Thrombophilia evaluation in pulmonary embolism

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Purpose of review
Patients with pulmonary embolism commonly undergo thrombophilia evaluation for a variety of reasons including risk stratification for recurrent venous thromboembolism (VTE) and treatment planning. However, the utility of thrombophilia testing in many clinical scenarios remains unclear. This review evaluates current recommendations for thrombophilia testing described in consensus VTE guidelines, recent literature on the clinical application of these recommendations, novel genetic assessments for hereditary thrombophilias, and studies evaluating use of direct oral anticoagulants (DOACs) in VTE patients with thrombophilias.

Recent findings
Current VTE guidelines advise limited use of thrombophilia testing, recognizing that testing may be misinterpreted and frequently does not lead to a change in management. Testing and test results are not necessarily benign, are frequently misinterpreted, and can lead to increased anxiety in both patients and clinicians. Recent studies have offered innovative techniques to better align clinical practice with these recommendations as well as expanded genomic assessments to improve the scope and predictive value of thrombophilia testing. There is also emerging literature on the appropriateness of direct oral anticoagulant therapy for VTE patients with hereditary thrombophilias or antiphospholipid syndrome.

Summary
Thrombophilia testing in its current form does not significantly impact clinical management or improve outcomes for most VTE patients. Therefore, it should be employed judiciously and only in patients for whom it is likely to alter clinical management. Novel expanded genomic thrombophilia testing approaches and additional studies evaluating optimal anticoagulant treatment in various thrombophilia subpopulations will make thrombophilia testing more useful for patients moving forward.

Keywords
direct oral anticoagulant, pulmonary embolism, thrombophilia, venous thromboembolism, venous thromboembolism guidelines

INTRODUCTION

Over the past 30 years, the incidence of pulmonary embolism has risen dramatically. Much of this increase is attributed to advances in detection, as improved laboratory markers and imaging modalities have led to a near doubling of the pulmonary embolism detection rate [1]. Although the frequency of pulmonary embolism can at times make the diagnosis feel mundane, there continues to be a high mortality rate associated with the diagnosis. Despite the introduction of direct oral anticoagulants (DOACs), the 30-day and 1-year mortality rates for pulmonary embolism are 4 and 13%, respectively, with approximately 100 000 annual deaths in the United States attributed to pulmonary embolism [2,3].

The acute management of newly diagnosed pulmonary embolism is the same regardless of provoking factors and venous thromboembolism (VTE) risks, with anticoagulation as the mainstay of treatment. In the setting of massive or sub-massive pulmonary embolism, thrombolysis may also be considered. However, the duration of anticoagulation after the initial 3–6 months depends on an assessment of the risk of recurrent VTE. Thrombophilia testing is often part of this risk stratification and is intended to identify individuals at an increased risk of recurrent thrombotic events. In clinical practice, thrombophilia testing often

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KEY POINTS

- Updated consensus VTE guidelines recommend more limited thrombophilia testing in VTE patients. Thrombophilia testing is generally advised only in clinical situations where test results are likely to change clinical management.
- New electronic ordering procedures offer the potential to better align the clinical use of thrombophilia testing with recommendations from consensus VTE guidelines.
- Direct oral anticoagulants should not be used to treat VTE in the setting of a high-risk antiphospholipid syndrome, the 'triple positive APS' patient. Whether DOACs should be used in patients with low-risk APS is uncertain, given the limited data available. For patients with an inherited thrombophilia, whereas most studies have demonstrated no difference between DOACs and other anticoagulants, robust data is lacking.

includes testing for hereditary thrombophilias [protein C deficiency, protein S deficiency, factor V Leiden mutation (FVL), prothrombin *G20210* gene mutation (PGM), and antithrombin deficiency] as well as the acquired thrombophilia antiphospholipid syndrome (APS). Although the presence of a hereditary thrombophilia increases the risk of a first VTE [4,5], its impact on recurrence risk is much lower. This contrasts with APS, which is associated with high increased recurrence risk if anticoagulation is stopped. The prevalence, impact on thrombosis risk, and pathophysiology of the hereditary thrombophilias is illustrated in Table 1 and Fig. 1.

