fewer) PS: 1.94 fewer per 1,000 (from 0.11 to 8.03 fewer) Effect estimates for VTE in second-degree relatives -

		Combined HRT: FVL: 2.89 fewer per 1,000 (from 0.86 to 7.64 fewer) PT: 1.80 fewer per 1,000 (from 0.35 to 6.97 fewer) AT: 8.66 fewer per 1,000 (from 2.51 to 23.89 fewer) PC: 6.64 fewer per 1,000 (from 1.86 to 19.13 fewer) PS: 5.21 fewer per 1,000 (from 1.41 to 15.01 fewer)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	See Evidence Profile.	Undesirable effect = intangible as they fall into a wider scope than VTE. The panel considered labeling as thrombophilia positive, and potential other consequences of testing.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows: Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(2, 1, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3)	The values of potential undesirable effects are not included here.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		FVL and prothrombin mutation: Does not favor either the intervention or comparison, for first- and second-degree relatives. Antithrombin, protein C, and protein S deficiency: Probably favors the intervention, for first- and second-degree relatives.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		The panel considered that the costs would be much lower than testing in the general population, but not negligible as many women will have a first- or second-degree relative with a history of VTE and known thrombophilia in the family.

Intervention Costs:

Test (source)	Approximate Cost (2005)	Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016)	(14/12/2016) £1 = $1,27
Full Blood Count	£2.55	£3.29	$4,18
Protein C	£11.67	£15.5	$19,12
Free Protein S	£11.67	£15.5	$19,12
Antithrombin	£11.67	£15.5	$19,12
APCR	£10.73	£13.84	$17,58
Factor V Leiden	£85.00	£109.65	$141,45
Prothrombin gene mutation	£85.00	£109.65	$141,45
Lupus Anticoagulant	£10.73	£13.84	$17,58
Antiphospholipid antibodies	£12.30	£15.87	$20,15
Anti Beta-2 GP1 antibody	£9.50	£12.25	$15,81
The potential cost of a full thrombophilia screen	£250.82,	£323.56	$410,92

Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Based on a hypothetical model of 10,000 patients, in the absence of thrombophilia screening, adverse clinical complications would be found in approximately 104 women on HRT at cost of £1,185,428. When taking effectiveness of screening into account, universal screening of patients prior to prescribing HRT and restricting prescription to those tested negative for thrombophilia would prevent 42 VTE events and was the most cost-effective strategy (ICER £6824). Irrespective of patient groups, selective screening based on the presence of previous personal or family history of VTE prevented fewer cases of adverse clinical complications but was more cost effective than universal screening in all four screening scenarios.(6)	

Equity

What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(7)	The panel considered that the health system/service coverage/access to care will be the main aspect affecting health equity. USA is an example where promotion of testing that is not covered by insurance would generate inequities. I.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Research studies suggested the following regarding acceptability and barriers associated with testing and treatment: **Patients:** A survey was conducted in members of a large family with heritable protein C deficiency. For those who had not been tested before, using a 7-point scale (1 - not at all interested; 7 extremely interested), the mean score for interest in testing interest was 4.6 (standard deviation 2.4). Patients in general were willing to take the test for thrombophilia.(8) A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(9) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(10) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers:** A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(11) **Payers:** At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	**Patients:** the panel agreed that acceptability can vary importantly according to patient preference. **Health care providers**: most panel members agree that testing is acceptable to health care providers, although in some thrombophilias multiple tests need to be performed and knowledge about pitfalls and interpretation of thrombophilia testing is required. **Health care payers:** testing all women with family history of VTE considered for HRT would probably not be acceptable due to the cost.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(12) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending.(13) In addition, an external quality	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation.

	assurance program among USCAP laboratories showed that 98% of tests for anithrombin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(14) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(15) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(16)	External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories. Testing is feasible as it is currently being done, but it may be less feasible if this required rolling out a program to test all women considered for HRT who have a family history of VTE and a known thrombophilia in the family.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention

○	○	○	○	○

CONCLUSIONS

Recommendation

Factor V Leiden or prothrombin mutation

In first- and second-degree relatives of patients with VTE and known factor V Leiden or prothrombin mutation in the family (low risk thrombophilia), the ASH guideline panel suggests not testing for the known familial thrombophilia to guide prescription of HRT (conditional recommendation based on very low certainty in the evidence about effects)

Antithrombin, protein C, or protein S deficiency

In first- and second-degree relatives of patients with VTE and known antithrombin, protein C or protein S deficiency in the family (high risk thrombophilia), the ASH guideline panel suggests testing for the known familial thrombophilia and avoidance of HRT in women for thrombophilia over no testing for thrombophilia and HRT in all women (conditional recommendation based on very low certainty in the evidence about effects)

Remarks:

- A strategy with selective testing for the known familial thrombophilia would mean that positive women would avoid HRT, and negative women would use HRT.

- These recommendations do not address homozygous defects, or combinations of thrombophilia types.

Justification

The considered the small to moderate benefit in terms of VTE prevention, unknown harmful effects, and the moderate costs involved in testing women who are considered for HRT and who have a family history of VTE and known thrombophilia in the family.

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation.

Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

No research priorities.

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Wu, O., Robertson, L., Twaddle, S., Lowe, G. D., Clark, P., Greaves, M., Walker, I. D., Langhorne, P., Brenkel, I., Regan, L., Greer, I.. Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. Health Technol Assess; Apr 2006.
7. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
8. van Korlaar, I. M., Vossen, C. Y., Rosendaal, F. R., Bovill, E. G., Naud, S., Cameron, L. D., Kaptein, A. A.. Attitudes toward genetic testing for thrombophilia in asymptomatic members of a large family with heritable protein C deficiency. Journal of Thrombosis & Haemostasis; Nov 2005.
9. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
10. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
11. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
12. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
13. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
14. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
15. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
16. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In asymptomatic women with a family history of VTE (first or second degree) and known thrombophilia in the family, should selective testing for the known familial thrombophilia and subsequent avoidance of hormone replacement therapy (HRT) in women positive for thrombophilia and HRT in women negative for thrombophilia compared to no thrombophilia testing and HRT in all be used?

Setting:

Bibliography: See reference list and footnotes. [1,2,3,4]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
VTE - Factor V Leiden - Estrogen alone HRT - First-degree relatives (follow up: 12 months; assessed with: any first-time DVT or PE)									
4 [a,b,c,d]	observational studies	not serious	not serious	serious [e]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and factor V Leiden (FVL) in the family for FVL and avoiding hormone replacement therapy (HRT) with estrogen alone in the 500 positives, 3.35 VTE events will occur per year (ranging from 2.55 to 6.18). When not testing 1,000 women and treating all of them with estrogen alone HRT, 5.55 VTE events will occur per year (95% CI: 2.80 to 10.98). Therefore, a selective thrombophilia testing strategy is associated with 500 fewer women treated with estrogen alone HRT and **2.20 fewer VTE events (ranging from 0.25 to 4.79)** per 1,000 women per year compared with a no testing strategy. [f]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Factor V Leiden - Combined HRT - First-degree relatives (follow up: 12 months; assessed with: any first-time DVT or PE)									
4 [a,b,c,d]	observational studies	not serious	not serious	serious [e]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and factor V Leiden (FVL) in the family for FVL and avoiding combined hormone replacement therapy (HRT) in the 500 positives, 4.78 VTE events will occur per year (ranging from 3.10 to 9.39). When not testing 1,000 women and treating all of them with combined HRT, 10.70 VTE events will occur per year (95% CI: 6.23 to 18.35). Therefore, a selective thrombophilia testing strategy is associated with 500 fewer women treated with combined HRT and **5.92 fewer VTE events (ranging from 3.12 to 8.96)** per 1,000 women per year compared with a no testing strategy. [g]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Prothrombin mutation - Estrogen alone HRT - First-degree relatives (follow up: 12 months; assessed with: any first-time DVT or PE)									
4 [a,b,c,d]	observational studies	not serious	not serious	serious [e]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and protthrombin mutation (PT) in the family for PT and avoiding hormone replacement therapy (HRT) with estrogen alone in the 500 positives, 4.19 VTE events will occur per year (ranging from 2.59 to 9.02). When not testing 1,000 women and treating all of them with estrogen alone HRT, 5.55 VTE events will occur per year (95% CI: 2.80 to 10.98). Therefore, a selective thrombophilia testing strategy is associated with 500 fewer women treated with estrogen alone HRT and **1.36 fewer VTE events (ranging from 0.21 to 1.96)** per 1,000 women per year compared with a no testing strategy. [h]	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
VTE - Prothrombin mutation - Combined HRT - First-degree relatives (follow up: 12 months; assessed with: any first-time DVT or PE)									
4 [a,b,c,d]	observational studies	not serious	not serious	serious [e]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and prothrombin mutation (PT) in the family for PT and avoiding combined hormone replacement therapy (HRT) in the 500 positives, 7.06 VTE events will occur per year (ranging from 3.66 to 14.69). When not testing 1,000 women and treating all of them with combined HRT, 10.70 VTE events will occur per year (95% CI: 6.23 to 18.35). Therefore, a selective thrombophilia testing strategy is associated with 500 fewer women treated with combined HRT and **3.64 fewer VTE events (ranging from 2.56 to 3.66)** per 1,000 women per year compared with a no testing strategy. [i]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Antithrombin deficiency - Estrogen alone HRT - First-degree relatives (follow up: 12 months; assessed with: any first-time DVT or PE)									
4 [a,b,c,d]	observational studies	not serious	not serious	serious [e]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and antithrombin deficiency (AT) in the family for AT and avoiding hormone replacement therapy (HRT) with estrogen alone in the 500 positives, 12.20 VTE events will occur per year (ranging from 8.64 to 23.39). When not testing 1,000 women and treating all of them with estrogen alone HRT, 18.65 VTE events will occur per year (95% CI: 9.41 to 36.88). Therefore, a selective thrombophilia testing strategy is associated with 500 fewer women treated with estrogen alone HRT and **6.45 fewer VTE events (ranging from 0.77 to 13.49)** per 1,000 women per year compared with a no testing strategy. [j]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Antithrombin deficiency - Combined HRT - First-degree relatives (follow up: 12 months; assessed with: any first-time DVT or PE)									
4 [a,b,c,d]	observational studies	not serious	not serious	serious [e]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and antithrombin deficiency (AT) in the family for AT and avoiding combined hormone replacement therapy (HRT) in the 500 positives, 18.60 VTE events will occur per year (ranging from 11.38 to 36.43). When not testing 1,000 women and treating all of them with combined HRT, 35.95 VTE events will occur per year (95% CI: 20.92 to 61.66). Therefore, a selective thrombophilia testing strategy is associated with 500 fewer women treated with combined HRT and **17.35 fewer VTE events (ranging from 9.54 to 25.23)** per 1,000 women per year compared with a no testing strategy. [k]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Protein C deficiency - Estrogen alone HRT - First-degree relatives (follow up: 12 months; assessed with: any first-time DVT or PE)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
4 [a,b,c,d]	observational studies	not serious	not serious	serious [e]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and protein C deficiency (PC) in the family for PC and avoiding hormone replacement therapy (HRT) with estrogen alone in the 500 positives, 9.05 VTE events will occur per year (ranging from 6.46 to 17.54). When not testing 1,000 women and treating all of them with estrogen alone HRT, 13.99 VTE events will occur per year (95% CI: 7.06 to 27.66). Therefore, a selective thrombophilia testing strategy is associated with 500 fewer women treated with estrogen alone HRT and **4.94 fewer VTE events (ranging from 0.60 to 10.12)** per 1,000 women per year compared with a no testing strategy. [l]	⨁◯◯◯ VERY LOW	CRITICAL

VTE - Protein C deficiency - Combined HRT - First-degree relatives (follow up: 12 months; assessed with: any first-time DVT or PE)

4 [a,b,c,d]	observational studies	not serious	not serious	serious [e]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and protein C deficiency (PC) in the family for PC and avoiding combined hormone replacement therapy (HRT) in the 500 positives, 13.68 VTE events will occur per year (ranging from 8.26 to 27.32). When not testing 1,000 women and treating all of them with combined HRT, 26.96 VTE events will occur per year (95% CI: 15.69 to 46.24). Therefore, a selective thrombophilia testing strategy is associated with 500 fewer women treated with combined HRT and **13.28 fewer VTE events (ranging from 7.43 to 18.92)** per 1,000 women per year compared with a no testing strategy. [m]	⨁◯◯◯ VERY LOW	CRITICAL

VTE - Protein S deficiency - Estrogen alone HRT - First-degree relatives (follow up: 12 months; assessed with: any first-time DVT or PE)

4 [a,b,c,d]	observational studies	not serious	not serious	serious [e]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and protein S deficiency (PS) in the family for PS and avoiding hormone replacement therapy (HRT) with estrogen alone in the 500 positives, 6.96 VTE events will occur per year (ranging from 5.02 to 13.64). When not testing 1,000 women and treating all of them with estrogen alone HRT, 10.88 VTE events will occur per year (95% CI: 5.49 to 21.51). Therefore, a selective thrombophilia testing strategy is associated with 500 fewer women treated with estrogen alone HRT and **3.92 fewer VTE events (ranging from 0.47 to 7.87)** per 1,000 women per year compared with a no testing strategy. [n]	⨁◯◯◯ VERY LOW	CRITICAL

VTE - Protein S deficiency - Combined HRT - First-degree relatives (follow up: 12 months; assessed with: any first-time DVT or PE)

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
4 [a,b,c,d]	observational studies	not serious	not serious	serious [e]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and protein S deficiency (PS) in the family for PS and avoiding combined hormone replacement therapy (HRT) in the 500 positives, 10.44 VTE events will occur per year (ranging from 6.33 to 21.25). When not testing 1,000 women and treating all of them with combined HRT, 20.97 VTE events will occur per year (95% CI: 12.20 to 35.97). Therefore, a selective thrombophilia testing strategy is associated with 500 fewer women treated with combined HRT and **10.53 fewer VTE events (ranging from 5.87 to 14.72)** per 1,000 women per year compared with a no testing strategy. [o]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE, 1 study; Risk association for thrombophilia positive versus negative, 2 studies; Effect of HRT, 1 systematic review

b. Overall risk for VTE: Couturaud 2009

c. Thrombophilia positive vs negative risk association: Cushman 2004, Cushman 2018

d. Effect of HRT: Marjoribanks 2017

e. The effect was indirectly calculated using separate studies for overall risk, thrombophilia prevalence, relative risk of thrombophilia positives vs negatives, and the effect of HRT avoidance.

