

*Medical Progress***GENETIC SUSCEPTIBILITY TO VENOUS THROMBOSIS**

URI SELIGSOHN, M.D., AND AHARON LUBETSKY, M.D.

THE annual incidence of venous thrombosis, one of the leading causes of mortality and morbidity, increases from 1 per 100,000 during childhood to 1 per 100 in old age.¹ In this article we will discuss conditions involving a genetic predisposition to venous thrombosis. The clinical relevance of this topic has increased with new evidence of the high prevalence of mutant genes that increase susceptibility to thrombosis.

Of the three mechanisms of thrombosis defined by Virchow in the 19th century — vessel-wall injury, stasis, and “changes in the composition of blood” (hypercoagulability) — the last two predominate in venous thrombosis. Hypercoagulability can be inherited or acquired (Table 1). The inherited type, which is also termed inherited thrombophilia, should be suspected when a patient has recurrent or life-threatening venous thromboembolism, has a family history of venous thrombosis, is younger than 45 years of age, or has no apparent acquired risk factors, or if the patient is a woman who has a history of multiple abortions, stillbirth, or both. Acquired and genetic causes frequently interact, which makes it difficult to decide which patients should be tested for inherited thrombophilia, what tests to perform and when to order them, whether the results of the tests will affect the duration of anticoagulant therapy, and whether to examine family members. This review addresses these and other topics related to hereditary thrombophilia.

HISTORICAL PERSPECTIVE

Antithrombin deficiency and dysfibrinogenemia, the first inherited thrombophilias to be described, were found in studies of families in which several members were affected by venous thrombosis.^{2,3} Later, heterozygous deficiencies of protein C⁴ and protein S⁵ were identified as causes of inherited thrombophilia. Initially, searches for inherited thrombophilias among patients with idiopathic venous thrombosis were disappointing, since only 5 to 20 percent of such patients had inherited thrombophilias.⁶ The situation changed remarkably in 1993, after the discov-

From the Institute of Thrombosis and Hemostasis and the National Hemophilia Center, Department of Hematology, Chaim Sheba Medical Center, Tel Hashomer, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv — both in Israel. Address reprint requests to Dr. Seligsohn at the Institute of Thrombosis and Hemostasis, Chaim Sheba Medical Center, Tel Hashomer 52621, Israel, or at zeligson@post.tau.ac.il.

TABLE 1. INHERITED AND ACQUIRED CAUSES OF VENOUS THROMBOSIS.

Inherited
Common
G1691A mutation in the factor V gene (factor V Leiden)
G20210A mutation in the prothrombin (factor II) gene
Homozygous C677T mutation in the methylenetetrahydrofolate reductase gene
Rare
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Very rare
Dysfibrinogenemia
Homozygous homocystinuria
Probably inherited
Increased levels of factor VIII, factor IX, factor XI, or fibrinogen*
Acquired
Surgery and trauma
Prolonged immobilization
Older age
Cancer
Myeloproliferative disorders
Previous thrombosis
Pregnancy and the puerperium
Use of contraceptives or hormone-replacement therapy
Resistance to activated protein C that is not due to alterations in the factor V gene
Antiphospholipid antibodies
Mild-to-moderate hyperhomocysteinemia

*Levels of factor VIII and fibrinogen may also increase as part of the acute-phase response.

ery of resistance to activated protein C. This condition is the most common cause of inherited thrombophilia.⁷ In most cases it results from the substitution of adenine for guanine at nucleotide 1691 of the factor V gene (G1691A), which causes the arginine in residue 506 of the factor V protein to be replaced by glutamine (Arg506Gln). The resulting protein is called factor V Leiden.⁸ In 1996, the substitution of adenine for guanine at nucleotide 20210 of the prothrombin gene (G20210A) was found to be another cause of thrombophilia.⁹ Homocystinuria, a rare type of thrombophilia, is manifested by both venous and arterial thrombosis.¹⁰ Familial venous thrombosis has also been associated with the occurrence of two or more inherited thrombophilias in the same person.¹¹

MECHANISMS OF THROMBOSIS IN INHERITED THROMBOPHILIA

In most inherited thrombophilias, impaired neutralization of thrombin or a failure to control the generation of thrombin causes thrombosis (Fig. 1). In these cases, there is a malfunction in a system of natural anticoagulants that maintain the fluidity of the blood. One such anticoagulant is antithrombin, which, when bound to heparan sulfate on endothelial cells, neutralizes the procoagulants thrombin, factor XIa, factor IXa, and factor Xa. Protein C, another natural anticoagulant, controls the generation of thrombin.