In this article, we will outline the current guidelines for thrombophilia testing in VTE patients as specific guidelines for pulmonary embolism do not exist. We will then discuss our own practice of testing, how these guidelines are applied in clinical practice, recent research to improve the predictive value of

Table 1. Summary of prevalence of hereditary thrombophilias and impact of initial and recurrent venous thromboembolism risk

Thrombophilia	Affected Gene	Prevalence	Approximate risk of initial VTE	Approximate risk of recurrent VTE
Factor V Leiden heterozygote	*F5*	1 in 20[a]	3–4-fold	1.5-fold
Factor V Leiden homozygote		1 in 400[a]	11-fold	Uncertain
Prothrombin G20210A heterozygote	*F2*	1 in 50[a]	3–4-fold	Not significantly increased
Prothrombin G20210A homozygote		1 in 2500[a]	7-fold	Uncertain
Protein C deficiency	*PROC*	1 in 200 to 1 in 500	7–30-fold	Uncertain
Protein S deficiency	*PROS1*	Uncertain	5–30-fold	Uncertain
Antithrombin deficiency	*SERPINC1*	1 in 600 to 1 in 5000	15–30-fold	Uncertain

Data from [39–47]. VTE, venous thromboembolism.
[a]In the Caucasian population.

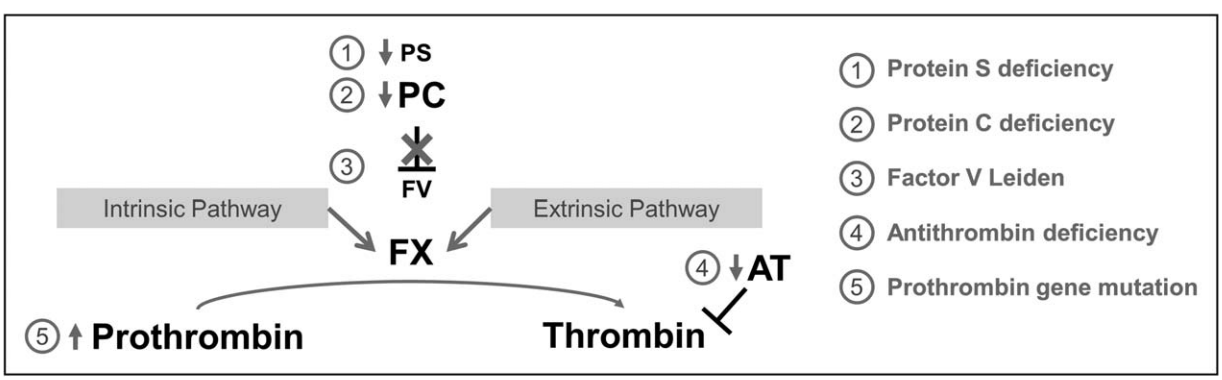

FIGURE 1. Pathophysiology of hereditary thrombophilias. (1) Protein S (PS) is a critical cofactor for activated protein C (PC); in protein S-deficient states, a functional protein C deficiency ensues. (2) Protein C is a natural anticoagulant that inactivates factor V (FV), a critical cofactor for factor X (FX), thereby halting thrombin generation. (3) Factor V Leiden is a mutation in factor V rendering it resistant to inactivation from activated protein C. (4) Antithrombin (AT) is a natural anticoagulant that inhibits several procoagulant factors, most notably thrombin. Antithrombin deficiency results in inadequate thrombin inactivation. (5) The prothrombin *G20210A* gene mutation results in production of excess prothrombin (approximately 25 and 50% in heterozygotes and homozygotes, respectively) [48–52].

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thrombophilia testing, and studies evaluating DOAC therapy in the setting of known thrombophilia, with a focus on pulmonary embolism where specific data are available. We will not discuss arterial thromboembolism or cancer-associated thrombosis, which are beyond the scope of this review.

