Thrombophilia Screening
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What is This?
Thrombophilia Screening

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Abstract
Although controversial, screening for thrombophilia has become common. Testing for antiphospholipid antibodies is indicated in order to guide treatment decisions if there is clinical suspicion for antiphospholipid syndrome. The utility of identifying other thrombophilias in symptomatic venous thromboembolism (VTE) is questionable, as the risk of recurrence does not appear to be increased by an appreciable degree with the most common disorders (heterozygosity for factor V Leiden or prothrombin mutation). Although recurrence appears to be increased in those with homozygous or multiple abnormalities and potentially deficiencies in natural anticoagulants, screening to detect these conditions is difficult to justify based on their rarity. The American College of Chest Physicians’ current guidelines note the increased risk of recurrence with idiopathic, proximal events regardless of thrombophilia status. They suggest duration of anticoagulation therapy be based on location and provoking factors rather than whether or not the individual has a thrombophilia. Because routine prophylaxis in asymptomatic individuals with thrombophilia is not recommended, screening of asymptomatic family members is difficult to justify. Screening prior to prescribing combination oral contraceptives is not cost effective, may result in unwanted pregnancies, and may have little effect on the overall rate of VTE.

Keywords
thrombophilia, screening, factor V Leiden, prothrombin mutation, protein C deficiency, protein S deficiency, antithrombin deficiency, antiphospholipid antibodies, inherited thrombophilia

Learning Objectives
1. List reasons for which many clinicians conduct thrombophilia screening.
2. Discuss the arguments against routine thrombophilia screening in patients with symptomatic VTE.
3. Describe the limitations of available literature regarding the risk of recurrent VTE and clinical outcomes related to thrombophilia screening.
4. Recognize the arguments for and against thrombophilia screening in asymptomatic family members of those with VTE and a known thrombophilia.
5. Explain the arguments for and against thrombophilia screening in women prior to administering combination oral contraceptives (COCs).
6. Identify factors that contribute to inaccurate results when screening for thrombophilia is conducted.

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**Introduction**

Although screening for thrombophilia has increased significantly over the last decade, the clinical utility of such practice is of considerable debate. In 2005, an International Consensus Statement from various organizations including the International Union of Angiology recommended screening in all patients with a first spontaneous (or idiopathic) venous thromboembolism (VTE), VTE at a young age (<50), recurrent VTE, or VTE at an unusual site in individuals less than 50. They also recommended screening in asymptomatic first-degree relatives of those with symptomatic VTE and a known thrombophilia. These recommendations were updated in 2013 suggesting routine screening for first spontaneous events, but only in patients less than 60 years of age and in any VTE in individuals under 40, but are otherwise similar to the 2005 recommendations. The rationale for thrombophilia screening varies. Many clinicians are simply in search of an underlying cause of VTE, while others feel the results should guide therapeutic decisions regarding duration of anticoagulation therapy. Some propose genetic testing is warranted in order to identify asymptomatic family members at an increased risk of thrombosis in order to provide adequate prophylaxis in high-risk situations. Regardless of the rationale, testing should only be conducted if results will affect either current or future clinical decisions and ultimately patient outcomes. This however has not been consistently demonstrated for all thrombophilias and recognized in recent guidelines developed by the British Committee for Standards in Haematology as well as the American College of Chest Physicians. This article will discuss the evidence regarding the utility of screening for various thrombophilias in nonpregnant patients with VTE, in asymptomatic family members of those with VTE and thrombophilia, and in women prior to the use of combination oral contraceptives (COCs).

**Screening in Symptomatic VTE**

Although screening for thrombophilia is often conducted based on the premise that positive results warrant an extended duration of anticoagulant therapy, this practice is of considerable controversy. Extended therapy would only be warranted in the presence of thrombophilia that convey an increased risk of recurrence. Although thrombophilia is known to increase the risk of initial events, their effect on recurrence is not as well established. With the exception of antiphospholipid syndrome (APS), most thrombophilias have failed to show an association with increased recurrence or, at most, have shown a weak association.

