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Titolo relazione Profili genetici di rischio trombotico

Ordering thrombophilia tests is easy....

Case report

Gupta A, JAMA 2017

Case report

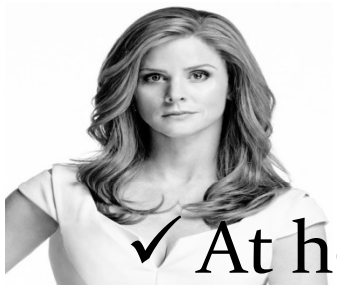
Gupta A, JAMA 2017

- ✓ A 52-year-old woman with hypertension and type 2 diabetes presented with right-sided groin pain after a fall.
- ✓ Her medications included lisinopril,pravastatin, andglipizide.
- ✓ Examination and imaging findings were consistent with fracture of the right femoral neck and she subsequently underwent successful total hip arthroplasty.
- ✓ On postoperative day 4, she developed pain and swelling of the right calf, and duplex ultrasonography demonstrated thrombosis of the right popliteal vein.
- ✓ She reported no personal or family history of thrombosis or complications with prior pregnancies, and she was up to date on routine cancer screening.
- ✓ Anticoagulation therapy with heparin and warfarin was initiated.

Gupta A, JAMA 2017

- ✓ Thrombophilia testing was performed 48 hours later and included factor V Leiden and prothrombin gene mutations, protein C, protein S, and antithrombin activity, and antiphospholipid antibodies (IgG and IgM anticardiolipin, antibeta2 glycoprotein 1, and lupus anticoagulant)
- ✓ Results demonstrated decreased activity of proteinC (25%;reference range, 70%-160%), protein S (34%; reference range, 65%-160%), and antithrombin (45%; reference range, 80%-130%).

She was discharged home with warfarin treatment and referred to the hematology clinic for follow-up



- ✓ At her follow-up visit 2 weeks later, she was told that because these laboratory test blood samples had been drawn in the context of a recent thrombus and concurrent anticoagulation therapy, the results were spurious, and 3 months of anticoagulation was advised.
- ✓ Prior to having these results explained to her in the hematology clinic, the patient experienced significant worry about possibly suffering from rare disorders and the prospect of passing these on to her children. …

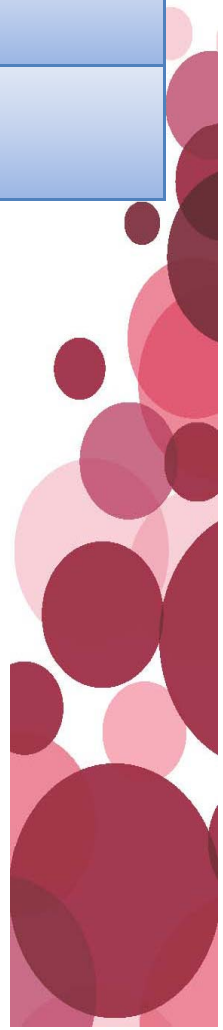
Gupta A, JAMA 2017

She remains without recurrent venous thromboembolism (VTE) at 1-year follow-up

Thrombophilia Type

Inherited	
Increased procoagulant activity (common)	Factor V leiden
	Prothrombin gene mutation
Decreased anticoagulant activity (uncommon)	Protein C
	Protein S
	Antithrombin

Acquired
Lupus anticoagulant



Although inherited and acquired thrombophilias are acknowledged to increase the risk of venous thromboembolism

The majority of patients with VTE should not be tested for thrombophilia.

According to Medicare data,280 000 tests for inherited thrombophilia were claimed in 2014, costing an estimated $300 to $670 million, and up to 55% of patients with provoked VTE have been reported to undergo thrombophilia testing

Thrombophilia tests and prevalence of risk factors

Table 3. Thrombophilia Tests and Prevalence of Risk Factors.*

Thrombophilia Type	Assay	Prevalence
Inherited		
Increased procoagulant activity (common)		
Factor V Leiden	APCR and PCR	White, 5.0% Hispanic, 2.2% Black, 1.2% Native American, 1.2% Asian, 0.4%
Prothrombin gene mutation	PCR	White, 3%
Decreased anticoagulant activity (uncommon)		
Protein C	Activity assay	<0.5%
Protein S	Activity assay	<0.5%
Antithrombin	Activity assay	<0.5%
Acquired		
Lupus anticoagulants†	In vitro clotting assay: PTT-LA, dRVVT, silica clotting time ELISA: ACL IgG and IgM, beta-2 glycoprotein 1 IgG and IgM	Overall, 0–5% Patients with VTE, 10–12% Patients with SLE, 35%

Factor V Leiden

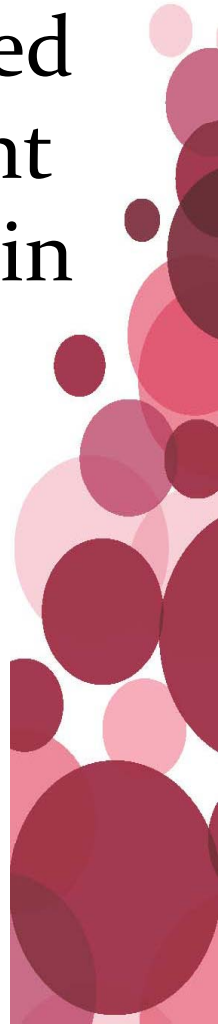
The most common known inherited risk factor for thrombosis, results from a base change from G to A at position1691 of the gene encoding coagulation Factor V. The associated amino acid substitution eliminates one of three activated Protein C cleavage sites in the Factor V protein, resulting in ***Factor V being inactivated more slowly and generating more thrombin, thereby enhancing the potential for clot formation***.

Factor V Leiden frequency

- An FVL mutation is present in 15–20% of individuals with an initial episode of VTE, making it the most common known heritable thrombophilic risk factor
- Population studies have suggested that a single FVL variant (heterozygosity) increases risk for an initial episode of VTE by 4- to 7-fold over the annual background risk of less than one per thousand, whereas two copies (homozygosity) increase that risk by 9- to 80-fold

Prothrombin

The second most common known inherited risk factor for thrombosis, is a gene variant that produces an amino acid substitution in the PT protein, which results in higher circulating PT levels and an enhanced potential for clot formation.



Prothrombin frequency

- ✓ The PT mutation is the second most common heritable risk factor for VTE. The variant of gene produces an amino acid substitution in the PT protein, which results in higher circulating PT levels and an enhanced potential for clot formation.
- ✓ In the United States, approximately 2.2%, 2.2%, and 0.6% of non-Hispanic white, Hispanic white, and African American populations, respectively, are heterozygous for the PT mutation.
- ✓ Individuals homozygous for this mutation are rare (< 1 per 100,000 individuals, respectively).
- ✓ The PT mutation is present in 6% of individuals with an initial episode of venous thrombosis and seems to increase risk for VTE by 2- to 4-fold.