CURRENT GUIDELINES ON HEREDITARY THROMBOPHILIA TESTING

Since 2009, at least eight clinical practice guidelines on VTE have been issued within the United States and Europe [6–13,14▪]. Two additional guidelines, an original set of guidelines from the American Society of Hematology and an updated set of guidelines from the National Institute for Health and Clinical Excellence are forthcoming in the end of 2019 [15,16]. The currently available guidelines vary in their discussion of thrombophilia testing. For example, the ninth edition of the American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines for antithrombotic therapy and its associated 2016 VTE update do not provide recommendations on the appropriateness of thrombophilia testing [6,7]. When guidelines do offer recommendations, they rely heavily on expert opinion.

Whenever the guidelines are taken together, consensus recommendations do emerge. First, there is a recognition that hereditary thrombophilia testing may have negative consequences. Negative hereditary thrombophilia testing can be falsely reassuring and positive testing can lead to overtreatment [17]. Second, there is an appreciation that thrombophilia testing is difficult to interpret and often misunderstood by clinicians [18]. Therefore, if thrombophilia testing is undertaken immediately after a VTE diagnosis or while a patient is on therapeutic anticoagulation, the recommendation is to limit testing to genotype-based tests (for FVL and PGM) and antibody titers (cardiolipin and beta-2 glycoprotein) as acute thrombosis and antithrombotic therapy alter functional thrombophilia assays and may lead to inaccurate results (Table 2) [17]. Third, there is consensus that thrombophilia testing should be ordered only when it will change clinical management. Although testing for APS frequently meets this criteria, testing for hereditary thrombophilias does not. In the case of a provoked VTE, clot formation is driven primarily by a major transient VTE risk factor and anticoagulation should be time-limited regardless of whether a hereditary thrombophilia is identified [19]. In the case of an unprovoked VTE, the presence of a common thrombophilia (such as FVL or PGM) does not significantly impact recurrence risk [20]. In addition, given the importance of the family history in the diagnosis of protein S, protein C, or antithrombin deficiencies, patients with VTE lacking a clear family history of VTE are unlikely to harbor a deficiency in any of these natural anticoagulants. As such, hereditary thrombophilia testing rarely alters the primary clinical assessment of risk of recurrent VTE [17,20].

The differences that exist across guidelines often involve clinical scenarios where the benefits of thrombophilia testing are uncertain. For example, guidelines diverge on whether hereditary thrombophilia testing should be obtained in a patient with VTE and a close relative who is considering oral contraceptive use or pregnancy. Some guidelines recommend testing broadly in this situation, given the additive or synergistic risk of increased estrogen levels in combination with a hereditary thrombophilia [12]. In contrast, other guidelines recommend testing narrowly, using personal and family VTE history rather than thrombophilia status to guide clinical decision-making [8]. Similarly, guidelines disagree over the appropriateness of hereditary thrombophilia testing for a VTE patient with a strong family history of VTE. The 2012 NICE guidelines do not recommend testing in such a clinical scenario [13]. In opposition, the 2010 British Committee for Standards in Haematology guidelines state that, in such a scenario, thrombophilia testing is reasonable with 'a view to enhanced prophylaxis at times of high risk in affected [family] members' [9].

In our own practice, we do not to test for hereditary or acquired thrombophilias at the time of VTE diagnosis and, if testing is indicated, we test only

Table 2. Potential pitfalls of functional hereditary thrombophilia testing

Assay	Potential impact of acute thrombosis	Potential impact of anticoagulant drugs	Potential impact of pregnancy or estrogen use
Activated protein C resistance screen		✓	
Protein C activity and antigen assays	✓	✓	✓
Protein S activity and antigen assays	✓	✓	✓
Antithrombin activity assay	✓	✓	

Data from [18].

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after anticoagulation has been stopped. Although we consider testing for APS in all patients with an unprovoked VTE, we will consider hereditary thrombophilia testing in patients with VTE and one of the following scenarios: young age with no provoking factors or minor provoking factors, family member of childbearing age who may consider exogenous estrogen use or pregnancy, strong family history of VTE, or a personal history of recurrent VTE.

