The real value of thrombophilia markers in identifying patients at high risk of venous thromboembolism


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Thrombophilia is defined as a condition predisposing to the development of venous thromboembolic complications. Over the past decades, there have been great advances in the understanding of the pathogenesis of venous thromboembolism (VTE) through the identification of several inherited and acquired risk factors. However, in spite of such progress, a number of questions remain unanswered. In particular, it is well known that some subjects carrying several risk factors for VTE will never experience a thrombotic episode while other individuals developed recurrent thromboembolic events with no known risk factor. In this review, we summarize the current knowledge on the various thrombophilia markers, and also discuss their role in the development of thrombotic complications.

KEYWORDS: acquired • arterial thrombosis • inherited • thrombophilia • venous thrombosis

Thrombophilia is defined as a hypercoagulable state leading to a thrombotic tendency [1–3]. In 1856, the German physician Rudolf Virchow conceived the theory of the triad, that is, endothelial injury, stasis of blood flow and hypercoagulability, to explain the etiology of thrombosis [4]. This concept was prophetic in that it has now been shown that all three components of the triad play active roles in the development of thrombotic events. During the past two decades, progress has been made in the identification and characterization of the cellular and molecular mechanisms that interdependently influence the Virchow’s triad. It is now accepted that the combination of stasis and hypercoagulability, more than endothelial damage, is crucial for the occurrence of venous thromboembolism (VTE), venous thrombi being mainly constituted by fibrin and red blood cells and less by platelets. In contrast, platelets are essential for primary hemostasis, repair of the damaged endothelium and play a pivotal role in the development of arterial thrombosis [5].

Thrombophilic abnormalities can be inherited, acquired or mixed (both congenital and acquired) and the risk of VTE is different according to each abnormality (Table 1). Inherited thrombophilias include deficiencies of the natural anticoagulant proteins antithrombin, protein C and protein S, as well as the gain-of-function mutations in the factor V gene (FV G1691A Leiden) and prothrombin gene (prothrombin G20210A). Acquired thrombophilia is mainly represented by the presence of antiphospholipid antibodies, while the most frequently investigated mixed abnormality is mild-to-moderate hyperhomocysteinemia. In this review, we discuss the role of the main thrombophilia markers in the development of thrombotic events.

Antithrombin deficiency
Antithrombin is a single chain glycoprotein synthesized in the liver, belonging to the serine protease inhibitor (serpin) superfamily [6], which functions as a natural anticoagulant by binding to, and inactivating, thrombin and other serine proteases, such as activated factor X [7]. The result of this activity is a reduction in both the generation and the half-life of thrombin. In addition to the active site responsible for coagulation factor inactivation, the antithrombin molecule contains a heparin-binding site [8]. When exogenous heparin or endogenous heparan sulfate bind to this site, the ability of antithrombin to inactivate the
Antithrombin deficiency is mainly transmitted as an autosomal dominant trait and patients usually present with recurrent VTE episodes during the second to third decade of life. The penetrance of this disease is very high, since most affected family members experience a thrombotic event by the age of 45 [10,11]. Antithrombin deficiency is probably the most severe of the inherited thrombophilias, causing more than 50-fold increased risk for VTE compared with that of individuals not carrying this defect [11]. In the general population, the estimated prevalence of antithrombin deficiency ranges from 2 to 17 per 10,000 individuals, and in patients with VTE is around 1% [12-14]. More than 250 gene variations have been identified in antithrombin deficiency, including missense and nonsense point mutations, insertions and deletions [15].

Two types of antithrombin deficiency can be distinguished. In type I, antithrombin activity and antigen level are both reduced in plasma owing to a lack of protein production or secretion by the mutant allele. In type II, low antithrombin activity contrasts with normal antigen levels, indicating functional defects in the molecule. Type II can be further subdivided into three subtypes characterized by impairment of the enzyme reactive site, of the heparin-binding site or by pleiotropic defects affecting antigen concentration and heparin-binding or enzyme activity [16]. The only individuals homozygous for antithrombin deficiency described so far carry heparin-binding site defects, suggesting that the other subtypes are associated with embryonic lethality [16].

