

Should Patients with Venous Thromboembolism Be Screened for Thrombophilia?

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ABSTRACT

In the mid-19th century, Virchow identified hypercoagulability as part of the triad leading to venous thrombosis, but the specific causes of hypercoagulability remained a mystery for another century. The first specific cause to be identified was antithrombin III deficiency. Many other causes of thrombophilia, both genetic and acquired, have been discovered since then. The 2 most common genetic causes of thrombophilia are the Leiden mutation of factor V and the G20210A mutation of prothrombin. The most common acquired cause is antiphospholipid syndrome. These factors increase the relative risk of an initial episode of venous thromboembolism (VTE) by a factor of 2 to 10, but the actual risk remains relatively modest. Therefore, thrombophilia screening to prevent initial episodes of VTE is not indicated, except possibly in women with a family history of idiopathic VTE who are considering oral contraceptive therapy. Some physicians screen for thrombophilia to aid decision making concerning the duration of anticoagulant therapy. However, several studies have demonstrated that, with the exception of antiphospholipid syndrome, thrombophilia does not significantly increase the risk of recurrent VTE. On the other hand, idiopathic VTE significantly increases the risk of recurrence in patients with or without thrombophilia.

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Hypercoagulability, stasis, and venous trauma comprise the triad that leads to venous thrombosis. Although hypercoagulability was first implicated in venous thrombosis by Virchow in 1856,¹ its causes remained unknown until the mid-20th century.

CAUSES OF THROMBOPHILIA

Deficiency of Naturally Occurring Coagulation Inhibitors

The first specific cause of thrombophilia (the propensity to develop thrombosis because of abnormalities in coagulation) was described in 1965 by Egeberg.² He found that thrombophilia could be caused by a deficiency of antithrombin III, a naturally occurring protein that inhibits the coagulation cascade² by inactivating procoagulant factors.³ An-

antithrombin III deficiency is an autosomal dominant trait found in less than 1% of the population.

Deficiencies in 2 other naturally occurring coagulation inhibitors also are known to cause thrombophilia. These inhibitors are protein C, which inactivates procoagulant factors Va and VIIIa,⁴ and protein S,⁵ which may be decreased by pregnancy and oral contraceptive agents.³ These deficiencies are rare, also occurring in less than 1% of the population (Table 1).³

Coagulation inhibitor deficiencies are present in approximately 2.5% to 5% of all episodes of venous thromboembolism (VTE),^{6,7} but their rarity has prevented quantitation of their effects on the relative risk (RR) of an initial thromboembolic episode. In studies of antithrombin III-, protein C-, or protein S-deficient relatives of patients who had an initial episode of VTE, Brouwer et al⁸ found an increased risk of thromboembolism (RR = 16-18), whereas van Vlijmen et al⁹ found that the risk of thromboembolism was not increased unless the relatives took oral contraceptive agents.

In a study of 474 patients with an initial episode of VTE, Koster et al¹⁰ found that antithrombin III or protein S

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deficiency did not pose a significantly increased risk of VTE, whereas protein C deficiency did increase risk (RR = 6.5, 95% confidence interval [CI], 1.8-24).¹⁰ In another study of patients with an initial episode of VTE and an antithrombin III, protein C, or protein S deficiency, van Vlijmen et al⁹ found that those patients who were taking oral contraceptive agents had an increased risk of VTE (RR = 9.7), as shown in Table 2. They advised that patients with coagulation inhibitor deficiencies should not take oral contraceptive agents.⁹

Abnormal Functions of Naturally Occurring Coagulants

Other dysfunctions in the coagulation cascade also can cause thrombosis.¹¹ The most common of these dysfunctions is resistance to activated protein C. Rarely, such resistance can result from pregnancy, oral contraceptive use, or cancer,¹² but in most cases it is caused by the Leiden mutation of factor V.¹³

Factor V Leiden, which was first described in 1994,¹⁴ is the most common genetic risk factor for VTE. Its prevalence varies in different populations, averaging 2% to 10% for the heterozygous form^{15,16} and 1.5% for the homozygous form.¹⁷ Heterogeneous factor V Leiden is present in approximately 20% of patients with a first thromboembolism (Table 1)^{6,7} and is homozygous in 2% of these patients.⁶

Factor V Leiden increases the risk of an initial VTE. For the heterozygous and homozygous forms of factor V Lei-

den, the RR is 3 to 10 and 79, respectively (Table 2).^{12,16,17} The risk also increases significantly during pregnancy and with oral contraceptive use or hormone replacement therapy (Table 2).^{12,18}