f. Based on the following estimates: Overall risk for VTE recurrence, 2.5 per 1,000; Prevalence of FVL, 50%; Relative risk for VTE in thrombophilia positives versus negatives, RR 2.6 (95%CI: 1.3-5.2); Relative risk of estrogen only HRT, RR 2.22 (1.12-4.39). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the higher CI of the Relative risk for VTE, and the smallest treatment effect (lower CI).

g. Based on the following estimates: Overall risk for VTE recurrence, 2.5 per 1,000; Prevalence of FVL, 50%; Relative risk for VTE in thrombophilia positives versus negatives, RR 2.6 (95%CI: 1.3-5.2); Relative risk of combined HRT, RR 4.28 (2.49-7.34). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the higher CI of the Relative risk for VTE, and the smallest treatment effect (lower CI).

h. Based on the following estimates: Overall risk for VTE recurrence, 2.5 per 1,000; Prevalence of PT, 50%; Relative risk for VTE in thrombophilia positives versus negatives, RR 0.8 (95%CI: 0.3-2.2); Relative risk of estrogen only HRT, RR 2.22 (1.12-4.39). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the higher CI of the Relative risk for VTE, and the smallest treatment effect (lower CI).

i. Based on the following estimates: Overall risk for VTE recurrence, 2.5 per 1,000; Prevalence of PT, 50%; Relative risk for VTE in thrombophilia positives versus negatives, RR 0.8 (95%CI: 0.3-2.2); Relative risk of combined HRT, RR 4.28 (2.49-7.34). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the higher CI of the Relative risk for VTE, and the smallest treatment effect (lower CI).

j. Based on the following estimates: Overall risk for VTE recurrence, 8.4 per 1,000; Prevalence of AT, 50%; Relative risk for VTE in thrombophilia positives versus negatives, RR 1.7 (95%CI: 0.9-3.2); Relative risk of estrogen only HRT, RR 2.22 (1.12-4.39). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the higher CI of the Relative risk for VTE, and the smallest treatment effect (lower CI).

k. Based on the following estimates: Overall risk for VTE recurrence, 8.4 per 1,000; Prevalence of AT, 50%; Relative risk for VTE in thrombophilia positives versus negatives, RR 1.7 (95%CI: 0.9-3.2); Relative risk of combined HRT, RR 4.28 (2.49-7.34). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the higher CI of the Relative risk for VTE, and the smallest treatment effect (lower CI).

l. Based on the following estimates: Overall risk for VTE recurrence, 6.3 per 1,000; Prevalence of PC, 50%; Relative risk for VTE in thrombophilia positives versus negatives, RR 1.8 (95%CI: 0.9-3.8); Relative risk of estrogen only HRT, RR 2.22 (1.12-4.39). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the higher CI of the Relative risk for VTE, and the smallest treatment effect (lower CI).

m. Based on the following estimates: Overall risk for VTE recurrence, 6.3 per 1,000; Prevalence of PC, 50%; Relative risk for VTE in thrombophilia positives versus negatives, RR 1.8 (95%CI: 0.9-3.8); Relative risk of combined HRT, RR 4.28 (2.49-7.34). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the higher CI of the Relative risk for VTE, and the smallest treatment effect (lower CI).

n. Based on the following estimates: Overall risk for VTE recurrence, 4.9 per 1,000; Prevalence of PS, 50%; Relative risk for VTE in thrombophilia positives versus negatives, RR 1.9 (95%CI: 0.9-4.1); Relative risk of estrogen only HRT, RR 2.22 (1.12-4.39). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the higher CI of the Relative risk for VTE, and the smallest treatment effect (lower CI).

o. Based on the following estimates: Overall risk for VTE recurrence, 4.9 per 1,000; Prevalence of PS, 50%; Relative risk for VTE in thrombophilia positives versus negatives, RR 1.9 (95%CI: 0.9-4.1); Relative risk of combined HRT, RR 4.28 (2.49-7.34). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the lower CI of the Relative risk for VTE, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the higher CI of the Relative risk for VTE, and the smallest treatment effect (lower CI).

References

1. Couturaud, F., Leroyer, C., Julian, J. A., Kahn, S. R., Ginsberg, J. S., Wells, P. S., Douketis, J. D., Mottier, D., Kearon, C.. Factors that predict risk of thrombosis in relatives of patients with unprovoked venous thromboembolism. Chest; Dec 2009.

2. Cushman, M., Kuller, L. H., Prentice, R., Rodabough, R. J., Psaty, B. M., Stafford, R. S., Sidney, S., Rosendaal, F. R., Women's Health Initiative, Investigators. Estrogen plus progestin and risk of venous thrombosis. Jama; Oct 6 2004.

3. Cushman, M., Larson, J. C., Rosendaal, F. R., Heckbert, S. R., Curb, J. D., Phillips, L. S., Baird, A. E., Eaton, C. B., Stafford, R. S.. Biomarkers, menopausal hormone therapy and risk of venous thrombosis: The Women's Health Initiative. Res Pract Thromb Haemost; Apr 2018.

4. Marjoribanks, Jane, Farquhar, Cindy, Roberts, Helen, Lethaby, Anne, Lee, Jasmine. Long-term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database of Systematic Reviews; 2017.

QUESTION

Should testing for the known familial thrombophilia and subsequent antepartum thromboprophylaxis in women positive for thrombophilia and no antepartum thromboprophylaxis in women negative for thrombophilia vs. no thrombophilia testing and no antepartum thromboprophylaxis in all be used for asymptomatic women who have a family history of VTE and a known thrombophilia in the family?

POPULATION:	asymptomatic women who have a family history of VTE and a known thrombophilia in the family
INTERVENTION:	testing for the known familial thrombophilia and subsequent antepartum thromboprophylaxis in women positive for thrombophilia and no antepartum thromboprophylaxis in women negative for thrombophilia
COMPARISON:	no thrombophilia testing and no antepartum thromboprophylaxis in all
MAIN OUTCOMES:	VTE (first-time any DVT or PE); Major Bleeding
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Inherited thrombophilia can be identified in many patients with a venous thromboembolism (VTE). Consequently, relatives of these patients are also at increased risk to have inherited thrombophilia which may put them at higher risk of VTE during pregnancy. The currently most commonly tested inherited thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. Thrombophilia testing is often performed in relatives of patients with VTE and known thrombophilia in the family, particularly if they intend to become or are pregnant. Although testing relatives of patients with a VTE and known thrombophilia in the family has a high chance of finding a positive test result, the relevant question and aim of the current guideline is to assess whether thrombophilia testing and tailoring management to the test result would improve patient important outcomes. This question addresses whether selective testing for the same thrombophilia type as the proband and subsequent thromboprophylaxis in positive women improves patient important outcomes in pregnant relatives of patients with VTE and known inherited thrombophilia in the family, as compared with no thrombophilia testing and no thromboprophylaxis in all. Since no randomized controlled trials have addressed this question, we used a modeling exercise based on observational evidence for baseline risk, prevalence of thrombophilia and associated risk of events with thrombophilia, and RCTs with evidence for the effect of thromboprophylaxis on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		As the ASH guidelines on VTE in the context of pregnancy suggested to use antepartum thromboprophylaxis in women with a family history of VTE and antithrombin deficiency, homozygous factor V Leiden or combined thrombophilias, this question is primarily relevant for

		women with these thrombophilia types in the family. A separate question in this guideline addressed selective testing for the known familial thrombophilia in the postpartum period.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	See Evidence Profile.	Desirable effect = preventing VTE. VTE would be avoided in relatives who are positive for thrombophilia by using thromboprophylaxis. The panel assumed that antepartum thromboprophylaxis would be administered during 8 months. The panel considered that during pregnancy, DVT's are more severe and that PE's occur more frequently than in other populations. FVL homozygous, combination of FVL + PT, Antithrombin: Small effect Protein C and S: Trivial effect <u>Second-degree relatives:</u> For modeling the effect in second-degree relatives we assumed a prevalence of 25% or 50% of the same thrombophilia type as the proband. Effect was not

		calculated for homozygous FVL. Effect estimates for VTE in second-degree relatives, per antepartum period (8 months): Combination of FVL + PT: 4.52 fewer per 1,000 (from 1.84 to 7.16 fewer) AT: 4.82 fewer per 1,000 (from 2.19 to 6.69 fewer) PC: 0.99 fewer per 1,000 (from 0.24 to 1.59 fewer) PS: 1.96 fewer per 1,000 (from 0.39 to 3.38 fewer)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	See Evidence Profile.	Undesirable effect = causing major bleeding. Major bleedings would be caused in patients who are positive for thrombophilia by using thromboprophylaxis. Trivial: no increase in bleeding, in first- and second-degree relatives. Other potential adverse effects the panel considered, but were not quantified: skin reactions, reduced QoL, complications for planning the delivery.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows using a scale from 0 (worst possible scenario, usually death), to 1 (best possible scenario, usually perfect health): Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(1, 2, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3) **Gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off)(2, 3) **Minor intracranial bleeding event:** 0.75 (standard gamble)(2) **Major intracranial bleeding event:** 0.15 (standard gamble)(2) **Anticoagulant therapy** Patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome.(3) Patients would favor efficacy and safety over convenience of route of administration.(6) Also, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events.(7, 6, 8)	The panel considered clinicians may value avoiding major bleedings more (they do not want to cause harm), while patients may value avoiding VTE events and pregnancy complications more.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Homozygous FVL, combination of FVL + PT, Antithrombin: probably favors intervention. Protein C and S: does not favor either the intervention or comparison.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Intervention Costs: <table><tr><th>Test (source)</th><th>Approximate Cost (2005)</th><th>Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016)</th><th>(14/12/2016) £1 = $1,27</th></tr><tr><td>Full Blood Count</td><td>£2.55</td><td>£3.29</td><td>$4,18</td></tr><tr><td>Protein C</td><td>£11.67</td><td>£15.5</td><td>$19,12</td></tr><tr><td>Free Protein S</td><td>£11.67</td><td>£15.5</td><td>$19,12</td></tr><tr><td>Antithrombin</td><td>£11.67</td><td>£15.5</td><td>$19,12</td></tr><tr><td>APCR</td><td>£10.73</td><td>£13.84</td><td>$17,58</td></tr><tr><td>Factor V Leiden</td><td>£85.00</td><td>£109.65</td><td>$141,45</td></tr><tr><td>Prothrombin gene mutation</td><td>£85.00</td><td>£109.65</td><td>$141,45</td></tr><tr><td>Lupus Anticoagulant</td><td>£10.73</td><td>£13.84</td><td>$17,58</td></tr><tr><td>Antiphospholipid antibodies</td><td>£12.30</td><td>£15.87</td><td>$20,15</td></tr><tr><td>Anti Beta-2 GP1 antibody</td><td>£9.50</td><td>£12.25</td><td>$15,81</td></tr><tr><td>The potential cost of a full thrombophilia screen</td><td>£250.82,</td><td>£323.56</td><td>$410,92</td></tr></table> Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx	- Cost for testing: 400$ -2000$ per patient - Thromboprophylaxis cost: 1000 $- 4500 per patient per year Costs for selective testing and 8 months course of thromboprophylaxis, as compared to no testing and no thromboprophylaxis. Costs for selective testing would be less than running full thrombophilia panels.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	In a prospective, unselected study with 113 pregnant women with a personal or family history of VTE, of whom only one had **FVL** and a VTE, selective FVL screening in these women resulted in an ICER of £7,535 assuming 50% reduction with prophylaxis, and £4,418 assuming 75% reduction with prophylaxis.(9) Based on a hypothetical model of 10,000 unselected pregnant women, in the absence of **thrombophilia** testing, adverse clinical complications would be found in 2921 pregnant women at a cost of £509,364. Universal testing of pregnant women would prevent 59 VTE events for an ICER of £81,554, and selective testing would prevent 7 VTE events for an ICER of £81,250.(10)	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(11)	The panel considered that the health system/service coverage/access to care will be the main aspect affecting health equity. USA is an example where promotion of testing that is not covered by insurance would generate inequities. I.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Pregnancy specific** Research studies suggested the following regarding acceptability and barriers associated with treatment in pregnancy: Four studies assessed several categories of acceptability depicted as compliance / adherence of different interventions for the prevention of thromboembolism during delivery(12), adherence to enoxaparin(13), and for adherence to guidelines recommendations in general in obstetric patient population(14). Compliance or acceptability was deemed rather adequate for postnatal thromboprophylaxis (83%), enoxaparin (93%) and for guidelines in obstetric patients in general (69%). No studies assessed effect on people's autonomy, disapproval of interventions, or disagreements with the values, costs, harms, or benefits.	The panel considered testing acceptable for many doctors, although maybe not for all. Patients are in general willing to undergo thrombophilia testing.

	Generic - Testing Research studies suggested the following regarding acceptability and barriers associated with testing and treatment: **Patients:** A survey was conducted in members of a large family with heritable protein C deficiency. For those who had not been tested before, using a 7-point scale (1 - not at all interested; 7 extremely interested), the mean score for interest in testing interest was 4.6 (standard deviation 2.4). Patients in general were willing to take the test for thrombophilia.(15) A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(16) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(17) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers:** A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(18) **Payers:** At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(19) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending.(20) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(21) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(22) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(23)	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation. External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

Homozygous factor V Leiden, combination of factor V Leiden and prothrombin mutation, or antithrombin deficiency in first-degree relatives:

In first-degree relatives of patients with VTE and known homozygous factor V Leiden, combination of factor V Leiden and prothrombin mutation, or antithrombin deficiency in the family, the ASH guideline panel suggests testing for the known familial thrombophilia and antepartum thromboprophylaxis in first-degree relatives positive for thrombophilia over no testing for thrombophilia and no antepartum thromboprophylaxis in all first-degree relatives (conditional recommendation based on very low certainty in the evidence about effects)

Combination of factor V Leiden and prothrombin mutation, or antithrombin deficiency in second-degree relatives:

In second-degree relatives of patients with VTE and known combination of factor V Leiden and prothrombin mutation, or antithrombin deficiency in the family, the ASH guideline panel suggests testing for the known familial thrombophilia and antepartum thromboprophylaxis in second-degree relatives positive for thrombophilia over no testing for thrombophilia and no antepartum thromboprophylaxis in all second-degree relatives (conditional recommendation based on very low certainty in the evidence about effects)

Protein C or protein S deficiency in first- and second-degree relatives:

In first- and second-degree relatives of patients with VTE and known protein C or protein S deficiency in the family, the ASH guideline panel suggests either testing for the known familial thrombophilia and antepartum thromboprophylaxis in relatives positive for thrombophilia or not testing for thrombophilia and no antepartum thromboprophylaxis in all relatives (conditional recommendation based on very low certainty in the evidence about effects)

Remarks:

- Pharmacological thromboprophylaxis based on antepartum thrombophilia testing is often continued postpartum.

