

THROMBOPHILIA EVALUATION AND TESTING

SYED HAIDER, MD

June, 2009

QUESTIONS:

1. Who should be tested for thrombophilia?

All are currently recommended indications except:

- A. First episode of venous thromboembolism VTE at a young age (<45 for venous and <55 for arterial thrombosis).
- B. Venous thrombosis at unusual vascular territory e.g. (cerebral, hepatic, portal, mesenteric or renal vein thrombosis.)
- C. Strong family history of venous thrombosis at a young age.
- D. Recurrent VTE
- E. Unprovoked first episode of VTE
- F. Neonatal purpura fulminans
- G. Warfarin induced skin necrosis
- H. VTE in a young patient after major lower extremity orthopedic surgery

2. Many patients with VTE with an inherited thrombophilia do not have a family history of thrombosis.

True or False

3. Thrombophilia Testing should be done in all first degree relatives of a patient identified with hereditary thrombophilia.

True or False.

4. When counseling a patient or family member regarding the risk of thrombosis with a thrombophilia it is 'most useful' to provide

- a. absolute risk
- b. relative risk

5. What is the order of increased risk for the following independent risk factors for DVT: highest to lowest, rank the conditions.

- a. Hospitalization
 - i. Acute medical illness
 - ii. Major surgery
- b. Trauma
- c. Malignancy without chemotherapy
- d. Malignancy with chemotherapy
- e. Prior CVAD or TV pacemaker
- f. Prior superficial venous thrombosis
- g. Neurologic disease with paresis
- h. Serious liver disease

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6. Which of the following is correct about the recurrence risk (%) of VTE at 30day/180day/5yr/10yr intervals after the initial DVT?

- a. 1.6/8.3/12.9/16.6
- b. 5.2/10.1/22.8/30.4
- c. 8.3/10.1/16.6/20.1

7. Please rank the following inherited thrombophilic conditions in the order of relative risk of incident (new onset) VTE. Highest to lowest.

AT III deficiency

Protein S Deficiency

Protein C Deficiency

FVL mutation

Prothrombin 20210 mutation

Combined FVL and prothrombin gene mutation

8. What is a cost effective way of screening for FVL mutation.

9. Among the following conditions which are also regarded as a cause for arterial thromboembolic events as well (not counting paradoxical embolism in ASD or VSD) besides being a reason for VTE.

- a. AT III deficiency
- b. Protein S Deficiency
- c. Protein C Deficiency
- d. Polycythemia vera/ ET / MPD myeloproliferative disorders
- e. FVL mutation
- f. Prothrombin 20210 mutation
- g. Antiphospholipid syndrome (APS)
- h. Heparin induced thrombocytopenia (HIT)
- i. Combined FVL and prothrombin gene mutation
- j. PNH
- k. Hyperhomocysteinemia
- l. Elevated FVIII levels

10. Following are the indications of secondary prophylaxis i.e. Chronic oral anti coagulation (OAC) except:

- i. Idiopathic (unprovoked) VTE

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- ii. Life threatening VTE
- iii. Persistent clinical risk factors
- iv. Cancer
 - v. Chronic neurologic disease with extremity paresis
- vi. Transient lupus anti coagulant/ anti cardiolipin antibodies
- vii. Compound heterozygotes for more than one familial thrombophilic condition.
- viii. Residual post treatment venous obstruction
- ix. Persistently increased d- dimer

11. Rank the following conditions in the order of prevalence among the general population, most common to least common

AT III deficiency

Protein S Deficiency

Protein C Deficiency

FVL mutation

Prothrombin 20210 mutation

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ANSWERS:

1. Who should be tested for thrombophilia?

All are currently recommended indications except:

- I. First episode of venous thromboembolism VTE at a young age (<45 for venous and <55 for arterial thrombosis).
- J. Venous thrombosis at unusual vascular territory e.g. (cerebral, hepatic, portal, mesenteric or renal vein thrombosis.)
- K. Strong family history of venous thrombosis at a young age.
- L. Recurrent VTE
- M. Unprovoked first episode of VTE
- N. Neonatal purpura fulminans
- O. Warfarin induced skin necrosis
- P. VTE in a young 20 year old patient after major lower extremity orthopedic surgery

Answer. H In this instance there is a definite identifiable acquired risk factor and no further work up is necessary in the absence of other suggestive risk indicators for a familial thrombophilia condition presence.

2. Many patients with VTE with an inherited thrombophilia do not have a family history of thrombosis.

True or False

A. True. Recent evidence suggests that a family history of VTE does not increase the likelihood that a recognized familial thrombophilia will be identified. Consequently thrombophilia testing should not be limited to symptomatic patients with a family history of VTE.

3. Thrombophilia Testing should be done in all first degree relatives of a patient identified with hereditary thrombophilia.

True or False.

- A. False. Testing should be done if the results are likely to change management. The risk of unprovoked thrombosis associated with thrombophilia although increased, is still insufficient to warrant chronic primary prophylaxis, even for thrombophilias with high penetrance (AT III deficiency, FVL mutation) with the possible exception of Paroxysmal Nocturnal hemoglobinuria (PNH).

