Thrombophilia Testing – Guidance and Considerations

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BOTTOM LINE

DO	DON'T	CONSIDER	CAUTION
• Have institutional protocols to limit and guide thrombophilia testing • Obtain a personal and family venous thromboembolism (VTE) history	• Routinely order thrombophilia tests • Perform tests at the time of acute VTE event (Except anti-phospholipid antibody testing in patients with a high pre-test probability of APS) • Perform functional and clot-based tests while patient is on anticoagulation • Routinely prescribe anticoagulation for patients with a positive thrombophilia test without a personal history of thrombosis	• The most common inherited thrombophilias are mild risk factors for VTE recurrence. The absence of risk factors (unprovoked) or persistent risk factors are associated with a high risk of recurrence after discontinuing anticoagulation. • Negative thrombophilia testing does not specifically indicate low VTE risk.	• When assessing ongoing anticoagulation **or** assuming management of a patient with a known thrombophilia, confirm confirmatory testing was appro-priately performed and interpreted (i.e. performed off anticoag-ulation, not at the time of acute thrombosis, no interfering medical conditions such as coagulopathy of liver disease or DIC). • Discuss with an expert if testing was performed in the setting of potential influencing anticoagulants or medical conditions.

Common Types of Thrombophilia[1–3]

Mild Thrombophilia*†	Strong Thrombophilia*†
Heterozygous factor V Leiden (FVL)	Homozygous FVL
Heterozygous factor II G20210A (Prothrombin Gene Mutation -PTGM)	Homozygous factor II G20210A
	Antithrombin deficiency
	Protein C deficiency
	Protein S deficiency
	Antiphospholipid syndrome (APS)
	Combined heterozygous FVL and heterozygous factor II G20210A thrombophilias

It is important to consider the relative and absolute increase in risk associated with thrombophilia testing. For example, the risk of first episode of VTE in the general population is about 1/1000 per year. Heterozygosity for factor V Leiden increases this risk by ~5-fold to 5/1000 per year. Factor V Leiden and PTGM are mild risk factors for recurrent VTE (odds ratio ~1.3). Natural anticoagulant deficiencies are infrequent and usually associated w/strong family history.

* Strong and mild refer to the relative increase in the risk of recurrent VTE w/o anticoagulation.
† Presence of a thrombophilia generally should not impact decisions regarding anticoagulation type or duration, with the exception of high-risk antiphospholipid syndrome (APS; see APS guidance on opposite page).

Situations to generally avoid performing thrombophilia testing[2–5]	Situations where thrombophilia testing may be considered[2–4,6]
During the initial or primary phase of VTE treatment	Embolic strokes of unknown source in patients <50 years of age
Patients >60 years of age	VTE in rare thrombosis (e.g. cerebral vein thrombosis, splanchnic vein thrombosis) sites w/o provoking risk factors
In the setting of a provoked VTE	Unexplained recurrent unprovoked thromboses while on appropriate antithrombotic therapy
Arterial thrombosis or systemic embolism associated with a known risk factors (e.g. stroke in patients with Afib, peripheral arterial thrombosis)	When APS is suspected (e.g., concurrent autoimmune disease, pregnancy morbidity; see APS guidance on opposite page)

Common Thrombophilia Tests[7–11]

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 & test results w/ thrombosis experts familiar w/institutional testing procedures.

