Inherited thrombophilia: a double-edged sword

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Inherited thrombophilia is a blood coagulation disorder that increases the risk for venous thromboembolism (VTE). During the last decades, the practice of testing has evolved from testing selected populations, leading to high perceived risks, to broad testing for various conditions that included VTE, arterial thrombosis, and pregnancy complications. Because results of such tests usually do not guide treatment decisions, not testing patients with VTE for inherited thrombophilia is on the "Choosing Wisely" list endorsed by multiple specialty societies, including ASH. Inherited thrombophilia can be regarded a double-edged sword, as despite the rationale not to test, it is still being performed frequently. Another way of seeing inherited thrombophilia as a double-edged sword lies in its 2-sided association with reproduction, both in men and in women. Current areas of research are whether women with inherited thrombophilia and pregnancy complications benefit from anticoagulant therapy with regard to improving the chance of a successful pregnancy. Potential effects of inherited thrombophilia, most notably factor V Leiden, on improved embryo implantation in women and sperm counts in men are intriguing, but are currently poorly understood.

Learning Objectives

Upon completion of this activity, participants will be able to:

- Describe the evolution of research into inherited thrombophilia during the last decades
- Know the absolute risk for VTE associated with inherited thrombophilia
- Know the association of inherited thrombophilia with non-VTE clinical manifestations, including reproduction, in men and women
- Understand the Choose Wisely recommendation not to test patients for inherited thrombophilia, and justify rational exceptions to this rule

Introduction

For the Ham-Wasserman lecture, I have been given the privilege of providing my perspective on inherited thrombophilia and the clinical role of testing for these conditions. In 1994, when I was a second-year resident in internal medicine, the most prevalent inherited thrombophilia, now called factor V Leiden, was reported by 4 groups independent of each other over a time frame of about 6 weeks.[1-4] A year earlier, Dahlbäck had described the phenomenon of activated protein C (APC) resistance in a Swedish family with a high tendency toward VTE that followed a Mendelian inheritance pattern.[5] He found that the poor anticoagulant response to APC in affected relatives was best explained by an inherited deficiency of what was until then an "unrecognized cofactor to APC." After having ruled out several possible mechanisms, including deficiencies of protein S, protein C, or linkage with polymorphisms in the factor VIII or Von Willebrand factor genes, Dahlbäck showed that this alleged "cofactor" was identical to coagulation factor V.[6] The underlying genetic defect turned out to be a single G to A substitution in the gene of factor V at nucleotide position 1691, resulting in an amino acid change at position 506, the first cleavage site of factor Va for APC (FV Q506, or FV Leiden).[1-4] It was in these exciting times that I was looking for a clinical research project that would meet a requirement (ie, writing 1 peer-reviewed research paper) for my training as an internist. The fact that this factor V mutation was present in about 20% of patients with VTE[1] compared with the combined total of 8% of the then-known deficiencies of the natural anticoagulants antithrombin, protein C, and protein S[7] raised frequently occurring clinical questions about the relevance for patients with VTE , as well as for their relatives, and these questions formed the basis of my first research project.

Here I share my perspective of how the field of inherited thrombophilia evolved from excitement to potential diagnostic and therapeutic nihilism. I also discuss some intriguing aspects of inherited thrombophilia that could be regarded as double edges of a sword.

Thrombophilia: from description to diagnosis

The familial tendency of thromboembolic disease has been recognized for many decades and was extensively reviewed by Jordan and Nandorff in 1956.[8] Even earlier, in 1937, the term "thrombophilia" was first used by Nygaard and Brown, when they described sudden occlusion of large arteries, sometimes with coexistent VTE.[9] Research into causes of thrombophilia started by investigating families with a strong tendency to VTE. In this way, in 1965, Egeberg showed that deficiency of antithrombin caused VTE at a young age (ie, thrombophilia) in several members of a Norwegian family.[10] In the early 1980s, deficiencies of the other anticoagulant proteins, protein C and protein S, were discovered as hereditary risk factors for VTE.[11,12] Numerous mutations in the genes encoding antithrombin, protein C, and protein S have been identified as underlying

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Table 1. Prevalence of inherited thrombophilia and relative risk estimates for various clinical manifestations