Factor V Leiden and Prothrombin

- In the general population, individuals with both an FVL mutation and PT mutation (compound heterozygotes) occur at the rate of 22 per 100,000.
- In such individuals, there is an estimated 20-fold increased risk for an initial episode of VTE.
- Among patients with VTE who are heterozygous for FVL, 12% will also be heterozygous for PT

My talk today

Whom to test

How to use the results

- ✓ Data showing the clinical usefulness and benefits of testing are limited or nonexistent, as are data supporting the benefit of primary or secondary VTE prophylaxis based on thrombophilia status alone.
- ✓ No validated testing guidelines have been published

The American College of Chest Physicians does not give guidance on thrombophilia testing in its ninth edition of clinical practice guidelines for antithrombotic therapy or its 2016 VTE update

"In cases of first provoked events, as with this patient, guidelines recommend against anticoagulating for more than 3 months"

"Unprovoked VTEs require longer anticoagulation"

- ✓ The **American Society of Hematology's 2013 Choosing Wisely campaign** recommends not testing for thrombophilia in adults with VTE who have major transient risk factors

- ✓ **Clinical Guidelines for Testing for Heritable Thrombophilia, published by the British Committee for Standards in Haematology**, "It is not possible to give a validated recommendation as to how such patients (and families) should be selected" for testing

- ✓ Similar guidelines advise limiting testing to a narrow range of specific clinical situations and patients

The first steps in deciding whether to test a patient are to determine why the tests are being ordered and how the results will be used.

- ✓ As the etiology of thrombosis is multifactorial, the presence of a thrombophilic defect is only one of many elements that determine risk
- ✓ Test results should not affect decisions about the duration of anticoagulant therapy for the management of VTE
- ✓ A negative thrombophilia evaluation is not a sufficient basis to stop anticoagulants following an episode of unprovoked VTE in a patient with low bleeding risk and willingness to continue therapy
- ✓ Patients with inherited thrombophilia can often be identified by coagulation experts on the basis of the patient's personal and family history of VTE, even without knowledge of test results

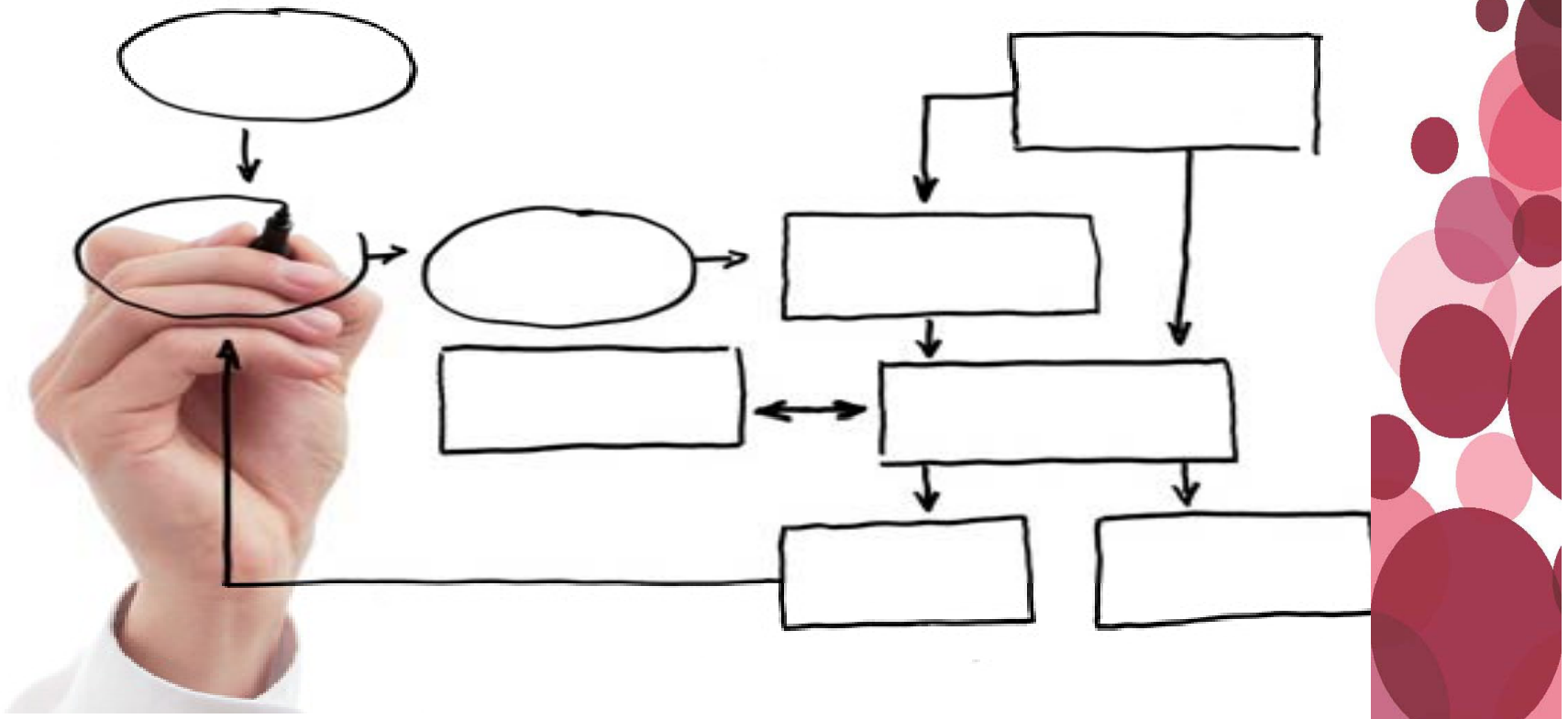
Clinical Characteristics Suggestive of Inherited Thrombophilia in Patients with Venous Thromboembolism (VTE).

