Thrombophilias:

who to test

1. 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. 2003;362:523–526.

Definitions

Thrombophilia: hypercoagulable state generally due to one of several inherited conditions

- Factor V Leiden
- Prothrombin 20210A
- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency
- Dyfibrinogenemia
- "Alleged" thrombophilias: heparin cofactor 2 deficiency, plasminogen deficiency, factor XII deficiency

- All predispose to venous thrombosis
- Worth mentioning: APLS. Acquired "thrombophilia"

1. 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. 2003;362:523–526.

- I will tell you the truth , Pure and simple . “ My friend the truth is rarely pure and never simple” Oscar WIld

Who NOT to test

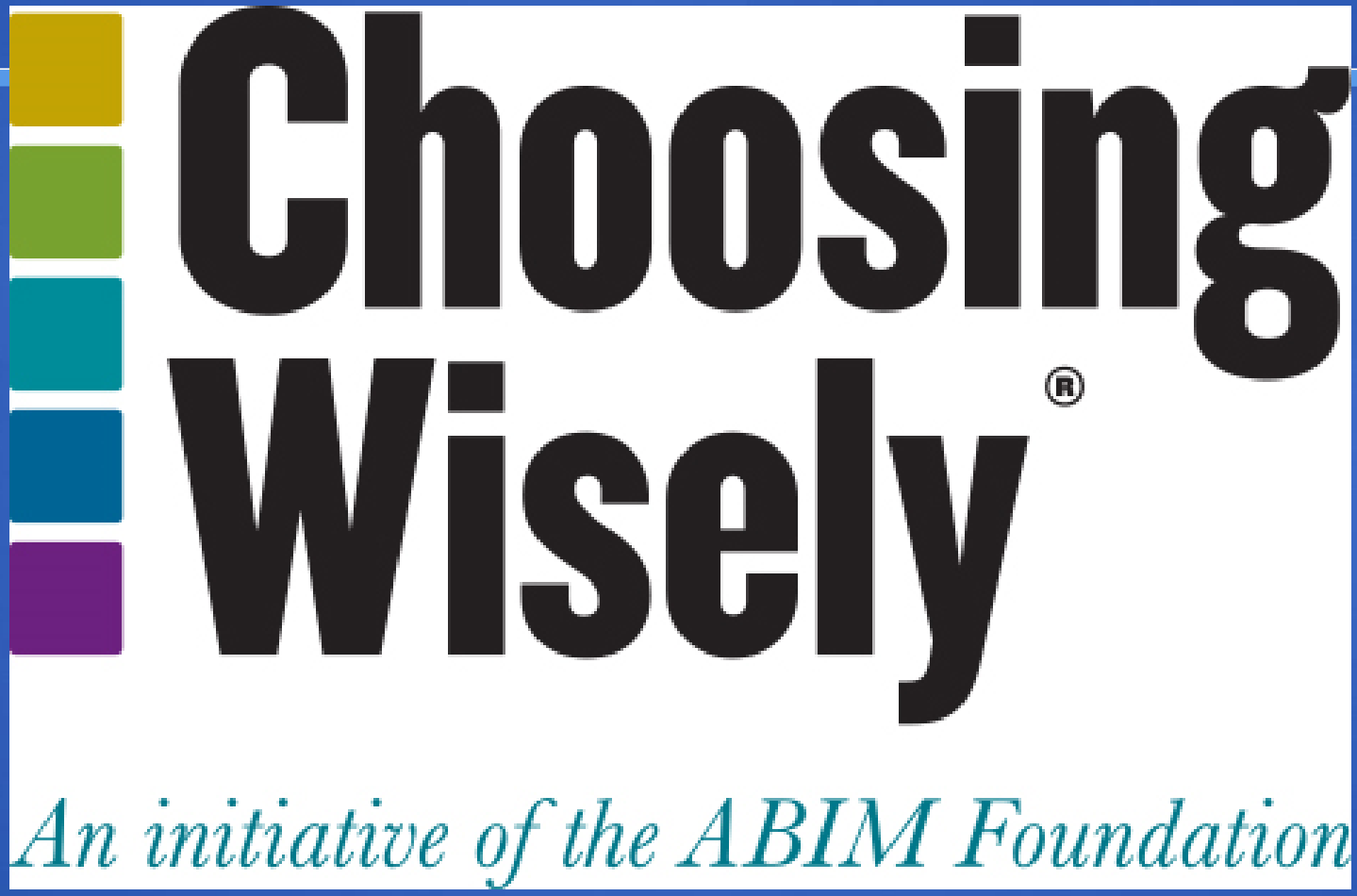
- Just about everyone

1. Coppens M, Reijnders JH, Middeldorp S, Doggen CJ, Rosendaal FR. Testing for inherited thrombophilia does not reduce the recurrence of venous thrombosis. J Thromb Haemost. 2008;6:1474–1477.