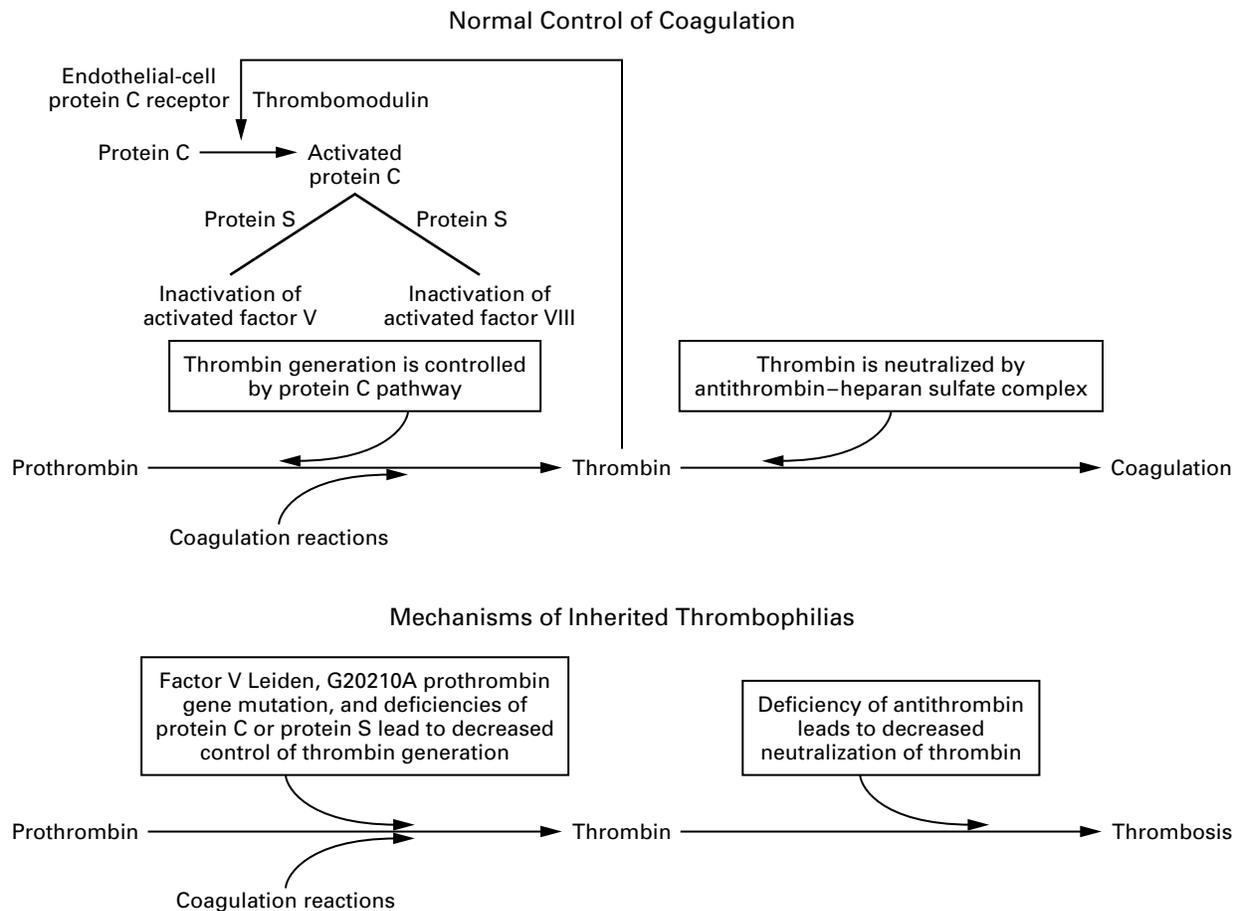


Figure 1. Major Mechanisms Involved in the Normal Control of Coagulation and Inherited Thrombophilias. Control of coagulation is achieved by the protein C pathway and antithrombin. In the protein C pathway thrombin bound to thrombomodulin activates protein C, which in turn inactivates activated factor V and factor VIII in the presence of protein S, thereby down-regulating the generation of thrombin. The neutralization of thrombin is achieved by antithrombin bound to heparin sulfate. In the inherited thrombophilias, a deficiency of antithrombin, protein C, or protein S, aberrant activity of factor V, or increased activity of prothrombin results in decreased neutralization of thrombin or increased generation of thrombin.

The binding of thrombin to thrombomodulin on endothelial cells of small blood vessels neutralizes the procoagulant activities of thrombin and activates protein C. In large blood vessels, protein C binds to a specific receptor, and the binding augments the activation of protein C by thrombin. Activated protein C inactivates factors Va and VIIIa in the presence of free protein S and phospholipids, thereby inhibiting the generation of thrombin. Free protein S itself has anticoagulant effects: it inhibits the prothrombinase complex (factor Xa, factor Va, and phospholipid), which converts prothrombin to thrombin, and the tenase complex (factor IXa, factor VIIIa, and phospholipid), which converts factor X to factor Xa. A decrease in antithrombin activity impairs the neutralization of thrombin, and the reduced activity of protein C or protein S diminishes the control of thrombin

generation. Both these mechanisms increase susceptibility to venous thrombosis (Fig. 1).

The control of thrombin generation is also compromised by mutations in the gene for factor V or prothrombin. The Arg506Gln substitution in factor V Leiden involves the first of three sites on factor Va that are cleaved by activated protein C. This mutation slows down the proteolytic inactivation of factor Va, which in turn leads to the augmented generation of thrombin.¹² Moreover, the mutant factor V has diminished cofactor activity in the inactivation of factor VIIIa by activated protein C.¹³ Both these abnormalities in factor V cause the in vitro phenomenon of resistance to activated protein C, resulting in the failure of activated protein C to prolong the activated partial-thromboplastin time. For unknown reasons, the G20210A mutation in the 3' untranslated region

of the prothrombin gene is associated with an increased level of plasma prothrombin, an effect that promotes the generation of thrombin and impairs the inactivation of factor Va by activated protein C.^{14,15} The mechanisms by which increased levels of factor VIII, factor IX, factor XI, fibrinogen, and homocysteine enhance venous thrombosis are unknown.

**EPIDEMIOLOGIC AND GENETIC
FEATURES OF INHERITED
THROMBOPHILIA**

The frequency of the major inherited thrombophilias varies substantially within healthy populations and among patients with venous thrombosis. Factor V Leiden and the G20210A mutation in the prothrombin gene are common among healthy whites but are extremely rare among Asians and Africans. Founder effects have been demonstrated for both mutations, suggesting that they occurred after the separation of non-Africans from Africans and after the divergence of whites and Asians.^{16,17} The frequency of all inherited thrombophilias is significantly higher in unselected consecutive patients with venous thrombosis than in healthy subjects.¹⁸⁻⁴⁷ This difference is striking in selected patients with venous thrombosis who are also likely on clinical grounds to have an inherited thrombophilia (Table 2).

Since factor V Leiden and the G20210A mutation in the prothrombin gene are relatively common, their coinheritance with other thrombophilias is not rare.

Four studies that together enrolled 677 members of families with deficiencies of protein C, protein S, or antithrombin demonstrated that the prevalence of venous thrombosis was 13 to 25 percent among subjects with only factor V Leiden, 19 to 57 percent among subjects with only one of the three deficiencies, and 73 to 92 percent among subjects who co-inherited one of the deficiencies and factor V Leiden.⁴⁸⁻⁵¹ Similar interactions were observed between factor V Leiden and the G20210A mutation in the prothrombin gene.⁵² Hyperhomocysteinemia also interacts with factor V Leiden and the G20210A mutation in the prothrombin gene; the combination of hyperhomocysteinemia with either factor significantly increases the risk of venous thrombosis.^{53,54}

Numerous mutations have been described in patients with a deficiency of protein C, protein S, or antithrombin (Table 3). Type I defects (low activity and low antigen level) predominate in patients with a deficiency of protein C or S, whereas both type I and type II (low activity and normal antigen level) defects are common in patients with antithrombin deficiency. In these three disorders, heterozygotes are susceptible to venous thrombosis, except for those with type II antithrombin deficiency involving the heparin-binding site.⁵⁵ Homozygous antithrombin deficiency is probably incompatible with life unless it is a type II defect involving the heparin-binding site, in which the susceptibility to venous thrombosis is indistinguishable from that of persons with hetero-

TABLE 2. FREQUENCY OF INHERITED THROMBOPHILIAS AMONG HEALTHY SUBJECTS AND UNSELECTED AND SELECTED PATIENTS WITH VENOUS THROMBOSIS.

INHERITED THROMBOPHILIA	HEALTHY SUBJECTS		UNSELECTED PATIENTS		SELECTED PATIENTS*		REFERENCES
	NO. EXAMINED	% AFFECTED	NO. EXAMINED	% AFFECTED	NO. EXAMINED	% AFFECTED	
Protein C deficiency	15,070	0.2-0.4	2008	3.7	767	4.8	Miletich et al., ¹⁸ Tait et al., ¹⁹ Koster et al., ²⁰ Heijboer et al., ²¹ Pabinger et al., ²² Tabernero et al., ²³ Ben-Tal et al., ²⁴ Horellou et al., ²⁵ Gladson et al., ²⁶ Melissari et al., ²⁷ Salomon et al. ²⁸
Protein S deficiency	—	—	2008	2.3	649	4.3	Koster et al., ²⁰ Heijboer et al., ²¹ Pabinger et al., ²² Tabernero et al., ²³ Ben-Tal et al., ²⁴ Gladson et al., ²⁶ Melissari et al., ²⁷ Salomon et al. ²⁸
Type I antithrombin deficiency	9,669	0.02	2008	1.9	649	4.3	Heijboer et al., ²¹ Pabinger et al., ²² Tabernero et al., ²³ Ben-Tal et al., ²⁴ Melissari et al., ²⁷ Tait et al. ²⁹
Factor V Leiden	16,150†	4.8	1142	18.8	162	40	Salomon et al., ²⁸ De Stefano et al. ³⁰
G20210A prothrombin gene mutation	2,192‡	0.05	2884	7.1	551	16	Poort et al., ⁹ Salomon et al., ²⁸ Ehrenforth et al., ³¹ Hillarp et al., ³² Eichinger et al., ³³ Ferraresi et al., ³⁴ Tosetto et al., ³⁵ Leroyer et al., ³⁶ Souto et al., ³⁷ Alhenc-Gelas et al., ³⁸ Corral et al., ³⁹ Brown et al., ⁴⁰ Hainaut et al., ⁴¹ Howard et al., ⁴² Ridker et al., ⁴³ Margaglione et al., ⁴⁴ Rosendaal et al., ⁴⁵ Rees et al., ⁴⁶ De Stefano et al. ⁴⁷
	11,932†	2.7					
	1,811‡	0.06					

*Nonconsecutive patients who met the following criteria were selected: an age of less than 50 years, a family history of venous thrombosis, a history of recurrent events, and the absence of acquired risk factors except for pregnancy or the use of oral contraceptives.