Table 2 reports epidemiological data and association with VTE risk of the different thrombophilic risk factors. It should be outlined that risk estimates are generally based on selected family studies, so that the risk of venous thrombosis may not necessarily reflect the risk of thrombophilia in the general population.

**Protein C deficiency**

Protein C, described for the first time in 1979 [17], is a vitamin-K-dependent glycoprotein synthesized in the liver in an inactive form. Under physiological conditions, once activated by the thrombin–thrombomodulin complex, protein C acts as an anticoagulant by means of the proteolytic degradation of activated coagulant factors Va and VIIIa. As for other physiological inhibitors of coagulation, any mutation leading to a reduction of protein C activity increases the risk of VTE [18].

Inherited protein C deficiency is transmitted as a dominant autosomal trait [19] and more than 200 mutations in the protein C gene (PROC), which lies on 2q13-q14 chromosome, have been reported so far [20]. Heterozygous deficient people experience recurrent episodes of VTE, often before the age of 45. Homozygous individuals have a more severe clinical picture, not infrequently leading to neonatal purpura fulminans, a potentially fatal condition characterized by multiple thrombosis in small vessels leading to skin necrosis [14]. The penetrance of the disease is less than that of antithrombin deficiency, thus heterozygotes have a 15-fold increased risk for thrombosis compared with the general population [15]. However, the disorder is quite rare with prevalence in the population of only 0.2–0.4 and of 3% in patients selected for VTE. Similar to antithrombin deficiency, protein C deficiency can be divided in two subtypes. Type I, which is the most common, is characterized by a parallel reduction in plasma antigen level and activity, reflecting a reduced synthesis of a functional protein. The rarer type II is characterized by normal antigen level with reduced functional activity, reflecting normal synthesis of a dysfunctional protein. In type I, the majority of mutations are of the missense variety, leading to premature termination of synthesis or disruption of protein folding, whereas deletions and insertions occur with a much lower frequency (~10%). In type II, missense mutations are located mainly in the γ-carboxyglutamic acid and protease domains [21].

**Protein S deficiency**

Protein S is a vitamin-K-dependent protein of liver synthesis, which circulates in plasma in equilibrium between an inactive form, bound to a carrier called C4b-binding protein, and a free, functionally active form, which accounts for approximately 40% of the total plasma protein S [18]. Protein S functions as a cofactor of activated protein C (APC) for the degradation of activated factors Va and VIIIa. In addition, protein S acts as a cofactor of tissue factor pathway inhibitor in the inhibition of factor Xa. The bioavailability of protein S is closely linked to the concentration of the acute phase reactant C4b-binding protein, which acts as an important regulatory protein. Thus, all conditions (i.e., pregnancy, oral contraceptive use, acute thrombosis, inflammatory states and cancers) associated with increased C4b-binding protein levels also cause an increase in bound protein S and hence a reduction of the unbound free form [22].

Transmitted as an autosomal dominant trait, familial protein S deficiency has a clinical presentation very similar to that observed for protein C deficiency [23]. Thus, heterozygotes experience early recurrent VTE episodes and sometimes warfarin-induced skin necrosis, while rare homozygotes exhibit a very severe clinical picture with neonatal purpura fulminans. The penetrance of the disease is also similar to that of protein deficiency.
Table 2. Prevalence of thrombophilia abnormalities and relative risk of thrombosis.

<table>
<thead>
<tr>
<th>Thrombophilia abnormality</th>
<th>Prevalence (%)</th>
<th>Relative risk</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>General population</td>
<td>Patients with VTE</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>0.02–0.17</td>
<td>1.1</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>0.2–0.4</td>
<td>3.2</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>0.03–0.1</td>
<td>2.2</td>
</tr>
<tr>
<td>Heterozygous factor V Leiden</td>
<td>2–10</td>
<td>20–50</td>
</tr>
<tr>
<td>Heterozygous prothrombin G20210A</td>
<td>1–4</td>
<td>5–10</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>1–2</td>
<td>5–15</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>5</td>
<td>10–15</td>
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VTE: Venous thromboembolism.

C deficiency, causing a nearly 10-fold increased VTE risk in affected individuals compared with the normal population. The prevalence of protein S deficiency in the general population is estimated at 0.03–0.1%, while it occurs in 2% of patients with VTE [14]. The risk of recurrence is similar to that of the other natural anticoagulant deficiencies (2.5-fold).