- Conditions can include the duration and burden of the treatment, which involves injections, and patient preference.

- A strategy with selective testing for the known familial thrombophilia type would mean that positive relatives would receive thromboprophylaxis, and negative relatives would receive no thromboprophylaxis.

- For homozygous FVL, these recommendations only concern siblings, not children. Management of second-degree relatives was not addressed.

- These recommendations do not address heterozygous FVL or PT mutation alone, as the ASH guidelines on the management of VTE in the context of pregnancy suggest not to prescribe thromboprophylaxis in these patients, and patient outcomes would not be affected by thrombophilia testing.

Justification

The panel considered that thrombophilia testing and thromboprophylaxis in positive women likely has some benefit in terms of prevention of VTE that outweighs the risk of major bleeding in pregnant relatives of patients with VTE and who have a very high risk thrombophilia in the family (homozygous FVL, combination of FVL & PT, or antithrombin), but no clear benefit in relatives of patients with VTE and who have a somewhat lower risk thrombophilia in the family (protein C or S).

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation. This includes testing for protein S, protein C and antithrombin deficiency during pregnancy.

Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

Future research will need to provide higher certainty evidence on the effect of selective testing for thrombophilia, and consequent antepartum prophylaxis in positive women.

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
7. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
8. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
9. Clark, P., Twaddle, S., Walker, I. D., Scott, L., Greer, I. A.. Cost-effectiveness of screening for the factor V Leiden mutation in pregnant women. Lancet; Jun 1 2002.
10. Wu, O., Robertson, L., Twaddle, S., Lowe, G. D., Clark, P., Greaves, M., Walker, I. D., Langhorne, P., Brenkel, I., Regan, L., Greer, I.. Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. Health Technol Assess; Apr 2006.
11. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
12. Hordern, C. E., Bircher, C. W., Prosser-Snelling, E. C., Fraser, F. K., Smith, R. P.. Patient compliance with postnatal thromboprophylaxis: An observational study. J Obstet Gynaecol; 2015.
13. Patel, J. P., Auyeung, V., Patel, R. K., Marsh, M. S., Green, B., Arya, R., Davies, J. G.. Women's views on and adherence to low-molecular-weight heparin therapy during pregnancy and the puerperium. Journal of Thrombosis & Haemostasis; Dec 2012.
14. Cregan, A., Higgins, J. R., O'Shea, S.. Implementation of thromboprophylaxis guidelines. Ir Med J; Mar 2013.
15. van Korlaar, I. M., Vossen, C. Y., Rosendaal, F. R., Bovill, E. G., Naud, S., Cameron, L. D., Kaptein, A. A.. Attitudes toward genetic testing for thrombophilia in asymptomatic members of a large family with heritable protein C deficiency. Journal of Thrombosis & Haemostasis; Nov 2005.
16. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
17. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
18. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
19. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
20. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
21. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
22. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
23. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In asymptomatic women who have a family history of VTE and a known thrombophilia in the family, should testing for the known familial thrombophilia and subsequent antepartum thromboprophylaxis in women positive for thrombophilia and no antepartum thromboprophylaxis in women negative for thrombophilia compared to no thrombophilia testing and no antepartum thromboprophylaxis in all be used?

Setting:

Bibliography: See reference list and footnotes. [1,2,3,4,5,6,7,8,9]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
VTE - Homozygous Factor V Leiden - First-degree relatives (follow up: antepartum period (8 months); assessed with: any first-time DVT or PE)									
3 [a,b,c]	observational studies	not serious	not serious	serious [d]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and homozygous factor V Leiden (FVL) in the family for homozygous FVL and treating the 250 positives with antepartum pharmacological thromboprophylaxis, 18.15 VTE events will occur per antepartum period (ranging from 13.36 to 25.34). When not testing 1,000 asymptomatic women and treating none of them with antepartum pharmacological thromboprophylaxis, 37.5 VTE events will occur per antepartum period. Therefore, a selective thrombophilia testing strategy is associated with 250 more women treated with pharmacological thromboprophylaxis and **19.35 fewer VTE events (ranging from 12.16 to 24.14)** per 1,000 women per antepartum period compared with a no testing strategy. [e]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Antithrombin deficiency - First-degree relatives (follow up: antepartum period (8 months); assessed with: any first-time DVT or PE)									
5 [c,f,g]	observational studies	not serious	not serious	serious [d]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and antithrombin deficiency (AT) in the family for AT and treating the 500 positives with antepartum pharmacological thromboprophylaxis, 8.30 VTE events will occur per antepartum period (ranging from 6.03 to 12.10). When not testing 1,000 asymptomatic women and treating none of them with antepartum pharmacological thromboprophylaxis, 18.0 VTE events will occur per antepartum period. Therefore, a selective thrombophilia testing strategy is associated with 500 more women treated with pharmacological thromboprophylaxis and **9.70 fewer VTE events (ranging from 5.90 to 11.97)** per 1,000 women per antepartum period compared with a no testing strategy. [h]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Protein C deficiency - First-degree relatives (follow up: antepartum period (8 months); assessed with: any first-time DVT or PE)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
4 [c,i,j]	observational studies	not serious	not serious	serious [d]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and protein C deficiency (PC) in the family for PC and treating the 500 positives with antepartum pharmacological thromboprophylaxis, 1.98 VTE events will occur per antepartum period (ranging from 1.34 to 3.18). When not testing 1,000 asymptomatic women and treating none of them with antepartum pharmacological thromboprophylaxis, 4 VTE events will occur per antepartum period. Therefore, a selective thrombophilia testing strategy is associated with 500 more women treated with pharmacological thromboprophylaxis and **2.02 fewer VTE events (ranging from 0.82 to 2.66)** per 1,000 women per antepartum period compared with a no testing strategy. [k]	⨁◯◯◯ VERY LOW	CRITICAL

VTE - Protein S deficiency - First-degree relatives (follow up: antepartum period (8 months); assessed with: any first-time DVT or PE)

4 [c,i,j]	observational studies	not serious	not serious	serious [d]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and protein S deficiency (PS) in the family for PS and treating the 500 positives with antepartum pharmacological thromboprophylaxis, 4.06 VTE events will occur per antepartum period (ranging from 2.68 to 6.66). When not testing 1,000 asymptomatic women and treating none of them with antepartum pharmacological thromboprophylaxis, 8 VTE events will occur per antepartum period. Therefore, a selective thrombophilia testing strategy is associated with 500 more women treated with pharmacological thromboprophylaxis and **3.94 fewer VTE events (ranging from 1.34 to 5.32)** per 1,000 women per antepartum period compared with a no testing strategy. [l]	⨁◯◯◯ VERY LOW	CRITICAL

VTE - Combination of Factor V Leiden & Prothrombin mutation combination - First-degree relatives (follow up: antepartum period (8 months); assessed with: any first-time DVT or PE)

3 [a,b,c]	observational studies	not serious	not serious	serious [d]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and the combination of factor V Leiden (FVL) plus prothrombin mutation (PT) in the family for the same combination and treating the 250 positives with antepartum pharmacological thromboprophylaxis, 11.20 VTE events will occur per antepartum period (ranging from 7.92 to 15.62). When not testing 1,000 asymptomatic women and treating none of them with antepartum pharmacological thromboprophylaxis, 20.3 VTE events will occur per antepartum period. Therefore, a selective thrombophilia testing strategy is associated with 250 more women treated with pharmacological thromboprophylaxis and **9.05 fewer VTE events (ranging from 4.63 to 12.33)** per 1,000 women per antepartum compared with a no testing strategy. [m]	⨁◯◯◯ VERY LOW	CRITICAL

Major Bleeding - Antithrombin, Protein C, or Protein S deficiency - First-degree relatives (follow up: antepartum period (8 months))

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
2 [n]	observational studies	not serious	not serious	serious [o]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and antithrombin, protein C, or protein S deficiency (AT, PC, PS) in the family for the same thrombophilia, and treating the 500 positives with antepartum pharmacological thromboprophylaxis, 4.25 major bleedings will occur per antepartum period (ranging from 3.30 to 13.35). When not testing 1,000 asymptomatic women and treating none of them with antepartum pharmacological thromboprophylaxis, 6.34 major bleedings will occur per antepartum period. Therefore, a selective thrombophilia testing strategy is associated with 500 more women treated with pharmacological thromboprophylaxis and **2.09 fewer major bleedings (ranging from 3.04 fewer to 7.01 more)** per 1,000 women per antepartum period compared with a no testing strategy. [p]	⨁◯◯◯ VERY LOW	CRITICAL

Major Bleeding - Homozygous Factor V Leiden (FVL), or combination of FVL & Prothrombin mutation - First-degree relatives (follow up: antepartum period (8 months))

2 [n]	observational studies	not serious	not serious	serious [o]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and either homozygous Factor V Leiden (FVL), or combination of FVL and prothrombin mutation (PT) in the family for the same thrombophilia, and treating the 250 positives with antepartum pharmacological thromboprophylaxis, 5.29 major bleedings will occur per antepartum period (ranging from 4.82 to 9.84). When not testing 1,000 asymptomatic women and treating none of them with antepartum pharmacological thromboprophylaxis, 6.34 major bleedings will occur per antepartum period. Therefore, a selective thrombophilia testing strategy is associated with 250 more women treated with pharmacological thromboprophylaxis and **1.05 fewer major bleedings (ranging from 1.52 fewer to 3.50 more)** per 1,000 women per antepartum period compared with a no testing strategy. [q]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE & Risk association for FVL homozygous positive versus negative, 2 studies; Thromboprophylaxis effect, 1 RCT

b. Overall risk for VTE & FVL homozygous positive vs negative risk association: Martinelli 2001, Tormene 2001

c. Effect of thromboprophylaxis: Hull 2001

d. The effect was indirectly calculated using separate studies for overall risk for first-time VTE, relative risk of thrombophilia positives vs negatives, and the effect of thromboprophylaxis.

e. Based on the following estimates: Overall risk for VTE recurrence, 37.5 per 1,000; Prevalence of same thrombophilia, 25%; Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 20.96 (95%CI: 7.17-53.34); Relative risk of VTE recurrence with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.41 (0.32-0.54). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

f. Number of studies used in calculations: Overall risk for VTE & Risk association for FVL homozygous positive versus negative, 4 studies; Thromboprophylaxis effect, 1 RCT

g. Overall risk for VTE & AT positive vs negative risk association: Folkeringa 2007, Friederich 1996, Mahmoodi 2010, van Boven 1999

h. Based on the following estimates: Overall risk for VTE recurrence, 18 per 1,000; Prevalence of same thrombophilia, 50%; Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 10.51 (95%CI: 2.48-44.54); Relative risk of VTE recurrence with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.41 (0.32-0.54). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

i. Number of studies used in calculations: Overall risk for VTE & Risk association for FVL homozygous positive versus negative, 3 studies; Thromboprophylaxis effect, 1 RCT

j. Overall risk for VTE & PC positive vs negative risk association: Folkeringa 2007, Friederich 1996, Mahmoodi 2010

k. Based on the following estimates: Overall risk for VTE recurrence, 4 per 1,000; Prevalence of same thrombophilia, 50%; Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 6.04 (95%CI: 0.81-45.19); Relative risk of VTE recurrence with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.41 (0.32-0.54). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

l. Based on the following estimates: Overall risk for VTE recurrence, 8 per 1,000; Prevalence of same thrombophilia, 50%; Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 5.03 (95%CI: 0.57-44.51); Relative risk of VTE recurrence with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.41 (0.32-0.54). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

m. Based on the following estimates: Overall risk for VTE recurrence, 20.25 per 1,000; Prevalence of same thrombophilia, 25%; Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 9.36 (95%CI: 2.97-25.66); Relative risk of VTE recurrence with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.41 (0.32-0.54). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

n. Number of studies used in calculations: Overall risk & effect of anticoagulation, 1 systematic review

o. The effect was calculated using a systematic review on an indirect population, without family history of VTE and thrombophilia

p. Based on the following estimates: Overall risk for Major bleeding of 6.34 per 1,000; Prevalence of same thrombophilia, 50%; Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.34 (0.04-3.21). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the smallest treatment effect (lower CI).

q. Based on the following estimates: Overall risk for Major bleeding of 6.34 per 1,000; Prevalence of same thrombophilia, 25%; Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.34 (0.04-3.21). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the smallest treatment effect (lower CI).

References

1. Folkeringa, N., Brouwer, J. L., Korteweg, F. J., Veeger, N. J., Erwich, J. J., van der Meer, J.. High risk of pregnancy-related venous thromboembolism in women with multiple thrombophilic defects. Br J Haematol; Jul 2007.

2. Friederich, P. W., Sanson, B. J., Simioni, P., Zanardi, S., Huisman, M. V., Kindt, I., Prandoni, P., Buller, H. R., Girolami, A., Prins, M. H.. Frequency of pregnancy-related venous thromboembolism in anticoagulant factor-deficient women: implications for prophylaxis. Ann Intern Med; Dec 15 1996.

3. Hull, R. D., Pineo, G. F., Stein, P. D., Mah, A. F., MacIsaac, S. M., Dahl, O. E., Butcher, M., Brant, R. F., Ghali, W. A., Bergqvist, D., Raskob, G. E.. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. Ann Intern Med; Nov 20 2001.

4. Mahmoodi, B. K., Brouwer, J. L., Ten Kate, M. K., Lijfering, W. M., Veeger, N. J., Mulder, A. B., Kluin-Nelemans, H. C., Van Der Meer, J.. A prospective cohort study on the absolute risks of venous thromboembolism and predictive value of screening asymptomatic relatives of patients with hereditary deficiencies of protein S, protein C or antithrombin. Journal of Thrombosis & Haemostasis; Jun 2010.

5. Martinelli, I., Legnani, C., Bucciarelli, P., Grandone, E., De Stefano, V., Mannucci, P. M.. Risk of pregnancy-related venous thrombosis in carriers of severe inherited thrombophilia. Thromb Haemost; Sep 2001.

6. Middeldorp, S., Libourel, E. J., Hamulyak, K., Van der Meer, J., Buller, H. R.. The risk of pregnancy-related venous thromboembolism in women who are homozygous for factor V Leiden. Br J Haematol; May 2001.

7. Tormene, D., Simioni, P., Prandoni, P., Luni, S., Zerbinati, P., Sartor, D., Franz, F., Girolami, A.. Factor V Leiden mutation and the risk of venous thromboembolism in pregnant women. Haematologica; Dec 2001.