	Antithrombin deficiency	Protein C deficiency	Protein S deficiency	Factor V Leiden	Prothrombin 20210A mutation
Prevalence in the general population*	0.02%	0.2%	0.03%-0.13%	3%-7%	0.7%-4%
Prevalence in consecutive patients with VTE*	1%	3%	2%	20%	5%
Relative risk for a first VTE†	5-10	4-6.5	1-10	3-5	2-3
Relative risk for recurrent VTE	1.9-2.6	1.4-1.8	1.0-1.4	1.4	1.4
Relative risk for arterial thrombosis	No association	No consistent association	No consistent association	1.3	0.9
Relative risk for pregnancy complications	1.3-3.6	1.3-3.6	1.3-3.6	1.0-2.6	0.9-1.3

Figures are derived from studies that are reviewed in detail elsewhere.[60]
*Population prevalences vary with geographic regions.
†Relative risks were derived, where possible, from family studies comparing the risk for a first VTE in thrombophilic relatives vs in nonthrombophilic relatives. Hence, the relative risk is not consistent with the ratio between the prevalence in consecutive VTE patients and in the general population.

causes.[13-15] Soon after the elucidation of APC resistance caused by factor V Leiden, genetic analysis of candidate factor prothrombin revealed a G to A transition at position 20210 that was linked to VTE, as well as to elevated levels of prothrombin.[16] Since then, additional common genetic variants that increase the risk for VTE to a minor extent have been identified.[17] Elevated levels of several coagulation factors including factors VIII, IX, and XI, as well as increased levels of thrombin activatable fibrinolysis inhibitor, also increase the risk for VTE.[18-21] Although the levels of coagulation factors are in part determined genetically, factor VIII also increases with age and during various inflammatory diseases, including VTE.

Thrombophilia: from etiology to clinical application

Thus, in the 1990s, inherited thrombophilia evolved from a very rare genetic disorder to a highly prevalent trait (Table 1, Figure 1). The association between thrombophilia and VTE was confirmed in case–control studies, which yielded relative risk increases compared with individuals from the general population who did not have thrombophilia. These high relative risk estimates raised a lot of attention. The effect of factor V Leiden was shown to be strongly enhanced by use of oral contraceptives (relative risk, 35 vs noncarriers not using oral contraceptives),[22] homozygosity of factor V Leiden (80-fold increased risk),[23] or carriership of multiple defects.[24,25]

In addition, the association of inherited thrombophilia with other clinical manifestations, as were known to occur in the acquired antiphospholipid syndrome (ie, arterial thrombosis and pregnancy complications), was heavily investigated (Table 1).[26,27]

The observed associations led to widespread testing of thrombophilia for various indications, but left the clinician with many unanswered questions regarding the clinical implications for thrombophilic individuals.[28]

The risk for VTE in individuals with thrombophilia

Despite the excitement of identifying new thrombophilic defects with a strong relative risk increase, absolute risk estimates in relevant populations were needed to guide decisions regarding prevention or treatment. My first research project was a family study in which we aimed to obtain absolute risk estimates for VTE in family members of consecutive probands who had had a VTE and carried factor V Leiden. We identified 437 first-degree relatives of 112 heterozygous probands and 30 relatives of 6 homozygous probands.[29] Before DNA testing, information on previous VTE and concomitant risk factors was obtained. The annual incidence of VTE in relatives of heterozygous probands was 0.45% in those with factor V Leiden compared with 0.10% in those without the mutation (relative risk, 4.2; 95% confidence interval [CI], 1.8-9.9). Among carriers, the incidence increased from 0.25% in the 15- to 30-year-old age group to 1.1% in individuals older