In individuals with APS who were not receiving anticoagulation therapy, Derksen et al reported a 50% probability of recurrence at 2 years and a 78% probability at 7 years. Schulman et al reported a recurrence rate of 29% over a 4-year period in patients with anticardiolipin antibodies as compared to 14% in those negative for antibodies (relative risk [RR] 2.1, 95% confidence interval [CI] 1.3-3.3). Recurrence was highest in individuals with APS during the first 6 months after discontinuation of warfarin in a trial by Khamashta et al. An increased risk has also been shown with anti-β2-glycoprotein antibodies. Therefore, screening for antiphospholipid antibodies would be warranted in the presence of clinical signs suggesting APS, especially if discontinuation of therapy is being considered, as indefinite therapy is usually recommended in these individuals. The overall risk of thrombosis associated with specific antiphospholipid antibodies is discussed in a separate article in this issue.

The risk of recurrence in regard to the 2 most common thrombophilias, factor V Leiden (FVL) and prothrombin mutation, has been evaluated in 3 systematic reviews. FVL (heterozygosity) was associated with a small increase in the risk of recurrence, while prothrombin mutation (heterozygosity) either failed to show an increased risk or at most was found to result in a small increase (Tables 1 and 2). In the reviews by Ho et al and Marchiori et al, the population attributable risk of VTE recurrence conferred by FVL (heterozygosity) was estimated at 9.0% (95% CI 4.5%-13.2%) and 6.2% (95% CI 2.6%-10.1%), respectively. The risk of prothrombin mutation (heterozygosity) was estimated at 6.7% (95% CI 3.4%-9.9%) and 1.4% (95% CI 0%-4%). The highest risk of recurrence was found in those homozygous for FVL (odds ratio [OR] 2.65, 95% CI 1.18-5.97).

When evaluating individuals with initial events determined to be idiopathic, the analysis by Segal et al found no difference in the risk of recurrence related to FVL status (OR 1.17, 95% CI 0.63-2.18). A trial by Eichinger et al evaluating the effect of FVL in initial idiopathic, proximal deep vein thrombosis (DVT) or pulmonary embolism (PE) found similar results. Of the 287 patients followed for 6 years, the risk of recurrence did not differ between those with FVL and those without (RR 0.9, 95% CI 0.5-1.5). The effect of FVL remained insignificant when comparing recurrence in those receiving anticoagulation therapy for less than 6 months as compared to greater than 6 months.

A trial by DeStefano et al did not find an increased risk of recurrence in those with FVL alone (RR 1.1, 95% CI 0.7-1.6) but did find an increased risk of recurrence in those heterozygous for both FVL and the prothrombin mutation as compared to FVL alone (RR 2.6, 95% CI 1.3-5.1). Although the risk remained significant for those with idiopathic recurrence (RR 3.7, 95% CI 1.7-7.7), this difference was lost when evaluating those with transient, provoking risk factors.

The risk of recurrence with anticoagulant deficiencies has been difficult to assess due to their rarity and lack of well-designed clinical trials. Although recurrence rates have been estimated between 10% and 17% for antithrombin (AT) deficiency, 8% and 16% for protein S deficiency, and 10% for protein C deficiency, it is unclear whether these thrombophilias affect the overall rate of recurrence after an initial event as compared to those without deficiencies. One trial reported a small, but significant, increase in the risk of recurrence, while 3 trials failed to find a difference. One trial reported 355 patients for 8 years and reported a significant increase in the risk of recurrence with anticoagulant deficiencies (hazard ratio [HR] 1.44, 95% CI 1.02-2.01). This trial however did not...
exclude patients with malignancies nor did they account for FVL or prothrombin mutation.