8. van Boven, H. H., Vandenbroucke, J. P., Briet, E., Rosendaal, F. R.. Gene-gene and gene-environment interactions determine risk of thrombosis in families with inherited antithrombin deficiency. Blood; Oct 15 1999.

9. Rodger, M. A., Gris, J. C., de Vries, J. I. P., Martinelli, I., Rey, E., Schleussner, E., Middeldorp, S., Kaaja, R., Langlois, N. J., Ramsay, T., Mallick, R., Bates, S. M., Abheiden, C. N. H., Perna, A., Petroff, D., de Jong, P., van Hoorn, M. E., Bezemer, P. D., Mayhew, A. D., Low-Molecular-Weight Heparin for Placenta-Mediated Pregnancy Complications Study, Group. Low-molecular-weight heparin and recurrent placenta-mediated pregnancy complications: a meta-analysis of individual patient data from randomised controlled trials. Lancet; Nov 26 2016.

QUESTION

Should testing for the known familial thrombophilia and subsequent postpartum thromboprophylaxis in women positive for thrombophilia and no postpartum thromboprophylaxis in women negative for thrombophilia vs. no thrombophilia testing and no postpartum thromboprophylaxis in all be used for asymptomatic women who have a family history of VTE and a known thrombophilia in the family?

POPULATION:	asymptomatic women who have a family history of VTE and a known thrombophilia in the family
INTERVENTION:	testing for the known familial thrombophilia and subsequent postpartum thromboprophylaxis in women positive for thrombophilia and no postpartum thromboprophylaxis in women negative for thrombophilia
COMPARISON:	no thrombophilia testing and no postpartum thromboprophylaxis in all
MAIN OUTCOMES:	VTE - Homozygous Factor V Leiden - First-degree relatives; VTE - Antithrombin deficiency - First-degree relatives; VTE - Protein C deficiency - First-degree relatives; VTE - Protein S deficiency - First-degree relatives; VTE - Combination of Factor V Leiden & Prothrombin mutation combination - First-degree relatives; Major Bleeding - Antithrombin, Protein C, or Protein S deficiency - First-degree relatives; Major Bleeding - Homozygous Factor V Leiden (FVL), or combination of FVL & Prothrombin mutation - First-degree relatives;
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Inherited thrombophilia can be identified in many patients with a venous thromboembolism (VTE). Consequently, relatives of these patients are also at increased risk to have inherited thrombophilia which may put them at higher risk of VTE during pregnancy as well as after delivery. The currently most commonly tested inherited thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. Thrombophilia testing is often performed in relatives of patients with VTE and known thrombophilia in the family, particularly if they are pregnant. Although testing relatives of patients with a VTE and known thrombophilia in the family has a high chance of finding a positive test result, the relevant question and aim of the current guideline is to assess whether thrombophilia testing and tailoring management to the test result would improve patient important outcomes. This question addresses whether selective testing for the same thrombophilia type as the proband and subsequent thromboprophylaxis for 6 weeks in positive women improves patient important outcomes in postpartum relatives of patients with VTE and known inherited thrombophilia in the family, as compared with no thrombophilia testing and no thromboprophylaxis in all. Since no randomized controlled trials have addressed this question, we used a modeling exercise based on observational evidence for baseline risk, prevalence of thrombophilia and associated risk of events with thrombophilia, and RCTs with evidence for the effect of thromboprophylaxis on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes		As the ASH guidelines on VTE in the context of pregnancy recommended to use postpartum thromboprophylaxis in women with a family history of VTE and antithrombin deficiency, and suggested to use postpartum

○ Varies ○ Don't know		thromboprophylaxis in those with protein C, protein S, homozygous factor V Leiden or combined thrombophilias, this question is primarily relevant for women with these thrombophilia types in the family. A separate question in this guideline addressed selective testing in the antepartum period.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	See Evidence Profile.	Desirable effect = preventing VTE. VTE would be avoided in relatives who are positive for thrombophilia by using thromboprophylaxis. The panel assumed that postpartum thromboprophylaxis would be administered during 6 weeks. The panel considered that during pregnancy/postpartum period, DVT's are more severe and that PE's occur more frequently than in other populations. FVL homozygous, combination of FVL + PT, antithrombin: Moderate effect Protein C and S: Small effect <u>Second-degree relatives:</u> For modeling the effect in second-degree relatives we

		assumed a prevalence of 25% or 50% of the same thrombophilia type as the proband. Effect was not calculated for homozygous FVL. Effect estimates for VTE in second-degree relatives, per antepartum period (8 months): Combination of FVL + PT: 4.52 fewer per 1,000 (from 1.84 to 7.16 fewer) AT: 4.82 fewer per 1,000 (from 2.19 to 6.69 fewer) PC: 0.99 fewer per 1,000 (from 0.24 to 1.59 fewer) PS: 1.96 fewer per 1,000 (from 0.39 to 3.38 fewer)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	See Evidence Profile	Undesirable effect = causing major bleeding. Major bleedings would be caused in patients who are positive for thrombophilia by using thromboprophylaxis. Trivial: no increase in bleeding, in first- and second-degree relatives. Other potential adverse effects the panel considered, but were not quantified: skin reactions, reduced QoL, complications for planning the delivery.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows using a scale from 0 (worst possible scenario, usually death), to 1 (best possible scenario, usually perfect health): Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(1, 2, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3) **Gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off)(2, 3) **Minor intracranial bleeding event:** 0.75 (standard gamble)(2) **Major intracranial bleeding event:** 0.15 (standard gamble)(2) **Anticoagulant therapy** Patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome.(3) Patients would favor efficacy and safety over convenience of route of administration.(6) Also, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events.(7, 6, 8)	The panel considered clinicians may value avoiding major bleedings more (they do not want to cause harm), while patients may value avoiding VTE events and pregnancy complications more.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Homozygous FVL, combination of FVL + PT, Antithrombin, protein C, protein S: Probably favors the intervention.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Intervention Costs: <table><tr><th>Test (source)</th><td>Approximate Cost (2005)</td><td>Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016)</td><td>(14/12/2016) £1 = $1,27</td></tr><tr><td>Full Blood Count</td><td>£2.55</td><td>£3.29</td><td>$4,18</td></tr><tr><td>Protein C</td><td>£11.67</td><td>£15.5</td><td>$19,12</td></tr><tr><td>Free Protein S</td><td>£11.67</td><td>£15.5</td><td>$19,12</td></tr><tr><td>Antithrombin</td><td>£11.67</td><td>£15.5</td><td>$19,12</td></tr><tr><td>APCR</td><td>£10.73</td><td>£13.84</td><td>$17,58</td></tr><tr><td>Factor V Leiden</td><td>£85.00</td><td>£109.65</td><td>$141,45</td></tr><tr><td>Prothrombin gene mutation</td><td>£85.00</td><td>£109.65</td><td>$141,45</td></tr><tr><td>Lupus Anticoagulant</td><td>£10.73</td><td>£13.84</td><td>$17,58</td></tr><tr><td>Antiphospholipid antibodies</td><td>£12.30</td><td>£15.87</td><td>$20,15</td></tr><tr><td>Anti Beta-2 GP1 antibody</td><td>£9.50</td><td>£12.25</td><td>$15,81</td></tr><tr><td>The potential cost of a full thrombophilia screen</td><td>£250.82,</td><td>£323.56</td><td>$410,92</td></tr></table>Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx	- Cost for testing: 400$ -2000$ per patient - Thromboprophylaxis cost: 1000 $- 4500 per patient per year Costs for selective testing and 6 weeks course of thromboprophylaxis, as compared to no testing and no thromboprophylaxis. Costs for selective testing would be less than running full thrombophilia panels.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	In a prospective, unselected study with 113 pregnant women with a personal or family history of VTE, of whom only one had FVL and a VTE, selective FVL screening in these women resulted in an ICER of £7,535 assuming 50% reduction with prophylaxis, and £4,418 assuming 75% reduction with prophylaxis.(9) Based on a hypothetical model of 10,000 unselected pregnant women, in the absence of thrombophilia testing, adverse clinical complications would be found in 2921 pregnant women at a cost of £509,364. Universal testing of pregnant women would prevent 59 VTE events for an ICER of £81,554, and selective testing would prevent 7 VTE events for an ICER of £81,250.(10)	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(11)	The panel considered that the health system/service coverage/access to care will be the main aspect affecting health equity. USA is an example where promotion of testing that is not covered by insurance would generate inequities. I.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Pregnancy specific** Research studies suggested the following regarding acceptability and barriers associated with treatment in pregnancy: Four studies assessed several categories of acceptability depicted as compliance / adherence of different interventions for the prevention of thromboembolism during delivery(12), adherence to enoxaparin(13), and for adherence to guidelines recommendations in general in obstetric patient population(14). Compliance or acceptability was deemed rather adequate for postnatal thromboprophylaxis (83%), enoxaparin (93%) and for guidelines in obstetric patients in general (69%). No studies assessed affection of people's autonomy, disapproval of interventions, or disagreements with the values, costs, harms, or benefits. **Generic - Testing** Research studies suggested the following regarding acceptability and barriers associated with testing and treatment: **Patients:** A survey was conducted in members of a large family with heritable protein C deficiency. For those who had not been tested before, using a 7-point scale (1 - not at all interested; 7 extremely interested), the mean score for interest in testing interest was 4.6 (standard deviation 2.4). Patients in general were willing to take the test for thrombophilia.(15) A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(16) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in	The panel considered testing acceptable for many doctors, although maybe not for all. Patients are in general willing to undergo thrombophilia testing.

	the studies were limited to short-term follow-up, or lacked methodological accuracy.(17) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers:** A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(18) **Payers:** At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(19) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about proper indications might be a barrier causing overuse and overspending.(20) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(21) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(22) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(23)	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major potential problems or barriers for implementation. External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			

	JUDGEMENT						
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

Homozygous factor V Leiden, combination of factor V Leiden and prothrombin mutation, antithrombin, protein C, or protein S deficiency in first-degree relatives:

In first-degree relatives of patients with VTE and known homozygous factor V Leiden, combination of factor V Leiden and prothrombin mutation, antithrombin deficiency, protein C deficiency, or protein S deficiency in the family, the ASH guideline panel suggests testing for the known familial thrombophilia and postpartum thromboprophylaxis in first-degree relatives positive for thrombophilia over no testing for thrombophilia and no postpartum thromboprophylaxis in all first-degree relatives (conditional recommendation based on very low certainty in the evidence about effects)

Combination of factor V Leiden and prothrombin mutation, or antithrombin deficiency in second-degree relatives:

In second-degree relatives of patients with VTE and known combination of factor V Leiden and prothrombin mutation, or antithrombin deficiency in the family, the ASH guideline panel suggests testing for the known familial thrombophilia and postpartum thromboprophylaxis in second-degree relatives positive for thrombophilia over no testing for thrombophilia and no postpartum thromboprophylaxis in all second-degree relatives

(conditional recommendation based on very low certainty in the evidence about effects)

Protein C or protein S deficiency in first- and second-degree relatives:

In first- and second-degree relatives of patients with VTE and known protein C or protein S deficiency in the family, the ASH guideline panel suggests either testing for the known familial thrombophilia and postpartum thromboprophylaxis in relatives positive for thrombophilia or not testing for thrombophilia and no postpartum thromboprophylaxis in all relatives (conditional recommendation based on very low certainty in the evidence about effects)

Remarks:

- Pharmacological hromboprophylaxis postpartum continues until 6 weeks after delivery.

- Conditions can include the duration and burden of the treatment, which involves injections, and patient preference.

- A strategy with selective testing for the known familial thrombophilia type would mean that positive relatives would receive thromboprophylaxis, and negative relatives would receive no thromboprophylaxis.

- For homozygous FVL, these recommendations only concern siblings, not children. Management of second-degree relatives was not addressed.

- These recommendations do not address heterozygous FVL or PT mutation alone, as the ASH guidelines on the management of VTE in the context of pregnancy suggest not to prescribe thromboprophylaxis in these patients, and patient outcomes would not be affected by thrombophilia testing.

Justification

The panel considered that thrombophilia testing and thromboprophylaxis in positive women likely has some benefit in terms of prevention of VTE that outweighs the risk of major bleeding in relatives of patients with VTE and who have a very high risk thrombophilia in the family (homozygous FVL, combination of FVL + PT, antithrombin), and only in first-degree but not second-degree relatives of patients with VTE and who have a somewhat lower risk thrombophilia in the family (protein C or S).

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation. This includes testing for protein S, protein C and antithrombin deficiency during pregnancy.

Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

Future research will need to provide higher certainty evidence on the effect of selective testing for thrombophilias, and consequent postpartum prophylaxis in test positives.

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
7. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
8. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
9. Clark, P., Twaddle, S., Walker, I. D., Scott, L., Greer, I. A.. Cost-effectiveness of screening for the factor V Leiden mutation in pregnant women. Lancet; Jun 1 2002.
10. Wu, O., Robertson, L., Twaddle, S., Lowe, G. D., Clark, P., Greaves, M., Walker, I. D., Langhorne, P., Brenkel, I., Regan, L., Greer, I.. Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. Health Technol Assess; Apr 2006.
11. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
12. Hordern, C. E., Bircher, C. W., Prosser-Snelling, E. C., Fraser, F. K., Smith, R. P.. Patient compliance with postnatal thromboprophylaxis: An observational study. J Obstet Gynaecol; 2015.
13. Patel, J. P., Auyeung, V., Patel, R. K., Marsh, M. S., Green, B., Arya, R., Davies, J. G.. Women's views on and adherence to low-molecular-weight heparin therapy during pregnancy and the puerperium. Journal of Thrombosis & Haemostasis; Dec 2012.
14. Cregan, A., Higgins, J. R., O'Shea, S.. Implementation of thromboprophylaxis guidelines. Ir Med J; Mar 2013.
15. van Korlaar, I. M., Vossen, C. Y., Rosendaal, F. R., Bovill, E. G., Naud, S., Cameron, L. D., Kaptein, A. A.. Attitudes toward genetic testing for thrombophilia in asymptomatic members of a large family with heritable protein C deficiency. Journal of Thrombosis & Haemostasis; Nov 2005.
16. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
17. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
18. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
19. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
20. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
21. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
22. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
23. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In asymptomatic women who have a family history of VTE and a known thrombophilia in the family, should testing for the known familial thrombophilia and subsequent postpartum thromboprophylaxis in women positive for thrombophilia and no postpartum thromboprophylaxis in women negative for thrombophilia compared to no thrombophilia testing and no postpartum thromboprophylaxis in all be used?