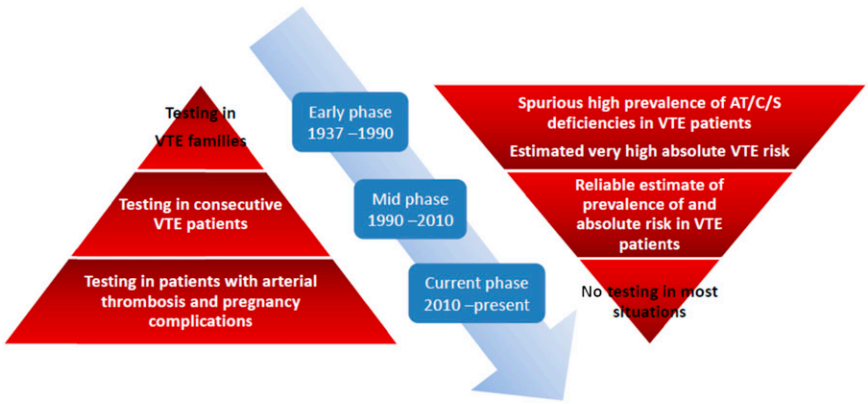

Figure 1. Evolution of inherited thrombophilia testing over time. The left pyramid indicates the evolution from testing in rare populations to testing in consecutive patients and for broader indications. The right inverted pyramid shows how the perceived prevalence and benefits of inherited thrombophilia and its associated risk evolved from very high to low, discouraging testing in most situations.

Table 2. Estimated incidence of a first episode of VTE in carriers of various thrombophilias (data apply to individuals with at least 1 symptomatic first-degree relative)

	Antithrombin, protein C, or protein S deficiency	Factor V Leiden, heterozygous	Prothrombin 20210A mutation	Factor V Leiden, homozygous
Overall, %/y (95% CI)	1.5 (0.7-2.8)	0.5 (0.1-1.3)	0.4 (0.1-1.1)	1.8 (0.1-4.0)*
Surgery, trauma, or immobilization, %/episode (95% CI)†	8.1 (4.5-13.2)	1.8 (0.7-4.0)	1.6 (0.5-3.8)	—
Pregnancy, %/pregnancy (95% CI)	4.1 (1.7-8.3)	2.1 (0.7-4.9)	2.3 (0.8-5.3)	16.3‡
During pregnancy, % (95% CI)	1.2 (0.3-4.2)	0.4 (0.1-2.4)	0.5 (0.1-2.6)	7.0‡
Postpartum period, % (95% CI)	3.0 (1.3-6.7)	1.7 (0.7-4.3)	1.9 (0.7-4.7)	9.3‡
Oral contraceptive use, %/y of use (95% CI)	4.3 (1.4-9.7)	0.5 (0.1-1.4)	0.2 (0.0-0.9)	—

Figures are derived from numerous family studies, reviewed in detail elsewhere.[60]

*Based on pooled OR of 18 (95% CI, 8-40) and an incidence of 0.1% in noncarriers.

†These risk estimates of symptomatic VTE for a large part reflect the situation before thrombosis prophylaxis was routine patient care.

‡Data from family studies, risk estimates lower in other settings.

than 60 years. Half of the episodes of VTE occurred spontaneously, 20% were related to surgery, and 30% were associated with pregnancy or use of oral contraceptives. For female factor V Leiden carriers in these families, the risk associated with oral contraceptives was 0.5% per year of use, and we also observed that the risk associated with pregnancy was 2%. On the basis of these results, we concluded that the observed low annual risk for VTE in persons carrying the factor V Leiden mutation did not seem to outweigh the risks for bleeding associated with vitamin K antagonist prophylaxis, or to justify discouragement of the use of oral contraceptives. Hence, a general policy of screening families of all patients with the factor V Leiden mutation did not seem to be indicated. The results were confirmed by retrospective and prospective studies that were performed in the Netherlands, Italy, France, and Canada.[30-33] We repeated the studies in carriers of the prothrombin 20210A mutation, and similar risk estimates were observed.[34,35]

Since the mid-1990s, studies with a similar design had been initiated in families of consecutive probands with antithrombin, protein C, or protein S deficiency.[30,36] As expected, the absolute risk for VTE, both unprovoked as well as provoked by high-risk situations, including use of oral contraceptives and pregnancy, were higher than in factor V Leiden carriers (Table 2). It also became apparent that absolute risks were somewhat higher than when deriving estimates from multiplying odds ratios from population-based case control studies that used age-specific baseline risks for VTE. In contrast, the observed risks in families with antithrombin, protein C, or protein S deficiency were markedly lower than in historical studies. A likely explanation is that in the early days of thrombophilia research, when the yield of finding a positive test result was very low,[7] only families with a strong tendency for VTE were tested (Figure 1). These families likely had cosegregated known and unknown genes, yielding a biased risk estimate.[24,25] How the setting in which testing is being performed is important is illustrated by estimates of absolute VTE risk in pregnant and postpartum women who are homozygous for factor V Leiden, in which the risk ranges from 0% (95% CI, 0%-19%) in carriers selected from the general population to 16.7% (95% CI, 5%-37%) in carriers selected from first-degree relatives of patients with VTE.[37]

