

Venous thrombosis: Preventing clots in patients at risk

Which test should you order for a patient with recurrent superficial thrombophlebitis? Which pregnant women need prophylaxis? Read on for these answers, and more.

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PRACTICE RECOMMENDATIONS

› *Testing for inherited hypercoagulable disorders should focus on the identification of individuals most likely to benefit from it. (C)*

› *Avoid testing asymptomatic individuals for the sole purpose of initiating long-term prophylactic therapy. (C)*

› *Long-term anticoagulant therapy may be warranted for patients with antithrombin III, protein C, or protein S deficiency, who may be at increased risk of recurrent thrombosis. (C)*

› *A definitive diagnosis of antiphospholipid antibody syndrome requires a history of either vascular thrombosis or pregnancy morbidity. (C)*

Strength of recommendation (SOR)

- A** Good-quality patient-oriented evidence
- B** Inconsistent or limited-quality patient-oriented evidence
- C** Consensus, usual practice, opinion, disease-oriented evidence, case series

Each year, venous thrombosis develops in approximately 1 in 1000 people.¹ The cause: An alteration in blood composition, venous stasis, or vascular damage—commonly known as Virchow's triad. Changes in blood composition are associated with hereditary thrombophilias, such as factor V Leiden mutation or a deficiency in protein C or S or antithrombin III (AT). Changes in blood flow (stasis) and vessel damage stem from acquired conditions that commonly lead to hypercoagulability—pregnancy, malignancy, and estrogen use among them.

Regardless of the reason a patient is at elevated risk, however, the goal is the same: to prevent the development of thrombi, thereby reducing the increased morbidity and mortality associated with thromboembolism. Achieving that goal requires an understanding of both inherited and acquired risk factors, familiarity with diagnostic tools, and knowledge of appropriate treatment. This review, which begins with hereditary hypercoagulable states before turning to acquired conditions associated with hypercoagulability, will help toward that end.

Keep these thrombophilias on your radar screen

Factor V Leiden mutation is the most common inherited hypercoagulable disorder, and the most common form of activated protein C resistance. The mutation is found in an estimated 5% to 10% of the general population.² Among patients with thromboembolic disorders, however, the incidence is considerably higher, with estimates ranging from 21% to 60%.^{3,4} Factor V Leiden mutation is more prevalent among Caucasian populations, and rarely found in people of Asian or African descent.²

■ **Prothrombin G20210A mutation**, an autosomal-dominant disorder, is the second most common inherited

> Hyperhomocysteinemia may be associated with a hereditary disorder or an acquired condition, such as vitamin B6 or B12 deficiency, chronic kidney disease, hypothyroidism, and certain malignancies.

hypercoagulable state.⁴ This mutation is associated with an increase in prothrombin levels, causing an elevation in thrombin and, in turn, a heightened risk of thrombosis.

Although prothrombin G20210A mutation is found in only 1% to 2% of the general population, its prevalence among those with a history of thromboembolic events is estimated at 5% to 19%.⁴ This disorder, too, varies significantly by ethnicity: People from southern Europe are twice as likely to be affected as northern Europeans, and the mutation is rarely found in people of Asian or African descent.^{2,5}

■ **Protein C deficiency.** Protein C, a vitamin K-dependent anticoagulant produced in the liver, is activated when thrombomodulin binds with thrombin in the presence of protein S, which serves as the cofactor. Protein C is required to inactivate clotting factors V and VIII.² The deficiency is an autosomal-dominant disorder, and is more likely to result in venous than arterial thrombosis.²

Protein C deficiency affects 1 in every 200 to 500 people in the general population; among patients with a history of venous thrombosis, its prevalence is 2% to 9%.^{2,3} Generally, people with a protein C deficiency begin developing thrombi in their late teens, and about 75% suffer from 1 or more thrombotic events during the course of their lives.²

There are 2 types of protein C deficiency: Patients with type I have a decreased production of protein C, while those with type II have normal levels of the protein, but in a form that is dysfunctional.⁶

■ **AT deficiency.** AT, a natural anticoagulant synthesized by the liver and endothelial cells, is responsible for inactivating several clotting factors, including thrombin and factors IXa, Xa, XIa, and XIIa. Like protein C deficiency, AT deficiency is an autosomal-dominant disorder with 2 subtypes. Individuals with type I deficiency have normal plasma levels of AT, but the anticoagulant has reduced biological activity or is dysfunctional; those with type II deficiency have decreased plasma levels of fully functional AT.² Both types are more likely to lead to venous than arterial thrombosis.