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4. When counseling a patient or family member regarding the risk of thrombosis with a thrombophilia it is 'most useful' to provide

- a. absolute risk
- b. relative risk

Answer a. absolute risk e.g. the relative risk of VTE with a heterozygous FVL carriers who receive oral contraceptives is increased about 30-fold; however the incidence is only 300 per 100,000 women years, or about 0.3% per woman-year.

5. What is the order of increased risk for the following independent risk factors for DVT : highest to lowest, rank the conditions.

- i. Hospitalization
 - a. Acute medical illness
 - b. Major surgery
- ii. Trauma
- iii. Malignancy without chemotherapy
- iv. Malignancy with chemotherapy
- v. Prior CVAD or TV pacemaker
- vi. Prior superficial venous thrombosis
- vii. Neurologic disease with paresis
- viii. Serious liver disease

Answer.

	Rank order	Odds ratio
Hospitalization		
i. Acute medical illness	3	7.98
ii. Major surgery	1	21.72
Trauma	2	12.69
Malignancy without chemotherapy	7	4.05
Malignancy with chemotherapy	4	6.53
Prior CVAD or TV pacemaker	5	5.55
Prior superficial venous thrombosis	6	4.32
Neurologic disease with paresis	8	3.04
Serious liver disease	9	0.10

6. Which of the following is correct about the recurrence risk (%) of VTE at 30day/180day/5yr/10yr intervals after the initial DVT?

- d. 1.6/8.3/12.9/16.6

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- e. 5.2/10.1/22.8/30.4
- f. 8.3/10.1/16.6/20.1

Answer. b. It is for that reason that oral anticoagulation is recommended for six months in most people after the first episode of DVT. However in provoked uncomplicated event a three month program may also be adequate. Beyond 6 months the aim of continued anticoagulation is not to prevent thrombosis extension or embolism but to prevent recurrent VTE.

7. Please rank the following inherited thrombophilic conditions in the order of relative risk of incident (new onset) VTE. Highest to lowest.

AT III deficiency
Protein S Deficiency
Protein C Deficiency
FVL mutation
Prothrombin 20210 mutation
Combined FVL and prothrombin gene mutation

Answer.

	Rank	Relative risk (95% CI)
AT III deficiency	2	17.5
Protein S Deficiency	3	11.3
Protein C Deficiency	1	32.4
FVL mutation	4	4.3
Prothrombin 20210 mutation	5	1.9
Combined FVL and prothrombin gene mutation	1	32.4

Please note the strongest risk factors as opposed to the least strong one. Recent literature does not suggest that significant a role for hyper-homocysteinemia and MTHFR mutations in VTE as by brought out in some earlier literature.

8. What is a cost effective way of screening for FVL mutation.

Answer. Ordering Activated protein C Resistance. If the initial screen for APC resistance is positive then it is worthwhile to order the FV Leiden mutation which is an expensive test and would be positive in cases of inherited causes of APC resistance constituting a cause for APC resistance, 95% of the times.

9. Among the following conditions which are also regarded as a cause for arterial thromboembolic events as well (not counting paradoxical embolism in ASD or VSD) besides being a reason for VTE.

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- e. FVL mutation
- f. Prothrombin 20210 mutation
- g. Antiphospholipid syndrome (APS)
- h. Heparin induced thrombocytopenia (HIT)
- i. Combined FVL and prothrombin gene mutation
- j. PNH
- k. Hyperhomocysteinemia
- l. Elevated FVIII levels

Answer. d, g, h, j, k?

APS, HIT, PNH, myeloproliferative disorders are definite causes of arterial thromboembolism.

AT III deficiency, Protein S Deficiency, Protein C Deficiency, FVL mutation, Prothrombin 20210 mutation, Combined FVL and prothrombin gene mutation, elevated FVIII levels despite the common concern have not been shown to cause arterial events, cerebro-vascular, coronary or other. There has been some literature suggesting some role of hyperhomocysteinemia in arterial stroke.

10. Following are the indications of secondary prophylaxis i.e. Chronic oral anti coagulation (OAC) except:
- i. Idiopathic (unprovoked) VTE
 - ii. Life threatening VTE
 - iii. Persistent clinical risk factors
 - iv. Cancer
 - v. Chronic neurologic disease with extremity paresis
 - vi. Transient lupus anti coagulant/ anti cardiolipin antibodies
 - vii. Compound heterozygotes for more than one familial thrombophilic condition.
 - viii. Residual post treatment venous obstruction
 - ix. Persistently increased d- dimer

Answer. vi. Transient ACA and LA once resolved do not constitute a reason for continued anticoagulation even if they caused a VTE during their presence.

11. Rank the following conditions in the order of prevalence among the general population, most common to least common

AT III deficiency

Protein S Deficiency

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Protein C Deficiency

FVL mutation

Prothrombin 20210 mutation

Answer.

	Rank	Prevalence (whites) %
AT III deficiency	5	0.02-0.04
Protein C Deficiency	4	0.02-0.05
Protein S Deficiency	3	0.01- 1
FVL mutation	1	3-7
Prothrombin 20210 mutation	2	1-3