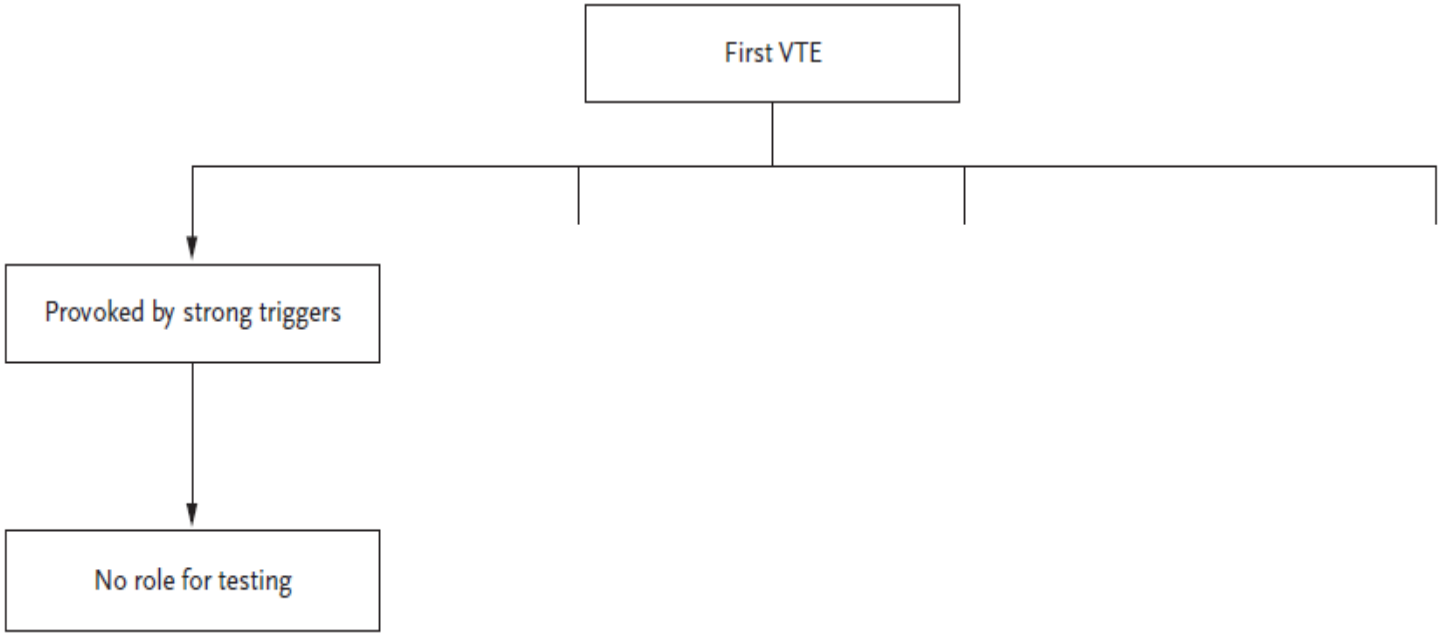
- ✓ Thrombosis at a young age (<50 yr), especially in association with weak provoking factors (minor surgery, prolonged air travel, combination oral contraceptives,) or unprovoked VTE
- ✓ Strong family history of VTE (first-degree family members affected at a young age)
- ✓ Recurrent VTE events, especially at a young age
- ✓ VTE in unusual sites such as splanchnic or cerebral veins

The severity of the VTE event can also be a factor in making decisions about testing.

A surgically provoked deep-vein thrombosis (DVT) in the calf is of less concern than an extensive lower-extremity DVT or a bilateral pulmonary embolism and is also of less concern than a fatal pulmonary embolism in a first-degree relative at a young age

Algorithm for Selecting Patients with a First Venous Thromboembolism (VTE) for Thrombophilia Testing

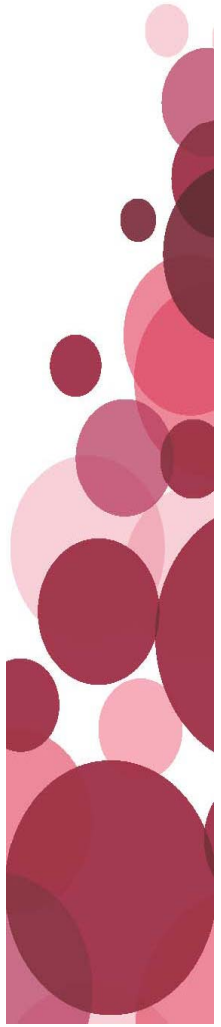


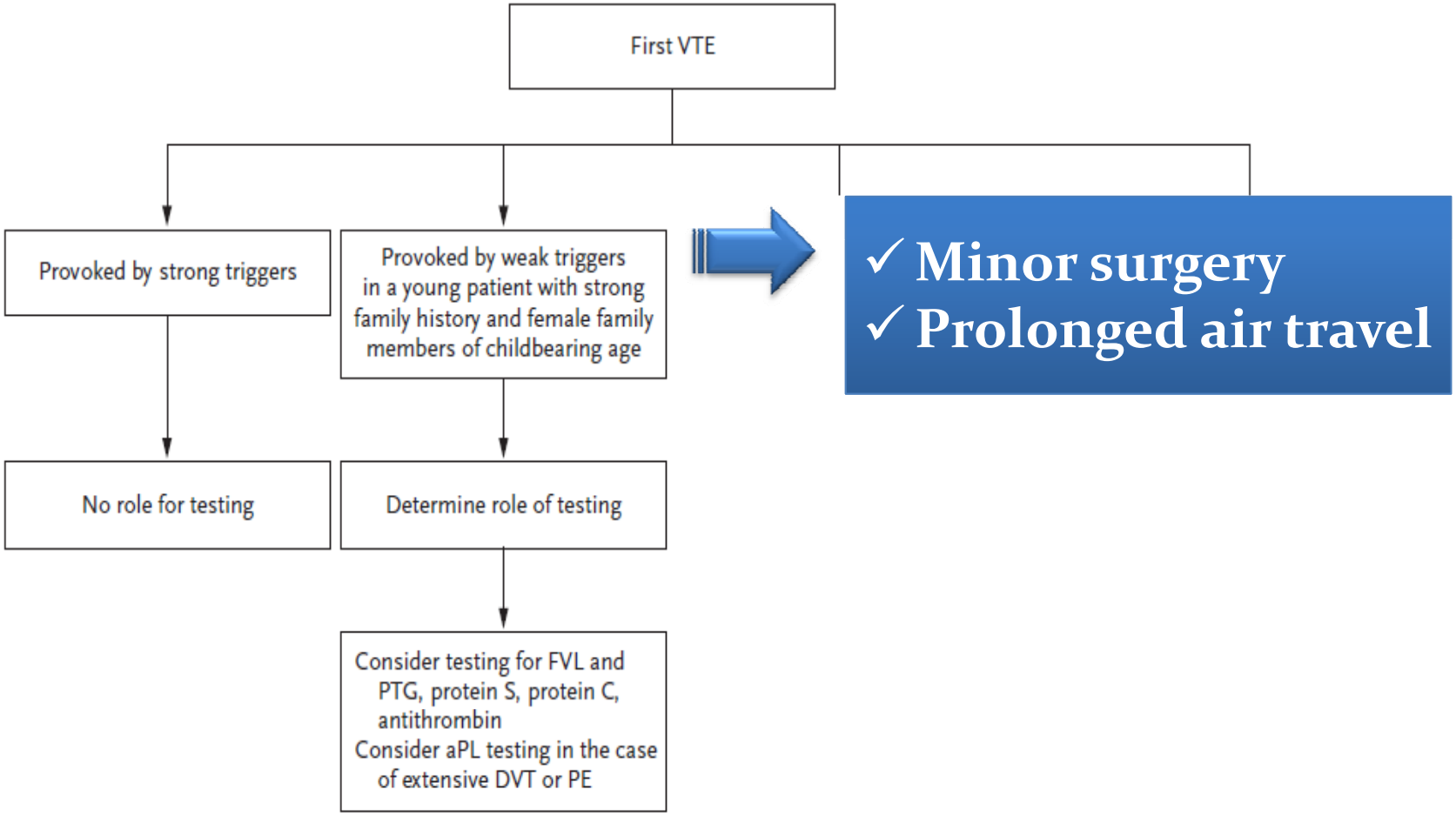


N England J, 2017

Provoked by strong triggers

- ✓ Fracture
- ✓ Cancer
- ✓ Oestrogen therapy
- ✓ Pregnancy
- ✓ Surgery within the preceding 3 months
- ✓ Immobility