Hypercoagulability also can be caused by the prothrombin mutation G20210A. This autosomal dominant mutation, which was first described in 1996,¹⁹ increases the plasma prothrombin concentration and the risk of an initial VTE (RR = 2~5).^{16,20} Its prevalence in the general population varies in different ethnic groups, averaging 1% to 5%,^{11,12} but its average prevalence in multiple reports of patients with an initial VTE^{6,7,11} is 9% (Table 1). The risk doubles when factor V Leiden also is present¹¹ and increases approximately 4-fold (RR = ~16) when combined with oral contraceptive use (Table 2).¹²

Hyperhomocysteinemia

An elevated level of homocysteine (hyperhomocysteinemia) increases the risk of venous and arterial thrombosis.²¹ This condition is heritable but also can be caused by a deficiency of folate, vitamin B₆, or vitamin B₁₂. Its prevalence is 5% to 10%^{12,17} in the general population and 18% in patients with an initial VTE.⁷ Hyperhomocysteinemia is thought to double the risk of an initial episode (RR ~ 2.5).¹⁷

In a randomized clinical trial, patients with known cardiovascular disease were treated with folic acid, vitamin B₆, and vitamin B₁₂. This treatment decreased serum homocysteine levels by 18% compared with placebo,²² but did not

CLINICAL SIGNIFICANCE

- The presence of thrombophilia (other than the antiphospholipid syndrome) has a minor impact on the rate of recurrent VTE.
- Recurrent VTE is nearly twice as frequent in patients with idiopathic VTE than in those with provoked VTE.
- Idiopathic VTE is a better predictor of recurrent VTE than the presence of thrombophilia.
- There are few clinical indications for thrombophilia screening.

Table 1 Prevalence of Thrombophilic States in Patients with Initial Venous Thromboembolism

Thrombophilia	Controls, % (Ref. No.)	Patients, % (Ref. No.)
Antithrombin III deficiency	<1 (11,12)	
Protein C deficiency	<1 (10,12)	2.5-5 (6,7)
Protein S deficiency	Uncertain	
FVL, heterozygous	2-10 (15,16)	20 (6,7)
FVL, homozygous	1.5 (17)	2 (6)
Prothrombin G20210A	1-3 (11,12)	9 (6,7,11)
Homocystinemia	5-10 (17)	18 (7)
Antiphospholipid syndrome	1-7 (12,24)	13 (25)
Elevated factor VIII	10 (11)	20-45 (6,7,27)
Elevated factor IX	10 (11)	18-26 (6,7)
Elevated factor XI	10 (11)	18 (7)
Elevated fibrinogen	10 (11)	18 (7)

FVL = factor V Leiden.

Table 2 Relative Risk of Initial Venous Thromboembolism

Condition	Relative Risk	Reference No.
Oral contraceptive use	2-4	18,20
Hyperhomocysteinemia	2.5	17
FVL, heterozygous	3-10	16,17,20
FVL, heterozygous + HRT	15	12
FVL, heterozygous + OCA	30-40	18,20
FVL, heterozygous + pregnancy	35	12
FVL, homozygous	79	17
FVL, homozygous + OCA	100	18
Prothrombin G20210A mutation	1-5	16,20
Prothrombin G20210A + FVL	6-10	11
Prothrombin G20210A + OCA	16	12
Protein C or S or ATIII Deficiency + OCA	9.7	9

FVL = factor V Leiden mutation; HRT = hormone replacement therapy; OCA = oral contraceptive agent; ATIII = antithrombin III deficiency.

affect the subsequent incidence of VTE in the total treatment group or in those with the highest baseline homocysteine levels.

A similar randomized clinical trial²³ examined patients with a first episode of idiopathic VTE (ie, without known risk factors of recent surgery, pregnancy, oral contraceptive use, cancer, trauma, or immobility). In patients with homocysteine levels greater than the 75th percentile ($n = 360$), treatment with folic acid and vitamins B₆ and B₁₂ decreased homocysteine levels by 46% compared with placebo. However, the rate of recurrence was unaffected over 2.5 years of follow-up.²³

Antiphospholipid Syndrome

Antiphospholipid syndrome is the most common acquired cause of thrombophilia. It is characterized by the presence of antiphospholipid antibodies, such as lupus anticoagulant antibodies or anticardiolipin antibodies.²⁴ This syndrome is usually secondary to cancer or an autoimmune disease, such as systemic lupus erythematosus, Sjögren's syndrome, or rheumatoid arthritis, but it also occurs as a primary syndrome. It may cause venous or arterial thrombosis, thrombocytopenia, recurrent fetal loss, or acute ischemic encephalopathy.²⁴

Schulman et al²⁵ found anticardiolipin antibodies in 13% of 897 patients with a first VTE. The antibody increased the risk of recurrence (RR = 2.5) and the 4-year mortality rate; in those with or without anticardiolipin antibodies the 4-year mortality rates were 6% and 15%, respectively.

