Journal of
Vascular Surgery
Venous and Lymphatic Disorders™

PRACTICE MANAGEMENT

# Thrombophilia testing has limited usefulness in clinical decision-making and should be used selectively

**Elna M. Masuda, MD,[a] Raymond W. Lee, MD,[b] Ian J. Okazaki, MD,[c] Pouya Benyamini, MD,[d]** and **Robert L. Kistner, MD,[e]** *Honolulu and Hilo, Hawaii*

**Management of venous thromboembolism (VTE) includes evaluation for hypercoagulable state, especially if the VTE occurs in young patients, is recurrent, or is associated with a positive family history. These laboratory tests are costly, and surprisingly, there is little evidence showing that testing leads to improved clinical outcomes. Evidence based on observational prospective studies suggests that optimal duration of anticoagulation should be based on clinical risks resulting in VTE, such as transient, permanent, and idiopathic or unprovoked risks, and less on abnormal thrombophilia values. Thrombophilia screening is important in a subgroup of clinical scenarios, such as when there is clinical suspicion of antiphospholipid antibody syndrome, heparin resistance, or warfarin necrosis; with thrombosis occurring in unusual sites (such as mesenteric or cerebral deep venous thrombosis); and for pregnant women or those seeking pregnancy or considering estrogen-based agents. Thrombophilia screening is *not* likely to be helpful in most cases of first-time unprovoked VTE in the setting of transient risks, active malignant disease, deep venous thrombosis of upper extremity veins or from central lines, two or more VTEs, or arterial thrombosis with preexisting atherosclerotic risk factors. The desire by both patient and physician for a scientific explanation of the clotting event may alone lead to testing, and if so, it should be with the understanding that an abnormal test result will likely not change management, and normal results do not accurately exclude a thrombophilic defect because there are likely factors yet to be discovered. Such false assumptions may lead to shorter durations of treatment than are optimal. (J Vasc Surg: Venous and Lym Dis 2015;3:228-35.)**

Thrombophilia abnormalities are common among those with venous thromboembolism (VTE) and can be present in >50% of those tested for first-time thrombosis.[1] However, recent reports suggest that thrombophilia testing does not appear to strongly alter VTE management and more specifically does not appear to reduce VTE recurrence any more than management based on clinical risk factors.[2,3] Because testing can be costly, ranging from $1000 to $3000, depending on tests ordered (Table I), determining the practical use of testing should be more clearly defined. The American Society of Hematology,[4] the National Institute for Health and Care Excellence,[5] and the Society for Vascular Medicine[6] all discourage thrombophilia testing in the presence of first-episode VTE in the setting of a known cause or transient risk factor. Specific guidelines regarding indications for thrombophilia screening in general VTE groups have not been published by the American College of Chest Physicians (ACCP) at the time of this publication, except for pregnancy-related groups.[7]

From the Department of Vascular Surgery[a] and Department of Hematology and Oncology,[c] Straub Clinic & Hospital, Hawaii Pacific Health, and John A. Burns School of Medicine, Honolulu; the Hilo Medical Center, Hilo[b]; the University of Hawaii John A. Burns School of Medicine, Department of Surgery, UH Surgery Residency Program, Honolulu[d]; and the Kistner Vein Clinic, Honolulu.[e]

Author conflict of interest: E.M.M. is on the speakers bureau for Janssen Pharmaceuticals.

Reprint requests: Elna M. Masuda, MD, Department of Vascular Surgery, Straub Clinic & Hospital, Hawaii Pacific Health, and John A. Burns School of Medicine, 888 S King St, Honolulu, HI 96821 (e-mail: emasuda@straub.net).

The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.
2213-333X



http://dx.doi.org/10.1016/j.jvsv.2015.01.001

## PREVALENCE OF THROMBOPHILIA

The most common thrombophilias are the hereditary gene polymorphisms for factor V Leiden (FVL) and prothrombin G20210 gene mutation (PTGM). These are inherited in an autosomal dominant pattern and can be found in up to 3% to 7% of the population with northern or southern European ancestry. FVL and PTGM are rare in the Asian and African populations. Whereas the inherited deficiencies mentioned are common, the inherited deficiencies of antithrombin III (AT), protein C (Pro C), and protein S (Pro S) are rare yet more strongly associated with thrombotic events[8] (Table II).