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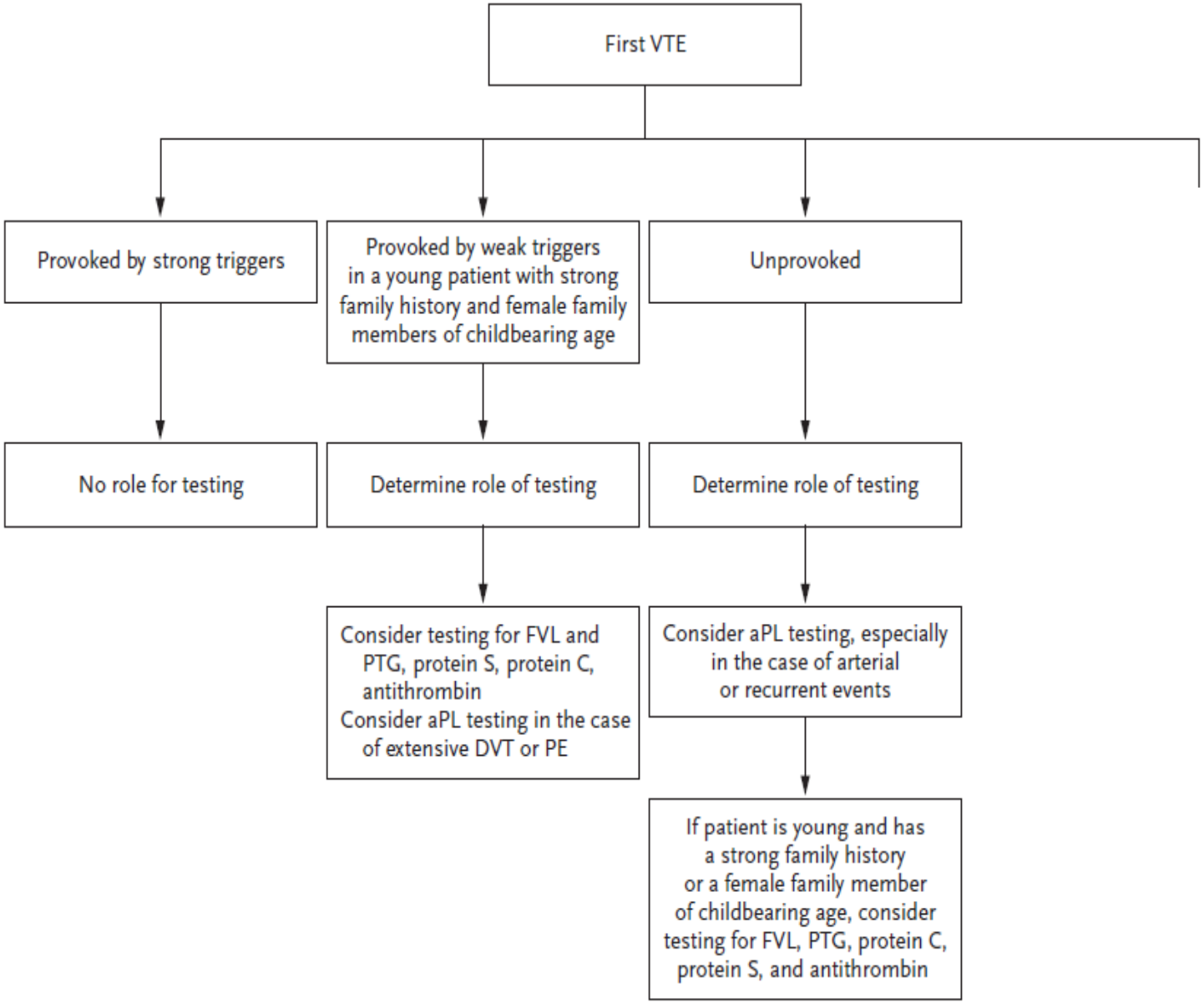

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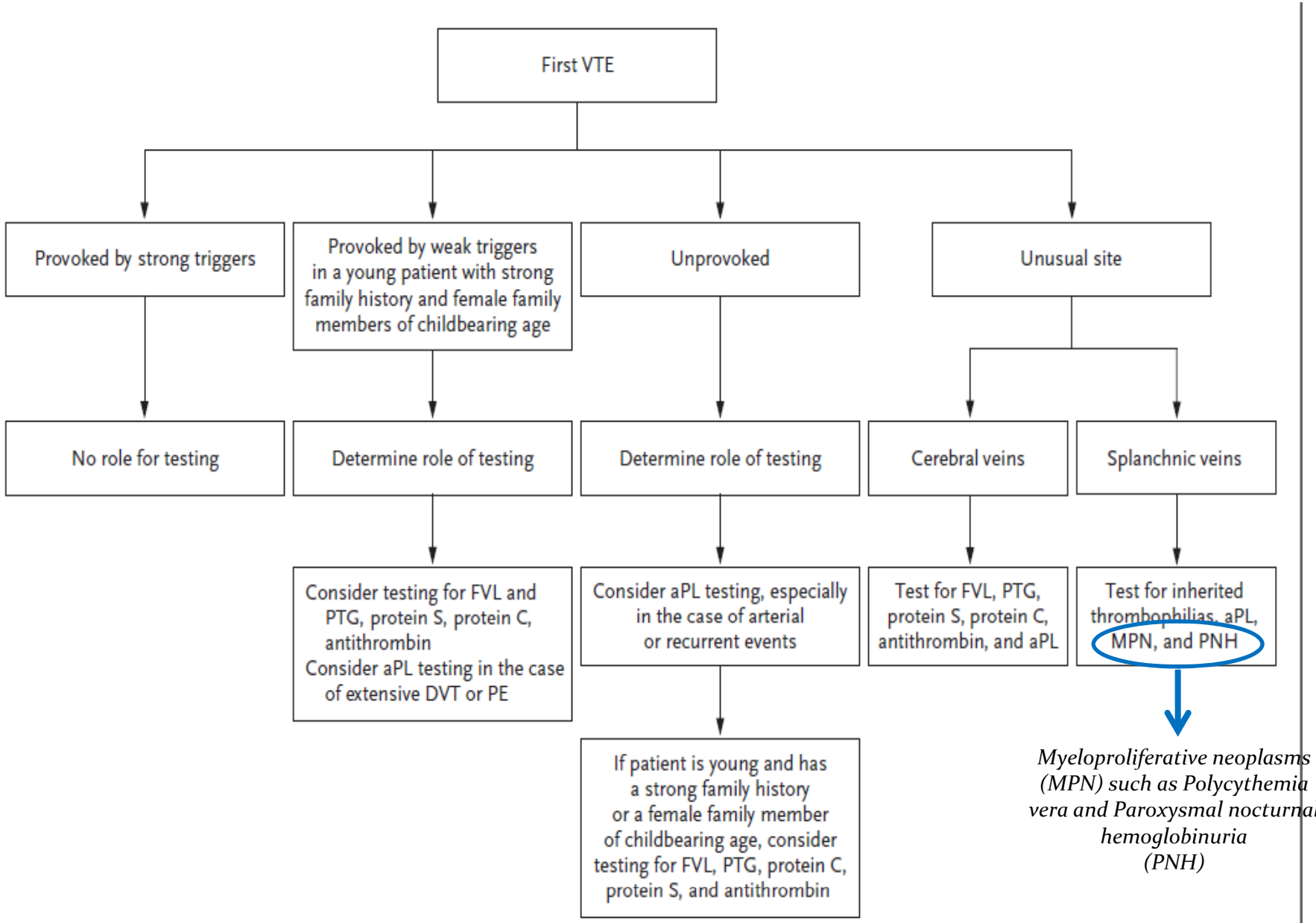