Of patients with active systemic lupus erythematosus, 15% to 34% have lupus anticoagulant antibodies and 12% to 30% have anticardiolipin antibodies. Thrombosis occurs in 30% to 50% of patients with lupus with circulating antiphospholipid antibodies. These antibodies are detected in 1% to 7% of healthy controls^{12,24} and do not require therapy in the absence of a history of venous or arterial embolism. If thrombosis has occurred, lifelong therapy with warfarin is recommended.²⁶

Elevated Levels of Naturally Occurring Coagulation Factors

Hypercoagulability also can be caused by elevated concentrations of coagulation factors VIII, IX, or XI, or fibrinogen.³ Whether the elevation of these levels is acquired or genetic in origin is uncertain. Elevated levels of these factors are found in approximately 20% of patients with an initial VTE.⁷ In patients whose initial episode was idiopathic ($n = 360$), Kyrle et al²⁷ found that a factor VIII level greater than the 90th percentile significantly increased the risk of recurrence compared with a factor VIII level less than the 90th percentile (RR = 6.7). Elevation of factor VIII also is seen in cancer, inflammatory disorders, and pregnancy.³ The risks associated with increased levels of factor IX, factor XI, or fibrinogen are not well established.

CLINICAL IMPLICATIONS

Prevention of Primary Venous Thromboembolism Through Thrombophilia Screening

Thrombophilia screening to facilitate primary prevention of VTE is a reasonable consideration only for women who are about to begin using oral contraceptives. The substantially increased risk of primary thromboembolism in women with deficiencies in protein C, protein S, or antithrombin III who take oral contraceptive agents is well documented, leading van Vlijmen et al⁹ to recommend that women with these deficiencies should not take oral contraceptive agents.

Should all women be screened for thrombophilia before receiving oral contraceptives? A 10-fold increase in the rate of VTE amounts to only 3 cases per 1000 people per year. Given the fact that thrombophilia screening can cost well more than \$1000, the cost-effectiveness of this screening is uncertain.

Others have suggested that only women who have a family history of thromboembolism should be screened before receiving oral contraceptives.^{6,28} However, the value of such a family history has been questioned. Legnani et al²⁰ reported that a family history of VTE had a positive-predictive value of only 20% for an inherited thrombophilia.²⁰

Legnani et al²⁰ and Santamaria et al²⁹ recommend that women should be informed that the risk of thrombosis during oral contraceptive therapy is increased significantly in those who carry thrombophilic conditions. Given this information, women can decide if they want to be screened before receiving oral contraceptives.

Prevention of Secondary Venous Thromboembolism Through Thrombophilia Screening

The recurrence rate of VTE after 3 to 6 months of therapy is substantial. Christiansen et al⁷ reported a rate of 2.6% per year, increasing to an average of 12.4% after 5 years in patients aged less than 70 years without cancer. Hansson et al³⁰ reported recurrence rates of 7.0% and 12.1% at 1 and 2 years, respectively. Prandoni et al³¹ reported a recurrence rate of 17.5% at 2 years.

The percentage of VTE patients whose initial episode is idiopathic is surprisingly high, as shown in Table 3. In each of 3 series of patients without cancer, more than one half of the VTE episodes were idiopathic.^{6,7,27} Because the recurrence rate is higher for the idiopathic disease than for the provoked disease,^{15,30,31,32} some investigators recommend that such patients undergo thrombophilia screening.^{12,17} However, given the prevalence of idiopathic VTE, screening all such patients would be expensive.

Whether idiopathic VTE is an accurate marker for the presence of thrombophilia is questionable. In the series reported by Baglin et al,³² 32% of 157 patients with idiopathic VTE had 1 or more heritable thrombophilic defects, but so did 26% of 330 patients with risk factors for VTE.