†All subjects were white.

‡All subjects were African or Asian (African Americans were excluded).

TABLE 3. DIAGNOSTIC TESTS FOR THROMBOPHILIAS.

TEST*	GENETIC BASIS FOR TEST RESULT	ACQUIRED CONDITIONS OR STATES THAT CAN ACCOUNT FOR TEST RESULT
High priority		
Increased resistance to activated protein C	Factor V Leiden, HR ₂ haplotype	Pregnancy, use of oral contraceptives, presence of lupus anticoagulant, use of oral anticoagulant therapy, stroke, increased factor VIII levels, presence of autoantibodies against activated protein C
Heterozygosity or homozygosity for factor V Leiden	G1691A in exon 10	—
Heterozygosity or homozygosity for G20210A prothrombin gene mutation	G20210A in the untranslated region of the gene	—
Increased level of homocysteine	Mutations in the genes for cystathionine β -synthase or methylenetetrahydrofolate reductase	Deficiencies of folic acid, vitamin B ₁₂ , or vitamin B ₆ ; older age; renal failure; smoking
Increased level of factor VIII	Unknown	Stress, exertion, pregnancy, use of oral contraceptives, older age, acute-phase response
Presence of lupus anticoagulant	—	—
Intermediate priority		
Decreased protein C activity	161 Different mutations†	Liver disease, childhood, use of oral anticoagulants, vitamin K deficiency, disseminated intravascular coagulation, presence of autoantibodies against protein C
Decreased level of free protein S antigen	131 Different mutations†	Liver disease, childhood, use of oral anticoagulants, vitamin K deficiency, disseminated intravascular coagulation, pregnancy, use of oral contraceptives, nephrotic syndrome, presence of autoantibodies against protein S
Decreased antithrombin activity	127 Different mutations‡	Liver disease, use of heparin therapy, disseminated intravascular coagulation, nephrotic syndrome
Increased titer of anticardiolipin antibodies	—	Infectious diseases
Low priority		
Dysfibrinogenemia (normal or low fibrinogen level and prolonged thrombin time)	20 Different mutations‡	Recent birth, liver disease, disseminated intravascular coagulation
Increased level of fibrinogen	Unknown	Acute-phase response, pregnancy, older age, atherosclerosis, smoking
Increased factor IX activity	Unknown	—
Increased factor XI activity	Unknown	—
Homozygosity for C677T mutation in methylenetetrahydrofolate reductase gene	C677T in exon 4	—

*Priority for testing is defined in the chart outlined in Figure 2.

†A compendium of the point mutations that have been described is available at <http://www.uwcm.ac.uk/uwcm/mg/hgmd0.html>.

‡A compendium of the point mutations that have been described is available at http://www.geht.org/pages/database_ang.html.

zygous antithrombin deficiency.⁵⁶ Persons with a homozygous deficiency of protein C or protein S are exceedingly rare and present soon after birth with purpura fulminans or massive venous thrombosis. Persons who are homozygous for factor V Leiden or the G20210A mutation in the prothrombin gene are more common and have a predisposition to venous thrombosis. The predisposition is greater in homozygotes for factor V Leiden than in heterozygotes.

Factor V Leiden is not the only cause of resistance to activated protein C. The HR₂ haplotype, a unique and relatively common haplotype of the factor V gene, causes resistance to activated protein C and increases the risk of venous thrombosis when coinherited with factor V Leiden.⁵⁷ There is also a rare mutation in the second of the three sites in factor V_A that activated protein C cleaves (Arg306Thr).⁵⁸ Additional causes of resistance to activated protein C, probably

genetic but as yet unidentified, also increase the risk of venous thrombosis.⁵⁹

Hyperhomocysteinemia, a risk factor for venous thrombosis,⁶⁰ can be caused by genetic disorders affecting the trans-sulfuration or remethylation pathways of homocysteine metabolism, or by folic acid deficiency, vitamin B₁₂ deficiency, vitamin B₆ deficiency, renal failure, hypothyroidism, increasing age, and smoking. A rare example of excessive hyperhomocysteinemia is homozygous homocystinuria due to cystathionine β -synthase deficiency; 50 percent of affected patients present with venous or arterial thrombosis by the age of 29 years.¹⁰ Homozygosity for the C677T mutation in the methylenetetrahydrofolate reductase gene is a cause of mild hyperhomocysteinemia in 5 to 15 percent of white and East Asian populations, but its relation to venous thrombosis is controversial.³⁸

Elevated levels of factor VIII, factor IX, factor XI,

or fibrinogen increase the risk of venous thrombosis, but so far no genetic alterations have been demonstrated in any of these conditions.⁶¹⁻⁶⁴

CLINICAL FEATURES OF INHERITED THROMBOPHILIA

Persons with a heterozygous deficiency of protein C, protein S, or antithrombin and those who are heterozygous or homozygous for factor V Leiden or the G20210A mutation in the prothrombin gene typically present with deep-vein thrombosis of the legs, pulmonary embolism, or both. Less common manifestations are superficial venous thrombosis and thromboses in the cerebral, visceral, and axillary veins. In more than half the cases, venous thrombosis is provoked by surgery, immobilization, advanced age, pregnancy, or the use of oral contraceptives or hormone-replacement therapy.

In most patients with inherited thrombophilia, the first thrombotic event occurs before the age of 45 years. The first event is even earlier in patients who have more than one inherited thrombophilia or who are homozygous for factor V Leiden or the G20210A mutation in the prothrombin gene.^{31,34,48-51,65} Asymptomatic heterozygotes who are relatives of index patients with inherited thrombophilia have a significant risk of venous thrombosis. The highest risk, 0.87 to 1.6 percent per year, was observed in persons who were heterozygous for antithrombin deficiency, and the lowest, 0.25 to 0.45 percent per year, was seen in persons who were heterozygous for factor V Leiden. Persons who are heterozygous for the G20210A mutation in the prothrombin gene, protein C deficiency, or protein S deficiency have an annual incidence of venous thrombosis of 0.55 percent, 0.43 to 0.72 percent, and 0.5 to 1.65 percent, respectively.⁶⁶⁻⁷⁰

RECURRENT VENOUS THROMBOSIS

All patients with venous thrombosis, whether or not they have a known inherited thrombophilia, are prone to recurrent thromboses for many years after the first incident. Recurrence is fatal in approximately 5 percent of patients,⁷¹ and in one third of patients, it is associated with the post-thrombotic syndrome.⁷² Recurrent venous thrombosis requires prolonged therapy with anticoagulants, which itself carries a significant risk of major hemorrhage. Recurrence is more common in men, the elderly, patients who are immobilized, patients with cancer, patients who have had an unprovoked thrombotic event, and patients who have already had a recurrent thrombosis.⁷²⁻⁷⁴ Increased levels of factor VIII and homocysteine also increase the risk of recurrence.^{75,76}