N England J, 2017

Arterial thrombosis

Testing for heritable thrombophilia is not indicated in patients with arterial thrombosis.

Antiphospholipid antibodies, antibeta 2 glycoprotein 1 and anticardiolipin antibodies.

Indications for these tests:

- ✓ History of recurrent first trimester miscarriage (>/= 3 consecutive miscarriages)
- ✓ >/=1 unexplained deaths of a morphologically normal foetus at or beyond 10/40
- ✓ >/=1 premature birth of a morphologically normal neonate before 34/40 because of eclampsia/severe preeclampsia or placental insufficiency
- ✓ Young adults (<50 years) with ischaemic stroke

Secondary prevention following provoked VTE

Should thrombophilia testing be performed to help determine duration of anticoagulation following provoked VTE?

- ✓ Of the many factors which predict the risk of recurrent thrombosis after an initial event, the presence of provoking factors is the most important
- ✓ A positive thrombophilia evaluation is not a sufficient basis to offer extended anticoagulation following an episode of provoked VTE.

Do not perform thrombophilia testing following an episode of provoked VTE.

Secondary prevention following provoked VTE

Should thrombophilia testing be performed to help determine duration of anticoagulation following unprovoked VTE?

- ✓ The absolute risk for recurrent VTE among patients with unprovoked thrombosis is higher than among those with provoked VTE, with 5-year risk approaching 30 % unless extended-duration anticoagulant therapy is provided
- ✓ Current guidelines from the American College of Chest Physicians (ACCP) recommend extended duration anticoagulation after unprovoked VTE unless the risk of bleeding is high or this is contrary to the patient's values and preferences.
- ✓ Other factors, such as the degree of post-thrombotic symptoms, D dimer levels after a minimum of 3 months of anticoagulant therapy, and residual vein thrombosis may also modify the risk of recurrence

Do not perform thrombophilia testing in patients following an episode of unprovoked VTE.

Primary prevention in relatives of VTE patients

Should family members of patients with VTE or hereditary thrombophilia undergo thrombophilia testing?

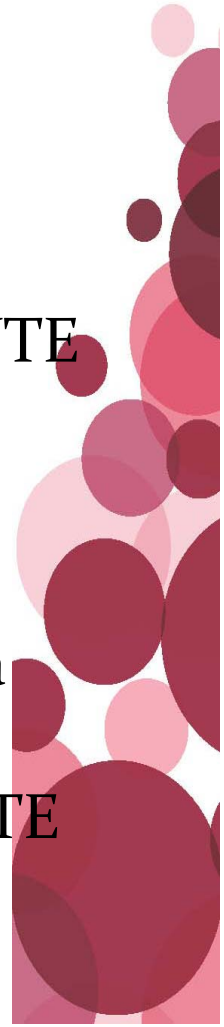
- ✓ Except for temporary prophylaxis during certain high risk situations (during hospitalization, following major surgery, and during long distance travel), anticoagulation for primary prevention of thrombosis is not advocated regardless of the genetic defect because the risk of bleeding may be higher than the absolute risk of a first thrombotic event
- ✓ However, a family history of thrombosis alone carries an increased risk, even in the absence of an identifiable thrombophilia
- ✓ Therefore, negative thrombophilia screening does not equate to normal VTE risk
- ✓ Family members who tested negative for a thrombophilic defect were less likely to use prophylaxis

Do not test for thrombophilia in asymptomatic family members of patients with VTE or hereditary thrombophilia.

Primary prevention in female relatives of VTE patients considering estrogen

Should female relatives of patients with VTE or hereditary thrombophilia who are considering using estrogen-containing medications be tested for thrombophilia?

- ✓ Although studies have shown that it is not practical or cost-effective to screen all women for thrombophilia before they use combination oral contraceptives, for women who are first-degree relatives of patients with VTE and known inherited thrombophilia, screening may provide guidance in making informed choices about contraceptive use.
- ✓ As with screening in any patient population, however, a strong family history of VTE with negative results of thrombophilia testing does not indicate a low risk of VTE



Do not test for thrombophilia in asymptomatic family members of patients with VTE or hereditary thrombophilia who are contemplating use of estrogen.

Family history of VTE in a first degree relative predicts an excess risk of thrombosis with estrogen use, even when thrombophilia testing is negative.

Combined oral contraceptives, thrombophilia and the risk of venous thromboembolism: a systematic review and meta-analysis

Results: We identified 12 case–control and three cohort studies. In COC-users, mild and severe thrombophilia increased the risk of VTE almost 6-fold (rate ratio [RR], 5.89; 95% confidence interval [CI], 4.21–8.23) and 7-fold (RR, 7.15; 95% CI, 2.93–17.45), respectively. The cohort studies showed that absolute VTE risk was far higher in COC-users with severe thrombophilia than in those with mild thrombophilia

Severe thrombophilia: anticoagulant deficiency

Mild thrombophilia: factor V Leiden (FVL) or prothrombin-G20210A (PT) mutation

Conclusion: These results support discouraging COC-use in women with severe hereditary thrombophilia. By contrast, additive VTE risk of mild thrombophilia is modest. When no other risk factors are present, (e.g. family history) COCs can be offered to these women when reliable alternative contraceptives are not tolerated.

F . W. VAN VLIJMEN, J. Thr. and Haemostasis, 2016

Primary prevention in female relatives of VTE patients who are contemplating pregnancy

Should female relatives of patients with VTE or hereditary thrombophilia who are contemplating pregnancy be tested for thrombophilia?