Table 3 Initial Episodes of Venous Thromboembolism: Percent Idiopathic

Report	No. of Cases VTE	Exclusions	Idiopathic
Kyrle et al ²⁷	608	Cancer	59%
Christiansen et al ⁷	474	Cancer, age > 70 y	55%
Hron et al ⁶	1969	Cancer; lupus; deficiency of protein C, protein S, or ATIII	76%

ATIII = antithrombin III; VTE = venous thromboembolism.

Risk of Venous Thromboembolism Recurrence in Patients with Thrombophilia

Christiansen et al,⁷ Baglin et al,³² and de Stefano et al³³ did follow-up studies to determine the rate of recurrence of VTE. Ho et al¹⁵ reviewed these 3 reports and 10 additional reports (Table 4), all of which included patients with idiopathic or provoked episodes of VTE.

Baglin et al³² and Christiansen et al,⁷ after 2- and 7-year follow-ups, respectively, reported a small, nonsignificant increase in the risk of recurrence in patients with factor V Leiden (Table 4), and de Stefano et al³³ found that factor V Leiden did not affect the risk of recurrence. However, in the combined series (n = 663), the increase was small but statistically significant (RR = 1.4, 95% CI, 1.1-1.8).¹⁵

Both Baglin et al³² and Christiansen et al⁷ reported an insignificant increase in recurrence in patients with prothrombin G20210A, whereas the combined series of Ho et al¹⁵ demonstrated a small but statistically significant increase (RR = 1.7, CI, 1.3-2.3). It is striking that patients with the factor V or prothrombin mutations have a smaller risk of having a second thromboembolism than of having an initial one.

The data on anticoagulant deficiencies are less extensive. Baglin et al³² and Christiansen et al⁷ reported that deficiencies in protein C or S or antithrombin III had insignificant effects on the risk of recurrent VTE. In contrast, these deficiencies are associated with a significant increase in the risk of an initial episode.^{8,9}

Christiansen et al⁷ did not find an increased risk of recurrence in patients with hyperhomocysteinemia or elevated factor VIII, IX, or XI levels. However, in patients above the 90th percentile for factor VIII levels, Kyrle et al²⁷ found a significant increase in risk (RR = 6.6, CI, 2.4-18.4). Christiansen et al⁷ found a marginally significant increase in risk with elevated fibrinogen (RR = 1.7, CI, 1.1-2.8).

Further evidence of the small impact of inherited thrombophilia on the risk of recurrent VTE is the finding that presence of a single thrombophilic factor confers only a statistically insignificant increase in risk (RR = 1.2 and 1.5 according to Christiansen et al⁷ and Baglin et al,³² respectively). In patients with 2 or more thrombophilias, risk increases modestly (RR = 1.2).^{7,33} On the other hand,

Table 4 Relative Risk of Recurrent Venous Thromboembolism

Condition	Reference	No. of Cases	Follow-Up (y)	Relative Risk (CI)
FVL, heterozygous	Ho et al ¹⁵	663	1-8	*1.4 (1.1-1.8)
	Christiansen et al ⁷	92	7.3	1.3
	de Stefano et al ³³	112		1.1
	Baglin et al ³²	77	2	1.4
Prothrombin G20210A	Ho et al ¹⁵	283	1-8	*1.7 (1.3-2.3)
	Christiansen et al ⁷	29	≥7	0.7
	Baglin et al ³²	20	2	1.7
Protein C deficiency	Baglin et al ³²	5	2	1.8
Protein S deficiency	Baglin et al ³²	27	2	1.0
ATIII deficiency	Baglin et al ³²	8	2	2.6
Proteins C and S +ATIII deficiency	Christiansen et al ⁷	25	≥7	1.8
Elevated homocysteine	Christiansen et al ⁷	83	≥7	0.9
Elevated factor VIII	Christiansen ⁷	110	≥7	1.3
	Kyrle et al ²⁷	36	≥2	*6.6 (2.4-18.4)
Elevated factor IX	Christiansen et al ⁷	86	≥7	1.2
Elevated factor I XI	Christiansen et al ⁷	92	≥7	0.6
Elevated fibrinogen	Christiansen et al ⁷	87	≥7	*1.7 (1.1-2.8)
Antiphospholipid syndrome	Shulman et al ²⁵	116	4	*2.5
	Christiansen et al ⁷	319	≥7	1.2
1 Abnormality	Baglin et al ³²	137	2	1.5
	Christiansen et al ⁷		≥7	*1.6 (1.0-2.7)
FVL + prothrombin G20210A	de Stefano et al ³³	17		*2.7 (1.4-5.0)

CI = confidence interval; FVL = factor V Leiden; ATIII = antithrombin III.