The effect of inherited thrombophilias on recurrent venous thrombosis has been assessed mainly in retrospective studies. Recurrent venous thrombosis is more common in patients with a deficiency of antithrombin, protein C, or protein S⁷⁷; in those with

more than one inherited thrombophilia^{52,78}; and in those who are homozygous for factor V Leiden.⁶⁵ Whether persons who are heterozygous for factor V Leiden or the G20210A mutation in the prothrombin gene have increased rates of recurrence of venous thrombosis is controversial.⁷⁹

INHERITED THROMBOPHILIAS DURING PREGNANCY AND THE PUERPERIUM

The predominant sites of thrombosis during pregnancy are the iliofemoral veins and the veins of the left leg. The risk of venous thrombosis in women with a deficiency of antithrombin, protein C, or protein S is substantially increased during pregnancy and the puerperium. A review of uncontrolled retrospective studies found that venous thrombosis occurred during pregnancy and the puerperium in up to 60 percent of women with an antithrombin deficiency and in up to 20 percent of women with a deficiency of either protein C or protein S.⁸⁰ A case-control study showed that among 129 asymptomatic female relatives of patients with a deficiency of antithrombin, protein C, or protein S, those who also had a deficiency of one of these proteins had a risk of venous thrombosis during pregnancy and the puerperium that was eight times as high as the risk in those without a deficiency.⁸¹ An increased risk of venous thrombosis during pregnancy is also associated with factor V Leiden (odds ratio, 16.3; 95 percent confidence interval, 4.8 to 54.9) and the G20210A mutation in the prothrombin gene (odds ratio, 10.2; 95 percent confidence interval, 4.0 to 25.9).⁸² Coinheritance of factor V Leiden and the G20210A mutation in the prothrombin gene further increases the risk (estimated odds ratio, 107).⁸³

Inherited thrombophilias also increase the risk of fetal loss. In a large cohort of women with a deficiency of antithrombin, protein C, or protein S or factor V Leiden, the odds ratios for fetal loss after 28 weeks of gestation (stillbirth) were 5.2, 2.3, 3.3, and 2.0, respectively; the odds ratio was 14.3 for women with more than one type of inherited thrombophilia.⁸⁴ Another study found that the risk of late fetal loss (after 20 weeks of gestation) was tripled in carriers of the G20210A mutation in the prothrombin gene or factor V Leiden.⁸⁵ An increased relative risk of early fetal loss (at less than 25 weeks of gestation) was also observed in women with a deficiency of protein C, protein S, or antithrombin⁸⁶ and in carriers of factor V Leiden.⁸⁷ In a more general case-control study, 52 percent of pregnant women with fetal growth retardation, preeclampsia, abruptio placentae, or stillbirth were heterozygous for factor V Leiden or the G20210A mutation in the prothrombin gene or homozygous for the C677T mutation in the gene for methylenetetrahydrofolate reductase, as compared with 17 percent of controls.⁸⁸ These data provide a rationale for screening women who intend to

become pregnant for inherited thrombophilias if they have a personal or family history of venous thrombosis or if they have three unexplained miscarriages, abruptio placentae, stillbirth, recurrent fetal growth retardation, or possibly preeclampsia.

ORAL CONTRACEPTIVES AND HORMONE-REPLACEMENT THERAPY

The use of oral contraceptives significantly increases the risk of venous thrombosis in a woman with an inherited thrombophilia. In a study of women using oral contraceptives, the risk was increased by a factor of 3.8 in normal women and by a factor of 34.7 in women who were heterozygous for factor V Leiden.⁸⁹ Increased risks were also conferred by heterozygosity for the G20210A mutation in the prothrombin gene, a deficiency of protein C, or a deficiency of protein S⁹⁰⁻⁹²; among women with antithrombin deficiency, the incidence of venous thrombosis was 27 percent per year in users of contraceptives, as compared with 3.4 percent per year in nonusers.⁹² Among women with factor V Leiden, the risk of venous thrombosis with the use of third-generation contraceptives is twice that with the use of second-generation contraceptives,⁹³ probably because the third-generation contraceptives result in a more pronounced resistance to activated protein C.⁹⁴

For these reasons, women with inherited thrombophilias should avoid using oral contraceptives, particularly when they have a personal or family history of venous thrombosis. Screening of healthy women for thrombophilias, however, is not recommended, since it would deny contraceptives to about 5 to 10 percent of white women with factor V Leiden or the G20210A mutation in the prothrombin gene, while preventing very few fatal venous thromboembolisms. Screening should be confined to women with a personal or family history of thrombosis.

Hormone-replacement therapy in healthy women increases the risk of venous thrombosis by a factor of two to four, but the increased risk probably disappears after one year of treatment.⁹⁵ A recent study found that the risk was significantly increased in women with antithrombin deficiency, resistance to activated protein C, or increased levels of factor IX.⁹⁶ Until more data are available, it is advisable to search for inherited thrombophilias only in women with a personal or family history of venous thrombosis and to avoid hormone-replacement therapy in affected women unless it is strongly indicated.

DIAGNOSIS OF INHERITED THROMBOPHILIA

With the identification of factor V Leiden and the G20210A mutation in the prothrombin gene, the proportion of patients with venous thrombosis in whom a diagnosis of inherited thrombophilia can be established has increased. In unselected patients, the

rate has increased from approximately 10 percent to approximately 30 percent, and in patients with a clinical likelihood of having an inherited thrombophilia, it has increased from approximately 17 percent to approximately 70 percent. What is the most economical way of testing for an inherited thrombophilia? Decisions regarding laboratory tests in a given patient can be made according to a set of priorities (Table 3) and individualized after the likelihood of inherited thrombophilia is assessed, taking into account that in a few cases the diagnosis will be missed (Fig. 2). The inclusion of all six high-priority tests in the evaluation (Table 3) should provide the highest diagnostic yield, because the six conditions being tested for are relatively frequent.^{75,76,97} Measurement of resistance to activated protein C in plasma diluted with factor V-deficient plasma is not only highly sensitive and specific for factor V Leiden but is also accurate in patients whose plasma contains lupus anticoagulant or increased levels of factor VIII and in patients taking oral anticoagulants. It is also advisable to confirm the diagnosis of factor V Leiden by a genetic test, because this information can be used in deciding whether family members should be examined. In patients with stroke or with antibodies to activated protein C, resistance to activated protein C can be delineated only by testing undiluted plasma (Table 3).^{98,99}

Tests of intermediate priority (Table 3) yield positive results less frequently, and low-priority tests only very rarely diagnose an inherited thrombophilia (e.g., dysfibrinogenemia). The association between venous thrombosis and the C677T mutation in the gene for methylenetetrahydrofolate reductase or increased levels of fibrinogen, factor IX, or factor XI has not been definitively established.⁶¹⁻⁶⁴