- ✓ Pregnancy is a period of particularly high risk for thrombosis, causing a relative risk increase of 5–10 times baseline.
- ✓ The presence of a thrombophilic defect amplifies this risk several-fold further
- ✓ Thrombophilia screening, if performed, would be most applicable to the setting of primary prevention, as women with a prior VTE that was unprovoked, or provoked by pregnancy or an OCP

Primary prevention in female relatives of VTE patients who are contemplating pregnancy

Should female relatives of patients with VTE or hereditary thrombophilia who are contemplating pregnancy be tested for thrombophilia?

- ✓ A personal history of a prior VTE provoked by surgery or trauma does not significantly increase the risk of VTE during pregnancy; and no special prophylaxis measures are indicated ante-partum
- ✓ The use of antepartum prophylaxis in women who have an inherited thrombophilia but no personal or family history of VTE is controversial, with varying recommendations because of extremely limited data.

Primary prevention in female relatives of VTE patients who are contemplating pregnancy

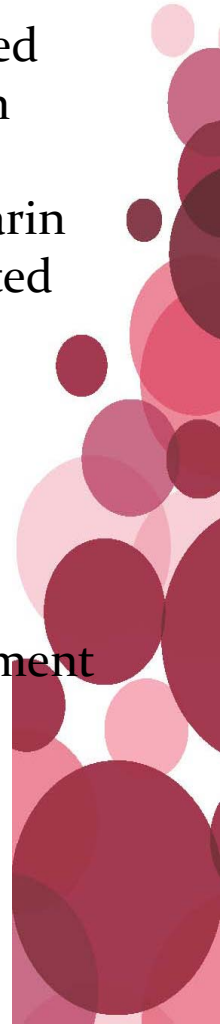
Should female relatives of patients with VTE or hereditary thrombophilia who are contemplating pregnancy be tested for thrombophilia?

- ✓ A recent multinational prospective, randomized, open-label trial compared prophylaxis with dalteparin versus no prophylaxis in 289 pregnant women with thrombophilia who were at increased risk of placenta-mediated pregnancy complications, VTE, or both. Antepartum prophylactic dalteparin did not reduce the occurrence of VTE, pregnancy loss, or placenta-mediated pregnancy complications, but increased minor bleeding.

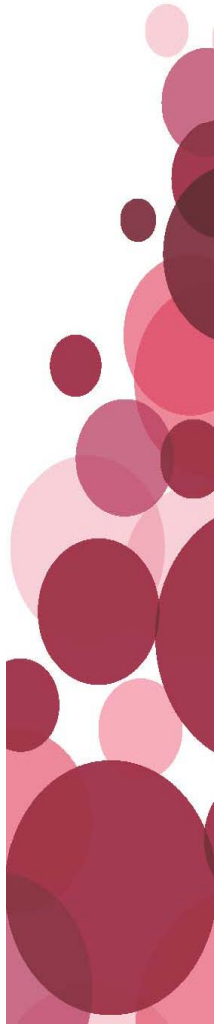
Rodger MA. Lancet 2014

- ✓ Systematic reviews have concluded that the evidence supporting management decisions for pregnant patients with FVL or PGM is low

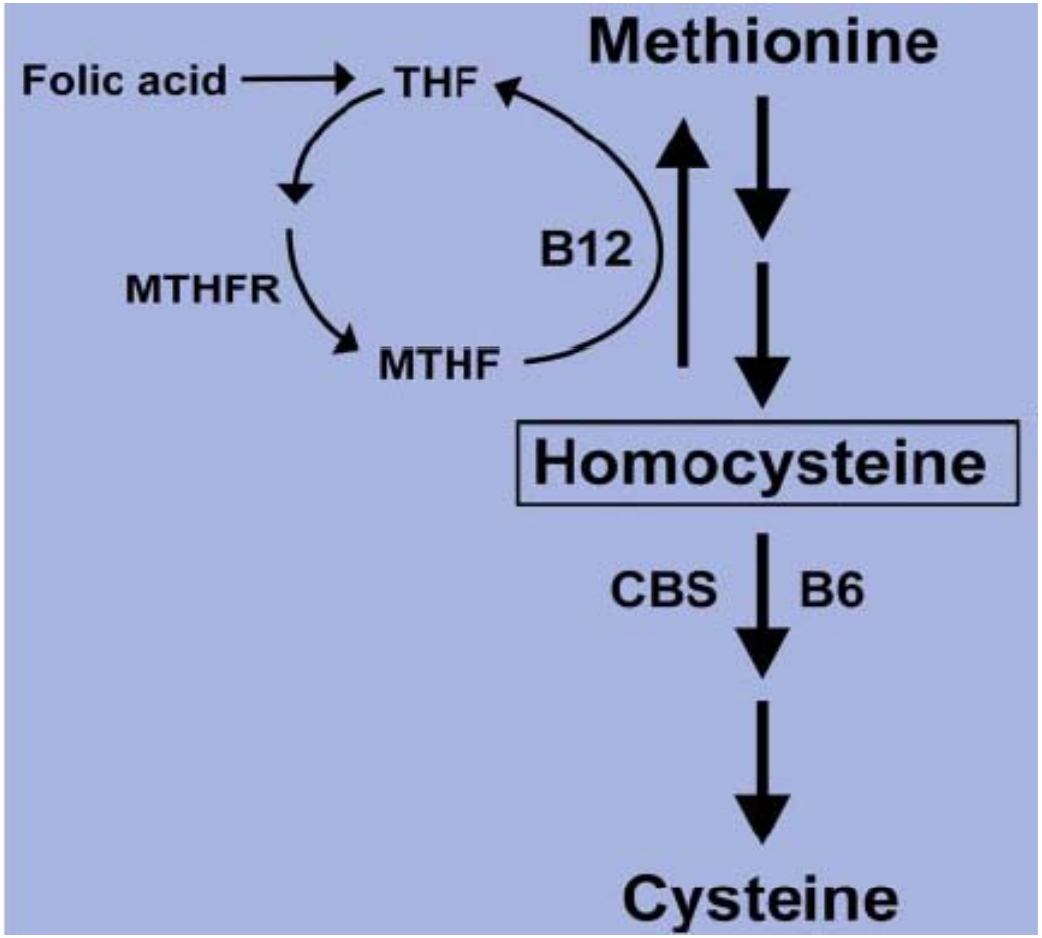
Bain E, Cochrane Database Syst Rev 2014



MTHFR polymorphism test

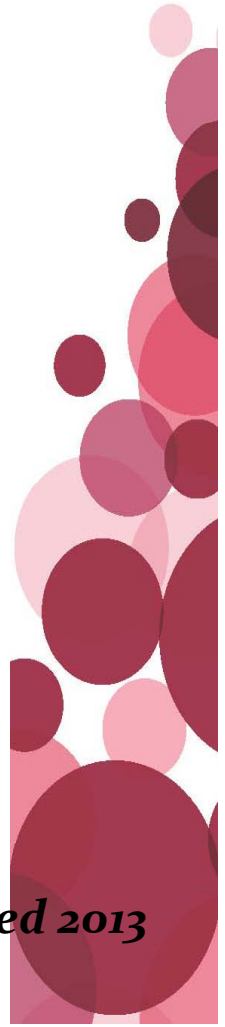


The 5,10-methylenetetrahydrofolate reductase (MTHFR) enzyme catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the primary circulatory form of folate, and a cosubstrate for homocysteine remethylation to methionine.