The Leiden Thrombophilia Study (LETS) prospectively evaluated 474 patients over an average of 7.3 years after an initial VTE to determine the effect of several factors on the risk of recurrence. Recurrence was found to be increased with initial idiopathic events (HR 1.9, 95% CI 1.2-2.9) but did not differ based on the presence of FVL, prothrombin mutation, hyperhomocysteinemia, or in those with an elevation in factors VIII, IX, and XI. Of the 25 patients included with anticoagulant deficiencies, the risk of recurrence was not significant (HR 1.8, 95% CI 0.9-3.7). Other studies with similar findings are noted. The small number of patients and the large CIs in the trials by Christiansen et al and Baglin et al suggest a potential lack of power to detect a difference in these rare conditions. In all, 3 trials included patients with provoked events and 1 included patients with events in the distal veins of the lower extremities, both of which are known to be associated with lower rates of recurrence. Two trials included patients with thrombosis of the upper extremities, which is often device associated; thus, a potential confounder as well. In the trial by Christiansen et al, patients were allowed to continue anticoagulation treatment at varying times during the study. Therefore, caution is warranted in the interpretation of these results.

To date, there are no prospective, randomized trials evaluating the benefits of screening in relation to treatment decisions based on the presence or absence of thrombophilia. A case–control trial of a subset of patients from the Multiple Environmental and Genetic Assessment (MEGA) study attempted to determine the effect of thrombophilia screening on the risk of recurrence after an initial proximal DVT or PE. The investigators hypothesized that patients found to have a thrombophilia would be more likely to receive extended durations of anticoagulation after an initial event or more aggressive prophylaxis during high-risk situations. Of the 197 cases and 324 controls, 35% of cases and 30% of controls were screened. The authors reported no difference in recurrence rates between those screened and those who were not (OR 1.2, 95% CI 0.9–1.8%). Although treatment decisions based on the results of thrombophilia status were not evaluated, there was no clinical benefit associated with screening. This trial highlights the

### Table 1. Systematic Reviews Evaluating the Risk of Recurrence With FVL.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of trials included</th>
<th>Carriers/first episode VTE</th>
<th>Duration of follow-up (range in years)</th>
<th>Risk of recurrence for heterozygous carriers</th>
<th>Risk of recurrence for homozygous carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ho et al[^19]</td>
<td>10</td>
<td>663/3104</td>
<td>1.6-8.3</td>
<td>1.41 (1.14-1.75)^a</td>
<td>NA</td>
</tr>
<tr>
<td>Marchiori et al[^20]</td>
<td>10</td>
<td>557/3203</td>
<td>0.75-8.3</td>
<td>1.39 (1.15-1.67)^b</td>
<td>NA</td>
</tr>
<tr>
<td>Segal et al[^18]</td>
<td>13</td>
<td>979 heterozygous/4730;</td>
<td>0.5-8.3</td>
<td>1.56 (1.14-2.12)^c</td>
<td>2.65 (1.18-5.97)^c</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; FVL, factor V Leiden; NA, not applicable; OR, odds ratio; RR, relative risk; VTE, venous thromboembolism.

[^1]: Reported as OR (95% CI) utilizing the fixed effects model.
[^2]: Reported as RR (95% CI) utilizing the fixed effects model.
[^3]: Reported as OR (95% CI).

### Table 2. Systematic Reviews Evaluating the Risk of Recurrence With Prothrombin Mutation.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of trials included</th>
<th>Carriers/first episode VTE</th>
<th>Duration of follow-up (range in years)</th>
<th>Risk of recurrence for heterozygous carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ho et al[^19]</td>
<td>9</td>
<td>283/2903</td>
<td>1.7-8.3</td>
<td>1.72 (1.27-2.31)^a</td>
</tr>
<tr>
<td>Marchiori et al[^20]</td>
<td>10</td>
<td>212/3208</td>
<td>0.75-8.3</td>
<td>1.20 (0.89-1.61)^b</td>
</tr>
<tr>
<td>Segal et al[^18]</td>
<td>10</td>
<td>281/3636</td>
<td>0.5-8.3</td>
<td>1.45 (0.96-2.21)^a</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio; RR, relative risk; VTE, venous thromboembolism.