The optimal time for performing tests in most patients is six months after the thrombotic event, when a decision should be made about continuing anticoagulant therapy (Fig. 2). The results of examinations performed earlier can be misleading, because thrombosis itself can cause low antithrombin levels and elevated levels of factor VIII. At six months, all high-priority tests and a test for antithrombin activity should be performed in patients who are most likely to have an inherited thrombophilia. These patients should then be switched to treatment with low-molecular-weight heparin for two weeks and subsequently tested for protein C activity and the level of free protein S antigen. If none of these test results are abnormal in a patient with a family history of venous thrombosis or a recurrent thrombosis, it is reasonable to perform low-priority tests (Table 3). In our algorithm (Fig. 2), patients likely to have thrombophilia undergo only high-priority tests, but if factor V Leiden, the G20210A mutation in the prothrombin gene, or a lupus anticoagulant is detected, intermediate-priority tests should also be performed. Patients with the least likelihood of having thrombophilia are not tested

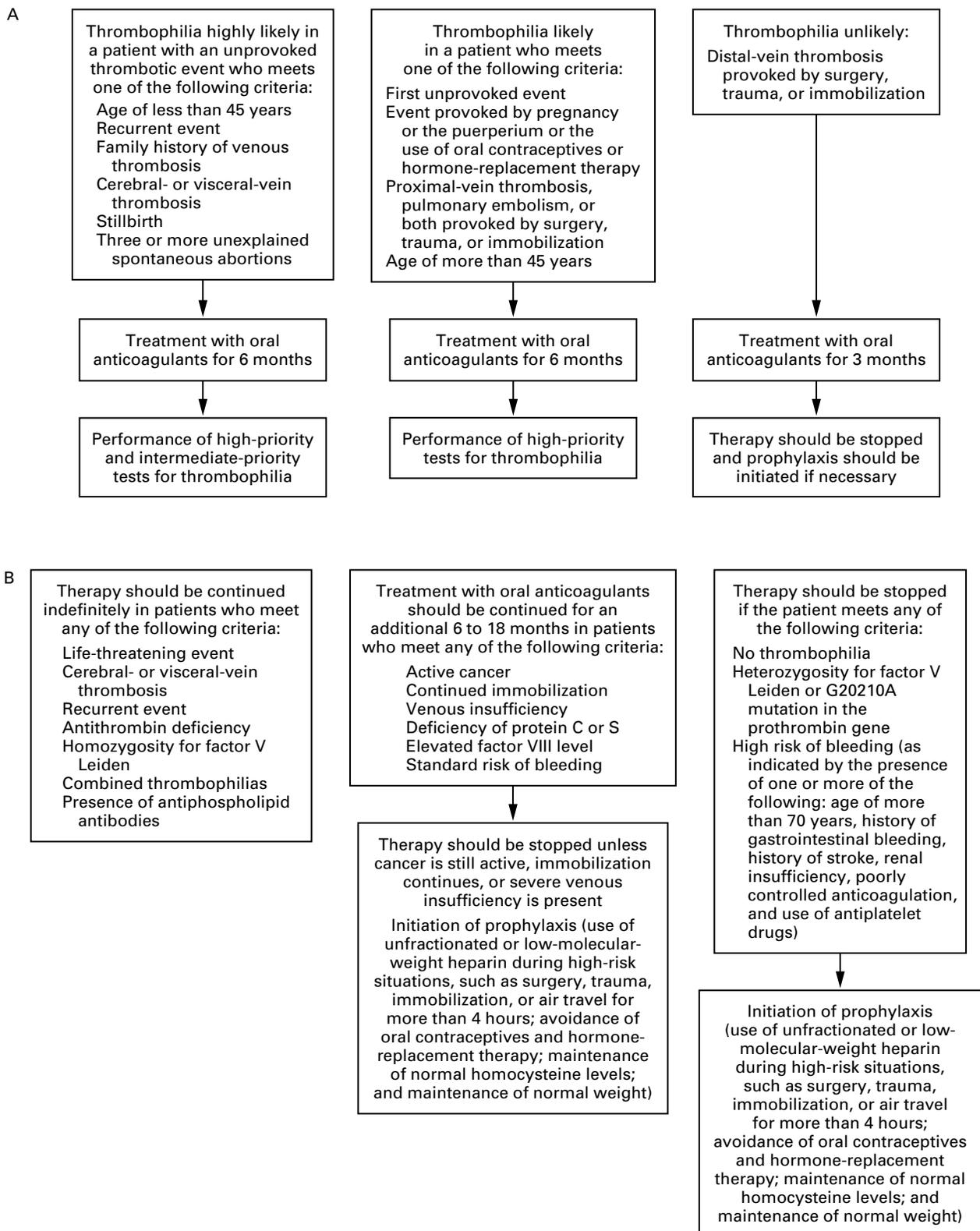


Figure 2. Approach to the Diagnosis and Treatment of Thrombophilia in Patients with Venous Thrombosis. Panel A shows the clinical evaluation of the likelihood of thrombophilia, initial anticoagulant therapy, and the performance of tests. Panel B shows the criteria for continuing therapy and for prophylaxis.

at all; the anticipated recurrence of venous thrombosis in them is low (1.5 percent per year) and does not outweigh the risk of bleeding due to the prolongation of anticoagulant therapy.¹⁰⁰

Before establishing the diagnosis of an inherited thrombophilia, it is essential to rule out acquired conditions that may produce similar results (Table 3); it is also advisable to repeat nongenotypic tests with abnormal results. Detection of the same abnormality in first-degree relatives of the patient provides evidence of a possible genetic defect.

First-degree relatives of patients with one or more abnormal test results should be examined to determine whether they should receive primary prophylaxis. A reasonable approach is to test for only the abnormal factor or factors found in the index patient when there is no family history of venous thrombosis and to perform all tests of high and intermediate priority when there is a family history.

THERAPY AND PROPHYLAXIS

Patients with a known or unknown inherited thrombophilia who present with venous thromboembolism should be treated with a standard regimen of heparin overlapped with warfarin until an international normalized ratio (INR) of 2.0 to 3.0 is obtained on two consecutive days. This regimen is sufficient for the prevention of skin necrosis, which may occur during the initiation of warfarin therapy in patients with a deficiency of protein C. The chief goals of therapy are to prevent recurrent venous thromboembolism, which is fatal in 5 percent of cases.⁷¹ Recurrent thromboses also increase the risk of venous insufficiency⁷² and impose a need for indefinite anticoagulant therapy, which carries a significant risk of bleeding. Warfarin therapy reduces the risk of recurrence by 90 to 95 percent, but the annual risk of fatal hemorrhage is 0.25 percent.¹⁰¹ Consequently, the benefits and hazards associated with increasing the duration of therapy should be carefully evaluated and discussed with each patient, with consideration of the patient's preference and clinical and laboratory risk factors that increase susceptibility to recurrent venous thrombosis or hemorrhage. Comprehensive, evidence-based guidelines for therapy cannot yet be formulated, but the substantial information reviewed in this article and our own experience lead us to an algorithm that applies to all patients with established venous thrombosis (Fig. 2).

During the initiation of therapy, patients are classified according to their likelihood of having thrombophilia. Patients with the lowest likelihood are treated for three months, and no tests for thrombophilia are performed. All other patients are treated with warfarin for six months, after which they are examined for the presence of thrombophilia and assessed for the risks of recurrence and hemorrhage. On the basis of this assessment, treatment is discontinued, con-

tinued for 6 to 18 more months, or continued indefinitely.

In patients with hyperhomocysteinemia, we recommend indefinite treatment with folic acid, supplemented by vitamins B₆ and B₁₂ if normal levels of homocysteine are not achieved with folic acid alone. Annual testing of serum vitamin B₁₂ levels is advisable to avoid potential deleterious effects of folic acid in patients with vitamin B₁₂ deficiency.