Who NOT to test

- Patients who have had their 1st DVT
  - No change in recurrence with testing [1]
    - Study pooled unprovoked and provoked
  - If unprovoked DVT already merits indefinite anticoagulation, presence of thrombophilia does not change therapy
  - Risk of recurrence is elevated with or without thrombophilia [2]

Coppens M, Reijnders JH, Middeldorp S, Doggen CJ, Rosendaal FR. Testing for inherited thrombophilia does not reduce the recurrence of venous thrombosis. J Thromb Haemost. 2008;6:1474–1477.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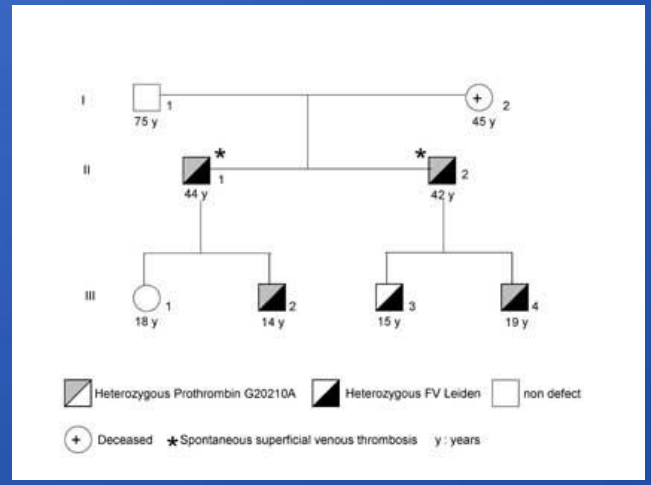
Who NOT to test

- Family members of those with Hx of VTE or known thrombophilia
  - FamHx of VTE increases probability of thrombosis with or without presence of thrombophilia [3]
  - Consider prophylaxis in high-risk circumstances (surgery, etc) for those with strong family history



Who NOT to test

- What if there's a family history of VTE/thrombophilia in a patient who wants to use OCPs/HRT?
  - Same story: family history should be enough to warrant consideration of alternate forms of contraception
  - Again, risk of thrombosis is elevated with or without detectable thrombophilia [?]

1. Skeith, L., Carrier, M., Kaaja, R., Martinelli, I., Petroff, D., Schleußner, E., Laskin, C. A., & Rodger, M. A. (2016). A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia. *Blood,* 127(13), 1650-1655.

Who NOT to test

- Women with Hx of unexplained spontaneous abortion or FamHx of thrombophilia
  - LMWH does not prevent loss of pregnancy in women with inherited thrombophilia [
  - Dalteparin does not prevent pregnancy-associated VTE nor placenta-mediated pregnancy complications in women with thrombophilia
  - APLA syndrome is the exception, since link with pregnancy loss and efficacy of therapy have been established

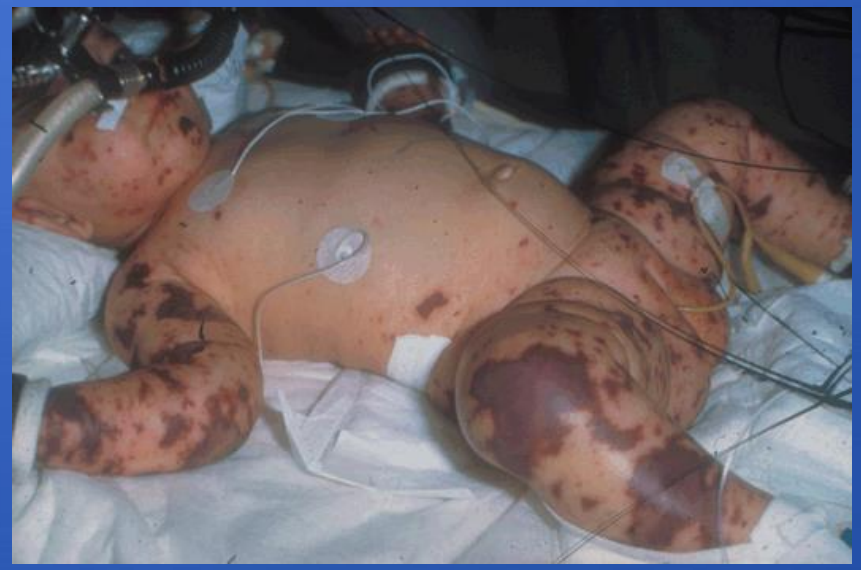
1. Skeith, L., Carrier, M., Kaaja, R., Martinelli, I., Petroff, D., Schleußner, E., Laskin, C. A., & Rodger, M. A. (2016). A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia. *Blood,* 127(13), 1650-1655.
2. Rodger MA, Hague WM, Kingdom J, et al. Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial. Lancet. 2014;384:1673–1683

Who NOT to test

- Others:
  - Patients with retinal vein thrombosis, CVC-related thrombosis, unselected patients with upper extremity venous thrombosis, arterial thrombosis, childhood stroke [7]

Who definitely to test

- Neonates with signs of purpura fulminans (for proteins C and S)
- Patients who have had warfarin-induced skin necrosis (proteins C & S)



Who maybe to test?