[^1]: Reported as OR (95% CI) utilizing the fixed effects model.
[^2]: Reported as RR (95% CI) utilizing the fixed effects model.
[^3]: Reported as OR (95% CI).
current prevalence of widespread testing, a practice that is consuming unnecessary health care dollars if not associated with improved outcomes.

Although the risk of VTE recurrence appears to be increased in those homozygous for FVL, or with a combination of disorders, and potentially with deficiencies in natural anticoagulants, the utility of routine testing to identify these rare conditions is questionable. In addition, data suggesting idiopathic events alone warrant consideration for extended therapy, despite thrombophilia status, would further question the clinical utility of routine screening.29 The most recent guidelines published by the American College of Chest Physicians for the prevention and treatment of thromboembolic events do not consider the presence of thrombophilia as a major determinant of recurrence but rather location (distal vs proximal) and cause (provoked vs unprovoked) of the event.4 Recurrence has been shown to be decreased in VTE secondary to a transient, provoking event as compared to idiopathic events (HR 0.55, 95% CI 0.41-0.74)26 with rates of 6.6% versus 15% at 1 year, 16.1% versus 40.8% at 5 years, and 22.5% versus 52.6% at 10 years.24 Proximal events have been associated with an increased risk of recurrence as compared to distal (RR 2.4, 95% CI 1.48-3.88).25,26 These guidelines therefore suggest consideration for extended anticoagulation therapy in all patients with an initial idiopathic, proximal event, regardless of thrombophilia status, taking into consideration individual bleeding risk and patient preference.4 They also suggest extended therapy in those with more than 1 event due to the increased risk of future recurrence. In such patients where continuation of therapy is planned, screening for thrombophilia would not alter treatment decisions, thus calling into question the recommendation for screening in those with recurrent events by the International Union of Angiology.2

It is also important to note the potential for additional thrombophilia yet to be identified. Before the discovery of FVL and prothrombin mutation in the 1990s, an underlying thrombophilia was identified in less than 10% of VTE cases.30 At present, over 50% of individuals with VTE, when screened, test positive for a thrombophilia.30,31 The lack of an increased risk of recurrence found in those with known thrombophilia as compared to those without, specifically in idiopathic events, could be explained by the presence of thrombophilia yet to be identified.

**Screening in Asymptomatic Family Members**

Trials evaluating the predictability of family history as a risk factor for VTE and/or the presence of a thrombophilia have reported conflicting information. Bezer et al reported the risk of VTE was increased by 2-fold in those with a history of at least 1 relative with VTE and by 4-fold in those with more than 1 affected relative.32 Noboa et al reported similar results with an OR of 2.7 (95% CI 1.8-3.8) for the risk of VTE with a positive family history.33 Neither trial however found an association with family history and the presence of FVL or prothrombin mutation.32,33 An additional trial by van Sluis et al also failed to find family history as a positive indicator for the presence of inherited thrombophilia,34 all of which may further support the idea for potential inherited thrombophilia not yet discovered.

Additional trials have evaluated the risk of VTE in asymptomatic family members of those with events and a known thrombophilia. A systematic review of both prospective and retrospective trials evaluated the risk of VTE in these individuals.35 In the 4 prospective studies, the annual incidence of VTE in asymptomatic family members representing 3641 patient-years was 0.58% to 0.67% for FVL, 1.0% to 2.5% for protein C deficiency, 0.7% to 2.2% for protein S deficiency, and 4% for AT deficiency. The rate of VTE was slightly lower in the retrospective trials ranging from 0.2% for FVL, 1.07% for AT deficiency, and 0.12% for prothrombin mutation. In the prospective trials, 20% to 75% of all events occurred during known high-risk periods, with lower rates of VTE in those receiving prophylaxis as compared to those who did not (5%-9% vs 17%-22%). FVL was associated with higher rates of provoked events as compared to those with anticoagulant deficiencies. In the retrospective trials, roughly half of all events occurred during high-risk periods; however, information regarding prophylaxis was not available. It is important to note, the overall incidence may be underestimated in these trials due to the relatively young age (highest mean age of 45) of participants as well as the potential effect of educational interventions and prophylaxis administered during high-risk situations to family members.35