CLINICAL APPLICATION OF THROMBOPHILIA TESTING GUIDELINES

Recent studies have assessed whether consensus guidelines are being followed in clinical practice. In 2014, according to Medicare Part B data, approximately 280 000 tests for hereditary thrombophilias were claimed in the United States with a cost of $300–672 million annually [21]. On the basis of published experiences from multiple large medical centers across the United States, it is likely that many of these 280 000 tests were obtained in a manner inconsistent with the guidelines. At the University of Texas Southwestern Medical Center, for example, Shen *et al.* [22] found that of the 173 patients who underwent hereditary and acquired thrombophilia testing in October and November of 2009, only 34% of the tests had indications considered appropriate by the authors. Similarly, at the University of Utah Healthcare University Hospital, Cox *et al.* [23] found that of the 1451 hereditary and acquired thrombophilia tests sent in 2014, 63% of tests were performed in situations of minimal clinical utility. Across both institutions, thrombophilia testing was frequently performed in the week following VTE diagnosis, concurrent with administration of therapeutic anticoagulation, or in the setting of provoked VTE [22,23]. Thrombophilia testing practices may be different in Europe. At the Lausanne University Hospital in Switzerland, Samim *et al.* [24▪] found that only 4.4% of patients admitted to the hospital with VTE between January 2013 and December 2015 underwent testing for a FVL or PGM, suggesting that thrombophilia testing is seldom performed in their institution.

To curtail thrombophilia testing that is inconsistent with VTE guidelines, several US hospitals have piloted new ordering procedures for thrombophilia testing. At the Stanford University Medical Center, for example, an electronic medical record-embedded best practice alert (BPA) for thrombophilia testing was introduced in 2016 [25]. The BPA cited the limited utility of thrombophilia testing in the setting of provoked VTE and was triggered when one of nine prespecified thrombophilias was ordered for a nonpregnant adult. The authors found that the BPA had a very high adherence rate and led to a significant decrease in thrombophilia testing in the outpatient setting. A similar decrease in testing was not found in the inpatient setting. Investigators from the Medical University of South Carolina (MUSC) implemented a similar system in the summer of 2017 [26▪]. When inpatient providers ordered a panel of hereditary and acquired thrombophilia tests, the providers were advised that inpatient testing for thrombophilia is suboptimal and should be deferred to the outpatient setting. If the providers moved forward with testing, a hematology consult was required for approval. In the 3 months following initiation of the advisory, inpatient thrombophilia testing dropped by 79%. Similar strategies to guide the appropriate ordering of thrombophilia tests could be easily replicated at other institutions.

ASSESSMENT OF NOVEL HEREDITARY THROMBOPHILIAS

A number of recent studies have attempted to broaden the scope of candidate thrombophilia genes and to improve the predictive value of thrombophilia testing. As currently constituted, standard hereditary thrombophilia testing is insufficient to impact management or improve outcomes for most VTE patients [20]. Fifty percent of patients with an unprovoked VTE test negative for hereditary thrombophilias [27]. In 30% of families with multiple family members affected by VTE, other genetic factors that predispose to thrombosis remain unknown [28▪]. Even when a hereditary thrombophilia is identified, it is rarely clear whether the thrombophilia has more than a modest effect on VTE occurrence [25].

Therefore, novel genetic assessments are now being undertaken to identify new hereditary thrombophilias and to improve the value of thrombophilia testing. In 2017, Lee *et al.* [29] performed whole-exome sequencing of 64 patients with VTE and 237 control patients without VTE. The authors focused their sequencing on a unique 55-gene extended thrombophilia panel that included genes encoding coagulation factors and genes reported in the literature as being associated with VTE. The panel successfully identified a probable disease-causing genetic variant or variant of unknown significance in 61% of the VTE patients as opposed to only 3% of control patients. Most variants had either been described previously in association with VTE or were novel variants disruptive of proteins relevant to hemostasis. By contrast, only 26% of the VTE patients tested positive for a hereditary

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thrombophilia by traditional clinical laboratory-based thrombophilia testing. De Haan *et al.* [28▪] in 2018, embarked on a similar study. The authors performed targeted DNA sequencing of the coding regions of 734 genes that were known to be or could be related to the hemostatic system in 899 DVT patients and 599 controls. They identified 20 054 high-quality variants including 5210 variants that had not previously been reported. Of the variants that had a significant statistical association with VTE, all 12 were on loci known to harbor genetic risk factors for VTE. Both of these studies demonstrate the potential for extended-spectrum genomic thrombophilia testing to improve the diagnostic value of hereditary thrombophilia evaluation.