- Patients with unprovoked DVT when assessment for other clinical risk factors as well as bleeding risk yields equivocal results
- When patient strongly desires testing
  - e.g. recurrent pregnancy loss, strong family history of PE
- Patients with thrombosis in unusual vascular beds
  - E.g. portal vein (JAK2 testing)

References

1. Coppens M, Reijnders JH, Middeldorp S, Doggen CJ, Rosendaal FR. Testing for inherited thrombophilia does not reduce the recurrence of venous thrombosis. J Thromb Haemost. 2008;6:1474–1477.

2. 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. 2003;362:523–526.

3. Couturaud F, Leroyer C, Tromeur C, et al. Factors that predict thrombosis in relatives of patients with venous thromboembolism. Blood. 2014;124:2124–2130

4. Skeith, L., Carrier, M., Kaaja, R., Martinelli, I., Petroff, D., Schleußner, E., Laskin, C. A., & Rodger, M. A. (2016). A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia. *Blood*, 127(13), 1650-1655.

5. Rodger MA, Hague WM, Kingdom J, et al. Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial. Lancet. 2014;384:1673–1683

6. Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e691S-e736S.

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7. Baglin, T., Gray, E., Greaves, M., Hunt, B. J., Keeling, D., Machin, S., Mackie, I., Makris, M., Nokes, T., Perry, D., Tait, R. C., Walker, I. and Watson, H. (2010), Clinical guidelines for testing for heritable thrombophilia. British Journal of Haematology, 149: 209–220.

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My Approach to Thrombophilia Testing

- The main reason to test patients with blood clots is to detect a stronger thrombophilia. There are 7 stronger thrombophilias:

1. antiphospholipid antibody syndrome
2. antithrombin deficiency
3. homozygous factor V Leiden
4. heterozygous factor V Leiden PLUS prothrombin 20210 mutation (i.e. both at the same time)
5. protein C deficiency
6. protein S deficiency
7. possibly homozygous prothrombin 20210 mutation

- Finding a weaker thrombophilia (i.e. heterozygous factor V Leiden alone or heterozygous prothrombin 20210 mutation alone) typically has no impact on the management of a patient who has had a blood clot. It does not influence the decision how long to treat the person with "blood thinners" (anticoagulants). However, finding of a stronger thrombophilia has a number of consequences in my practice:

Consequences for the patient:

- It decreases my threshold to recommend long-term "blood thinners" (anticoagulants) in a patient who has had an episode of unprovoked (= idiopathic) DVT or PE;
- It leads to discussion with the patient with an unexplained arterial, non-arteriosclerotic clot (heart attack, stroke, arm or leg arterial clot, etc) (create link to blog #4), whether "blood thinners" (anticoagulant drugs) or antiplatelet drugs might be the preferred treatment for prevention of another clot;

- *Consequences for family members* (Table 2 – Which family member to test)*:*

- It prompts me to recommend testing of the identified thrombophilia(s) in asymptomatic female family members and advice (a) against the use of estrogen birth control methods and (b) for anticoagulation prophylaxis during 6 weeks after delivery), and possibly during the 9 months of pregnancy.

- It prompts me to consider testing in some male and female family members and consideration for anticoagulation prophylaxis during (a) future long-distance airline travel, (b) casts and limb immobilizers/casts after fracture and trauma, and (c) non-major surgery, such as knee arthroscopy.

- The thrombophilia tests that I do when I embark on a thrombophilia work-up are listed in table 3 (Table 3 – What to test). I do not test for
- factor VIII levels
- levels of fibrinogen, factor IX, XI or other clotting factors
- parameters of fibrinolysis (PAI-1 level or mutations, tPA levels or mutations)
- the MTHFR polymorphisms (mutations)
- I limit homocysteine testing to the individual less than 30 years of age with thrombosis, to assess for the presence of homocysteinuria (very high homocysteine levels > 100 mg/dL).

- Table 4 – Which patient to test) lists the type of patients in whom I consider thrombophilia testing. However, individual decisions, typically in discussion with the patient, need to be made when deciding on whom to test and how extensively to test.