Genet Med 2013

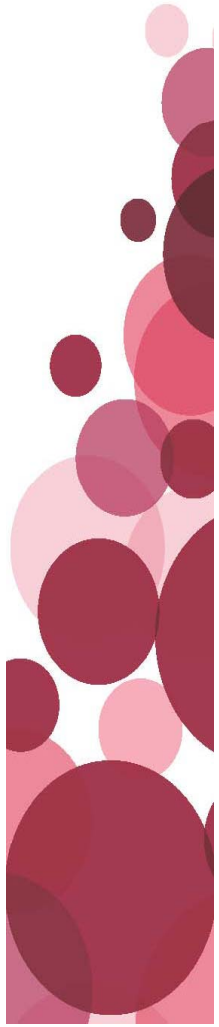
- ✓ Reduced enzyme activity of MTHFR is a genetic risk factor for hyperhomocysteinemia, especially in the presence of low serum folate levels.
- ✓ Mild to moderate hyperhomocysteinemia has been identified as a risk factor for venous thrombosis



Genet Med 2013

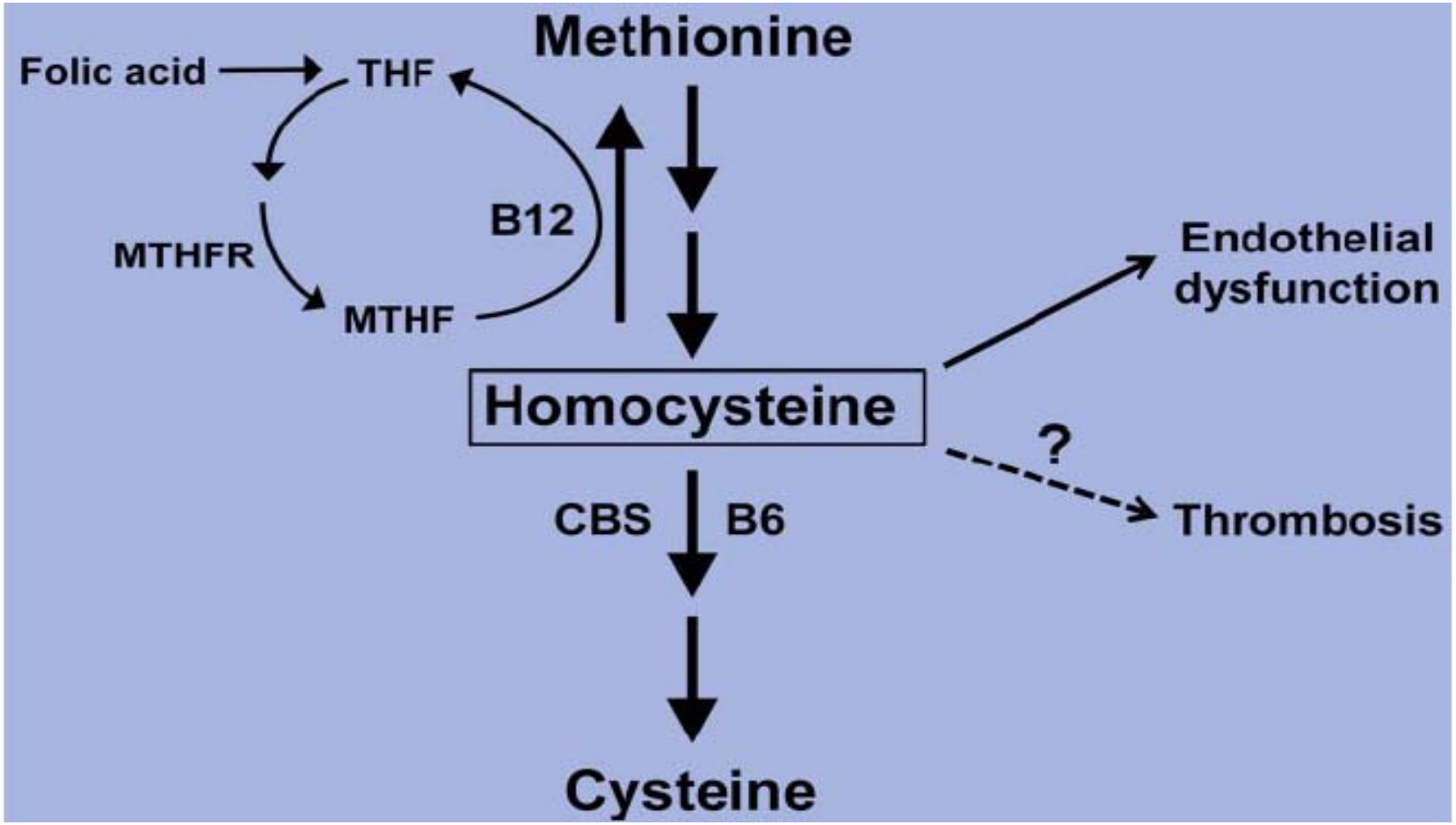
Homocysteine and venous thromboembolism—Is there any link?

Hirmerova J, 2013



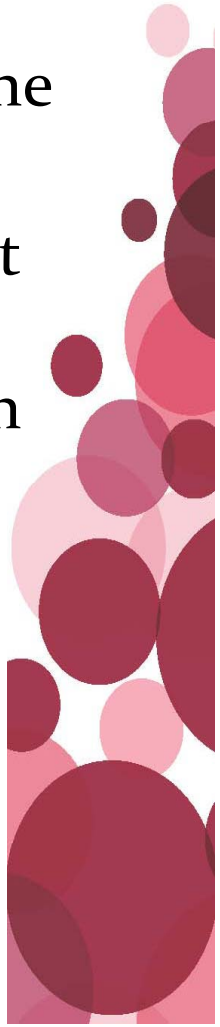
Homocysteine and thrombosis: guilt by association?

Blood,2012



Abnormal homocysteine metabolism is linked to vascular disease, including endothelial dysfunction, but is hyperhomocysteinemia sufficient to trigger thrombosis?

- ✓ The role of homocysteine in venous thrombosis has been studied less extensively than its role in arterial diseases and nowadays it seems quite controversial. It is also possible that hyperhomocysteinemia plays a role in the pathogenesis of VTE only as an additional risk factor in the presence of other thrombophilic disorders
- ✓ The results of epidemiologic studies are not so clear. Most of them found an association of hyperhomocysteinemia with venous thromboembolism (VTE) but the association was quite weak
- ✓ So far, the benefit of lowering homocysteine level in primary and secondary VTE prevention has not been clearly proven.