All patients with venous thrombosis of the legs should wear fitted compression stockings for at least two years; this measure reduces the incidence of the post-thrombotic syndrome by 50 percent.¹⁰² Other prophylactic measures for patients who discontinue therapy are given in Figure 2. Women with an inherited thrombophilia who have had venous thrombosis, stillbirth, or three unexplained spontaneous abortions should be treated throughout pregnancy and for six weeks post partum with low-molecular-weight heparin. Patients with antithrombin deficiency probably require a more intensive regimen.¹⁰³

First-degree relatives of index patients who are asymptomatic but who are affected by a thrombophilia should be advised of the risk of venous thrombosis. Primary prophylaxis in these persons includes the administration of low-molecular-weight heparin in high-risk conditions, such as during surgery, trauma, immobilization, and the six-week postpartum period; maintenance of normal weight and homocysteine levels; and avoidance of contraceptives and hormone-replacement therapy, with the patient's preference taken into account. Women with antithrombin deficiency, combined thrombophilia, or homozygosity for factor V Leiden or the G20210A mutation in the prothrombin gene should be treated throughout pregnancy and for six weeks post partum with low-molecular-weight heparin.

REFERENCES

1. Rosendaal FR. Thrombosis in the young: epidemiology and risk factors: a focus on venous thrombosis. *Thromb Haemost* 1997;78:1-6.
2. Egeberg O. Inherited antithrombin III deficiency causing thrombophilia. *Thromb Diath Haemorrh* 1965;13:516-30.
3. Beck EA, Charache P, Jackson DP. A new inherited coagulation disorder caused by an abnormal fibrinogen ('fibrinogen Baltimore'). *Nature* 1965;208:143-5.
4. Griffin JH, Evatt B, Zimmerman TS, Kleiss AJ, Wideman C. Deficiency of protein C in congenital thrombotic disease. *J Clin Invest* 1981;68:1370-3.
5. Comp PC, Esmon CT. Recurrent venous thromboembolism in patients with a partial deficiency of protein S. *N Engl J Med* 1984;311:1525-8.
6. Koeleman BP, Reitsma PH, Bertina RM. Familial thrombophilia: a complex genetic disorder. *Semin Hematol* 1997;34:256-64.
7. Dahlback B, Carlsson M, Svensson PJ. Familial thrombophilia due to a previously unrecognized mechanism characterized by poor anticoagulant response to activated protein C: prediction of a cofactor to activated protein C. *Proc Natl Acad Sci U S A* 1993;90:1004-8.
8. Bertina RM, Koeleman BP, Koster T, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature* 1994;369:64-7.
9. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood* 1996;88:3698-703.
10. Mudd SH, Skovby F, Levy HL, et al. The natural history of homocys-