In the largest prospective cohort trial in individuals with inherited thrombophilia, the European Prospective Cohort on Thrombophilia (EPCOT), 1575 asymptomatic carriers of family members with a history of VTE and known thrombophilia and 1118 controls were followed for up to 7 years (mean 5.7 years).36 VTE occurred in 4.5% of carriers and 0.6% of controls. The annual incidence of initial events was 0.8% (95% CI 0.5-1.2) in carriers and 0.1% (95% CI 0.0-0.2) in controls. Events were unprovoked in 58% of carriers and 43% of controls. The incidence was highest in those with AT deficiency (1.7%, 95% CI 0.8-3.3) and combined disorders (1.6%, 95% CI 0.5-3.7) and lowest for FVL (0.1%, 95% CI 0.0-0.6). The age of a first event was earlier in those with deficiencies in natural anticoagulants (~40) as compared to those with VTE and controls (both 63). Although the risk was higher for carriers, the overall incidence was low. The authors noted the increased risk of VTE would not outweigh the 1% to 3% incidence of bleeding associated with anticoagulation therapy.36

Because the risk of prophylaxis likely outweighs the benefits, proponents of testing family members agree that routine prophylaxis is not warranted. They do however cite benefits in the ability to provide more aggressive prophylaxis during high-risk situations such as surgery and to modify other known risk factors for thromboembolism such as obesity in these individuals.37 Although this approach may be beneficial in those with thrombophilia associated with a higher risk of thrombosis (homozygosity for FVL or prothrombin mutation, AT deficiency, and/or multiple defects), these conditions are extremely rare. Recommendations for all patients to receive primary
prophylaxis in certain high-risk situations, regardless of thrombophilia status, are also an argument against screening. Additional concerns with routine testing of family members include not only the anxiety associated with the detection of a thrombophilia that may carry an overall low risk of thrombosis but also a false sense of security that may come with negative results. The potential repercussions of a diagnosis in regard to a patient’s insurability must also be considered. Therefore, the best approach may not be to screen for thrombophilia in those reporting a family history of VTE but rather consider family history itself as a risk factor for VTE, when assessing the overall risk in asymptomatic individuals.

The British Committee for Standards in Haematology recommend against screening of asymptomatic relatives for FVL and prothrombin mutation. They also recommend against screening for rare disorders of homozgyosity or combination disorders due to their rarity and lack of predictability from family history. They do however suggest screening for AT, protein C, or S deficiency to be considered, but only in select thrombosis-prone families after the risk, benefits, and limitations are discussed. Despite this recommendation, they acknowledged that the best method for identifying these individuals is unknown. The consensus statement by the International Union of Angiology recommend screening in first-degree relatives of those with VTE and known thrombophilia with an emphasis on screening women of childbearing age. However, they do not provide a discussion of the clinical evidence to support this recommendation.

Screening Prior to Prescribing COCs

The increased risk of VTE in women with thrombophilia taking COCs suggests there may be utility in screening women prior to prescribing COCs. To evaluate this approach, Palareti et al estimated the cost of screening in order to detect 1 case of various thrombophilia. They reported the only cost-effective screening was for activated protein C resistance with a cost of US$433 to detect 1 case. When considering the incidence of events in those with FVL at a prevalence of 4% in the general population, it was noted that it would cost over US$150 000 to prevent 1 thrombotic event per year, resulting in a less favorable cost-effectiveness ratio. Vanderbrouncke et al provided various estimates regarding the cost-effectiveness for screening in this setting as well. Based on the proposed incidence of increased events, the case fatality rate for VTE in individuals <40 years of age, and a population incidence for FVL of 5% in the general population, it was determined that 400 000 women would need to be screened to find 20 000 women positive for FVL who would then be denied COCs in order to prevent 1 death related to fatal PE. This estimate translates into screening 8000 women to identify 400 with thrombophilia in order to potentially prevent 1 episode of VTE. The authors point out the negative aspects of denying COCs in women testing positive, primarily the potential increase in unwanted pregnancies, which may result in a similar number of VTE events due to the increased risk of VTE associated with pregnancy.