Homocysteine and venous thromboembolism—Is there any link?

Hirmerova J, 2013

Currently, there is not enough evidence to support the necessity of testing homocysteine level in VTE patients, neither is sufficient evidence of the benefit of vitamin supplementation in mild or moderate hyperhomocysteinemia. Therefore, such testing and supplementation should be performed only in selected cases

Table 1 – Causes of hyperhomocysteinemia [2,5,7].

Genetic causes	1. CBS deficiency 2. Inherited defects of folate metabolism 3. Inherited defects of cobalamin absorption, transport and metabolism 4. Polymorphisms of folate and cobalamin metabolism, including polymorphisms of following enzymes: (a) MTHFR (b) Methionine synthase (c) Methionine synthase-reductase
Acquired factors	1. Folate deficiency 2. Vitamin B12 deficiency 3. Vitamin B6 (pyridoxine) deficiency 4. Some diseases and disorders: (a) Renal insufficiency (b) Proliferative disorders: malignancy, psoriasis (c) Rheumatoid arthritis, systemic lupus erythematosus (d) Hypothyreoidism 5. Some medicaments: sex hormones, insulin, antiepileptics, fibrates, metformin, D-penicillamine, proton pump inhibitors, methotrexate, L-dopa, 6-mercaptopurin, sulfasalazin, cyclosporin, megadoses of vitamin C 6. Factors of life style: smoking, alcohol, sedentary life style, high consumption of animal proteins rich in methionine 7. Other: age, male sex, gastroplasty, Down syndrome, postmenopause

CBS—cystathionine beta-synthase.
MTHFR—methylentetrahydrofolate reductase.

Guideline: lack of evidence for *MTHFR* polymorphism testing and homocysteine measurement

- ✓ The American Congress of Obstetricians and Gynecologists does not recommend the measurement of homocysteine or MTHFR polymorphisms in the evaluation of the etiology of venous thromboembolism.
- ✓ The British Committee for Standards in Haematology and the British Society for Haematology do not include MTHFR polymorphism testing as part of their clinical guidelines for heritable thrombophilia testing.
- ✓ The ACMG (American College of Medical Genetics and Genomics) consensus statement on factor V Leiden testing briefly references the limited clinical utility of MTHFR polymorphism testing and that homocysteine measurement may be more informative

Genet Med 2013

Table 4. Diagnostic Criteria for the Antiphospholipid Syndrome.

The antiphospholipid syndrome is present if at least one of the two clinical criteria and at least one of the three laboratory criteria are met:

Clinical criteria

Vascular thrombosis: one or more documented clinical episodes of arterial or venous thrombosis in any organ or tissue (documented by means of imaging or histopathological assessment) in the absence of vasculitis

Pregnancy complication

- Unexplained death of a morphologically normal fetus at or beyond wk 10 of gestation
- Premature birth of a morphologically normal neonate before wk 34 of gestation as a result of eclampsia, severe preeclampsia, or placental insufficiency
- Three or more unexplained, consecutive, spontaneous abortions before wk 10 of gestation, not related to chromosomal or anatomical abnormalities in the parents

Laboratory criteria*

Lupus anticoagulant assay

IgG or IgM anticardiolipin antibody test

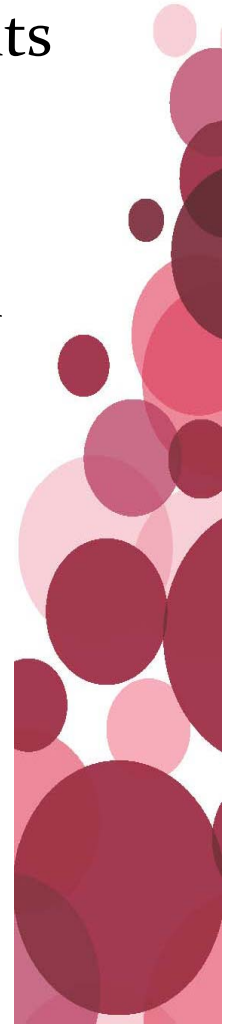
IgG or IgM anti–beta-2 glycoprotein 1 antibody test


MESSAGE

Do not test

Do not test

- ✓ Testing for heritable thrombophilia in unselected patients presenting with a first episode of venous thrombosis.
- ✓ Do not test if VTE is provoked by strong risk factors
- ✓ Testing is not recommended in unselected patients with upper limb venous thrombosis.
- ✓ Testing is not recommended in patients with central venous catheter (CVC)-related venous thrombosis.
- ✓ Testing is not indicated in patients with retinal vein occlusion.



Do not test at time of VTE event

Test at completion of anticoagulant therapy for provoked VTE; for unprovoked VTE, test after treatment for acute event if cessation of anticoagulant therapy is contemplated and test results might change management strategy

Do not test while patient is receiving anticoagulant therapy

Test when VKA has been stopped for at least 2 wk, DOAC has been stopped for at least 2 days (preferably longer), and UFH or LMWH for antithrombin levels has been stopped for more than 24 hr

Consider testing

Consider testing in patients in whom VTE occurs at a young age in association with weak provoking factors or a strong family history of VTE or in patients who have recurrent VTE

Identify goals of testing

Identify goals in order to aid decision making regarding future VTE prophylaxis, to guide testing of family members (especially regarding risk associated with COC or pregnancy in female family members), and to determine cause (especially for severe VTE, fatal VTE in family members, or VTE in an unusual location); test results alone should not be used for decision making regarding duration of anticoagulant therapy

Repeat testing

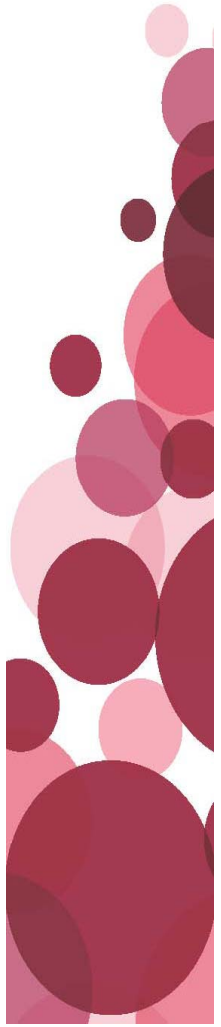
There is no benefit in repeating a normal thrombophilia screens. In the event of an abnormal result, requests for confirmatory testing should be limited to the relevant deficiency only.

If you do test

Known the 4 P:

- Patient selection
- Patient counseling
- Proper test interpretation
- Provision of education and advice

- ✓ Don't test while the patient is on anticoagulation
- ✓ Don't test during an acute thrombosis



Ordering thrombophilia tests is easy....

Determining whom to test and how to use the results is not!