- tinuria due to cystathionine beta-synthase deficiency. *Am J Hum Genet* 1985;37:1-31.
11. Seligsohn U, Zivelin A. Thrombophilia as a multigenic disorder. *Thromb Haemost* 1997;78:297-301.
 12. Heeb MJ, Kojima Y, Greengard JS, Griffin JH. Activated protein C resistance: molecular mechanisms based on studies using purified Gln506-factor V. *Blood* 1995;85:3405-11.
 13. Shen L, He X, Dahlback B. Synergistic cofactor function of factor V and protein S to activated protein C in the inactivation of the factor VIIIa-factor IXa complex — species specific interactions of components of the protein C anticoagulant system. *Thromb Haemost* 1997;78:1030-6.
 14. Butenas S, van't Veer C, Mann KG. "Normal" thrombin generation. *Blood* 1999;94:2169-78.
 15. Smirnov MD, Safa O, Esmon NL, Esmon CT. Inhibition of activated protein C anticoagulant activity by prothrombin. *Blood* 1999;94:3839-46.
 16. Zivelin A, Griffin JH, Xu X, et al. A single genetic origin for a common Caucasian risk factor for venous thrombosis. *Blood* 1997;89:397-402.
 17. Zivelin A, Rosenberg N, Faier S, et al. A single genetic origin for the common prothrombotic G20210A polymorphism in the prothrombin gene. *Blood* 1998;92:1119-24.
 18. Miletich J, Sherman L, Broze G Jr. Absence of thrombosis in subjects with heterozygous protein C deficiency. *N Engl J Med* 1987;317:991-6.
 19. Tait RC, Walker ID, Reitsma PH, et al. Prevalence of protein C deficiency in the healthy population. *Thromb Haemost* 1995;73:87-93.
 20. Koster T, Rosendaal FR, Briet E, et al. Protein C deficiency in a controlled series of unselected outpatients: an infrequent but clear risk factor for venous thrombosis (Leiden Thrombophilia Study). *Blood* 1995;85:2756-61.
 21. Heijboer H, Brandjes DPM, Büller HR, Sturk A, ten Cate JW. Deficiencies of coagulation-inhibiting and fibrinolytic proteins in outpatients with deep-vein thrombosis. *N Engl J Med* 1990;323:1512-6.
 22. Pabinger I, Brucker S, Kyrle PA, et al. Hereditary deficiency of antithrombin III, protein C and protein S: prevalence in patients with a history of venous thrombosis and criteria for rational patient screening. *Blood Coagul Fibrinolysis* 1992;3:547-53.
 23. Taberner MD, Tomas JE, Alberca I, Orfao A, Borrasca AI, Vicente V. Incidence and clinical characteristics of hereditary disorders associated with venous thrombosis. *Am J Hematol* 1991;36:249-54.
 24. Ben-Tal O, Zivelin A, Seligsohn U. The relative frequency of hereditary thrombotic disorders among 107 patients with thrombophilia in Israel. *Thromb Haemost* 1989;61:50-4.
 25. Horellou MH, Conard J, Bertina RM, Samama M. Congenital protein C deficiency and thrombotic disease in nine French families. *BMJ* 1984;289:1285-7.
 26. Gladson CL, Scharrer I, Hach V, Beck KH, Griffin JH. The frequency of type I heterozygous protein S and protein C deficiency in 141 unrelated young patients with venous thrombosis. *Thromb Haemost* 1988;59:18-22.
 27. Melissari E, Monte G, Lindo VS, et al. Congenital thrombophilia among patients with venous thromboembolism. *Blood Coagul Fibrinolysis* 1992;3:749-58.
 28. Salomon O, Steinberg DM, Zivelin A, et al. Single and combined prothrombotic factors in patients with idiopathic venous thromboembolism: prevalence and risk assessment. *Arterioscler Thromb Vasc Biol* 1999;19:511-8.
 29. Tait RC, Walker ID, Perry DJ, et al. Prevalence of antithrombin deficiency in the healthy population. *Br J Haematol* 1994;87:106-12.
 30. De Stefano V, Chiusolo P, Paciaroni K, Leone G. Epidemiology of factor V Leiden: clinical implications. *Semin Thromb Hemost* 1998;24:367-79.
 31. Ehrenforth S, von Depka Prondsinski M, Aygoren-Pursun E, Nowak-Gottl U, Scharrer I, Ganser A. Study of the prothrombin gene 20210 GA variant in FV:Q506 carriers in relationship to the presence or absence of juvenile venous thromboembolism. *Arterioscler Thromb Vasc Biol* 1999;19:276-80.
 32. Hillarp A, Zoller B, Svensson PJ, Dahlback B. The 20210A allele of the prothrombin gene is a common risk factor among Swedish outpatients with verified deep venous thrombosis. *Thromb Haemost* 1997;78:990-2.
 33. Eichinger S, Minar E, Hirschl M, et al. The risk of early recurrent venous thromboembolism after oral anticoagulant therapy in patients with the G20210A transition in the prothrombin gene. *Thromb Haemost* 1999;81:14-7.
 34. Ferraresi P, Marchetti G, Legnani E, et al. The heterozygous 20210 G/A prothrombin genotype is associated with early venous thrombosis in inherited thrombophilias and is not increased in frequency in artery disease. *Arterioscler Thromb Vasc Biol* 1997;17:2418-22.
 35. Tosetto A, Missaglia E, Frezzato M, Rodeghiero F. The VITA project: prothrombin G20210A mutation and venous thromboembolism in the general population. *Thromb Haemost* 1999;82:1395-8.
 36. Leroyer C, Mercier B, Oger E, et al. Prevalence of 20210 A allele of the prothrombin gene in venous thromboembolism patients. *Thromb Haemost* 1998;80:49-51.
 37. Souto JC, Coll I, Llobet D, et al. The prothrombin 20210A allele is the most prevalent genetic risk factor for venous thromboembolism in the Spanish population. *Thromb Haemost* 1998;80:366-9.
 38. Alhenc-Gelas M, Arnaud E, Nicaud V, et al. Venous thromboembolic disease and the prothrombin, methylene tetrahydrofolate reductase and factor V genes. *Thromb Haemost* 1999;81:506-10.
 39. Corral J, Gonzalez-Conejero R, Lozano ML, Rivera J, Heras I, Vicente V. The venous thrombosis risk factor 20210 A allele of the prothrombin gene is not a major risk factor for arterial thrombotic disease. *Br J Haematol* 1997;99:304-7.
 40. Brown K, Luddington R, Williamson D, Baker P, Baglin T. Risk of venous thromboembolism associated with a G to A transition at position 20210 in the 3'-untranslated region of the prothrombin gene. *Br J Haematol* 1997;98:907-9.
 41. Hainaut P, Gala JL, Lesage V, et al. The prothrombin gene G20210A variant in an unselected thromboembolic population: a Belgian prospective clinical study. *Acta Clin Belg* 1998;53:344-8.
 42. Howard TE, Marusa M, Boisza J, et al. The prothrombin gene 3'-untranslated region mutation is frequently associated with factor V Leiden in thrombophilic patients and shows ethnic-specific variation in the allele frequency. *Blood* 1998;91:1092.
 43. Ridker PM, Hennekens CH, Miletich JP. G20210A mutation in prothrombin gene and risk of myocardial infarction, stroke, and venous thrombosis in a large cohort of US men. *Circulation* 1999;99:999-1004.
 44. Margaglione M, Brancaccio V, Giuliani N, et al. Increased risk for venous thrombosis in carriers of the prothrombin G → A²⁰²¹⁰ gene variant. *Ann Intern Med* 1998;129:89-93.
 45. Rosendaal FR, Doggen CJM, Zivelin A, et al. Geographic distribution of the 20210 G to A prothrombin variant. *Thromb Haemost* 1998;79:706-8.
 46. Rees DC, Chapman NH, Webster MT, Guerreiro JE, Rochette J, Clegg JB. Born to clot: the European burden. *Br J Haematol* 1999;105:564-6.
 47. De Stefano V, Chiusolo P, Paciaroni K, et al. Prevalence of the factor II G20210A mutation in symptomatic patients with inherited thrombophilia. *Thromb Haemost* 1998;80:342-3.
 48. Koeleman BPC, Reitsma PH, Allaart CE, Bertina RM. Activated protein C resistance as an additional risk factor for thrombosis in protein C-deficient families. *Blood* 1994;84:1031-5.
 49. Zoller B, Berntsdotter A, Garcia de Frutos P, Dahlback B. Resistance to activated protein C as an additional genetic risk factor in hereditary deficiency of protein S. *Blood* 1995;85:3518-23.
 50. Koeleman BPC, van Rumpft D, Hamulyak K, Reitsma PH, Bertina RM. Factor V Leiden: an additional risk factor for thrombosis in protein S deficient families? *Thromb Haemost* 1995;74:580-3.
 51. van Boven HH, Vandembroucke JP, Briet E, Rosendaal FR. Gene-gene and gene-environment interactions determine risk of thrombosis in families with inherited antithrombin deficiency. *Blood* 1999;94:2590-4.
 52. De Stefano V, Martinelli I, Mannucci PM, et al. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. *N Engl J Med* 1999;341:801-6.
 53. Ridker PM, Hennekens CH, Selhub J, Miletich JP, Malinow MR, Stampfer MJ. Interrelation of hyperhomocyst(e)inemia, factor V Leiden, and risk of future venous thromboembolism. *Circulation* 1997;95:1777-82.
 54. De Stefano V, Zappacosta B, Persichilli S, et al. Prevalence of mild hyperhomocysteinemia and association with thrombophilic genotypes (factor V Leiden and prothrombin G20210A) in Italian patients with venous thromboembolic disease. *Br J Haematol* 1999;106:564-8.
 55. Finazzi G, Caccia R, Barbui T. Different prevalence of thromboembolism in the subtypes of congenital antithrombin III deficiency: review of 404 cases. *Thromb Haemost* 1987;58:1094.
 56. Boyer C, Wolf M, Vedrenne J, Meyer D, Larricau MJ. Homozygous variant of antithrombin III: AT III Fontainebleau. *Thromb Haemost* 1986;56:18-22.
 57. Faioni EM, Franchi F, Bucciarelli P, et al. Coinheritance of the HR2 haplotype in the factor V gene confers an increased risk of venous thromboembolism to carriers of factor V R506Q (factor V Leiden). *Blood* 1999;94:3062-6.
 58. Williamson D, Brown K, Luddington R, Baglin C, Baglin T. Factor V Cambridge: a new mutation (Arg³⁰⁶→Thr) associated with resistance to activated protein C. *Blood* 1998;91:1140-4.
 59. de Visser MCH, Rosendaal FR, Bertina RM. A reduced sensitivity for activated protein C in the absence of factor V Leiden increases the risk of venous thrombosis. *Blood* 1999;93:1271-6.
 60. Ray JG. Meta-analysis of hyperhomocysteinemia as a risk factor for venous thromboembolic disease. *Arch Intern Med* 1998;158:2101-6.

