Anticoagulation FORUM
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Antithrombotic Clinical Guidance

Thrombophilia Testing

Background[1]

- Thrombophilias affect approximately 10% of the population
- Depending on the type of thrombophilia, the risk of VTE can be either mildly or strongly increased
- Thrombophilias can be hereditary or acquired

$ Thrombophillia testing is costly and often does not change management

First VTE

Do Not Test

- In the initial phase of treatment (see below for the effects of AC on testing)
- Patient is ≥ 60 years old
- Arterial thrombus or systemic embolism with associated known risk factors (e.g. stroke in afib, peripheral arterial thrombosis)
- Provoked by surgery
- Unprovoked or unspecified if provoked

Consider Testing

- High estrogen states (e.g. pregnancy, postpartum, on combined oral contraception, on hormone replacement therapy, on gender affirming hormone therapy)
- Provoked by nonsurgical transient cause (e.g. hospitalized > 3 days)
- Embolic strokes of unknown source (ESUS) in patients < 50 years old
- Unusual site thrombosis (e.g. splanchnic vein thrombosis, cerebral vein thrombosis) without provoking factors (See Antithrombotic Clinical Guidance: Unusual Site Thrombosis)

Second VTE

Do Not Test

- Provoked and not on VTE prophylaxis

Consider Testing

- Unexplained, recurrent unprovoked thromboses while on appropriate antithrombotic therapy (could consider APS testing)

CVT or Splanchnic VTE

(See Antithrombotic Clinical Guidance: Unusual Site Thrombosis)

Do Not Test

- Will be on lifelong AC

Consider Testing

- Considering AC discontinuation

Common Thrombophilia Tests[2,3]

Thrombophilia Type	Test	Considerations
Inherited		
Increased procoagulant activity		
Factor V Leiden	APC resistance assay* and PCR	APC resistance assay may be inaccurate in the presence of DOACs or in patients with Lupus anticoagulant antibodies or inflammation. Of note: PCR assay may be clinically incorrect, depending on assay used, in patients who have had liver or bone marrow transplant (i.e., buccal swab vs whole blood); consultation with experts is advised
Prothrombin gene mutation	PCR	PCR for prothrombin G20210A mutation is the only test
Decreased anticoagulant activity		
Protein C (PC)	Activity assay*	Can also have acquired deficiencies with acute thrombosis and other medical conditions
Protein S (PS)	Activity assay*	Can also have acquired deficiencies acute thrombosis and other medical conditions
Antithrombin (AT)	Activity assay*	Can also have acquired deficiencies with heparin use, acute thrombosis, and other medical conditions
Acquired		
Antiphospholipid antibodies (See Antithrombotic Clinical Guidance: Antiphospholipid Syndrome)		
Lupus Anticoagulant	Screening followed by confirmatory tests*	Screening tests (e.g. sensitive PTT, DRVVT, Kaolin clotting time) Confirmatory tests (e.g. platelet neutralization test, hexagonal phase phospholipid) Can be affected by acute thrombosis and other medical conditions
Anticardiolipin	IgG and IgM antibodies	Can be affected by other medical conditions
Anti-β-2-glycoprotein 1	IgG and IgM antibodies	Can be affected by other medical conditions
Rare prothrombotic states		
Myeloproliferative neoplasms	JAK2 V617F	Polycythemia vera and essential thrombocytosis due to JAK2 mutations are prothrombotic states; consultation with experts is advised
Paroxysmal nocturnal hemoglobinuria	Flow cytometry	PNH is a prothrombotic state due to lack of complement regulation with resultant hemolysis and thrombosis; consultation with experts is advised

*Can be affected by presence of anticoagulants.