Others have suggested selective screening in women with a positive family history of VTE prior to prescribing COCs. Cosmi et al evaluated 324 women without a previous history of VTE to determine the positive predictive value of family history in detecting underlying common thrombophilia. Overall, 34 women reported a family history of VTE. Only 3 (9%) were found to have an underlying thrombophilia. Comparatively, of the 290 women without a family history, 16 (6%) women were found to have an underlying thrombophilia ($P = .44$). A later study by Eggert-Kruse et al verified the lack of a predictive value of family history in determining the presence of thrombophilia in women without a previous VTE. Therefore, screening in these women prior to prescribing COCs does not appear to be an effective strategy.

Timing Considerations For Screening

Although the benefit of routine screening is controversial, if conducted, it is important to ensure the accuracy of results. Screening at the time of an event may lead to numerous inaccuracies and inappropriate clinical decisions. At the time of an event, there is a transient decrease in natural anticoagulants. Patients may also test false positive for protein C deficiency or protein S deficiency in the presence of warfarin therapy and AT deficiency while receiving heparin. In contrast, screening for AT deficiency while on warfarin may result in false-negative results. Therefore, if screening for protein C, S, or AT deficiency is conducted, it should not be done within 3 weeks of the event or while patients are receiving anticoagulation therapy. Due to transient fluctuations, confirmatory testing should be conducted for all conditions other than FVL and prothrombin mutation. Diagnosis of APS requires confirmation of positive antibody testing separated specifically by 12 or more weeks in addition to clinical criteria that includes vascular thrombosis or pregnancy-related morbidity.

Suggested Future Research

Additional trials are needed to determine the clinical utility of thrombophilia screening, particularly in patients with symptomatic VTE. Large prospective trials, including patients with idiopathic PE and proximal DVT, with predetermined durations of anticoagulation therapy based on thrombophilia status, are warranted. Individuals with potential confounders such as upper extremity DVT and cancer should be excluded. An adequate duration of follow-up will be needed to adequately assess the risk of recurrence. Research should also be continued to determine additional risk factors, other than thrombophilia, associated with recurrence. This will aid clinicians in identifying patients that would benefit most from extended anticoagulation therapy while limiting the use of anticoagulants in those at low risk of VTE recurrence.
Conclusions

Thrombophilia screening should only be conducted if the results will be used to guide treatment decisions. Screening to confirm suspected APS is justified if discontinuation of anticoagulation therapy is planned. Although the risk of VTE recurrence appears to be increased in patients homozygous for either FVL or prothrombin mutation, in those with multiple thrombophilia, or with deficiencies in natural anticoagulants, the utility of routine testing to identify these rare conditions is debatable. The risk of recurrence with the most common thrombophilia appears to be only slightly increased. In addition, data suggesting all patients with idiopathic events or with recurrent VTE may benefit from long-term therapy despite thrombophilia status further question the clinical utility of routine screening in these individuals. Data to support screening in asymptomatic family members of patients with VTE and known thrombophilia are also lacking. Although these individuals may be at an increased risk of initial events, particularly in high-risk situations, using family history as a risk factor to ensure adequate prophylaxis may be more appropriate than thrombophilia screening. Although thrombophilia increases the risk of VTE in women taking COCs, screening for thrombophilia prior to their use does not appear to be a justified practice at this time.

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