

The Thrombophilias: Well-Defined Risk Factors with Uncertain Therapeutic Implications

Kenneth A. Bauer, MD

Discovery of the factor V Leiden and prothrombin G20210A mutations has greatly increased the percentage of patients in whom venous thrombosis can be attributed to hereditary thrombophilia. The first step in the diagnostic approach to all patients with venous thrombosis consists of a careful history and physical examination combined with routine laboratory testing to characterize the severity of the thrombotic condition and determine the presence of any of the acquired causes of hypercoagulability. The second step is to consider screening for the causes of hereditary and acquired thrombophilia in selected subsets of patients. The selection of patients for testing, the choice of tests to perform, and the timing of the testing are important and challenging issues to consider.

Routine testing would be warranted if the identification of abnormalities led to an alteration in the type or duration of initial anticoagulant therapy or the use of long-term prophylactic anti-

coagulation. The available data, however, do not yet indicate that most patients with defined thrombophilic states should be managed any differently than patients without identifiable abnormalities. On the basis of relative prevalences of the various thrombophilias, patients can be classified as “strongly” or “weakly” thrombophilic depending on their thrombotic histories. Management considerations and guidelines are offered for patients who are found to have one or more defined abnormalities, hereditary or otherwise. The future identification of additional laboratory abnormalities predisposing patients to thrombosis, coupled with prospective clinical trials, should enable us to better identify patients at high risk for recurrence who will benefit from prolonged anticoagulant prophylaxis.

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For the author affiliation and current address, see end of text.

Before 1993, a heritable cause of thrombophilia was detectable in a relatively small percentage (5% to 15%) of patients presenting with venous thromboembolism. Such abnormalities were confined to deficiencies of antithrombin, protein C, and protein S (1). However, the recent discovery of two prothrombotic mutations prevalent in white populations, the factor V Arg506Gln, or factor V Leiden, mutation (2) and the prothrombin G20210A mutation (3), has kindled renewed interest in this area of research. The factor V Leiden mutation causes resistance to activated protein C (4); both prothrombin antigen and activity are elevated by approximately 30% in heterozygotes with the prothrombin G20210A mutation compared with normal persons (3). Elevated plasma homocysteine levels also constitute a risk factor for venous as well as arterial thrombosis, sometimes on an inherited basis (5). One or more of these abnormalities, or the antiphospholipid antibody syndrome (a lupus anticoagulant or elevated cardiolipin antibody titers), can be identified in a substantial percentage of patients presenting with a first episode of idiopathic venous thromboembolism (that is, venous thromboembolism in the absence of a triggering risk factor, such as surgery, immobilization, or active malignancy). However, with the exception of the antiphospholipid antibody syndrome (6), the available data do

not indicate that most patients with defined thrombophilias should be managed any differently than patients without identifiable abnormalities. The following discussion will therefore focus on the question of who should be screened for hereditary and other thrombophilias and the implications of such a diagnosis on patient management.

IS THERE A RATIONALE FOR SCREENING?

Among unselected white patients presenting with an initial symptomatic episode of deep venous thrombosis, 12% to 20% will be heterozygous for the factor V Leiden mutation and 6% will be heterozygous for the prothrombin G20210A mutation, compared with 6% and 2%, respectively, of asymptomatic control populations (3, 7, 8). The relative and absolute risks for a first episode of deep venous thrombosis in persons carrying these abnormalities, along with the risk associated with oral contraceptive use, are shown in **Table 1**. The identification of either mutation in the setting of acute thrombosis does not alter the initial anticoagulant regimen. Similarly, the initial management of thrombotic patients with a diagnosis of one of the less common thrombophilias—deficiencies of antithrombin, protein C, or protein S—is generally identical to that of patients

Table 1. Risks for and Incidence of a First Episode of Venous Thrombosis

Variable (Reference)	Relative Risk	Annual Incidence, %
Normal	1	0.008
Hyperhomocysteinemia (5)	2.5	0.02
Homozygous MTHFR C677T mutation (9)	1	
Prothrombin G20210A mutation (3)	2.8	0.02
Oral contraceptive use (10)	4	0.03
Factor V Leiden heterozygote (7)	7	0.06
Oral contraceptive use and factor V Leiden mutation (10)	35	0.3
Factor V Leiden homozygotes (11)	80	0.5–1

without one of these defects. Also, these conditions can easily be misdiagnosed when testing is done in the acute setting. Therefore, it can be argued that there is little to be gained by immediate evaluation for the hereditary thrombophilias when patients present with their first thrombotic episodes.