Test	Meaning if Abnormal	Potential Medical Condition Influences	Anticoagulants with Potential Influence on Results*
Functional and Clot-Based Testing			
Protein C (PC) activity (chromogenic)	Decreased PC activity resulting in increased risk of thrombosis	Vitamin K deficiency, infection, liver disease, acute thrombosis, DIC, nephrotic syndrome, autoimmune syndromes[12,13]	Warfarin†
Protein C activity (functional)	Decreased PC activity resulting in increased risk of thrombosis	Vitamin K deficiency, infection, liver disease, acute thrombosis, DIC, nephrotic syndrome, autoimmune syndromes[12,13]	Warfarin, direct thrombin inhibitors (DTIs), factor Xa (FXa) inhibitors
Protein S (PS) activity (Should be evaluated via protein S antigen)	Decreased PS activity resulting in increased risk of thrombosis	Vitamin K deficiency, infection, liver disease, acute thrombosis, DIC, nephrotic syndrome, autoimmune syndromes, surgery, combined oral contraceptives, pregnancy[12]	Warfarin†
Activated protein C (APC) resistance	Suggests FVL mutation or acquired APC resistance resulting in increased risk of thrombosis	Acute inflammation/infection/malignancy, factor or PS deficiency, pregnancy, combined oral contraceptives , LA, protein C antibodies[14]	Warfarin, heparins, DTIs, FXa inhibitors
Antithrombin (AT) activity	Decreased AT activity resulting in increased risk of thrombosis	Liver disease, malnutrition, nephrotic syndrome, acute thrombosis, L-asparaginase therapy, surgery, pregnancy, extracorporeal circulation[15,16]	UFH, FXa inhibitors
Lupus Anticoagulant (LA) (including dRVVT and LA PTT) *Antiphospholipid Syndrome Test*	Prolonged clotting time is potentially suggestive of LA	Acute thrombosis, pregnancy, infection, malignancy[3,15,17,18] *	Warfarin, heparins, fondaparinux, DTIs, FXa inhibitors
Hold anticoagulation before performing these tests (VKA 2weeks; DOACs 2 days; heparins 24hrs)[9]		* Assay dependent. False negative (eg increased protein C/S activity with DOAC) or false positive diagnoses (e.g. positive LA with DOACs, warfarin) are possible.	
† Levels may be physiologically decreased by drug, but assay is not specifically affected by presence of drug.			
Non-functional – Antibody and Genetic Testing			
Anti-Beta-2 glycoprotein antibodies *Antiphospholipid Syndrome Test*	Presence of antibodies associated with increased risk of thrombosis	Infection, malignancy[3,15,17]	None
Anti-Cardiolipin antibodies *Antiphospholipid Syndrome Test*	Presence of antibodies associated with increased risk of thrombosis	Infection, malignancy[3,15,17]	None
Factor V Leiden mutation	Genetic mutation resulting in Factor V resistance to inactivation by Protein C	None	None
Factor II G20210A mutation (Prothrombin G20210A gene mutation)	Genetic mutation resulting in increased levels of prothrombin	None	None

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Antiphospholipid Syndrome – Diagnostic and Treatment Considerations

Background: Antiphospholipid syndrome (APS/APLS) is an acquired systemic autoimmune disease defined by vascular thrombosis and/or pregnancy loss or morbidity with persistently positive antiphospholipid antibodies (aPL)[1]

Treatment of Thrombotic APS – Guideline Recommendations

Guideline	Recommendation
2019 EULAR[5]	Definite APS and venous thrombosis: • VKA with a target INR 2-3 is recommended • Avoid rivaroxaban in patients with triple aPL positivity • DOACs may be considered if unable to achieve target INR despite good adherence to VKA or contraindications to VKA • First unprovoked venous thrombosis ➔ long-term anticoagulation recommended • Provoked first venous thrombosis ➔ continue anticoagulation for same duration recommended for patients without APS • If recurrent venous thrombosis despite adherence to VKA within target INR 2-3, addition of low-dose aspirin, increase of INR target to 3-4, or change to LMWH may be considered Definite APS and arterial thrombosis: • VKA is recommended over low-dose aspirin monotherapy • VKA with INR 2-3 or INR 3-4 is recommended, considering individual risk of bleeding and recurrent thrombosis. May also consider VKA with INR 2-3 + low-dose aspirin • Use of DOACs NOT recommended • If recurrent arterial thrombosis despite adherence to VKA, an increase of INR target to 3-4, addition of low-dose aspirin, or switch to LMWH can be considered
2020 ASH[3]	• Patients with APLS are not optimal candidates for DOACs
2020 ISTH[4]	• VKA preferred for "high-risk" APS patients: 1) triple positivity, 2) arterial thrombosis, 3) small vessel thrombosis or organ involvement, 4) heart valve disease according to Sydney criteria • DOACs should not be used in APS patients with recurrent thrombosis while on therapeutic VKA. Other therapeutic options in these cases: increased target INR range, treatment dose LMWH, or addition of antiplatelet therapy • DOACs should not be used in APS patients who are non-adherent to VKA therapy • In non-"high-risk" patients (single or double positive) who have been on DOACs with good adherence for several months for a first episode of VTE, recommend discussion of potential risks and uncertainties and shared-decision making regarding continued DOAC use
2020 Intl Congress on APL Antibodies Task Force[12]	DOACs should be avoided in APS patients with arterial thrombosis, and small vessel thrombosis. VKA should be first line DOACs should not be used in APS patients with recurrent thrombosis while on standard-intensity VKA. In these patients recommend either 1)increasing INR goal, 2) standard treatment dose LMWH (or fondaparinux if VKA/LMWH is not suitable), or 3) addition of antiplatelet agent Single- or Double-positive aPL following a first episode of VTE (in the acute setting or later in their course): Suggest continuation of the DOAC may be considered, while awaiting confirmation of persistence of aPL, based on testing after at least 12 weeks, and thereafter. Discussion with the patient and shared decision making regarding the perceived risks, benefits, and the uncertainties of choice of anticoagulant should be undertaken. Testing to distinguish patients with double- rather than triple aPL positivity should be performed if a DOAC is considered Triple positive aPL patients: if started on a DOAC upon initial presentation with a first episode of VTE, and upon considering limitations of testing (especially as it pertains to assessment for the presence of LA), recommend that therapy be switched to VKA. If the patient declines, then the DOAC may be continued, with clinical surveillance. Suggest that surveillance could include MRI brain imaging to identify ischemic lesions, which, if present, merit consideration of a switch to alternative anticoagulation, with the first option a VKA
2021 ESVS[13]	• For patients with unprovoked deep vein thrombosis, testing for antiphospholipid antibodies should be considered if a decision to stop anticoagulation is contemplated • For patients with deep vein thrombosis and antiphospholipid syndrome who are triple positive or have a history of arterial or small vessel thrombosis, DOAC should not be used • For patients with deep vein thrombosis and triple positive antiphospholipid syndrome, treatment with a VKA titrated to maintain a target INR between 2-3 should be considered