Three types of protein S defects have been described: type I is a quantitative deficiency, with decreased plasma levels of functional and immunoreactive total and free protein S; type II is a qualitative deficiency, with decreased cofactor activity but normal total and free protein S levels and type III is a quantitative deficiency, with reduced functional activity and free protein S antigen levels and normal total protein S levels [14]. The PROS1 gene database lists almost 200 different mutations associated with protein S deficiency, the majority being missense mutations or short deletions or insertions [24].

Factor V Leiden

In 1993, a poor anticoagulant response to APC was associated with an increased risk of VTE [25,26]. The so-called APC resistance is mainly caused by the G1691A mutation (chromosome 1q23) in the Arg506 cleavage site of FVa, described first in the city of Leiden in 1994 [27,28]. Factor V Leiden is inactivated by APC more slowly than wild-type FVa, thus promoting a hypercoagulable state and an increased susceptibility to VTE. The FV Leiden gain-of-function mutation has a dominant autosomal transmission and is the most common prothrombotic gene mutation in the Caucasian population, with a prevalence of about 3%, ranging from 2 to 10% with a gradient from Southern to Northern Europe [29]. This prevalence rises to 20–50% in patients presenting with a first episode of VTE. VTE risk is increased approximately sevenfold in heterozygous, while homozygotes exhibit a very high risk for VTE, up to 80-times the normal risk [30,31].

Prothrombin G20210A

This polymorphism was first described in 1996 by Poort et al. [32], who showed that a G to A transition at nucleotide 20210 of the prothrombin gene within the 3´ untranslated region caused increased basal levels of functionally normal prothrombin, thereby conferring to heterozygotes an increased risk (~three- to fourfold) of developing VTE. Thus, these individuals exhibit a relatively low thrombotic risk, and most of them will not develop a thrombotic episode by age 50 years. In contrast, homozygosity for prothrombin gene mutation is much rarer and causes a higher thrombotic risk. The risk of VTE recurrence is similar to that of FV Leiden (1.4-fold). Like FV Leiden, the prothrombin G20210A mutation has a dominant autosomal transmission and is the second most common coagulation abnormality, with a prevalence of heterozygotes in populations of Caucasian descent ranging from 1 to 4%, with a gradient from Northern to Southern Europe. Prothrombin G20210A is found in 5–10% of VTE patients [33].

Antiphospholipid antibodies

Antiphospholipid antibodies are one of the most important acquired risk factors for thrombosis [34,35]. The corresponding syndrome is characterized by the presence of circulating antiphospholipid antibodies in plasma and either arterial and/or venous thrombosis, or pregnancy complications, particularly fetal loss [36]. The clinically relevant antiphospholipid antibodies include lupus anticoagulant, anticardiolipin and anti-β2-glycoprotein I antibodies. These autoantibodies are directed against a wide variety of protein co-factors localized upon phospholipid membrane surfaces (β2-glycoprotein I, prothrombin, protein C, protein S, annexin V, coagulation factor XII, etc.). The resulting complexes interact with several cell types, including endothelial cells, monocytes and platelets, all of which play important roles in hemostasis and thrombogenesis [37]. The relative risk of thrombosis varies depending on the type of antibody and is higher in the presence of lupus anticoagulant with or without anticardiolipin antibodies (odds ratio [OR]: 11.0; 95% CI: 3.81–32.3) and lower if only anticardiolipin antibodies are present at a clinically significant titer (>40 IU) (OR: 3.21; 95% CI: 1.11–9.28), or at a low titer <40 IU (OR: 1.56;
Antiphospholipid antibodies can be idiopathic, drug-related or associated with autoimmune (e.g., systemic lupus erythematosus or rheumatoid arthritis), lymphoproliferative or inflammatory diseases. Incidental detection of antiphospholipid antibodies is not uncommon. In the case-control Leiden thrombophilia study, lupus anticoagulant was present in 0.9% of unaffected controls (and in 3.1% of the VTE cases) and β2-glycoprotein I antibodies in 3.4% of controls (and in 7.5% of the patients). However, incidental antiphospholipid antibodies are associated with a low risk of thrombosis: in a large study including 178 asymptomatic carriers of antiphospholipid antibodies followed up for 26 months, no episode of thrombosis was detected.