ANTICOAGULATION IN THE SETTING OF THROMBOPHILIA

There is emerging literature on the appropriateness of DOAC therapy for the treatment of patients with VTE and a known thrombophilia. Over the past 10 years, the use of DOACs to treat VTE has increased exponentially. In 2010, only 0.1% of patients with VTE in the United States were treated with DOACs. By 2016, this number had increased to 66% [30]. As was seen in a compelling subgroup analysis of the Hokusai VTE trial, is possible that DOACs may be better than warfarin to prevent VTE recurrence in patients with pulmonary embolism leading to right ventricular dysfunction [31]. Further data is needed to confirm these findings.

Despite the rise in DOAC use for treatment of VTE, there has been limited evidence to support the safety and efficacy of DOACs in patients with hereditary or acquired thrombophilias. For example, individual patient reports and small case series are conflicting on the effectiveness of DOACs to prevent recurrent VTE in the setting of protein C and protein S deficiencies [32–34]. Similarly, only small retrospective studies and a single clinical trial with a surrogate endpoint have provided evidence for DOAC use in the setting of VTE and antiphospholipid syndrome [35,36].

Recent studies have attempted to provide more clarity on this topic. In 2019, Elsebaie *et al.* [37▪] conducted a systematic review and meta-analysis on DOAC use in patients with VTE and thrombophilia. The authors included data from phase 2 and phase 3 randomized trials that had compared DOACs to vitamin K antagonists (VKAs) in patients with VTE, including patients with a hereditary thrombophilia or APS. The authors found that the rates of VTE recurrence and major/clinically relevant non-major bleeding events were similar between thrombophilia patients treated with DOACs and VKAs. This held true in a subgroup analysis that included only patients with hereditary thrombophilia, but the analysis was limited by the small number of clinical events.

Recently, Pengo *et al.* [38▪▪] published the results of the TRAPS trial, a randomized open label multicenter trial assessing rivaroxaban use vs. warfarin in high-risk patients with antiphospholipid antibody syndrome (APS). This was the first large randomized controlled trial comparing the use of a DOAC with VKA in the setting of VTE and APS. The trial enrolled patients who were 'triple-positive' for APS (positive for a lupus anticoagulant by a clot-based assay and positive for both cardiolipin and beta-2 glycoprotein antibodies) and randomized patients to receive rivaroxaban or warfarin. Planned enrollment was 536 patients, but the trial was stopped early by the data safety monitoring board after only 120 patients were enrolled because of excessive adverse events on the rivaroxaban arm. This included seven thrombotic events (four ischemic strokes, three myocardial infarctions) and four bleeding events on the rivaroxaban arm as compared with zero thrombotic events and two bleeding events on the warfarin arm.

The systematic review and the TRAPS trial highlight the continued need for high-quality evidence evaluating DOAC therapy for the treatment of pulmonary embolism in the setting of thrombophilia. This is especially true for patients with hereditary thrombophilias or low-risk antiphospholipid syndrome, for which there are no prospective randomized trials.

CONCLUSION

Given the high mortality rate associated with pulmonary embolism, thrombophilia evaluation is intended to aid in risk stratification and to improve outcomes. However, current thrombophilia testing is frequently unable to accomplish this goal even when performed and interpreted properly. Recognizing these limitations, recent clinical guidelines advise judicious use of thrombophilia testing in the setting of DVT and pulmonary embolism, with testing only in patients for whom it will alter clinical management. Recent studies have attempted to better align clinical practice with current VTE guidelines, improve the predictive value of thrombophilia testing, and better define treatments for patients with VTE and a known thrombophilia. However, further studies are needed to explore the potential prognostic benefits of extended-spectrum genomic thrombophilia testing and evaluate the utility of DOACs in the management of various thrombophilia subpopulations.

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