Setting:

Bibliography: See reference list and footnotes. [1,2,3,4,5,6,7,8,9]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
VTE - Homozygous Factor V Leiden - First-degree relatives (follow up: postpartum period (6 weeks); assessed with: any first-time DVT or PE)									
3 [a,b,c]	observational studies	not serious	not serious	serious [d]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and homozygous factor V Leiden (FVL) in the family for homozygous FVL and treating the 250 positives with postpartum pharmacological thromboprophylaxis, 18.15 VTE events will occur per postpartum period (ranging from 13.36 to 25.34). When not testing 1,000 asymptomatic women and treating none of them with postpartum pharmacological thromboprophylaxis, 37.5 VTE events will occur per postpartum period. Therefore, a thrombophilia testing strategy is associated with 250 more women treated with pharmacological thromboprophylaxis and **19.35 fewer VTE events (ranging from 12.16 to 24.14)** per 1,000 patients per postpartum period compared with a no testing strategy. [e]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Antithrombin deficiency - First-degree relatives (follow up: postpartum period (6 weeks); assessed with: any first-time DVT or PE)									
5 [c,f,g]	observational studies	not serious	not serious	serious [d]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and antithrombin deficiency (AT) in the family for AT and treating the 500 positives with postpartum pharmacological thromboprophylaxis, 8.30 VTE events will occur per postpartum period (ranging from 6.03 to 12.10). When not testing 1,000 asymptomatic women and treating none of them with postpartum pharmacological thromboprophylaxis, 18.0 VTE events will occur per postpartum period. Therefore, a selective thrombophilia testing strategy is associated with 500 more women treated with pharmacological thromboprophylaxis and **9.70 fewer VTE events (ranging from 5.90 to 11.97)** per 1,000 women per postpartum period compared with a no testing strategy. [h]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Protein C deficiency - First-degree relatives (follow up: postpartum period (6 weeks); assessed with: any first-time DVT or PE)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
4 [c,i,j]	observational studies	not serious	not serious	serious [d]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and protein C deficiency (PC) in the family for PC and treating the 500 positives with postpartum pharmacological thromboprophylaxis, 1.98 VTE events will occur per postpartum period (ranging from 1.34 to 3.18). When not testing 1,000 asymptomatic women and treating none of them with postpartum pharmacological thromboprophylaxis, 4 VTE events will occur per postpartum period. Therefore, a selective thrombophilia testing strategy is associated with 500 more women treated with pharmacological thromboprophylaxis and **2.02 fewer VTE events (ranging from 0.82 to 2.66)** per 1,000 women per postpartum period compared with a no testing strategy. [k]	⨁◯◯◯ VERY LOW	CRITICAL

VTE - Protein S deficiency - First-degree relatives (follow up: postpartum period (6 weeks); assessed with: any first-time DVT or PE)

4 [c,i,j]	observational studies	not serious	not serious	serious [d]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and protein S deficiency (PS) in the family for PS and treating the 500 positives with postpartum pharmacological thromboprophylaxis, 4.06 VTE events will occur per postpartum period (ranging from 2.68 to 6.66). When not testing 1,000 asymptomatic women and treating none of them with postpartum pharmacological thromboprophylaxis, 8 VTE events will occur per postpartum period. Therefore, a selective thrombophilia testing strategy is associated with 500 more women treated with pharmacological thromboprophylaxis and **3.94 fewer VTE events (ranging from 1.34 to 5.32)** per 1,000 women per postpartum period compared with a no testing strategy. [l]	⨁◯◯◯ VERY LOW	CRITICAL

VTE - Combination of Factor V Leiden & Prothrombin mutation combination - First-degree relatives (follow up: postpartum period (6 weeks); assessed with: any first-time DVT or PE)

3 [a,c]	observational studies	not serious	not serious	serious [d]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and the combination of factor V Leiden (FVL) plus prothrombin mutation (PT) in the family for the same combination and treating the 250 positives with postpartum pharmacological thromboprophylaxis, 11.20 VTE events will occur per postpartum period (ranging from 7.92 to 15.62). When not testing 1,000 asymptomatic women and treating none of them with postpartum pharmacological thromboprophylaxis, 20.3 VTE events will occur per postpartum period. Therefore, a selective thrombophilia testing strategy is associated with 250 more women treated with pharmacological thromboprophylaxis and **9.05 fewer VTE events (ranging from 4.63 to 12.33)** per 1,000 women per postpartum compared with a no testing strategy. [m]	⨁◯◯◯ VERY LOW	CRITICAL

Major Bleeding - Antithrombin, Protein C, or Protein S deficiency - First-degree relatives (follow up: postpartum period (6 weeks))

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
2 [n]	observational studies	not serious	not serious	serious [o]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and antithrombin, protein C, or protein S deficiency (AT, PC, PS) in the family for the same thrombophilia, and treating the 500 positives with postpartum pharmacological thromboprophylaxis, 4.25 major bleedings will occur per postpartum period (ranging from 3.30 to 13.35). When not testing 1,000 asymptomatic women and treating none of them with postpartum pharmacological thromboprophylaxis, 6.34 major bleedings will occur per postpartum period. Therefore, a selective thrombophilia testing strategy is associated with 500 more women treated with pharmacological thromboprophylaxis and **2.09 fewer major bleedings (ranging from 3.04 fewer to 7.01 more)** per 1,000 women per postpartum period compared with a no testing strategy. [p]	⨁◯◯◯ VERY LOW	CRITICAL

Major Bleeding - Homozygous Factor V Leiden (FVL), or combination of FVL & Prothrombin mutation - First-degree relatives (follow up: postpartum period (6 weeks))

2 [n]	observational studies	not serious	not serious	serious [o]	not serious	none	When testing 1,000 asymptomatic women with a family history of VTE and either homozygous Factor V Leiden (FVL), or combination of FVL and prothrombin mutation (PT) in the family for the same thrombophilia, and treating the 250 positives with postpartum pharmacological thromboprophylaxis, 5.29 major bleedings will occur per postpartum period (ranging from 4.82 to 9.84). When not testing 1,000 asymptomatic women and treating none of them with postpartum pharmacological thromboprophylaxis, 6.34 major bleedings will occur per postpartum period. Therefore, a selective thrombophilia testing strategy is associated with 250 more women treated with pharmacological thromboprophylaxis and **1.05 fewer major bleedings (ranging from 1.52 fewer to 3.50 more)** per 1,000 women per postpartum period compared with a no testing strategy. [q]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE & Risk association for FVL homozygous positive versus negative, 2 studies; Thromboprophylaxis effect, 1 RCT

b. Overall risk for VTE & thrombophilia positive vs negative risk association: Martinelli 2001, Tormene 2001

c. Effect of thromboprophylaxis: Hull 2001

d. The effect was indirectly calculated using separate studies for overall risk for first-time VTE, relative risk of thrombophilia positives vs negatives, and the effect of thromboprophylaxis.

e. Based on the following estimates: Overall risk for VTE recurrence, 37.5 per 1,000; Prevalence of same thrombophilia, 25%; Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 20.96 (95%CI: 7.17-53.34); Relative risk of VTE recurrence with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.41 (0.32-0.54). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

f. Number of studies used in calculations: Overall risk for VTE & Risk association for FVL homozygous positive versus negative, 4 studies; Thromboprophylaxis effect, 1 RCT

g. Overall risk for VTE & AT positive vs negative risk association: Folkeringa 2007, Friederich 1996, Mahmoodi 2010, van Boven 1999

h. Based on the following estimates: Overall risk for VTE recurrence, 18 per 1,000; Prevalence of same thrombophilia, 50%; Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 10.51 (95%CI: 2.48-44.54); Relative risk of VTE recurrence with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.41 (0.32-0.54). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

i. Number of studies used in calculations: Overall risk for VTE & Risk association for FVL homozygous positive versus negative, 3 studies; Thromboprophylaxis effect, 1 RCT

j. Overall risk for VTE & thrombophilia positive vs negative risk association: Folkeringa 2007, Friederich 1996, Mahmoodi 2010

k. Based on the following estimates: Overall risk for VTE recurrence, 4 per 1,000; Prevalence of same thrombophilia, 50%; Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 6.04 (95%CI: 0.81-45.19); Relative risk of VTE recurrence with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.41 (0.32-0.54). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

l. Based on the following estimates: Overall risk for VTE recurrence, 8 per 1,000; Prevalence of same thrombophilia, 50%; Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 5.03 (95%CI: 0.57-44.51); Relative risk of VTE recurrence with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.41 (0.32-0.54). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

m. Based on the following estimates: Overall risk for VTE recurrence, 20.25 per 1,000; Prevalence of same thrombophilia, 25%; Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 9.36 (95%CI: 2.97-25.66); Relative risk of VTE recurrence with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.41 (0.32-0.54). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, higher CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

n. Number of studies used in calculations: Overall risk & effect of anticoagulation, 1 systematic review.

o. The effect was indirectly calculated using separate studies for overall risk, thrombophilia prevalence and the effect of prophylaxis.

p. Based on the following estimates: Overall risk for Major bleeding of 6.34 per 1,000; Prevalence of same thrombophilia, 50%; Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.34 (0.04-3.21). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the smallest treatment effect (lower CI).

q. Based on the following estimates: Overall risk for Major bleeding of 6.34 per 1,000; Prevalence of same thrombophilia, 25%; Relative risk of Major bleeding with extended anticoagulation treatment versus discontinuation after the acute treatment period, RR 0.34 (0.04-3.21). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the smallest treatment effect (lower CI).

References

1. Rodger, M. A., Gris, J. C., de Vries, J. I. P., Martinelli, I., Rey, E., Schleussner, E., Middeldorp, S., Kaaja, R., Langlois, N. J., Ramsay, T., Mallick, R., Bates, S. M., Abheiden, C. N. H., Perna, A., Petroff, D., de Jong, P., van Hoorn, M. E., Bezemer, P. D., Mayhew, A. D., Low-Molecular-Weight Heparin for Placenta-Mediated Pregnancy Complications Study, Group. Low-molecular-weight heparin and recurrent placenta-mediated pregnancy complications: a meta-analysis of individual patient data from randomised controlled trials. Lancet; Nov 26 2016.

2. Folkeringa, N., Brouwer, J. L., Korteweg, F. J., Veeger, N. J., Erwich, J. J., van der Meer, J.. High risk of pregnancy-related venous thromboembolism in women with multiple thrombophilic defects. Br J Haematol; Jul 2007.

3. Friederich, P. W., Sanson, B. J., Simioni, P., Zanardi, S., Huisman, M. V., Kindt, I., Prandoni, P., Buller, H. R., Girolami, A., Prins, M. H.. Frequency of pregnancy-related venous thromboembolism in anticoagulant factor-deficient women: implications for prophylaxis. Ann Intern Med; Dec 15 1996.

4. Hull, R. D., Pineo, G. F., Stein, P. D., Mah, A. F., MacIsaac, S. M., Dahl, O. E., Butcher, M., Brant, R. F., Ghali, W. A., Bergqvist, D., Raskob, G. E.. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. Ann Intern Med; Nov 20 2001.

5. Mahmoodi, B. K., Brouwer, J. L., Ten Kate, M. K., Lijfering, W. M., Veeger, N. J., Mulder, A. B., Kluin-Nelemans, H. C., Van Der Meer, J.. A prospective cohort study on the absolute risks of venous thromboembolism and predictive value of screening asymptomatic relatives of patients with hereditary deficiencies of protein S, protein C or antithrombin. Journal of Thrombosis & Haemostasis; Jun 2010.

6. Martinelli, I., Legnani, C., Bucciarelli, P., Grandone, E., De Stefano, V., Mannucci, P. M.. Risk of pregnancy-related venous thrombosis in carriers of severe inherited thrombophilia. Thromb Haemost; Sep 2001.

7. Middeldorp, S., Libourel, E. J., Hamulyak, K., Van der Meer, J., Buller, H. R.. The risk of pregnancy-related venous thromboembolism in women who are homozygous for factor V Leiden. Br J Haematol; May 2001.

8. Tormene, D., Simioni, P., Prandoni, P., Luni, S., Zerbinati, P., Sartor, D., Franz, F., Girolami, A.. Factor V Leiden mutation and the risk of venous thromboembolism in pregnant women. Haematologica; Dec 2001.

9. van Boven, H. H., Vandenbroucke, J. P., Briet, E., Rosendaal, F. R.. Gene-gene and gene-environment interactions determine risk of thrombosis in families with inherited antithrombin deficiency. Blood; Oct 15 1999.

QUESTION

Should testing for any hereditary thrombophilia and subsequent thromboprophylaxis in patients positive for thrombophilia and no thromboprophylaxis in patients negative for thrombophilia vs. no thrombophilia testing and no thromboprophylaxis in all be used for ambulatory patients with cancer without a personal history of VTE and a family history of VTE, who are at low or intermediate risk for VTE?

POPULATION:	ambulatory patients with cancer without a personal history of VTE and a family history of VTE, who are at low or intermediate risk for VTE
INTERVENTION:	testing for any hereditary thrombophilia and subsequent thromboprophylaxis in patients positive for thrombophilia and no thromboprophylaxis in patients negative for thrombophilia
COMPARISON:	no thrombophilia testing and no thromboprophylaxis in all
MAIN OUTCOMES:	VTE (first-time); Major bleeding
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	**General background for the guideline**: Inherited thrombophilia can be identified in many patients with a venous thromboembolism (VTE). Consequently, relatives of these patients are also at increased risk to have inherited thrombophilia. The currently most commonly tested inherited thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or procoagulant pathways. Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel. Thrombophilia testing is often performed in relatives of patients with VTE, particularly if they are in a risk episode such as immobilization, or have a risk factor such as cancer. Although testing relatives of patients with a VTE has a high chance of finding a positive test result, the relevant question and aim of the current guideline is to assess whether thrombophilia testing and tailoring management to the test result would improve patient important outcomes. This question addresses whether testing for any inherited thrombophilia and subsequent thromboprophylaxis in positive relatives improves important outcomes in relatives of patients with VTE who also are being treated for cancer in the ambulatory setting and are at low or intermediate risk for VTE, as compared with no thrombophilia testing and no thromboprophylaxis in all. Since no randomized controlled trials have addressed this question, we used a modeling exercise based on observational evidence for baseline risk, prevalence of thrombophilia and associated risk of events with thrombophilia, and RCTs with evidence for the effect of thromboprophylaxis on patient-important outcomes.
CONFLICT OF INTEREST:	No COI

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		This question only addresses patients at low or intermediate risk for VTE. The ASH VTE guidelines on prevention and treatment in patients with cancer suggests to use DOAC prophylaxis in all ambulatory cancer patients with high VTE risk.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Evidence Profile.	Desirable effect = preventing VTE. VTE would be avoided in relatives who are positive for thrombophilia by using thromboprophylaxis.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	See Evidence Profile.	Undesirable effect = causing major bleeding. Major bleedings would be caused in patients who are positive for thrombophilia by using thromboprophylaxis.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes is as follows using a scale from 0 (worst possible scenario, usually death), to 1 (best possible scenario, usually perfect health): Pulmonary embolism:** 0.63-0.93 (different methods)(1, 2, 3) **Deep vein thrombosis:** 0.64-0.99 (different methods)(1, 2, 3, 4, 5) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off)(3) **Gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off)(2, 3) **Minor intracranial bleeding event:** 0.75 (standard gamble)(2) **Major intracranial bleeding event:** 0.15 (standard gamble)(2) **Anticoagulant therapy** Patients highly value the benefits of risk reduction in VTE recurrence and post-thrombosis syndrome.(3) Patients would favor efficacy and safety over convenience of route of administration.(6) Also, patients would like to avoid adverse events but most of them are "not afraid of" the adverse events.(7, 6, 8)	The panel considered clinicians may value avoiding major bleedings more (they do not want to cause harm), while patients may value avoiding VTE events more (they prefer avoiding a recurrence of clots).