AT deficiency affects approximately 1 in 2000 to 5000 people, including 2.8% of

patients who develop venous thrombosis.⁷ Nearly two-thirds of those with AT deficiency develop thrombi before the age of 35.²

■ **Protein S deficiency.** Endothelial cells are responsible for the synthesis of protein S, which, like protein C (for which it serves as a cofactor), is vitamin K-dependent. Protein S deficiency, also an autosomal-dominant disorder, has 3 subtypes: Type I, also known as classical deficiency, is characterized by reduced free and total levels of functional protein S; type II patients have a normal total level of protein S, but a decreased amount of free protein; and type III patients have normal levels of both free and total protein S, but the available proteins are dysfunctional.^{2,6}

The prevalence of this hypercoagulable state in the general population is unknown, and protein S deficiencies have been found in only 1% of patients with a history of deep vein thrombosis (DVT).^{3,8} Although this hypercoagulable state is less common than other hereditary thrombophilias, 74% of people with this disorder develop DVT—half of them before the age of 25.²

■ **Hyperhomocysteinemia.** Elevations in homocysteine may occur as a result of a hereditary disorder (deficiencies in cystathionine beta-synthase or methylene-tetrahydrofolate reductase). Hyperhomocysteinemia may also be an acquired condition, associated with deficiencies in vitamins B6, B12, or folic acid; chronic kidney disease; hypothyroidism; and certain malignancies.

The prevalence of hyperhomocysteinemia varies, based on the underlying disorder. Only about 0.3% of the general population has a cystathionine beta-synthase deficiency. Methylene-tetrahydrofolate reductase deficiency, however, is common among Italian and Hispanic populations (occurring in about 20%), but rare (<1%) among African American people.³

When to test for thrombophilias

Idiopathic venous thrombosis is probably the most common reason for ordering testing for inherited hypercoagulable states, and an underlying thrombophilia is found in about 50% of cases.⁹ Other indications for testing include thrombus development in an unusual site

(eg, splanchnic, renal, retinal, or ovarian veins; cerebral venous sinuses; or upper limbs), recurrent venous thromboembolism (VTE), venous thrombosis at an early age (<45 years) or in a patient with a strong family history of VTE, and unexplained recurrent pregnancy loss.

Testing may also be considered for relatives of patients with known inherited hypercoagulability disorders, but this should be done only if the results could affect a treatment decision: Can a man safely undergo surgery with a high postoperative risk for thrombosis, for example? Should a woman take oral contraceptives (OCs), start hormone replacement therapy (HRT), or attempt another pregnancy?

Overall, testing for inherited hypercoagulable states should focus on the identification of individuals most likely to benefit from it; only tests yielding useful data should be performed. Testing of asymptomatic individuals for the sole purpose of initiating long-term prophylactic therapy is not recommended.

Which tests for which patients?

In some cases, selective assays may be more useful than test panels, for reasons associated with patient presentation as well as cost. Proper selection of specific tests should be individualized based on the patient's age, thrombotic presentation, and family history, and on potential effects on patient management.

For patients with heparin resistance, cerebral vein thrombosis, intra-abdominal vein thrombosis, or recurrent superficial thrombophlebitis, AT testing may be in order. Patients with recurrent superficial thrombophlebitis may also benefit from testing for factor V Leiden mutation, and protein C and protein S testing may be beneficial for patients with warfarin skin necrosis, recurrent superficial thrombophlebitis, or neonatal purpura fulminans. Cerebral vein thrombosis in the general population and in women using OCs, in particular, is suggestive of a G20210A mutation,⁹ and is a possible indication for testing. Hyperhomocysteinemia testing may be considered for patients with premature arterial and venous thrombosis, as well as mental retardation, skeletal abnor-

malities, and vitamin B6 or B12 deficiency.

Many physicians prefer to order testing in stages, starting with tests for the most common thrombophilias. When ordering tests for the conditions detailed above and in the **TABLE**, be aware that test panels vary among facilities, so it may be necessary to check with the testing laboratory to ensure that it offers the tests that are indicated for a particular patient.