Hyperhomocysteinemia
The amino acid homocysteine is formed from the demethylation of dietary methionine and its plasma levels are controlled by two metabolic pathways. The first involves the enzyme cystathionine β-synthase and requires vitamin B6, the second involves the enzyme methionine synthase and requires both vitamin B12 and N5-methyltetrahydrofolate reductase. Both genetic (e.g., mutations in N5-methyltetrahydrofolate reductase and cystathionine β-synthase genes) and acquired factors (e.g., deficiencies of folate, vitamin B12 or vitamin B6, advanced age, chronic renal failure and the use of antifolic drugs) interact to determine plasma homocysteine concentrations. As a consequence, hyperhomocysteinemia is considered a mixed factor (i.e., genetic and/or acquired) for thrombosis. Moderately increased plasma levels of homocysteine have been associated with a modest (1.5-times) increased thrombotic risk and approximately 5% of the general population has higher than normal levels of homocysteine, while the prevalence among VTE patients is about 10–15%.

High levels of coagulation factors
An association between elevated levels of factor VIII, but also of factors IX, XI and fibrinogen, and an increased risk of VTE has been demonstrated in several studies. The plasma levels of these factors are not only influenced by age and inflammation, but are also under genetic control. However, although a heritable component has been described for these clotting factors, to date no gene variations have been discovered accounting for such elevated levels. Hence most laboratories include only factor VIII plasma levels in the thrombophilia test panel.

Inherited thrombophilia & thrombotic risk
A number of family studies have been conducted to investigate the risk and incidence of VTE in carriers of thrombophilia versus non-carriers. These studies consistently indicate that a thrombotic risk gradient does exist, being higher in individuals with antithrombin, protein C, protein S deficiencies, homozygous FV Leiden and prothrombin G20210A or multiple abnormalities of the latter (severe thrombophilia) than in heterozygotes for FV Leiden or prothrombin G20210A (mild thrombophilia). Thus, carriers of antithrombin, protein C or protein S deficiencies have a 4- to 30-fold increased risk of VTE compared with non-carriers, being the highest incidence of VTE (0.9–4.0 per 100 person-years) observed in carriers of antithrombin deficiency. Conversely, carriers of mild thrombophilic traits have a two- to sevenfold increased risk of VTE, with a much lower incidence of events than those with severe thrombophilia (0.14–0.67 per 100 person-years for FV Leiden; 0.05–0.42 per 100 person-years for prothrombin G20210A). Even low borderline plasma levels of antithrombin, protein C and protein S are associated with a twofold increased risk of VTE, to the same degree as that of mild thrombophilia. The degree of severity of the thrombophilic defect has been found to influence the age of occurrence of the first thrombotic episode. Indeed, in a large family cohort, relatives of probands with thrombosis and a thrombophilic defect, who themselves had an antithrombin, protein C, or protein S deficiency, had VTE at a younger age (median 29 years) than those with FV Leiden, prothrombin G20210A or elevated FVIII levels (median 40 years). The definition of different classes of thrombotic risk for thrombophilic defects is also of great clinical relevance, as indefinite duration of anticoagulation is actually recommended after an unprovoked VTE event in carriers of severe thrombophilia. A particular mention deserves the occurrence of VTE in pediatric population, whose incidence is increasing due to the improved survival of children with previously fatal disease and advances in pediatric care. VTE in children is rare, being in the great majority of cases associated with primary underlying diseases, such as cancers, sepsis, congenital cardiovascular disorders or with therapeutic interventions, such as central venous line placement. In this context, inherited thrombophilia has been described as an additional risk factor rather than a primary triggering factor, although a recent cohort study found that 9 of 21 (42.8%) antithrombin-deficient pediatric patients developed VTE spontaneously. A meta-analysis of observational studies published from 1970 to 2007 on the impact of thrombophilia traits on VTE development or recurrence in children reported that all the investigated traits showed a significant association with first-ever VTE with ORs ranging from 2.63 (95% CI: 1.61–4.29) for the prothrombin mutation to 9.44 (95% CI: 3.34–26.66) for antithrombin deficiency. A similar association between inherited thrombophilia and cerebrovascular occlusion (cerebral venous thrombosis and stroke) was found in another systematic review and meta-analysis. Only few published data are available on the risk of recurrence of VTE in pediatric patients, suggesting a recurrence rate between 3% in neonates and 21% in children with idiopathic VTE. However, it remains a controversial issue whether or not children from thrombophilia families should be screened for inherited thrombophilia.