Interpreting test results

- When interpreting thrombophilia laboratory test results, it is important to be aware of the circumstances that lead to abnormal test results without a true thrombophilia being present.
- Several results are temporarily abnormal in the patient with acute thrombosis and therapy with heparin and warfarin.
- When a thrombophilia is identified, educating the patient and the patient's family members is important.
- Finally, to avoid inappropriate testing, thrombophilia testing should only be ordered by health care providers who know how to
- (a) interpret the test results
- (b) counsel the patient and his/her family members as to what the results mean for him/her/them.

ACOG screening a patient for thrombophilia

- Only if test results are likely to alter management.
- Screening should be performed when the presence of a thrombophilia may alter the intensity or duration of anticoagulation therapy.
- Screening is unnecessary when treatment is indicated for other reasons.[19]

ACOG recommendation

- Screening for thrombophilia may be considered
- (1) in patients with a personal history of VTE that occurred in the setting of a transient nonrecurrent risk factor (eg, fractures, surgery, prolonged immobility) that was not estrogen- or pregnancy-related[19]
- (2) in patients with a first-degree relative with a prior VTE that occurred before age 50 years or with a prior diagnosis of high-risk thrombophilia.

- In the absence of thrombophilia, pregnant patients with prior VTE not associated with estrogen and/or pregnancy may undergo surveillance and postpartum anticoagulation therapy.[15] In patients with a low-risk thrombophilia who have a history of VTE, management includes surveillance or prophylactic or intermediate-dose heparin therapy antepartum. Postpartum anticoagulation is recommended.

- In patients with prior VTE and a high-risk thrombophilia, prophylactic or low- or intermediate-dose heparin therapy is recommended antepartum and postpartum.[15, 19]

- It is controversial whether thrombophilia is associated with adverse pregnancy events other than VTE. Few obstetric indications for screening exist. Indications for screening for antiphospholipid antibody syndrome are discussed above.

- There is currently insufficient evidence to suggest that thromboprophylaxis in patients with thrombophilia prevents recurrence of adverse pregnancy events such as recurrent pregnancy loss, IUFD, abruption, or preeclampsia.[15,

- Factor V Leiden: Second-generation activated protein C resistance assay is reliable in pregnancy; if results are abnormal, evaluate for genotype for factor V Leiden mutation; if the patient is on anticoagulation therapy, consider evaluation of factor V Leiden mutation via genotype testing
- Prothrombin G20210A mutation DNA analysis
- Protein C functional activity level
- Protein S free, total, and functional levels
- Antithrombin-heparin cofactor assay
- Antiphospholipid antibody syndrome (abnormalities must be present at least twice and at least 12 weeks apart; anticardiolipin antibodies and anti-beta2 glycoprotein I antibodies must be present in medium to high titers, corresponding to >99th percentile for the general population, or greater than 40 IgG phospholipid [GPL] or IgM phospholipid [MPL] units): (1) Lupus anticoagulant, (2) anticardiolipin antibodies (IgG and IgM), and (3) anti-beta2 glycoprotein antibodies (IgG and IgM)
- Diagnosis of antiphospholipid antibody syndrome: please see above. Diagnosis of this syndrome relies on both clinical and laboratory criteria.

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Screening for Occult Cancer in Unprovoked Venous Thromboembolism

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ABSTRACT

BACKGROUND

Venous thromboembolism may be the earliest sign of cancer. Currently, there is a great diversity in practices regarding screening for occult cancer in a person who has an unprovoked venous thromboembolism. We sought to assess the efficacy of a screening strategy for occult cancer that included comprehensive computed tomography (CT) of the abdomen and pelvis in patients who had a first unprovoked venous thromboembolism.

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Screening for Occult Cancer in Unprovoked Venous Thromboembolism

- Unprovoked venous thromboembolism may be the earliest sign of cancer
- up to 10% of patients with unprovoked venous thromboembolism receive a diagnosis of cancer in the year after their diagnosis of venous thromboembolism.
- More than 60% of occult cancers are diagnosed shortly after the diagnosis of unprovoked venous thromboembolism.6 Thereafter, the incidence rate of cancer diagnosis gradually declines and returns to the rate in the general population after 1 year.5-7

DISCUSSION

- In NJEM Trial
- a screening strategy for occult cancer that included comprehensive CT of the abdomen and pelvis did not lead to fewer missed cancers than the number missed with a limited screening strategy.
- The screening strategy that included CT did not appear to detect significantly more occult cancers (including early cancers), shorten the time to cancer diagnosis, or reduce cancer-related mortality.

(SOME) trial

Results suggest

limited screening strategy for occult cancer

(history taking,

physical examination,

basic blood testing, chest radiography,

and age-specific and sex-specific cancer screening) may be adequate for patients who have a first unprovoked venous thromboembolism. June 22, 2015, at NEJM.org.

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