Standard therapy for patients with deep venous thrombosis and pulmonary embolism typically includes anticoagulation with warfarin for 3 to 6 months, with the international normalized ratio maintained between 2 and 3. However, Prandoni and colleagues (12) found that in patients who presented with a first episode of symptomatic venous thromboembolism, the cumulative incidence of recurrent venous thrombosis after the cessation of initial therapy was 24.8% at 5 years and 30.3% at 8 years. Recurrences are less common when the initial event is associated with surgery or trauma. Other groups have shown that the recurrence rate is approximately 5% per year after standard therapy. However, a recent clinical trial in patients with a first episode of idiopathic venous thromboembolism (that is, thromboembolism without a major precipitating factor) found that persons randomly assigned to 3 months of anticoagulation had a much higher risk for recurrence (27% per patient-year) (13). Patients in that study who were randomly assigned to continue warfarin at an international normalized ratio of 2 to 3 experienced a 95% reduction in risk for recurrent venous thromboembolism.

Testing for prothrombotic abnormalities would clearly be helpful if it identified patients who are particularly prone to recurrences and thus are candidates for long-term antithrombotic prophylaxis. Unfortunately, the data disagree on whether the recurrence risk is higher among patients with first episodes of venous

thromboembolism associated with the factor V Leiden or prothrombin G20210A mutations than in those without a prothrombotic mutation (13–20). However, the risk for recurrence seems to be statistically significantly higher in the small subset of patients who are heterozygous for both mutations (21, 22). In other clinical settings, such as arterial thrombosis, the data are unclear about whether hereditary thrombophilia constitutes a risk factor. The ascertainment of thrombophilic genetic risk factors in these situations therefore often proves problematic because hereditary thrombophilia may be inappropriately interpreted as requiring anticoagulation, with its attendant bleeding risk, when it might not otherwise be prescribed. It is therefore advisable not to investigate for the hereditary thrombophilias in most patients who have only arterial thrombosis, particularly if they have other independent risk factors for arterial disease, such as hypertension, diabetes mellitus, smoking, or hyperlipidemia.

Several arguments, however, can be advanced in favor of screening for the hereditary thrombophilias in appropriate patients with venous thromboembolism. These include the benefits, for both patient and treating physician, of an improved understanding of the pathogenesis of deep venous thrombosis or pulmonary embolism when a specific prothrombotic abnormality is identified. The discovery can benefit the patient's family by leading to the identification of other affected relatives. It also focuses attention on antithrombotic prophylaxis during temporary periods of increased thrombotic risk (for example, during surgery or immobilization). In women with the factor V Leiden or prothrombin G20210A mutations, oral contraceptive use and pregnancy increase the risk for venous thrombosis another fourfold to eightfold (10, 23). Women with these mutations are also at increased risk for venous thrombotic complications associated with hormone replacement therapy and, very likely, tamoxifen and selective estrogen-receptor modulators (24–27). In healthy older patients with idiopathic deep venous thrombosis, the identification of a hereditary prothrombotic abnormality helps mitigate concern about an underlying occult malignancy and minimize the resulting tendency to order expensive diagnostic tests.

Several other coagulation abnormalities have been implicated as risk factors for venous thrombosis. In the Leiden Thrombophilia Study, 25% of patients with a

first episode of venous thrombosis and 11% of healthy controls had a factor VIII coagulant activity level greater than 150% of normal (28) at least 3 months after completing treatment with an oral anticoagulant. Persons with factor VIII coagulant activity levels greater than 150% of normal had a 4.8-fold increased risk for venous thrombosis compared with persons whose levels of factor VIII coagulant activity were under 100% of normal. The increased factor VIII coagulant activity levels were not associated with elevations in levels of acute-phase reactants (29). Several other groups (30, 31) have confirmed that high levels of factor VIII coagulant activity are a risk factor for venous thrombosis, and Austrian investigators (32) recently reported that the probability of thrombosis recurrence at 2 years in persons with factor VIII coagulant activity levels greater than 234% of normal (the 90th percentile of the values for the study sample) was 37% (95% CI, 16% to 57%), compared with 5% (CI, 2% to 8%) in patients with levels less than 120% of normal. Corroborating studies will be required before routine measurement of factor VIII coagulant activity levels can be recommended in patients with a previous venous thrombotic event. Elevated antigenic levels of several other coagulation factors, including factor XI (33), factor IX (34), and thrombin-activatable fibrinolysis inhibitor (35), also independently confer a significantly increased, albeit modest, risk for an initial episode of deep venous thrombosis. The mechanisms responsible for high levels of factor VIII coagulant activity and these other factors have yet to be explained, but family studies suggest that high factor VIII levels are often genetically determined (36).