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Logistical Considerations of Thrombophilia Testing & Tests Affected by Anticoagulation[1,2]

Test†	Anticoagulant	Anticoagulant Hold Considerations	Testing Considerations
PC activity (chromogenic)	Warfarin	**Warfarin:** Hold for at least 2 weeks	Thrombophilia testing is not recommended during emergent situations which includes acute thrombosis Perform testing (when indicated) after completion of initial therapy and if it might change management strategies
PC activity (functional)	Warfarin DOACs	**DOACs:** Hold for at least 48 hours, longer if renal dysfunction	
PS activity (should be evaluated via protein S antigen)	Warfarin*	**Heparins/LMWH:** Hold for at least 24 hours	
Activated PC resistance	Warfarin* Heparins/LMWH DOACs	**Fondaparinux:** Hold for at least 48 hours, longer if renal dysfunction	
AT activity	Heparins/LMWH DOACs Parenteral DTIs		
LA (including sensitive PTT, DRVVT, Kaolin clotting time)	Warfarin Heparins/LMWH DOACs Fondaparinux		

† Assay dependent. False negative (e.g. increased protein C/S activity with direct oral anticoagulants) or False positive (e.g. positive LA with direct oral anticoagulants, warfarin) are possible
*Levels may be physiologically decreased by drug, but assay is not specifically affected by presence of drug
Lists are not all inclusive. Other thrombophilia tests available from different laboratories may be differentially influenced by various medical conditions or anticoagulants. Recommend discussing testing and test results w/ thrombosis experts familiar w/institutional testing procedures

Management Considerations[1,4,5]

- All patients with a thromboembolic event should be treated with anticoagulation for at least 3-6 months
- For VTE provoked by major surgery, do not test for thrombophilia
- For unprovoked VTE, generally recommend indefinite treatment with anticoagulation and not performing thrombophilia testing (except can consider with heightened suspicion for APS)
- For patients with VTE provoked by non-surgical risk factors, pregnancy/postpartum, or with VTE associated with exogenous hormonal therapy (e.g. combined oral contraceptives, gender-affirming hormonal therapy, or hormone replacement therapy), thrombophilia testing after initial treatment can be considered if it would influence treatment duration decisions

Thrombophilia Bottom Line[1,6]

Do	• Obtain a personal and family thromboembolic history • Have institutional protocols to limit and guide thrombophilia testing
Don't	• Perform non-genetic tests in the setting of acute inflammation or with an active thrombosis (except with strong suspicion of APS) • Routinely perform thrombophilia tests • Routinely prescribe anticoagulation for patients with a positive thrombophilia test and without a personal history of thrombosis
Consider	• Negative thrombophilia testing does not specifically indicate low risk of thrombosis • The absence of risk factors (unprovoked) or persistent strong risk factors are associated with high risk of recurrence after discontinuing anticoagulation and should be considered in addition to thrombophilia test results, if performed
Caution	• When managing patients with a prior thrombophilia diagnosis, evaluate and consider the impact of whether prior testing may have been influenced by confounding factors including anticoagulant use, during periods of acute inflammation/thrombosis, etc. • For patients with strong thrombophilias or recurrent thrombotic events, collaboration with relevant specialists is recommended (e.g. hematology, neurology, cardiology, etc.)

Abbreviations: AC: Anticoagulation, Afib: Atrial Fibrillation, APC: Activated Protein C, APS: Antiphospholipid Syndrome, AT: Antithrombin, CVT: Cerebral Venous Thrombosis, DOACs: Direct Oral Anticoagulants, DRVVT: Dilute Russell Viper Venom Time, DTIs: Direct Thrombin Inhibitors, DVT: Deep Vein Thrombosis, ESUS: Embolic Strokes of Unknown Source, FVL: Factor V Leiden, IgG: Immunoglobulin G, IgM: Immunoglobulin M, JAK2: Janus Kinase 2, LA: Lupus Anticoagulant, PC: Protein C, PCR: Polymerase Chain Reaction, PNH: Paroxysmal Nocturnal Hemoglobinuria, PS: Protein S, PTG: Prothrombin Gene, PTT: Partial Thromboplastin Time, VTE: Venous Thromboembolism

References: 1. Blood Adv. 2023 Nov 28;7(22):7101-7138. 2. N Engl J Med. 2017 Sep 21;377(12):1177-1187. 3. N Engl J Med. 2017 Dec 7;377(23):2297-8. 4. Blood Adv. 2020 Oct 13;4(19):4693-4738. 5. Hematology Am Soc Hematol Educ Program. 2024 Dec 6;2024(1):664-671. 6. J Thromb Thrombolysis. 2016 Jan;41(1):154-64.

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