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		**The panel considered the following cost ranges:** - Cost for testing: $400 -$2,000 per patient - Cost for treatment: $1,000-$ 4,500 per patient per year Costs for testing all hereditary thrombophilia types and short course of thromboprophylaxis, as compared to no

	Intervention Costs: **Cost of the health outcomes:**(9) - **Recurrent VTE:** 11,000 to 15,000 USD - **Major bleeding:** 11,000 to 22,000 USD **Cost of interventions:**(10) - **Dabigatran:** Cost per month: $300.44–$600.88 USD - **Rivaroxaban:** Cost per month: $300.42–$600.84 USD - **Apixaban:** Cost per month: $300.44–$600.88	testing and no thromboprophylaxis.

Test (source)	Approximate Cost (2005)	Approximate Cost (2016) (£1 in 2005 = £1.29 in 2016)	(14/12/2016) £1 = $1,27
Full Blood Count	£2.55	£3.29	**$4,18**
Protein C	£11.67	£15.5	**$19,12**
Free Protein S	£11.67	£15.5	**$19,12**
Antithrombin	£11.67	£15.5	**$19,12**
APCR	£10.73	£13.84	**$17,58**
Factor V Leiden	£85.00	£109.65	**$141,45**
Prothrombin gene mutation	£85.00	£109.65	**$141,45**
Lupus Anticoagulant	£10.73	£13.84	**$17,58**
Antiphospholipid antibodies	£12.30	£15.87	**$20,15**
Anti Beta-2 GP1 antibody	£9.50	£12.25	**$15,81**
The potential cost of a full thrombophilia screen	£250.82,	£323.56	**$410,92**

Source: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/ThrombophilliaScreeningCG.aspx

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Qualitative research from one study suggests that patients from lower socioeconomic groups may be disadvantaged with respect to testing, with the following reasons for the disadvantage: The qualitative study conducted in the UK showed that patients undergoing genetic testing for thrombophilia (factor V Leiden) often experience difficulty understanding genetic information and interpreting results. Those from higher socio-economic groups had a better understanding of genetic testing and were more likely to look up prevention-related information than those from lower socioeconomic groups. Participants with a positive test result and more knowledge estimated their overall risks to be lower than those with a positive test result and limited knowledge.(11)	The panel considered that the health system/service coverage/access to care will be the main aspect affecting health equity. USA is an example where promotion of testing that is not covered by insurance would generate inequities. I.e. prothrombin testing fees were increasingly not being reimbursed by insurance companies.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Research studies suggested the following regarding acceptability and barriers associated with testing and treatment: **Patients:** A survey was conducted in members of a large family with heritable protein C deficiency. For those who had not been tested before, using a 7-point scale (1 - not at all interested; 7 extremely interested), the mean score for interest in testing interest was 4.6 (standard deviation 2.4). Patients in general were willing to take the test for thrombophilia.(12) A cross sectional survey found that 79% of patients who tested positive for factor V Leiden incorrectly estimated their risk for VTE. 64% indicated they did not receive enough information on the meaning and implications of the genetic test. Although a positive test result increased worry for 43%, 88% of patients were glad to know their test results.(13) Studies of psychological impact of genetic testing for thrombophilia report few negative results. However, no valid conclusions can be drawn since most assessments in the studies were limited to short-term follow-up, or lacked methodological accuracy.(14) Social effects including labelling and difficulty getting health insurance are a concern. A positive test result for hereditary thrombophilia also elicits questions and concerns about relatives. **Health care providers:** A Canadian survey found that family physicians were more likely than experts to order thrombophilia testing for males, obese patients, those with a family history of myocardial infarction or infertility, pediatric patients, or those with a recent event (p 0.043), but were significantly less likely than experts to test a patient with VTE after a long flight (p= 0.038).(15) **Payers:** At present, thrombophilia testing is discouraged and in some health care settings not reimbursed.	The panel considered testing acceptable for many doctors, although maybe not for all. Patients are in general willing to undergo thrombophilia testing, although adding one more test to patients receiving cancer care may be less acceptable.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Research studies reported the following regarding feasibility of thrombophilia testing: One study assessed implementation of local guidelines for appropriate thrombophilia testing, primarily to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, and showed that twenty-two months after guideline implementation, there was an 84% reduction in ordered tests. This study revealed that a significant proportion of thrombophilia testing was inappropriately performed.(16) Observational evidence showed that 19% of lupus anticoagulant testing was ordered for an improper indication, and inadequate provider awareness about	Provider “lack of awareness” of proper indications for thrombophilia testing and appropriate prescription, sampling modalities and laboratory determination of a panel of relevant thrombophilia tests could be a barrier to optimal implementation of thrombophilia testing recommendations. The panel did not see any other major

	proper indications might be a barrier causing overuse and overspending.(17) In addition, an external quality assurance program among USCAP laboratories showed that 98% of tests for anithrombin, protein C and protein S were within recommended ranges, with the highest accuracy being for antithrombin.(18) A non-randomized controlled study showed that the use of pre-printed order forms outlining the limitations of in-hospital heritable thrombophilia testing was associated with a reduction in Factor V Leiden test ordering.(19) A retrospective review of thrombophilia screening panels in a US hospital revealed an over-utilization of thrombophilia testing, with screening often done in suboptimal circumstances such as acute thrombosis, pregnancy, or anticoagulation. Of 200 panels reviewed, 62% were inappropriately ordered and 20% had abnormal protein C and S results (of which 63% were attributable to anticoagulation with warfarin, and 38% to pregnancy). VTE was the most common indication for screening (51.7%) of which 69.5% of results were negative. Females were tested much more frequently with a female/male ratio of 2:1.(20)	potential problems or barriers for implementation. External quality assurance programs can aid in ensuring standardized and accurate thrombophilia testing across laboratories.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

In ambulatory cancer patients without a personal history of VTE, and who are first-degree relatives of a patient with VTE and are at low or intermediate risk for VTE, the ASH guideline panel suggests testing for any hereditary thrombophilia and thromboprophylaxis in positive patients over no testing for thrombophilia and no thromboprophylaxis in all patients (conditional recommendation based on very low certainty of the evidence about effects)

Remarks

- This question only addresses patients at low or intermediate risk for VTE. The ASH VTE guidelines on prevention and treatment in patients with cancer suggest using direct oral anticoagulant prophylaxis in all ambulatory cancer patients with high VTE risk.

- Patient preference is an important condition to consider, as it can be an added burden for cancer patients in terms of undergoing the thrombophilia test, knowing the positive test result, and receiving additional medication

- A strategy with testing for any hereditary thrombophilia would mean that positive relatives receive thromboprophylaxis, and negative relatives would receive no thromboprophylaxis.

- This recommendation does not address homozygous defects, or combinations of thrombophilia types.

Justification

The panel considered that thrombophilia testing and prophylaxis in positive relatives likely has benefit in terms of prevention of VTE that outweighs the risk of major bleeding in cancer patients without a personal history of VTE and with a family history of VTE.

Subgroup considerations

No subgroup considerations.

Implementation considerations

In this guideline, the panel has not considered the existence of pitfalls in the testing results, but clinicians ordering testing will need to consider the knowledge of false positives, false negatives and inconclusive results demanding multiple test performance for their interpretation.

Provider lack of awareness of proper indications for thrombophilia testing could be a barrier to optimal implementation of thrombophilia testing recommendations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

No research priorities.

REFERENCES SUMMARY

1. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
4. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
5. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
6. Noble, S., Matzdorff, A., Maraveyas, A., Holm, M. V., Pisa, G.. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica; Nov 2015.
7. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
8. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
9. Grosse, S. D., Nelson, R. E., Nyarko, K. A., Richardson, L. C., Raskob, G. E.. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res; Jan 2016.
10. Biskupiak, J., Ghate, S. R., Jiao, T., Brixner, D.. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. J Manag Care Pharm; Nov-Dec 2013.
11. Saukko, P. M., Ellard, S., Richards, S. H., Shepherd, M. H., Campbell, J. L.. Patients' understanding of genetic susceptibility testing in mainstream medicine: qualitative study on thrombophilia. BMC Health Serv Res; Jun 12 2007.
12. van Korlaar, I. M., Vossen, C. Y., Rosendaal, F. R., Bovill, E. G., Naud, S., Cameron, L. D., Kaptein, A. A.. Attitudes toward genetic testing for thrombophilia in asymptomatic members of a large family with heritable protein C deficiency. Journal of Thrombosis & Haemostasis; Nov 2005.
13. Hellmann, E. A., Leslie, N. D., Moll, S.. Knowledge and educational needs of individuals with the factor V Leiden mutation. Journal of Thrombosis & Haemostasis; Nov 2003.
14. Cohn, D. M., Vansenne, F., Kaptein, A. A., De Borgie, C. A., Middeldorp, S.. The psychological impact of testing for thrombophilia: a systematic review. Journal of Thrombosis & Haemostasis; Jul 2008.
15. Schneider-MacRae, N., Jackson, S. C., Valentine, K. A., Lockyer, J., Poon, M. C.. A study of thrombophilia testing and counseling practices of family physicians using the script concordance method in Calgary, Canada. Clin Appl Thromb Hemost; Jul 2012.
16. Shen, Y. M., Tsai, J., Taiwo, E., Gavva, C., Yates, S. G., Patel, V., Frenkel, E., Sarode, R.. Analysis of Thrombophilia Test Ordering Practices at an Academic Center: A Proposal for Appropriate Testing to Reduce Harm and Cost. PLoS ONE [Electronic Resource]; 2016.
17. Aljabry, M. S.. Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources. Ann Saudi Med; Sep-Oct 2015.
18. Cunningham, M. T., Olson, J. D., Chandler, W. L., Van Cott, E. M., Eby, C. S., Teruya, J., Hollensead, S. C., Adcock, D. M., Allison, P. M., Kottke-Marchant, K. K., Smith, M. D.. External quality assurance of antithrombin, protein C, and protein s assays: results of the College of American Pathologists proficiency testing program in thrombophilia. Arch Pathol Lab Med; Feb 2011.
19. Smith, T. W., Pi, D., Hudoba, M., Lee, A. Y.. Reducing inpatient heritable thrombophilia testing using a clinical decision-making tool. J Clin Pathol; Apr 2014.
20. Somma, J., Sussman, ,II, Rand, J. H.. An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. Am J Clin Pathol; Jul 2006.

Question: In ambulatory patients with cancer without a personal history of VTE and a family history of VTE, who are at low or intermediate risk for VTE, should testing for any hereditary thrombophilia and subsequent thromboprophylaxis in patients positive for thrombophilia and no thromboprophylaxis in patients negative for thrombophilia compared to no thrombophilia testing and no thromboprophylaxis in all patients be used?

Setting:

Bibliography: See reference list and footnotes. [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
VTE - Low risk for VTE (5.0%) - First-degree relatives (follow up: 6 months; assessed with: any first-time DVT or PE)									
38 [a,b,c,d,e,f]	observational studies	not serious	not serious	serious [g]	serious [h]	none	When testing 1,000 low-risk patients with cancer who are without a personal history of VTE, and who are first-degree relatives of patients with VTE, for any hereditary thrombophilia, and treating the 142 positives with thromboprophylaxis (ranging from 99 to 201), 43.15 VTE events will occur per 6 months (ranging from 26.63 to 50.16). When not testing 1,000 low-risk cancer patients for thrombophilia, and treating none of them with thromboprophylaxis, 50 VTE events will occur per 6 months. Therefore, a thrombophilia testing strategy is associated with 142 more patients treated with thromboprophylaxis (ranging from 99 to 201) and **6.85 fewer VTE events (ranging from 23.37 fewer to 0.16 more)** per 1,000 cancer patients per 6 months compared with a no testing strategy. [i]	⨁◯◯◯ VERY LOW	CRITICAL
VTE - Intermediate risk for VTE (6.6%) - First-degree relatives (follow up: 6 months; assessed with: any first-time DVT or PE)									
38 [a,b,c,d,e,f]	observational studies	not serious	not serious	serious [g]	serious [h]	none	When testing 1,000 intermediate-risk patients with cancer without a personal history of VTE, and who are first-degree relatives of patients with VTE, for any hereditary thrombophilia, and treating the 142 positives with thromboprophylaxis (ranging from 99 to 201), 56.96 VTE events will occur per 6 months (ranging from 35.15 to 66.21). When not testing 1,000 intermediate-risk cancer patients for thrombophilia, and treating none of them with thromboprophylaxis, 66 VTE events will occur per 6 months. Therefore, a thrombophilia testing strategy is associated with 142 more patients treated with thromboprophylaxis (ranging from 99 to 201) and **9.04 fewer VTE events (ranging from 30.85 fewer to 0.21 more)** per 1,000 intermediate-risk patients per 6 months compared with a no testing strategy. [j]	⨁◯◯◯ VERY LOW	CRITICAL
Major Bleeding - Low risk for VTE (0.36%) - First-degree relatives (follow up: 6 months)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
24 [c,d,f,k,l]	observational studies	not serious	not serious	serious [m]	not serious	none	When testing 1,000 low-risk patients with cancer without a personal history of VTE, and who are first-degree relatives of patients with VTE, for any hereditary thrombophilia, and treating the 142 positives with thromboprophylaxis (ranging from 99 to 201), 3.93 major bleedings will occur per 6 months (ranging from 3.50 to 5.62). When not testing 1,000 low-risk cancer patients for thrombophilia and treating none of them with thromboprophylaxis, 3.6 major bleedings will occur per 6 months. Therefore, a thrombophilia testing strategy is associated with 142 more patients treated with thromboprophylaxis (ranging from 99 to 201) and **0.33 more major bleedings (ranging from 0.10 fewer to 2.02 more)** per 1,000 low-risk patients per 6 months compared with a no testing strategy. [n]	⨁◯◯◯ VERY LOW	CRITICAL