In the absence of the factor V Leiden mutation, a significantly increased risk for venous thrombosis is associated with a reduced sensitivity to activated protein C, as measured by a clotting assay that does not mix patient plasma with factor V-deficient plasma (37). However, this risk is lower than that in carriers of the factor V Leiden mutation. This increased risk remains after adjustment for elevated levels of factor VIII coagulant activity and oral contraceptive use, both of which are known to lead to a reduced response to activated protein C. Most clinical laboratories test for activated protein C resistance by mixing patient plasma with factor V-deficient plasma, a method that is highly sensitive and specific for the factor V Leiden mutation, or by using a genetic assay. Because commercially available

assays for activated protein C resistance that do not mix the patient's plasma with factor V-deficient plasma fail to replicate the performance characteristics of the assay used by de Visser and coworkers (37), such assays are not recommended as part of the laboratory evaluation. Several hemostatic gene polymorphisms besides factor V Leiden and the prothrombin G20210A mutation have been investigated as risk factors for venous or arterial thrombosis, but the data supporting the associations are either inconsistent or too preliminary to warrant inclusion in the laboratory evaluation (38).

Thus, we are faced with the paradox of being able to diagnose more and more prothrombotic abnormalities in patients who present with venous thrombosis while remaining uncertain if and how the test results should influence their care. Given that a complete laboratory evaluation for thrombophilia is costly, it is appropriate to base the decision to test for thrombophilic abnormalities on the patient's personal and family history and clinical evaluation. Because clinical diagnosis is inaccurate, however, it is essential to verify that thrombotic events were documented by objective tests. Acquired causes of hypercoagulability, such as major surgery, active malignancy, systemic lupus erythematosus, or a myeloproliferative disorder, should be sought. It has not been shown that patients with venous thrombosis in association with these disorders have a higher frequency of hereditary thrombophilia than controls; therefore, testing in such patients is not routinely recommended. This is in contradistinction to venous thromboembolism triggered by oral contraceptive use or pregnancy and the puerperium (10, 23, 39).

Along with venous or arterial thrombosis, recurrent miscarriages, including second-trimester fetal loss, have been recognized for many years as a cardinal feature of the antiphospholipid antibody syndrome, through the mechanism of placental infarction. Because warfarin is teratogenic in the first trimester, heparin is the anticoagulant of choice in North America during pregnancy. Adding heparin therapy to aspirin substantially increases the number of live births in women with the antiphospholipid antibody syndrome and recurrent pregnancy loss compared with aspirin alone (40, 41). Case-control and retrospective cohort studies indicate that the hereditary thrombophilias are associated with a statistically significant increased risk for recurrent late fetal loss (42-45). It is controversial, however, whether other compli-

Table 2. Characterization of Patients with Venous Thromboembolism as “Strongly” or “Weakly” Thrombophilic

Clinical History	“Weakly” Thrombophilic	“Strongly” Thrombophilic
Age at onset < 50 years	–	+
Recurrent thrombosis	–	+
Family history	–	+

* Plus signs indicate “present”; minus signs indicate “not present.”

cations of pregnancy, such as preeclampsia, are associated with hereditary thrombophilia (42, 46). Moreover, the efficacy of therapy with heparin or low-molecular-weight heparin in women with hereditary thrombophilias has not been rigorously evaluated. Thus, although screening for the hereditary thrombophilias seems reasonable in selected women with recurrent late pregnancy loss, the identification of a thrombophilic abnormality has uncertain therapeutic ramifications.

WHAT IS A REASONABLE DIAGNOSTIC APPROACH TO PATIENTS WITH THROMBOTIC DISEASE?