61. Kraaijenhagen RA, in't Anker PS, Koopman MMW, et al. High plasma concentration of factor VIIIc is a major risk factor for venous thromboembolism. *Thromb Haemost* 2000;83:5-9.
62. van Hylckama Vlieg A, van der Linden IK, Bertina RM, Rosendaal FR. High levels of factor IX increase the risk of venous thrombosis. *Blood* 2000;95:3678-82.
63. Meijers JCM, Tekelenburg WLH, Bouma BN, Bertina RM, Rosendaal FR. High levels of coagulation factor XI as a risk factor for venous thrombosis. *N Engl J Med* 2000;342:696-701.
64. Koster T, Rosendaal FR, Reitsma PH, van der Velden PA, Briet E, Vandenbroucke JP. Factor VII and fibrinogen levels as risk factors for venous thrombosis: a case-control study of plasma levels and DNA polymorphisms — the Leiden Thrombophilia Study (LETS). *Thromb Haemost* 1994;71:19-22.
65. Emmerich J, Alhence-Gelas M, Aillaud MF, et al. Clinical features in 36 patients homozygous for the ARG 506 → GLN factor V mutation. *Thromb Haemost* 1997;77:620-3.
66. Martinelli I, Mannucci PM, De Stefano V, et al. Different risks of thrombosis in four coagulation defects associated with inherited thrombophilia: a study of 150 families. *Blood* 1998;92:2353-8.
67. Middeldorp S, Henkens CM, Koopman MM, et al. The incidence of venous thromboembolism in family members of patients with factor V Leiden mutation and venous thrombosis. *Ann Intern Med* 1998;128:15-20.
68. Bucciarelli P, Rosendaal FR, Tripodi A, et al. Risk of venous thromboembolism and clinical manifestations in carriers of antithrombin, protein C, protein S deficiency, or activated protein C resistance: a multicenter collaborative family study. *Arterioscler Thromb Vasc Biol* 1999;19:1026-33.
69. Simioni P, Sanson BJ, Prandoni P, et al. Incidence of venous thromboembolism in families with inherited thrombophilia. *Thromb Haemost* 1999;81:198-202.
70. Sanson BJ, Simioni P, Tormene D, et al. The incidence of venous thromboembolism in asymptomatic carriers of a deficiency of antithrombin, protein C, protein S: a prospective cohort study. *Blood* 1999;94:3702-6.
71. Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. *JAMA* 1998;279:458-62.
72. Prandoni P, Lensing AWA, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996;125:1-7.
73. Lindmarker P, Schulman S, Sten-Linder M, Wiman B, Egberg N, Johnsson H. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. *Thromb Haemost* 1999;81:684-9.
74. Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med* 1999;340:901-7. [Erratum, *N Engl J Med* 1999;341:298.]
75. Kyrle PA, Minar E, Hirschl M, et al. High plasma levels of factor VIII and the risk of recurrent venous thromboembolism. *N Engl J Med* 2000;343:457-62.
76. den Heijer M, Blom HJ, Gerrits WBJ, et al. Is hyperhomocysteinemia a risk factor for recurrent venous thrombosis? *Lancet* 1995;345:882-5.
77. van den Belt AG, Sanson BJ, Simioni P, et al. Recurrence of venous thromboembolism in patients with familial thrombophilia. *Arch Intern Med* 1997;157:2227-32.
78. Makris M, Preston FE, Beauchamp NJ, et al. Co-inheritance of the 20210A allele of the prothrombin gene increases the risk of thrombosis in subjects with familial thrombophilia. *Thromb Haemost* 1997;78:1426-9.
79. Lensing AWA, Prins MH. Recurrent deep vein thrombosis and two coagulation factor gene mutations: quo vadis? *Thromb Haemost* 1999;82:1564-6.
80. Girling J, de Swiet M. Inherited thrombophilia and pregnancy. *Curr Opin Obstet Gynecol* 1998;10:135-44.
81. Friederich PW, Sanson BJ, Simioni P, et al. Frequency of pregnancy-related venous thromboembolism in anticoagulant factor-deficient women: implications for prophylaxis. *Ann Intern Med* 1996;125:955-60. [Errata, *Ann Intern Med* 1997;126:835, 127:1138.]
82. Grandone E, Margaglione M, Colaizzo D, et al. Genetic susceptibility to pregnancy-related venous thromboembolism: roles of factor V Leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase C677T mutations. *Am J Obstet Gynecol* 1998;179:1324-8.
83. Gerhardt A, Scharf RE, Beckmann MW, et al. Prothrombin and factor V mutations in women with a history of thrombosis during pregnancy and the puerperium. *N Engl J Med* 2000;342:374-80.
84. Preston FE, Rosendaal FR, Walker ID, et al. Increased fetal loss in women with heritable thrombophilia. *Lancet* 1996;348:913-6.
85. Martinelli I, Taioli E, Cetin I, et al. Mutations in coagulation factors in women with unexplained late fetal loss. *N Engl J Med* 2000;343:1015-8.
86. Sanson BJ, Friederich PW, Simioni P, et al. The risk of abortion and stillbirth in antithrombin-, protein C-, and protein S-deficient women. *Thromb Haemost* 1996;75:387-8.
87. Ridker PM, Miletich JP, Buring JE, et al. Factor V Leiden mutation as a risk factor for recurrent pregnancy loss. *Ann Intern Med* 1998;128:1000-3.
88. Kupfermink MJ, Eldor A, Steinman N, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy. *N Engl J Med* 1999;340:9-13. [Erratum, *N Engl J Med* 1999;341:384.]
89. Vandenbroucke JP, Koster T, Briet E, Reitsma PH, Bertina RM, Rosendaal FR. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. *Lancet* 1994;344:1453-7.
90. Martinelli I, Sacchi E, Landi G, Taioli E, Duca F, Mannucci PM. High risk of cerebral-vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives. *N Engl J Med* 1998;338:1793-7.
91. Pabinger I, Schneider B. Thrombotic risk in hereditary antithrombin III, protein C, or protein S deficiency: a cooperative, retrospective study. *Arterioscler Thromb Vasc Biol* 1996;16:742-8.
92. *Idem*. Thrombotic risk of women with hereditary antithrombin III-, protein C- and protein S-deficiency taking oral contraceptive medication. *Thromb Haemost* 1994;71:548-52.
93. Bloemenkamp KWM, Rosendaal FR, Helmerhorst FM, Buller HR, Vandenbroucke JP. Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen. *Lancet* 1995;346:1593-6.
94. Rosing J, Middeldorp S, Curvers J, et al. Low-dose oral contraceptives and acquired resistance to activated protein C: a randomised cross-over study. *Lancet* 1999;354:2036-40.
95. Hoiibraaten E, Abdelnoor M, Sandset PM. Hormone replacement therapy with estradiol and risk of venous thromboembolism — a population-based case-control study. *Thromb Haemost* 1999;82:1218-21.
96. Lowe G, Woodward M, Vessey M, Rumley A, Gough P, Daly E. Thrombotic variables and risk of idiopathic venous thromboembolism in women aged 45-64 years: relationships to hormone replacement therapy. *Thromb Haemost* 2000;83:530-5.
97. Schulman S, Svenungsson E, Granqvist S. Anticardiolipin antibodies predict early recurrence of thromboembolism and death among patients with venous thromboembolism following anticoagulant therapy. *Am J Med* 1998;104:332-8.
98. Fisher M, Fernandez JA, Ameriso SF, et al. Activated protein C resistance in ischemic stroke not due to factor V arginine506→glutamine mutation. *Stroke* 1996;27:1163-6.
99. Zivelin A, Gitel S, Griffin JH, et al. Extensive venous and arterial thrombosis associated with an inhibitor to activated protein C. *Blood* 1999;94:895-901.
100. Schulman S. Duration of anticoagulants in acute or recurrent venous thromboembolism. *Curr Opin Pulm Med* 2000;6:321-5.
101. Hirsh J, Kearon C, Ginsberg J. Duration of anticoagulant therapy after first episode of venous thrombosis in patients with inherited thrombophilia. *Arch Intern Med* 1997;157:2174-7.
102. Brandjes DPM, Buller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet* 1997;349:759-62.
103. De Stefano V, Finazzi G, Mannucci PM. Inherited thrombophilia: pathogenesis, clinical syndromes, and management. *Blood* 1996;87:3531-44.

Copyright © 2001 Massachusetts Medical Society.