Hyperhomocysteinemia is the result of vitamin B deficiencies (B6, B9 or folate, and B12) or mutations of specific enzymes, such as methylenetetrahydrofolate reductase or cystathionine β-synthase. Because elevated homocysteine levels are associated with thrombosis, studies demonstrating

**Table I.** List of commonly tested thrombophilias and costs at a single institution (Straub Clinic & Hospital, Hawaii)

| | |
|---|---|
| Factor V Leiden mutation | $408 |
| Activated protein C resistance | $206 |
| Prothrombin gene mutation | $408 |
| Cardiolipin IgG/IgM | $564 |
| Lupus anticoagulant screen | $243 |
| Antithrombin activity | $122 |
| Protein C activity | $139 |
| Protein S activity | $154 |
| Methylenetetrahydrofolate reductase | $899 |
| Factor VIII, functional | $206 |
| Total | $3349 |

*IgG*, Immunoglobulin G; *IgM*, immunoglobulin M.

that normalization of homocysteine levels reduces the risk of thrombosis would seem prudent but are lacking. A randomized controlled trial by den Heijer et al[9] failed to show reduction in venous thrombotic recurrence with treatment by folic acid and normalization of the homocysteine level, raising some doubt as to the clinical usefulness of testing for methylenetetrahydrofolate reductase.

Elevated factor VIII levels also incur a risk for thrombosis. However, laboratory detection of high levels is inconsistent, and its value in management is limited. Clinical reports comparing a longer duration of therapy vs standard therapy found no benefit.[10]

## CLINICAL RISK CATEGORIES ARE MORE IMPORTANT THAN THROMBOPHILIA ABNORMALITIES

Because VTE is multifactorial in etiology, the challenge is to identify the various causes and to optimize treatment based on all contributing factors. Thrombosis results from the culmination of clinical risk factors, including extrinsic factors and hypercoagulable states. In considering clinical risk factors without knowledge of the thrombophilia status, risks for recurrence can be categorized into three groups, each associated with a different risk for recurrence: transient or provoked VTE risk factors, unprovoked or idiopathic VTE, and permanent risk factors including active malignant disease[7] (Table III). Of these groups, the lowest risk for recurrence is found in those with transient risks, whereas the highest is in those with active malignant neoplasms. For each of these groups, duration of anticoagulation appears well established on the basis of numerous scientific studies.[11-13]

The group that could potentially benefit the most from thrombophilia testing is that with idiopathic or unprovoked VTE, in which the cause of thrombosis is unclear. In patients with idiopathic or unprovoked VTE, up to 74% have a documented thrombophilia.[14] In contrast, only 20% of those with transient risks possess a documented thrombophilic defect. However, sentinel reports in the 2000s[15-17] caused many to re-examine the validity of thrombophilia testing for unprovoked VTE. Four studies and one meta-analysis showed that thrombophilia testing does not decrease the risk of long-term VTE recurrence in these patients,[3,15-18] especially after adjusting for stronger predictors of recurrence including clinical risk factors.[15,16]

In a cohort study from Cambridge, United Kingdom, the presence of thrombophilic defects was not associated with a significantly higher risk of recurrence compared with noncarriers.[16] These findings were corroborated in the Leiden Thrombophilia Study (LETS),[15] in which overall recurrence rates were found to be no different between those with thrombophilia and those without. The authors of this study identified minimal or no increased risk of recurrence with FVL (hazard ratio [HR], 1.3; 95% confidence interval [CI], 0.8-2.1) and PTGM (HR, 0.7; 95% CI, 0.3-2.0). In contrast, deficiencies of the natural anticoagulants AT, Pro C, and Pro S showed a slightly higher incidence of VTE recurrence (HR, 1.8; 95% CI, 0.9-3.7). Similar results were observed in the Italian cohort study,[17] which showed that a mild increase in VTE recurrence was associated with AT deficiency (HR, 1.9; 95% CI, 1.0-3.9) and Pro C or Pro S deficiency (HR, 1.4; 95% CI, 0.9-2.2).

Because the risk for recurrence is greater in cases of unprovoked VTE compared with those with transient risks but lower than that for cancer[7] (Table III), extended duration of anticoagulation beyond 3 months is usually recommended for the unprovoked group. The risk of major bleeding is estimated at 1% to 2% annually and should be considered in determining the recommended duration of

**Table II.** Prevalence of inherited and acquired thrombophilias

| *Hypercoagulable state* | *General population* | *Patients with first VTE* | *Thrombophilic families* |
|---|---|---|---|
| Factor V Leiden | 3%-7%[a] | 20% | 50% |
| Prothrombin G20210A | 1%-3% | 6% | 18% |
| Protein C deficiency | 0.2%-0.4% | 3% | 6%-8% |
| Protein S deficiency | N/A | 1%-2% | 3%-13% |
| Antithrombin deficiency | 0.02% | 1% | 4%-8% |
| Mild hyperhomocysteinemia | 5%-10% | 10%-25% | N/A |
| Elevated factor VIII | 11% | 25% | N/A |
| Lupus anticoagulant | 0%-3% | 5%-15% | N/A |
| Elevated anticardiolipin antibodies | 2%-7% | 14% | N/A |

*N/A*, Not available or unknown; *VTE*, venous thromboembolism.
From Deitcher and Gomes,[8] with permission from SAGE.
[a]Prevalence as high as 15% in northern Europe.