Timing of tests, and other specifics

Acute thrombosis, anticoagulation therapy, and some disease states—eg, liver disease, nephritic syndrome, disseminated intravascular coagulation, and acute illness—can affect levels of AT, protein C, and protein S. Within the first 48 hours of warfarin therapy, for example, a patient's protein C and protein S levels decline about 50%; after 2 weeks, the levels rise to about 70% of their normal range. Because of warfarin's effect on these proteins, evaluation for these deficiencies should be performed at least 1 week to 10 days after cessation of a 3- to 6-month course of anticoagulation therapy. Abnormal findings should be confirmed with a second test approximately 3 weeks later.^{2,3,9}

Several tests are used to detect factor V Leiden mutation, including the polymerase chain reaction-based test and the modified activated partial thromboplastin time (aPTT)-based test. The latter can be given to patients who are receiving anticoagulants. The results indicate the ratio of activated protein C (APC), and a finding of <2.0 is considered abnormal.⁸ The presence of lupus anticoagulant—autoantibodies that bind to phospholipids and proteins associated with the cell membrane—may yield a false-positive result on the modified aPTT test.

While the prothrombin G20210A mutation is linked to elevations in prothrombin, measuring prothrombin levels is not an accurate way to test for this hypercoagulable state. The prothrombin G20210A mutation generally is detected through DNA analysis instead.^{2,8}

Hyperhomocysteinemia is diagnosed by measuring fasting plasma levels of homocysteine. Although the results are not standardized, they generally correlate with the severity of disease (mild, 15-30 $\mu\text{mol/L}$; moderate, >30-100 $\mu\text{mol/L}$;

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TABLE

**Suspect a hereditary hypercoagulable disorder?
Testing considerations to keep in mind^{2,3,8,9,11,12}**

Disorder	Potential indication(s) for testing	Timing of test	Interaction with warfarin	Interaction with LMWH and UFH
Factor V Leiden mutation	Recurrent superficial thrombophlebitis	Not during an acute event	Modified aPTT test does <i>not</i> interact	Modified aPTT test does <i>not</i> interact
Prothrombin G20210A mutation	Cerebral vein thrombosis	Not during an acute event	No	No
Protein C deficiency	<ul style="list-style-type: none"> • Warfarin skin necrosis • Recurrent superficial thrombophlebitis • Neonatal purpura fulminans 	7-10 days after cessation of warfarin therapy	Yes	No
Antithrombin III deficiency	<ul style="list-style-type: none"> • Heparin resistance • Cerebral vein thrombosis • Intra-abdominal vein thrombosis • Recurrent superficial thrombophlebitis 	7-10 days after cessation of warfarin therapy	Yes	Yes
Protein S deficiency	<ul style="list-style-type: none"> • Warfarin skin necrosis • Recurrent superficial thrombophlebitis • Neonatal purpura fulminans 	7-10 days after cessation of warfarin therapy	Yes	No
Hyperhomocysteinemia	<ul style="list-style-type: none"> • Premature arterial/venous thrombosis • Skeletal abnormalities • Vitamin B6 or B12 deficiency 	Not during an acute event	No	No

aPTT, activated partial thromboplastin time; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

severe, >100 μmol/L). However, plasma levels may be falsely elevated during an acute thrombotic episode and decreased by supplementation with folic acid, B6 and B12. The decrease, however, does not indicate a reduction in the risk of thrombosis.

Treatment, yes, but for how long?

Most thrombotic events are initially treated with a combination of a heparin product (low-molecular-weight heparin [LMWH] or unfractionated heparin [UFH]) and warfarin—commonly known as bridging therapy. The heparin is discontinued once the patient's international normalized ratio (INR) has been maintained at a therapeutic level for more than 24 hours, which usually takes

about 5 days. Warfarin therapy, however, should continue for at least 3 to 6 months, depending on the severity and cause of the thrombosis.

Individuals with an AT, protein C, or protein S deficiency may be at increased risk of recurrence, and long-term anticoagulant therapy may be warranted.⁵ Under current guidelines from the American College of Chest Physicians (ACCP), however, hereditary thrombophilias are not considered to be major determinants of recurrence or a major factor guiding the duration of anticoagulation therapy.¹⁰ Practitioners must use their judgment to determine the need for treatment; if anticoagulation therapy is initiated, the duration should be based on an individual assessment of benefit and risk.

Recognizing and responding to acquired risks

Several conditions associated with vessel wall changes and venous stasis—the hallmarks of acquired hypercoagulable states—put patients at increased risk of venous thrombosis. Following is a review of the most likely risk factors, including antiphospholipid antibody syndrome (APS), previously known as lupus anticoagulant syndrome; heparin-induced thrombocytopenia (HIT); pregnancy; trauma; estrogen; and malignancy.