It is useful to characterize patients as “strongly” or “weakly” thrombophilic on the basis of thrombotic history as a guide to the extensiveness of laboratory evaluation. Patients are considered strongly thrombophilic if they sustained their first venous thromboembolic event before 50 years of age, have a history of recurrent thrombotic episodes, or have first-degree family members with documented venous thromboembolic events occurring before 50 years of age (Table 2). If one or more of these features are present, a complete evaluation for hereditary thrombophilia is appropriate (Table 3), including assays for the factor V Leiden and prothrombin G20210A mutations. Testing for the factor V Leiden mutation is most often done by screening for resistance to activated protein C with a clotting assay and then confirming positive results by genetic analysis. Strongly thrombophilic patients should also be tested for deficiencies of antithrombin, protein C, and protein S. Although molecular genetic techniques are used to diagnose the factor V Leiden mutation and the prothrombin G20210A mutation, heterozygous deficiencies of antithrombin, protein C, and protein S are caused by many different mutations. These three abnormalities must therefore be diagnosed by using specific functional or immunologic assays.

It is also helpful to measure free and total protein S by immunoassay. Low levels of antithrombin or protein C can occur in the setting of acute thrombosis, making a reliable diagnosis of a hereditary deficiency difficult. Approximately 60% of plasma protein S normally circulates bound to C4b-binding protein, a complement protein that increases in the setting of acute thrombosis or inflammatory processes, thereby leading to increased protein S binding and decreased plasma protein S activity. Furthermore, antithrombin levels can be reduced in association with heparin therapy, and levels of protein C and protein S are reduced by warfarin. It is therefore optimal to test for these three deficiencies at least 2 weeks after anticoagulation is discontinued.

Weakly thrombophilic patients include patients 50 years of age or older with a first episode of idiopathic venous thromboembolism in the absence of family history. In the Physicians’ Health Study, 26% of men older than 60 years of age with a first episode of idiopathic venous thromboembolism were found to have the factor V Leiden mutation (8). Thus, screening for this abnormality along with the prothrombin G20210A mutation has a reasonable diagnostic yield in such patients. On the other hand, the likelihood of establishing a diagnosis of hereditary antithrombin, protein C, or protein S deficiency in this population is so low (<5%) that screening for these abnormalities can be omitted.

Both strongly and weakly thrombophilic patients should be tested for markers of the antiphospholipid antibody syndrome and hyperhomocysteinemia. It is also appropriate to test for these two entities in patients with unexplained arterial thrombosis. Testing is widely available for the common homozygous mutation

Table 3. Screening Laboratory Evaluation for Thrombophilic Patients

Screen for resistance to activated protein C with a clotting assay that dilutes patient plasma in factor V–deficient plasma or perform a genetic test for factor V Arg506Gln mutation (factor V Leiden mutation)
Confirm positive results on clotting assay genetically
Perform genetic test for prothrombin G20210A mutation
Perform functional assay of antithrombin (heparin cofactor assay)*
Perform functional assay of protein C*
Perform functional assay of protein S along with immunologic assays of total and free protein S*
Perform clotting assay for lupus anticoagulant and enzyme-linked immunosorbent assay for antiphospholipid antibodies
Measure fasting total plasma homocysteine levels

* Omit in weakly thrombophilic patients because deficiencies of antithrombin, protein C, and protein S are rarely identified.

(C677T) encoding the heat-labile form of methylene tetrahydrofolate reductase, which is associated with hyperhomocysteinemia. Studies have shown, however, that this genetic variant either is not a prothrombotic risk factor (9) or carries a lower relative risk for thrombosis than a simple elevation of fasting plasma homocysteine level. Therefore, testing for this genetic abnormality is not recommended.

HOW SHOULD PATIENTS WITH THROMBOTIC DISEASE BE MANAGED?

With respect to management (Table 4), it is generally recommended that asymptomatic patients with hereditary thrombophilia identified through family studies do not receive long-term oral anticoagulation; however, they should receive counseling about their diagnosis, the need for prophylaxis during high-risk situations, and symptoms that require immediate medical attention. However, there are potential drawbacks to screening. Asymptomatic persons who are identified as having a genetic abnormality can sometimes be denied some types of insurance (for example, life or disability insurance), and asymptomatic persons identified as having the factor V Leiden or prothrombin G20210A mutation may be prescribed overaggressive anticoagulation in situations that carry a relatively low risk for venous thromboembolism (47, 48). These issues are particularly relevant for weakly thrombophilic patients and their families and should be openly discussed with them before screening.