Thrombophilia testing in high-risk situations
Clinical and epidemiological studies on the prevalence of the aforementioned thrombophilic traits, as well as on their...
The real value of thrombophilia markers in identifying patients at high risk of VTE

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Several prospective studies have investigated the risk of VTE recurrence in carriers of either mutations, with conflicting results [60–63]. The risk of recurrence among heterozygotes for FV Leiden or prothrombin G20210A has been recently revised by at least three meta-analyses [64–66], and it was found to be 1.4- to 1.6-fold higher in patients with FV Leiden and 1.3- to 1.4-fold higher in those with the prothrombin mutation. Data on natural anticoagulant deficiencies are less extensive, because only a few studies with a limited number of patients assessed the risk of recurrence. However, in probands and their deficient relatives belonging to the EPCOT prospective cohort, the incidence of recurrent VTE was 10.5% per patient-year in patients with antithrombin deficiency and 3.5% per patient-year in carriers of FV Leiden [67]. In a retrospective investigation on probands with a deficiency of natural anticoagulants and their deficient relatives, the incidence of recurrent VTE was confirmed to be high, being 7.7% per patient-year (10% for antithrombin deficiency, 6% for protein C deficiency and 8.4% for protein S deficiency) [68].

Another important issue regards the screening of asymptomatic relatives of patients with inherited thrombophilia. The rationale for this approach consists in the possibility of identifying those individuals carrying of a thrombophilic trait who may benefit from targeted thromboprophylaxis in high-risk situations (pregnancy, puerperium, surgery, immobilization and trauma). A number of prospective and retrospective studies have specifically investigated the VTE risk among relatives of individuals with inherited thrombophilia [69,70]. Collectively, these studies reported that the VTE incidence among relatives was higher in carriers of an antithrombin, protein C or protein S defect (with a range of 0.36–4.0% per individual-year) than in carriers of FV Leiden (0.19–0.58% per individual-year) and prothrombin G20210A (0.11–0.37% per individual-year) [69].

Considering these data globally, while a screening in asymptomatic relatives of patients with severe thrombophilia is warranted, more uncertainty exists regarding the usefulness of a familial screening among the relatives of probands with mild thrombophilia. However, as the risk of VTE has been consistently reported to be higher in asymptomatic carriers of mild thrombophilia who have a family history of VTE than in those with no family history [69–72], this approach to testing seems to be reasonable.

As regards the gender-related risk factors for VTE, a universal screening for thrombophilia before exposure to environmental risk circumstances such as oral contraceptives or pregnancy, has been demonstrated not to be cost-effective, but it should be considered in well-selected cases [73–75]. For instance, the use of third-generation combined oral contraceptives is associated with a twofold increased risk of VTE [76] and a supra-additive effect is observed (up to fivefold) when an inherited thrombophilic risk factor is also present [77]. However, because the expected absolute incidence of VTE among unselected carriers is relatively low, not exceeding 6.2 events per 1000 women-years, screening has a limited value in women with no personal

Box 1. Authors’ suggested indications for thrombophilia testing.

**Clinical condition**
- Idiopathic thrombosis and/or age <50 years at the time of first venous thrombosis
- Unusual sites of venous thrombosis (hepatic, mesenteric, splenic, portal, cerebral)
- History of recurrent venous thrombosis
- Asymptomatic relatives of patients with severe thrombophilia
- Venous thrombosis during pregnancy or in women taking oral contraceptives or under hormone replacement therapy