When to test for—and treat—APS

APS, a systemic autoimmune disorder that can result in arterial or venous thrombosis or pregnancy loss and morbidity, is characterized by the presence of autoantibodies. Patients of all ages may be affected by APS, one of the most common acquired hypercoagulability disorders. APS affects an estimated 28% of the general population.² About 15% of recurrent pregnancy losses and 20% of recurrent thromboses in young adults are attributed to this autoimmune disorder.¹¹

A definitive diagnosis of APS requires a history of either vascular thrombosis or pregnancy morbidity—defined as miscarriage after the 10th gestational week, consecutive fetal losses before the 10th gestational week, or placental insufficiency and premature birth before 34 weeks.^{11,12} APS testing may be useful in patients with cerebral vein thrombosis, intra-abdominal vein thrombosis, or unexplained recurrent fetal loss.⁹

In addition to clinical criteria, a diagnosis of APS is based on the presence of plasma antibodies on 2 or more occasions at least 12 weeks apart. APS encompasses 3 types of antiphospholipid antibodies—lupus anticoagulant antibodies, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies—which can be detected with 2 different tests. Coagulation assays are used to identify lupus anticoagulant antibodies because they prolong clotting time; however, immunoassays are used to measure immunologic reactivity to phospholipids to determine the presence of anticardiolipin antibodies and anti-beta 2-glycoprotein I antibodies.^{11,12}

■ **Treatment for APS** generally involves anticoagulant therapy for the prevention and

treatment of acute thrombotic events, or as prophylaxis during pregnancy. ACCP guidelines call for initiating warfarin therapy with a target INR of 2.5 (range 2.0-3.0) in patients with no other risk factors. In patients who have had recurrent thromboembolic events or have additional risk factors, a target INR of 3.0 (range 2.5-3.5) is suggested.¹⁰ LMWH and UFH are also options for use in the event of recurrence or for prophylaxis during pregnancy.^{11,13,14}

HIT can be benign, or life threatening

HIT—defined by a decrease in platelet count to less than 150,000 (or a 50% drop from baseline) after initiation of heparin therapy—may or may not be benign. HIT type I (previously called heparin-associated thrombocytopenia), which affects approximately 10% of patients treated with heparin, is transient, asymptomatic, and not associated with an increased risk of thrombosis. Type I typically occurs within the first 2 days of heparin therapy.¹⁵

HIT type II is an immune-mediated response that does increase the risk of thrombosis. Patients usually develop type II 5 to 12 days after initiation of heparin, but in rare instances onset is delayed, occurring up to 40 days after heparin therapy. Approximately 5% of patients on heparin develop HIT type II, and the risk increases with frequent heparin use. Unlike other states of thrombocytopenia, HIT rarely causes bleeding. However, patients with HIT type II are at risk for a paradoxical thrombotic syndrome that may become life threatening.^{13,15}

To diagnose HIT, an enzyme-linked immunosorbent assay or other specific blood tests must be used to confirm the presence of circulating antibodies.¹³ The diagnosis is based on the following criteria: (1) thrombocytopenia, (2) exclusion of other possible causes of thrombocytopenia, and (3) resolution of thrombocytopenia after discontinuation of heparin.^{13,15}

■ **When HIT is suspected**, all heparin-containing products must be discontinued immediately and alternative anticoagulant therapy (typically, with danaparoid, lepirudin, or argatroban) should be initiated to reduce the risk of thrombosis. Warfarin alone should not be used for the treatment of HIT

➤ **Antiphospholipid antibody syndrome (APS) testing may be useful for patients with cerebral vein thrombosis, intra-abdominal vein thrombosis, or unexplained recurrent fetal loss.**

➤ Pharmacologic prophylaxis is not recommended for pregnant patients with thrombophilias, but no history of thrombotic events.

because of its association with worsening thrombosis and venous limb gangrene.¹³ However, warfarin *should* be initiated while the patient is receiving danaparoid or a thrombin-specific inhibitor—with at least 5 days of overlapping therapy recommended. Duration of therapy has not been well defined, but an overall course of at least 2 to 3 months is recommended to reduce the risk of recurrent thrombosis.^{13,15}