Since no controlled trials have evaluated the duration of anticoagulant therapy in patients with the hereditary thrombophilias, therapy must be tailored to the individual patient (49). For most patients with a first venous thrombotic event in the setting of a transient triggering factor, anticoagulation can be discontinued after 3 to 6 months if the triggering factor is no longer present. Patients with venous thromboembolism in the absence of triggering factors should be treated for 6 months. Criteria for indefinite anticoagulation include a single idiopathic venous thrombotic event in the presence of more than one allelic abnormality (homozygosity for the factor V Leiden mutation or combined heterozygosity for the factor V Leiden mutation and the prothrombin G20210A mutation), an initial life-threatening thrombosis (massive pulmonary embolism or ce-

Table 4. Management of Patients with Venous Thromboembolism

Risk Classification	Management
High risk Two or more spontaneous events One spontaneous life-threatening event (near-fatal pulmonary embolism; cerebral, mesenteric, or portal venous thrombosis) One spontaneous event in association with the antiphospholipid antibody syndrome,* antithrombin deficiency, or more than one genetic or allelic abnormality	Indefinite anticoagulation
Moderate risk One event with a known provocative stimulus Asymptomatic	Vigorous prophylaxis in high-risk settings

* To attain adequate antithrombotic prophylaxis while taking warfarin, patients with the antiphospholipid antibody syndrome seem to require an international normalized ratio target range that exceeds 2 to 3.

rebral, mesenteric, portal, or hepatic venous thrombosis), and two or more spontaneous thromboses. It is uncertain whether patients with a single allelic abnormality warrant indefinite anticoagulation after a first spontaneous episode of venous thromboembolism. Many clinicians with expertise in this area recommend indefinite anticoagulation for patients with heterozygous antithrombin deficiency because they seem more thrombosis-prone than patients with other single heritable abnormalities. Some clinicians also recommend such an approach for patients with heterozygous deficiencies of protein C and protein S.

Although prolonged anticoagulation at an international normalized ratio of 2 to 3 is highly effective in preventing thrombotic recurrences, this benefit is partially offset by major bleeding, which occurs at a rate of 2% to 3% per year (50). Among elderly patients, it has been reported that the rate of serious or fatal bleeding is even higher, at 7% to 9% per year (51). Therefore, patients with several idiopathic venous thrombotic events are the ones most likely to benefit from long-term anticoagulant prophylaxis at an international normalized ratio of 2 to 3.

Patients with the common thrombophilias—that is, heterozygotes with the factor V Leiden or prothrombin G20210A mutation as well as patients with idiopathic venous thromboembolism without an identifiable biological abnormality—should be counseled about the approximate magnitude of the recurrence risk as well as the risk for bleeding complications associated with long-term warfarin treatment. Given the present data regard-

ing the overall benefits and risks of indefinite anticoagulation, even among patients with two or more episodes of venous thromboembolism, well-informed patients can become active participants in the decision-making process along with their physicians. Fewer than 10% of strongly thrombophilic and 3% of weakly thrombophilic patients will be found to have several genetic abnormalities. However, in the coming years, more information about the effect of recently identified abnormalities (for example, elevated levels of factor VIII coagulant activity) on recurrence risk will become available and other prothrombotic mutations will certainly be discovered. This should enable us to identify a greater percentage of patients with several genetic abnormalities who are likely at highest risk for recurrences.

Several ongoing randomized clinical trials involving patients with idiopathic venous thromboembolism are evaluating the efficacy of indefinite low-intensity warfarin therapy at an international normalized ratio of 1.5 to 2 in preventing recurrent events (the Prevention of Venous Thromboembolism [PREVENT] Trial in the United States [52] and the Extended Low-Intensity Anticoagulation in Idiopathic Thromboembolism [ELATE] Trial in Canada). It is hypothesized that a regimen targeting an international normalized ratio of 1.5 to 2 will provide substantial antithrombotic protection but fewer major bleeding complications; therefore, the overall benefit of prolonged anticoagulation will be more favorable than that of today's conventional-intensity anticoagulation. If this proves to be the case, it will be important to determine whether low-intensity anticoagulation is effective in trial participants who have the common hereditary thrombophilias.

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Requests for Single Reprints: Kenneth A. Bauer, MD, Veterans Affairs Boston Healthcare System, 1400 VFW Parkway, West Roxbury, MA 02132; e-mail, kbauer@caregroup.harvard.edu.

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