**P* < .05.

antiphospholipid syndrome with circulating anticardiolipin antibodies definitely increases the risk of recurrence.^{25,26}

Implications for Thrombophilia Screening

Christiansen et al⁷ concluded that “. . . extensive, if any, thrombophilic work-up after a first thrombotic event is not likely to confer a clinical benefit on the patient.” Baglin et al³² were equally pessimistic, stating that “. . . in unselected patients presenting with a first episode of venous thromboembolism, testing for heritable thrombophilia does not allow prediction of a new event during the highest risk period—that is, for the first 2 years after anticoagulant therapy is stopped.” Finally, in referring to the factor V and prothrombin mutations, Ho et al¹⁵ concluded that the data “. . . call into question the cost-effectiveness of routine testing for these common inherited thrombophilic polymorphisms among patients with a first episode of venous thromboembolism.”

The only thrombophilic states that seem to have a significant impact on the risk of recurrence of VTE are anticardiolipin antibodies, high levels of factor VIII (in 1 report),²⁷ and the presence of 2 or more thrombophilic defects. Anticardiolipin antibodies should be assessed in patients with clinical characteristics consistent with antiphospholipid syndrome.

Routine testing of patients with idiopathic VTE in search of those with multiple thrombophilic defects would rarely be productive, because the incidence of patients with more than 1 defect is low (2.7% in the studies of both de Stefano³³ [n = 624] and Legnani²⁰ [n = 301]) and the increase in risk is modest.^{7,33}

Implications for Vitamin K Antagonist Therapy

Because thrombophilic patients have a modestly increased risk of recurrent VTE,^{6,7,15,32,33} routine thrombophilia screening to determine the appropriate length of warfarin therapy is not warranted. For patients with an initial thromboembolism, the risk of recurrent VTE is greater if the episode was idiopathic than if it occurred with thrombophilia. As shown in Table 5, the rate of recurrence in patients with thrombophilia (2.5%) was the same as in the

Table 5 Incidence of Recurrent Venous Thromboembolism

Patient Group	Recurrence of VTE per Year
Total group	2.6%
With 1 thrombophilia	2.5%
Initial VTE provoked	1.8%
Initial VTE idiopathic	3.3%
Idiopathic with thrombophilia	3.4%
Idiopathic without thrombophilia	3.2%

VTE = venous thromboembolism.
Data from Christiansen et al.⁷
Total group = 474 patients with a first episode of VTE.

Table 6 Suggested Duration of Warfarin Therapy in Patients with Venous Thromboembolism Without Routine Thrombophilia Screening

Clinical Status	Recommended Duration of Warfarin Therapy
Initial VTE with reversible risk factors	3 mo
Initial VTE, idiopathic	1 y
VTE with cancer	Indefinite*
VTE with antiphospholipid syndrome	Indefinite†
≥2 VTE episodes	Indefinite

VTE = venous thromboembolism.
*0r until cancer resolved.
†0r until condition resolved.

total group (2.6%), but the rate of recurrence in patients with idiopathic VTE (3.3%) was almost double that in patients with provoked VTE (1.8%). In patients with idiopathic thromboembolism, thrombophilia did not further increase the rate of recurrence.⁷

Similar findings were reported by Baglin et al.³² For patients with an initial episode of idiopathic (n = 193) or provoked (n = 377) VTE, the 2-year recurrence rates were 19.4% and 6.6%, respectively. Again, thrombophilia did not significantly increase the rate of recurrence (RR = 1.5, 95% CI, 0.82-2.77).³²

Patients with unprovoked VTE who have persistent D-dimer elevation after completion of anticoagulant therapy are at increased risk of recurrence. Palareti et al³⁴ reported that after completion of at least 3 months of vitamin K antagonist therapy, patients with normal or abnormal D-dimer levels had 1-year recurrence rates of 4.4% and 10.9%, respectively. After a year of treatment, 1-year recurrence in those with elevated D-dimer levels was 2.0%.³⁴

The findings of Christiansen et al,⁷ Baglin et al,³² and Palareti et al³⁴ suggest that rather than screening all patients with idiopathic VTE, it is more appropriate to lengthen their course of treatment. A suggested approach to determining the duration of warfarin therapy without the aid of thrombophilia screening is shown in Table 6. This approach differs from that proposed by the 2004 American College of Chest Physicians' Conference on Antithrombotic and Thrombolytic Therapy²⁶ in that it recommends that patients with idiopathic VTE be treated for 12 months, regardless of thrombophilic status.

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