Pregnancy raises risk, but limits Tx options

By altering the body's normal physiologic state in a way that may lead to hypercoagulability, pregnancy increases the risk of VTE 6-fold.¹⁶ The risk continues throughout pregnancy and peaks during puerperium, the 6-week period after delivery. Cesarean delivery, prolonged immobility, and obesity elevate the risk.^{13,16}

Treatment options for acute thrombotic events during pregnancy are limited because warfarin is contraindicated. Current ACCP guidelines recommend substituting UFH or LMWH for oral anticoagulant therapy when treatment for an acute thrombotic event is required.¹⁰ While no pharmacologic prophylaxis is currently recommended for pregnant patients with thrombophilias but no history of thrombotic events,^{10,17} there are cases when it may be necessary. Patients with an AT deficiency, for example, may require prenatal and postpartum prophylaxis,¹⁰ and patients who deliver by cesarean and have 1 or more additional risk factors should receive prophylaxis for the duration of their hospitalization. Women with multiple risk factors, in addition to pregnancy and cesarean section, should receive pharmacologic prophylaxis for up to 4 to 6 weeks postpartum.

■ Choices for postpartum anticoagulation for the treatment of an acute thrombotic event should be based on guidelines developed for nonpregnant patients, with this caveat: For women who are breastfeeding, safety during lactation must be considered. Neither UFH nor warfarin enters breast milk, so both are safe for such patients.¹⁸ LMWH, although smaller in molecular weight than UFH, is considered moderately safe during breastfeeding, as well.¹⁸

Prophylaxis is vital for trauma patients

Trauma and major injuries increase the risk of thrombosis by approximately 50%. Patients who are hospitalized after a major trauma are at high risk for the development of a VTE. At the greatest risk are those with spinal cord injuries (62%), pelvic fractures (61%), and leg fractures (80%).¹⁶ Current ACCP guidelines recommend the use of LMWH as soon as it is safe for trauma patients, and continuing it until discharge in patients with no apparent contraindication. If a patient has an active bleed or other contraindication, mechanical thromboprophylaxis is indicated until the bleeding risk decreases.¹⁵

Estrogens increase platelet aggregation

Estrogens are considered a risk factor because of their effect on both natural anticoagulants and clotting factors. A reduction in AT activity and increasing concentrations of clotting factors VII, X, and XII result from the use of estrogens. Estrogen is also thought to be responsible for the increase in platelet count and aggregation associated with the use of combination OCs.¹⁹ In fact, OC use is associated with about a 3-fold overall risk of thrombosis, a risk reported to be highest during the first year of use.¹⁶ Among hormonal contraceptives, the transdermal formulation has the highest risk.²⁰⁻²² Hormone replacement therapy taken during menopause confers approximately a 2- to 4-fold increase in risk for VTE, and selective estrogen receptor modulators are associated with a 2-fold risk.¹⁶ Physicians should educate patients about the risks associated with these agents and signs and symptoms of thrombosis.

Cancer and hypercoagulability: Which patients need treatment?

Although the pathophysiologic process is not fully understood, a link between cancer and hypercoagulability has long been recognized. In fact, malignancy—the second most common cause of acquired hypercoagulability—is associated with 10% to 20% of spontaneous DVTs.²

One possible mechanism is the interaction of tumor cells with thrombin and plasmin-generating systems, directly influencing thrombus formation.⁷

Cancer patients also have an elevated risk for thrombosis related to immobilization, infection, treatment with antineoplastic agents, surgery, and the insertion of central venous catheters. Approximately 30% of patients with central venous catheters develop a DVT of the arm.¹⁶

Anticoagulant therapy in cancer patients varies, depending on the severity and circumstances of the patient. According to American Society of Clinical Oncology, National Comprehensive Cancer Center Network, and ACCP guidelines, LMWH is the preferred initial treatment for thromboses in patients with cancer—that is, in the first 3 to 6 months of therapy after a thrombotic event.^{17,23,24} The guidelines also

mention warfarin as an alternative for long-term (>6 months) anticoagulant therapy, if no contraindications exist.

Because cancer is usually a long-term illness, anticoagulant therapy should be continued indefinitely, or until the cancer has resolved.^{10,23,24} Prophylaxis is recommended for cancer patients who are bedridden with an acute medical illness, but should not be routinely used in patients with indwelling venous catheters or those receiving chemotherapy or hormonal therapy.^{13,15} **JFP**

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LMWH is the preferred initial treatment for thromboses in patients with cancer.



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