Whether or not the presence of a thrombophilic abnormality is able to predict VTE recurrence is still a matter of debate [60]. The estimated risk of recurrence for VTE is approximately 5% per year, although idiopathic cases tend to recur more frequently (~20% in the first 2 years) than unprovoked cases [57]. Several prospective studies have investigated the risk of VTE recurrence in carriers of either mutations, with conflicting results [60–63]. The risk of recurrence among heterozygotes for FV Leiden or prothrombin G20210A has been recently revised by at least three meta-analyses [64–66], and it was found to be 1.4- to 1.6-fold higher in patients with FV Leiden and 1.3- to 1.4-fold higher in those with the prothrombin mutation. Data on natural anticoagulant deficiencies are less extensive, because only a few studies with a limited number of patients assessed the risk of recurrence. However, in probands and their deficient relatives belonging to the EPCOT prospective cohort, the incidence of recurrent VTE was 10.5% per patient-year in patients
or family history of VTE [73]. By contrast, testing for inherited thrombophilia before the prescription of oral contraceptives might be beneficial for women who are relatives of symptomatic carriers of severe thrombophilia, because in this category the absolute incidence of VTE is much higher (4–10 events per 100 women-years for antithrombin, protein C and protein S deficiencies) [78]. However, it should be outlined that in these families, women without such deficiencies also have a markedly increased risk of oral contraceptive-related VTE compared with the general population (0.7 vs 0.04% per year of use) [79]. This phenomenon, which identifies families with a strong thrombotic tendency probably due to co-segregation of still unknown thrombophilia defects, should be carefully taken into account when oral contraceptives are prescribed.

The absolute incidence of VTE among post-menopausal women on hormone replacement therapy is higher than among oral contraceptive users, due to their older age. Accordingly, unrestricted or family-driven screening before prescribing hormone replacement therapy has been proposed by a number of investigators, because this therapeutic procedure is associated in thrombophilic carriers with a relatively high VTE risk [73]. Finally, pregnant women with asymptomatic inherited thrombophilia are considered at high VTE risk, and thus eligible for prophylaxis with low molecular weight heparin during antenatal and the 6-week puerperium periods, but only if they have a family history of VTE, severe thrombophilia or a mild thrombophilia with additional risk factors (family history of VTE, immobility, obesity, age >35 years, gross varicose veins) [80,81].

Expert commentary & five-year view

During the past 30–40 years, our knowledge on the genetic abnormalities predisposing to VTE has dramatically increased. Thus, from the analysis of the available data it appears that the thrombotic risk is higher in carriers of natural anticoagulant deficiencies and in the presence of homozygous defects or multiple abnormalities (severe thrombophilia) than in heterozygotes for FV Leiden and prothrombin G20210A (mild thrombophilia). This thrombotic risk gradient should be evaluated in the framework of other (genetic and/or acquired) coexisting risk factors for first or recurrent VTE when assessing the need and duration of primary or secondary antithrombotic prophylaxis. Future research should be focused on the identification of novel thrombophilic factors in order to explain (and prevent) more cases of unprovoked thrombosis, and to clarify the molecular mechanisms underlying the complex interaction between genetic and environmental risk factors for thrombosis.

Perhaps methods such as next-generation sequencing may help to detect new very rare traits associated with a high risk of VTE.

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Key issues

- Thrombophilia is defined a hypercoagulable state leading to a thrombotic tendency.
- Thrombophilic abnormalities can be inherited, acquired or mixed (both congenital and acquired).
- Thrombophilic abnormalities cause blood hypercoagulability through the impairment of the anticoagulant or the potentiation of procoagulant pathways.
- During the past 30–40 years, our knowledge on genetic abnormalities causing thrombophilia has greatly expanded.
- Both inherited and acquired risk factors should be taken into account when assessing the individual risk of thrombosis.
- Universal screening for inherited thrombophilia is unjustified.
- Screening asymptomatic relatives of carriers of severe thrombophilia is recommended.

References

Papers of special note have been highlighted as:

- of considerable interest
- ** A recent extensive review of the literature on genetic risk factors for venous thromboembolism.


[Reviewer's note: Image 489x15 to 599x29]
absolute thrombotic risk for currently known thrombophilic defects in 2479 relatives. Blood 2009;113(21):5314-22


**An extensive review of the literature describing the various risk factors for venous thromboembolism recurrence.**


78. Mahmoodi BK, Brouwer JL, Ten Kate MK, et al. A prospective cohort study on the absolute risks of venous thromboembolism and predictive value of screening...