Major Bleeding - Intermediate risk for VTE (0.8%) - First-degree relatives (follow up: 6 months)

24 [c,d,f,k,l]	observational studies	not serious	not serious	serious [m]	not serious	none	When testing 1,000 intermediate-risk patients with cancer without a personal history of VTE, and who are first-degree relatives of patients with VTE, for any hereditary thrombophilia, and treating the 142 positives with thromboprophylaxis (ranging from 99 to 201), 8.74 major bleedings will occur per 6 months (ranging from 7.78 to 12.49). When not testing 1,000 intermediate-risk cancer patients for thrombophilia, and treating none of them with thromboprophylaxis, 8 major bleedings will occur per 6 months. Therefore, a thrombophilia testing strategy is associated with 142 more patients treated with thromboprophylaxis (ranging from 99 to 201) and **0.74 more major bleedings (ranging from 0.22 fewer to 4.49 more)** per 1,000 intermediate-risk patients per 6 months compared with a no testing strategy. [o]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Number of studies used in calculations: Overall risk for VTE, 1 systematic review; Prevalence, 20 studies; Risk association for thrombophilia positive versus negative, 14 studies (all also reported Prevalence); Extended anticoagulation effect, 3 RCTs

b. Overall risk for VTE: Mulder 2019

c. Thrombophilia prevalence in VTE patients, used for calculation: Bezemer 2009, Cebi 2009, Di Minno 2014, Garcia-Fuster 2005, Heit 2010, Kearon 1999, Kearon 2018, Lim 2017, Mello 2010, Meyer 2015, Olie 2011, Palareti 2003, Prandoni 2007, Roldan 2009, Rossi 2008, Santamaria 2005, Schattner 1997, Schulman 2006, Sundquist 2015, Weingarz 2015

d. Prevalence of specific thrombophilia types in VTE patients, used to verify calculation estimate: Ahmad 2016, Ahmad 2016, Ahmad 2017, Asim 2017, Baarslag 2004, Baglin 2003, Brouwer 2009, Bruwer 2016, Christiansen 2005, De Stefano 1999, De Stefano 2006, Eichinger 1999, Eichinger 2002, Eischer 2017, Gonzalez-Porras 2006, Heijboer 1990, Hirmerova 2014, Hoibraaten 2000, Kearon 2008, Laczkovics 2007, Lee 2017, Lijfering 2010, Lindmarker 1999, Marcucci 2003, Mateo 1997, Miles 2001, Ridker 1995, Rodger 2008, Roupie 2016, Rupa-Matysek 2014, Simioni 2000, Sonnevi 2013, Strandberg 2007, Sveinsdottir 2012, The Procare group 2003, Wahlander 2006

e. Thrombophilia positive vs negative risk association: Bank 2004, Brouwer 2005, Brouwer 2006, Cohen 2012, Coppens 2006, Couturaud 2006, Faioni 1999, Lensen 2001, Mahmoodi 2010, Martinelli 1998, Martinelli 2000, Middeldorp 1998, Simioni 1999, Simioni 2002

f. Effect of DOAC thrombopohylaxis: Carrier 2019, Khorana 2019, Levine 2012

g. The effect was indirectly calculated using separate studies for overall risk, thrombophilia prevalence, relative risk of thrombophilia positives vs negatives, and the effect of thromboprophylaxis

h. There is a clinically important difference between the smallest and largest possible effect of the testing strategy

i. Based on the following estimates: Overall risk for VTE, 50 per 1,000 per 6 months; Prevalence of any inherited thrombophilia, 14.2% (min 9.9 - max 20.1); Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 3.26 (95%CI: 1.65-7.77); Relative risk of VTE with thromboprophylaxis versus no thromboprophylaxis, RR 0.61 (0.31-1.21). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, upper CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

j. Based on the following estimates: Overall risk for VTE, 66 per 1,000 per 6 months; Prevalence of any inherited thrombophilia, 14.2% (min 9.9 - max 20.1); Relative risk for VTE recurrence in thrombophilia positives versus negatives, RR 3.26 (95%CI: 1.65-7.77); Relative risk of VTE with thromboprophylaxis versus no thromboprophylaxis, RR 0.61 (0.31-1.21). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, upper CI of the Relative risk for VTE recurrence, and the largest treatment effect (lower CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, lower CI of the Relative risk for VTE recurrence, and the smallest treatment effect (upper CI).

k. Number of studies used in calculations: Overall risk, 1 systematic review; Prevalence, 20 studies; Effect of thromboprophylaxis, 3 RCTs

l. Overall risk for major bleeding: van Es 2020

m. The effect was indirectly calculated using separate studies for overall risk, thrombophilia prevalence and the effect of thromboprophylaxis

n. Based on the following estimates: Overall risk for Major bleeding of 3.6 per 1,000 per 6 months; Prevalence of any inherited thrombophilia, 14.2% (min 9.9 - max 20.1); Relative risk of Major bleeding with thromboprophylaxis versus no thromboprophylaxis, RR 1.65 (0.72-3.80). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the smallest treatment effect (lower CI).

o. Based on the following estimates: Overall risk for Major bleeding of 8.0 per 1,000 per 6 months; Prevalence of any inherited thrombophilia, 14.2% (min 9.9 - max 20.1); Relative risk of Major bleeding with thromboprophylaxis versus no thromboprophylaxis, RR 1.65 (0.72-3.80). To calculate the range of effects of a testing strategy versus a strategy without testing: 1) for a 'largest possible' difference between a strategy with testing vs without testing we used the maximum Prevalence, and the largest treatment effect (upper CI); 2) for a 'smallest possible' difference between a strategy with testing vs without testing we used the minimum Prevalence, and the smallest treatment effect (lower CI).

References

1. Ahmad, A., Sundquist, K., Zoller, B., Dahlback, B., Svensson, P. J., Sundquist, J., Memon, A. A.. Identification of polymorphisms in Apolipoprotein M gene and their relationship with risk of recurrent venous thromboembolism. Thromb Haemost; Aug 30 2016.

2. Asim, M., Al-Thani, H., El-Menyar, A.. Recurrent Deep Vein Thrombosis After the First Venous Thromboembolism Event: A Single-Institution Experience. Med Sci Monit; May 20 2017.

3. Baarslag, H. J., Koopman, M. M., Hutten, B. A., Linthorst Homan, M. W., Buller, H. R., Reekers, J. A., van Beek, E. J.. Long-term follow-up of patients with suspected deep vein thrombosis of the upper extremity: survival, risk factors and post-thrombotic syndrome. Eur J Intern Med; Dec 2004.

4. Baglin, T., Luddington, R., Brown, K., Baglin, C.. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet; Aug 16 2003.

5. Bank, I., Libourel, E. J., Middeldorp, S., Van Pampus, E. C., Koopman, M. M., Hamulyak, K., Prins, M. H., Van Der Meer, J., Buller, H. R.. Prothrombin 20210A mutation: a mild risk factor for venous thromboembolism but not for arterial thrombotic disease and pregnancy-related complications in a family study. Archives of Internal Medicine; Sep 27 2004.

6. Bezemer, I. D., van der Meer, F. J., Eikenboom, J. C., Rosendaal, F. R., Doggen, C. J.. The value of family history as a risk indicator for venous thrombosis. Archives of Internal Medicine; Mar 23 2009.

7. Brouwer, J. L., Lijfering, W. M., Ten Kate, M. K., Kluin-Nelemans, H. C., Veeger, N. J., van der Meer, J.. High long-term absolute risk of recurrent venous thromboembolism in patients with hereditary deficiencies of protein S, protein C or antithrombin. Thromb Haemost; Jan 2009.

8. Brouwer, J. L., Veeger, N. J., Kluin-Nelemans, H. C., van der Meer, J.. The pathogenesis of venous thromboembolism: evidence for multiple interrelated causes. Ann Intern Med; Dec 5 2006.

9. Brouwer, J. L., Veeger, N. J., van der Schaaf, W., Kluin-Nelemans, H. C., van der Meer, J.. Difference in absolute risk of venous and arterial thrombosis between familial protein S deficiency type I and type III. Results from a family cohort study to assess the clinical impact of a laboratory test-based classification. Br J Haematol; Mar 2005.

10. Bruwer, G., Limperger, V., Kenet, G., Klostermeier, U. C., Shneyder, M., Degenhardt, F., Finckh, U., Heller, C., Holzhauer, S., Trappe, R., Kentouche, K., Knoefler, R., Kurnik, K., Krumpel, A., Lauten, M., Manner, D., Mesters, R., Junker, R., Nowak-Gottl, U.. Impact of high risk thrombophilia status on recurrence among children and adults with VTE: An observational multicenter cohort study. Blood Cells Mol Dis; Nov 2016.

11. Carrier, M., Abou-Nassar, K., Mallick, R., Tagalakis, V., Shivakumar, S., Schattner, A., Kuruvilla, P., Hill, D., Spadafora, S., Marquis, K., Trinkaus, M., Tomiak, A., Lee, A. Y. Y., Gross, P. L., Lazo-Langner, A., El-Maraghi, R., Goss, G., Le Gal, G., Stewart, D., Ramsay, T., Rodger, M., Witham, D., Wells, P. S., Investigators, Avert. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. N Engl J Med; Feb 21 2019.

12. Cebi, N., Tanriverdi, S.. Aetiology of deep vein thrombosis in 63 turkish patients. Turkish Journal of Medical Sciences; April 2009.

13. Christiansen, S. C., Cannegieter, S. C., Koster, T., Vandenbroucke, J. P., Rosendaal, F. R.. Thrombophilia, clinical factors, and recurrent venous thrombotic events. Jama; May 18 2005.

14. Cohen, W., Castelli, C., Alessi, M. C., Aillaud, M. F., Bouvet, S., Saut, N., Brunet, D., Barthet, M. C., Tregouet, D. A., Lavigne, G., Morange, P. E.. ABO blood group and von Willebrand factor levels partially explained the incomplete penetrance of congenital thrombophilia. Arterioscler Thromb Vasc Biol; Aug 2012.

15. Coppens, M., van de Poel, M. H., Bank, I., Hamulyak, K., van der Meer, J., Veeger, N. J., Prins, M. H., Buller, H. R., Middeldorp, S.. A prospective cohort study on the absolute incidence of venous thromboembolism and arterial cardiovascular disease in asymptomatic carriers of the prothrombin 20210A mutation. Blood; Oct 15 2006.

16. Couturaud, F., Kearon, C., Leroyer, C., Mercier, B., Abgrall, J. F., Le Gal, G., Lacut, K., Oger, E., Bressollette, L., Ferec, C., Lamure, M., Mottier, D., Groupe d'Etude de la Thrombose de Bretagne, Occidentale. Incidence of venous thromboembolism in first-degree relatives of patients with venous thromboembolism who have factor V Leiden. Thromb Haemost; Dec 2006.

17. De Stefano, V., Martinelli, I., Mannucci, P. M., Paciaroni, K., Chiusolo, P., Casorelli, I., Rossi, E., Leone, G.. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med; Sep 9 1999.

18. De Stefano, V., Simioni, P., Rossi, E., Tormene, D., Za, T., Pagnan, A., Leone, G.. The risk of recurrent venous thromboembolism in patients with inherited deficiency of natural anticoagulants antithrombin, protein C and protein S. Haematologica; May 2006.

19. Di Minno, M. N., Dentali, F., Lupoli, R., Ageno, W.. Mild antithrombin deficiency and risk of recurrent venous thromboembolism: a prospective cohort study. Circulation; Jan 28 2014.

20. Eichinger, S., Minar, E., Hirschl, M., Bialonczyk, C., Stain, M., Mannhalter, C., Stumpflen, A., Schneider, B., Lechner, K., Kyrle, P. A.. The risk of early recurrent venous thromboembolism after oral anticoagulant therapy in patients with the G20210A transition in the prothrombin gene. Thromb Haemost; Jan 1999.

21. Eichinger, S., Weltermann, A., Mannhalter, C., Minar, E., Bialonczyk, C., Hirschl, M., Schonauer, V., Lechner, K., Kyrle, P. A.. The risk of recurrent venous thromboembolism in heterozygous carriers of factor V Leiden and a first spontaneous venous thromboembolism. Archives of Internal Medicine; Nov 11 2002.

22. Eischer, L., Kammer, M., Traby, L., Kyrle, P. A., Eichinger, S.. Risk of cancer after anticoagulation in patients with unprovoked venous thromboembolism: an observational cohort study. Journal of Thrombosis and Haemostasis; July 2017.

23. Faioni, E. M., Franchi, F., Bucciarelli, P., Margaglione, M., De Stefano, V., Castaman, G., Finazzi, G., Mannucci, P. M.. Coinheritance of the HR2 haplotype in the factor V gene confers an increased risk of venous thromboembolism to carriers of factor V R506Q (factor V Leiden). Blood; Nov 1 1999.

24. Garcia-Fuster, M. J., Forner, M. J., Fernandez, C., Gil, J., Vaya, A., Maldonado, L.. Long-term prospective study of recurrent venous thromboembolism in patients younger than 50 years. Pathophysiol Haemost Thromb; 2005.

25. Gonzalez-Porras, J. R., Garcia-Sanz, R., Alberca, I., Lopez, M. L., Balanzategui, A., Gutierrez, O., Lozano, F., San Miguel, J.. Risk of recurrent venous thrombosis in patients with G20210A mutation in the prothrombin gene or factor V Leiden mutation. Blood Coagul Fibrinolysis; Jan 2006.

26. Group, The,Procare. Is recurrent venous thromboembolism more frequent in homozygous patients for the factor V Leiden mutation than in heterozygous patients?. Blood Coagulation and Fibrinolysis; September 2003.

27. Heijboer, H., Brandjes, D. P., Buller, H. R., Sturk, A., ten Cate, J. W.. Deficiencies of coagulation-inhibiting and fibrinolytic proteins in outpatients with deep-vein thrombosis. N Engl J Med; Nov 29 1990.