BOTTOM LINE

DO	DON'T	CONSIDER	CAUTION
• Ensure accuracy of APS diagnosis including retesting to confirm persistently positive aPL antibodies at least 12 weeks apart • Favor VKA for management of thrombotic APS, particularly in triple positive patients and arterial thrombosis	• Perform LAC testing while patient on anticoagulant therapy, results can potentially be false positive or false negative • Anticoagulate APS patients with no history of thrombosis	• Periprocedural bridging during VKA interruption in patients with APS, especially high risk	• VKAs are considered first-line therapy for the treatment of thrombotic events in the setting of APS, especially for "triple-positive" APS, APS associated with arterial thrombotic events (e.g., stroke), or when therapeutic failure to a DOAC has occurred. The use of DOAC in the setting of any confirmed APS diagnosis is controversial and a shared decision making approach should be used.

Diagnosis of APS – Revised Sapporo Criteria[1]

Clinical Criteria

Vascular thrombosis
- Clinical episode of arterial, venous, or small vessel thrombosis

OR

Pregnancy morbidity
- Unexplained death of a normal fetus at or beyond 10th week of gestation
- Premature births due to preeclampsia or placental insufficiency
- ≥ 3 unexplained consecutive spontaneous abortions before the 10th week of gestation

AND

Laboratory Criteria*

Lupus anticoagulant (LAC) present in plasma

IgG and/or IgM anticardiolipin antibody (aCL) in a medium (>40GPL or MPL) or high titer >99th percentile

IgG and/or IgM anti-beta-2 Glycoprotein-I antibody (anti-β2 GPI) in titer >99th percentile

Two or more occasions at least 12 weeks apart

Diagnostic Interpretation

Key concepts
- Transient aPL positivity is common during infections or other acute illness
- Presence of a large thrombus may falsely normalize LA testing, but not aCL or anti-β2 GPI
- False positivity of LA testing can occur in patients on anticoagulants (heparin, VKA, or DOACs)

***Important to confirm persistence of aPL positivity via repeat testing at least 12 weeks after initial test**

Classification	Thrombosis Risk	Criteria to Meet
Triple positive[a]	High	Positive for all three laboratory criteria
Double positive[a]	Moderate-High	Positive for two out of three laboratory criteria
Single positive[b]	Low	Positive for only one laboratory criteria

[a]Same isotype (IgG or IgM) reinforces reliability of the result; [b]LA is considered higher risk than aCL or anti-β2 GPI
*Higher titer levels also tend to indicate higher thrombotic risk5

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