28. Heit, J. A., Beckman, M. G., Bockenstedt, P. L., Grant, A. M., Key, N. S., Kulkarni, R., Manco-Johnson, M. J., Moll, S., Ortel, T. L., Philipp, C. S., Thrombosis, C.,D.,C., Hemostasis Centers, Research, Prevention, Network. Comparison of characteristics from White- and Black-Americans with venous thromboembolism: a cross-sectional study. Am J Hematol; Jul 2010.

29. Hirmerova, J., Seidlerova, J., Subrt, I.. The association of factor V Leiden with various clinical patterns of venous thromboembolism-the factor V Leiden paradox. Qjm; Sep 2014.

30. Hoibraaten, E., Qvigstad, E., Arnesen, H., Larsen, S., Wickstrom, E., Sandset, P. M.. Increased risk of recurrent venous thromboembolism during hormone replacement therapy--results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). Thromb Haemost; Dec 2000.

31. Kearon, C., Gent, M., Hirsh, J., Weitz, J., Kovacs, M. J., Anderson, D. R., Turpie, A. G., Green, D., Ginsberg, J. S., Wells, P., MacKinnon, B., Julian, J. A.. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med; Mar 25 1999.

32. Kearon, C., Julian, J. A., Kovacs, M. J., Anderson, D. R., Wells, P., Mackinnon, B., Weitz, J. I., Crowther, M. A., Dolan, S., Turpie, A. G., Geerts, W., Solymoss, S., van Nguyen, P., Demers, C., Kahn, S. R., Kassis, J., Rodger, M., Hambleton, J., Gent, M., Ginsberg, J. S., Investigators, Elate. Influence of thrombophilia on risk of recurrent venous thromboembolism while on warfarin: results from a randomized trial. Blood; Dec 1 2008.

33. Kearon, C., Parpia, S., Spencer, F. A., Baglin, T., Stevens, S. M., Bauer, K. A., Lentz, S. R., Kessler, C. M., Douketis, J. D., Moll, S., Kaatz, S., Schulman, S., Connors, J. M., Ginsberg, J. S., Spadafora, L., Bhagirath, V., Liaw, P. C., Weitz, J. I., Julian, J. A.. Antiphospholipid antibodies and recurrent thrombosis after a first unprovoked venous thromboembolism. Blood; May 10 2018.

34. Khorana, A. A., Soff, G. A., Kakkar, A. K., Vadhan-Raj, S., Riess, H., Wun, T., Streiff, M. B., Garcia, D. A., Liebman, H. A., Belani, C. P., O'Reilly, E. M., Patel, J. N., Yimer, H. A., Wildgoose, P., Burton, P., Vijapurkar, U., Kaul, S., Eikelboom, J., McBane, R., Bauer, K. A., Kuderer, N. M., Lyman, G. H., Investigators, Cassini. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. N Engl J Med; Feb 21 2019.

35. Laczkovics, C., Grafenhofer, H., Kaider, A., Quehenberger, P., Simanek, R., Mannhalter, C., Lechner, K., Pabinger, I.. Risk of recurrence after a first venous thromboembolic event in young women. Haematologica; Sep 2007.

36. Lee, S. Y., Kim, E. K., Kim, M. S., Shin, S. H., Chang, H., Jang, S. Y., Kim, H. J., Kim, D. K.. The prevalence and clinical manifestation of hereditary thrombophilia in Korean patients with unprovoked venous thromboembolisms. PLoS ONE [Electronic Resource]; 2017.

37. Lensen, R., Bertina, R. M., Vandenbroucke, J. P., Rosendaal, F. R.. High factor VIII levels contribute to the thrombotic risk in families with factor V Leiden. Br J Haematol; Aug 2001.

38. Levine, M. N., Gu, C., Liebman, H. A., Escalante, C. P., Solymoss, S., Deitchman, D., Ramirez, L., Julian, J.. A randomized phase II trial of apixaban for the prevention of thromboembolism in patients with metastatic cancer. Journal of Thrombosis & Haemostasis; May 2012.

39. Lijfering, W. M., Middeldorp, S., Veeger, N. J., Hamulyak, K., Prins, M. H., Buller, H. R., van der Meer, J.. Risk of recurrent venous thrombosis in homozygous carriers and double heterozygous carriers of factor V Leiden and prothrombin G20210A. Circulation; Apr 20 2010.

40. Lim, H. Y., Chua, C. C., Tacey, M., Sleeman, M., Donnan, G., Nandurkar, H., Ho, P.. Venous thromboembolism management in Northeast Melbourne: how does it compare to international guidelines and data?. Intern Med J; Sep 2017.

41. Lindmarker, P., Schulman, S., Sten-Linder, M., Wiman, B., Egberg, N., Johnsson, H.. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. DURAC Trial Study Group. Duration of Anticoagulation. Thromb Haemost; May 1999.

42. Mahmoodi, B. K., Brouwer, J. L., Ten Kate, M. K., Lijfering, W. M., Veeger, N. J., Mulder, A. B., Kluin-Nelemans, H. C., Van Der Meer, J.. A prospective cohort study on the absolute risks of venous thromboembolism and predictive value of screening asymptomatic relatives of patients with hereditary deficiencies of protein S, protein C or antithrombin. Journal of Thrombosis & Haemostasis; Jun 2010.

43. Marcucci, R., Liotta, A. A., Cellai, A. P., Rogolino, A., Gori, A. M., Giusti, B., Poli, D., Fedi, S., Abbate, R., Prisco, D.. Increased plasma levels of lipoprotein(a) and the risk of idiopathic and recurrent venous thromboembolism. Am J Med; Dec 1 2003.

44. Martinelli, I., Bucciarelli, P., Margaglione, M., De Stefano, V., Castaman, G., Mannucci, P. M.. The risk of venous thromboembolism in family members with mutations in the genes of factor V or prothrombin or both. Br J Haematol; Dec 2000.

45. Martinelli, I., Mannucci, P. M., De Stefano, V., Taioli, E., Rossi, V., Crosti, F., Paciaroni, K., Leone, G., Faioni, E. M.. Different risks of thrombosis in four coagulation defects associated with inherited thrombophilia: a study of 150 families. Blood; Oct 1 1998.

46. Mateo, J., Oliver, A., Borrell, M., Sala, N., Fontcuberta, J.. Laboratory evaluation and clinical characteristics of 2,132 consecutive unselected patients with venous thromboembolism--results of the Spanish Multicentric Study on Thrombophilia (EMET-Study). Thromb Haemost; Mar 1997.

47. Mello, T. B., Orsi, F. L., Montalvao, S. A., Ozelo, M. C., de Paula, E. V., Annichinno-Bizzachi, J. M.. Long-term prospective study of recurrent venous thromboembolism in a Hispanic population. Blood Coagul Fibrinolysis; Oct 2010.

48. Meyer, M. R., Witt, D. M., Delate, T., Johnson, S. G., Fang, M., Go, A., Clark, N. P.. Thrombophilia testing patterns amongst patients with acute venous thromboembolism. Thromb Res; Dec 2015.

49. Middeldorp, S., Henkens, C. M., Koopman, M. M., van Pampus, E. C., Hamulyak, K., van der Meer, J., Prins, M. H., Buller, H. R.. The incidence of venous thromboembolism in family members of patients with factor V Leiden mutation and venous thrombosis. Ann Intern Med; Jan 1 1998.

50. Miles, J. S., Miletich, J. P., Goldhaber, S. Z., Hennekens, C. H., Ridker, P. M.. G20210A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. J Am Coll Cardiol; Jan 2001.

51. Mulder, F. I., Candeloro, M., Kamphuisen, P. W., Di Nisio, M., Bossuyt, P. M., Guman, N., Smit, K., Buller, H. R., van Es, N., collaborators, C.,AT-prediction. The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis. Haematologica; Jun 2019.

52. Olie, V., Plu-Bureau, G., Conard, J., Horellou, M. H., Canonico, M., Scarabin, P. Y.. Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. Menopause; May 2011.

53. Palareti, G., Legnani, C., Cosmi, B., Valdre, L., Lunghi, B., Bernardi, F., Coccheri, S.. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation; Jul 22 2003.

54. Prandoni, P., Noventa, F., Ghirarduzzi, A., Pengo, V., Bernardi, E., Pesavento, R., Iotti, M., Tormene, D., Simioni, P., Pagnan, A.. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica; Feb 2007.

55. Ridker, P. M., Miletich, J. P., Stampfer, M. J., Goldhaber, S. Z., Lindpaintner, K., Hennekens, C. H.. Factor V Leiden and risks of recurrent idiopathic venous thromboembolism. Circulation; Nov 15 1995.

56. Rodger, M. A., Kahn, S. R., Wells, P. S., Anderson, D. A., Chagnon, I., Le Gal, G., Solymoss, S., Crowther, M., Perrier, A., White, R., Vickars, L., Ramsay, T., Betancourt, M. T., Kovacs, M. J.. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. Cmaj; Aug 26 2008.

57. Roldan, V., Lecumberri, R., Munoz-Torrero, J. F., Vicente, V., Rocha, E., Brenner, B., Monreal, M., Investigators, Riete. Thrombophilia testing in patients with venous thromboembolism. Findings from the RIETE registry. Thromb Res; Jun 2009.

58. Rossi, E., Za, T., Ciminello, A., Leone, G., De Stefano, V.. The risk of symptomatic pulmonary embolism due to proximal deep venous thrombosis differs in patients with different types of inherited thrombophilia. Thromb Haemost; Jun 2008.

59. Roupie, A. L., Dossier, A., Goulenok, T., Perozziello, A., Papo, T., Sacre, K.. First venous thromboembolism in admitted patients younger than 50years old. Eur J Intern Med; Oct 2016.

60. Rupa-Matysek, J., Gil, L., Wojtasinska, E., Ciepluch, K., Lewandowska, M., Komarnicki, M.. The relationship between mean platelet volume and thrombosis recurrence in patients diagnosed with antiphospholipid syndrome. Rheumatol Int; Nov 2014.

61. Santamaria, M. G., Agnelli, G., Taliani, M. R., Prandoni, P., Moia, M., Bazzan, M., Guazzaloca, G., Ageno, W., Bertoldi, A., Silingardi, M., Tomasi, C., Ambrosio, G. B., Warfarin Optimal Duration Italian Trial, Investigators. Thrombophilic abnormalities and recurrence of venous thromboembolism in patients treated with standardized anticoagulant treatment. Thromb Res; 2005.

62. Schattner, A., Kasher, I., Berrebi, A.. Causes and outcome of deep-vein thrombosis in otherwise-healthy patients under 50 years. Qjm; Apr 1997.

63. Schulman, S., Lindmarker, P., Holmstrom, M., Larfars, G., Carlsson, A., Nicol, P., Svensson, E., Ljungberg, B., Viering, S., Nordlander, S., Leijd, B., Jahed, K., Hjorth, M., Linder, O., Beckman, M.. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. Journal of Thrombosis & Haemostasis; Apr 2006.

64. Simioni, P., Prandoni, P., Lensing, A. W., Manfrin, D., Tormene, D., Gavasso, S., Girolami, B., Sardella, C., Prins, M., Girolami, A.. Risk for subsequent venous thromboembolic complications in carriers of the prothrombin or the factor V gene mutation with a first episode of deep-vein thrombosis. Blood; Nov 15 2000.

65. Simioni, P., Sanson, B. J., Prandoni, P., Tormene, D., Friederich, P. W., Girolami, B., Gavasso, S., Huisman, M. V., Buller, H. R., Wouter ten Cate, J., Girolami, A., Prins, M. H.. Incidence of venous thromboembolism in families with inherited thrombophilia. Thromb Haemost; Feb 1999.

66. Simioni, P., Tormene, D., Prandoni, P., Zerbinati, P., Gavasso, S., Cefalo, P., Girolami, A.. Incidence of venous thromboembolism in asymptomatic family members who are carriers of factor V Leiden: a prospective cohort study. Blood; Mar 15 2002.

67. Sonnevi, K., Tchaikovski, S. N., Holmstrom, M., Antovic, J. P., Bremme, K., Rosing, J., Larfars, G.. Obesity and thrombin-generation profiles in women with venous thromboembolism. Blood Coagul Fibrinolysis; Jul 2013.

68. Strandberg, K., Svensson, P. J., Ohlin, A. K.. Venous thromboembolism in carriers of the Factor V Leiden mutation and in patients without known thrombophilic risk factor; prediction of recurrence and APC-PCI complex concentration and/or soluble thrombomodulin antigen and activity. Thromb Res; 2007.

69. Sundquist, K., Sundquist, J., Svensson, P. J., Zoller, B., Memon, A. A.. Role of family history of venous thromboembolism and thrombophilia as predictors of recurrence: a prospective follow-up study. Journal of Thrombosis & Haemostasis; Dec 2015.

70. Sveinsdottir, S. V., Saemundsson, Y., Isma, N., Gottsater, A., Svensson, P. J.. Evaluation of recurrent venous thromboembolism in patients with Factor V Leiden mutation in heterozygous form. Thromb Res; Sep 2012.

71. van Es, N., Ventresca, M., Di Nisio, M., Zhou, Q., Noble, S., Crowther, M., Briel, M., Garcia, D., Lyman, G. H., Macbeth, F., Griffiths, G., Iorio, A., Lawrence, M., Neumann, I., Brozek, J., Guyatt, G., Streiff, M. B., Baldeh, T., Florez, I. D., Alma, O. G., Agnelli, G., Ageno, W., Marcucci, M., Bozas, G., Zulian, G., Maraveyas, A., Lebeau, B., Lecumberri, R., Sideras, K., Loprinzi, C., McBane, R., Pelzer, U., Riess, H., Solh, Z., Perry, J., Kahale, L. A., Bossuyt, P. M., Klerk, C., Buller, H. R., Akl, E. A., Schunemann, H. J., group, Ipdma,heparin,use,in,cancer,patients,research. The Khorana score for prediction of venous thromboembolism in cancer patients: an individual patient data meta-analysis. Journal of Thrombosis & Haemostasis; Apr 26 2020.

72. Wahlander, K., Eriksson, H., Lundstrom, T., Billing Clason, S., Wall, U., Nystrom, P., Wessman, P., Schulman, S., Investigators, Thrive,Iii. Risk of recurrent venous thromboembolism or bleeding in relation to thrombophilic risk factors in patients receiving ximelagatran or placebo for long-term secondary prevention of venous thromboembolism. Br J Haematol; Apr 2006.

73. Weingarz, L., Schindewolf, M., Schwonberg, J., Hecking, C., Wolf, Z., Erbe, M., Lindhoff-Last, E., Linnemann, B.. Thrombophilia and risk of VTE recurrence according to the age at the time of first VTE manifestation. Vasa; Jul 2015.