Inherited thrombophilia and pregnancy complications

In 1995, my fellow junior researchers in the department noted a high number of miscarriages and stillbirth in women who participated in their family study that was set up to estimate the absolute risk for VTE in families with antithrombin, protein C, or protein S deficiency. Indeed, they found the risk in deficient women to be increased 2-fold compared with in nondeficient relatives[38] In our factor V Leiden family study,[39] but not in our prothrombin 20210A study,[34] we observed a similar phenomenon. Numerous studies since then have investigated the association between inherited thrombophilia and various pregnancy complications, ranging from a single miscarriage to intrauterine fetal death, preeclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelets), and placental abruption.[27,40] Testing women with pregnancy complications soon became common clinical practice, but no evidence-based answer on subsequent therapeutic consequences was available. This frequent clinical question fueled my interest not only in the associations and absolute risks but also in testing the frequently discussed hypothesis that anticoagulation with low-molecular-weight heparin (LMWH) might improve pregnancy outcome in women with and without inherited thrombophilia and otherwise unexplained recurrent miscarriage. This was my first personal experience with successfully setting up and leading a multicenter, investigator-initiated randomized clinical trial, which was called ALIFE.[41] Even though the trial recruitment and conduct was challenging, and the result was negative, I regard its completion, publication, and effect on clinical practice as a highlight of my career. After about 15 years of various clinical trials performed by colleagues around the world, we now know that LMWH does not improve the chance of live birth in women with unexplained recurrent miscarriage.[42-45] However, we are still uncertain whether this is also the case for women with inherited thrombophilia.[46,47] In the ALIFE study, the subgroup of women with inherited thrombophilia (n = 47) showed a trend toward a benefit of LMWH and aspirin (relative risk for live birth, 1.31 [95% CI, 0.74-2.33] for the LMWH and aspirin vs placebo; relative risk for live birth, 1.22 [95% CI, 0.69-2.16] for aspirin, with corresponding absolute difference in live birth rates of 16.3% [95% CI, −18.2% to 50.8%] and 11.8% [95% CI, −21.1% to 44.6%], respectively).[41] On the basis of these results, we initiated the ALIFE2 trial, which has been recruiting patients since 2013 in the Netherlands, United Kingdom, and Belgium, and hopefully soon in the United States and Slovenia.[48]

For other placenta-mediated pregnancy complications, the results of the AFFIRM individual patient data meta-analysis included 963 women who had participated in 8 randomized, controlled trials, including the TIPPS trial that was dedicated entirely to women with thrombophilia.[49-51] LMWH did not significantly reduce the risk of recurrent placenta-mediated pregnancy complications (14% vs 22%; relative risk, 0.64; 95% CI 0.36-1.11). There was significant heterogeneity between single-center and multicenter trials. In subgroup analyses, LMWH significantly reduced the primary outcome in

Table 3. The double-edged sword of thrombophilia: evolutionary disadvantages and advantages of factor V Leiden

	Estimated incidence*	Probable trend in incidence since premodern times	Relevant to chances of offspring†
Hemostasis			
Disadvantages			
Venous thromboembolism	Common	Increased	Yes
Acute myocardial infarction	Common	Increased	Yes
Ischemic colitis	Uncommon	Increased	No
Ischemic stroke in children	Rare	—	Yes
Legg-Calvé-Perthes disease	Rare	—	Yes
Advantages			
Excessive intrapartum blood loss	Common	Decreased	Yes
Lower menstrual blood loss	Common	Decreased	Yes
Reduced blood loss	Common	Decreased	Yes
Spontaneous intracranial hemorrhage	Uncommon	Increased	No
Hemorrhagic disease of the newborn	Uncommon	Decreased	Yes
Milder hemophilia phenotype	Rare	Stable	Yes
Inflammation			
Disadvantages			
Procoagulant state in sepsis	Common	Decreased	Yes
Mortality severe sepsis	Common	Decreased	Yes
Purpura fulminans	Rare	Decreased	Yes
Advantages			
Survival severe sepsis	Common	Decreased	Yes
Susceptibility severe sepsis	Common	Decreased	Yes
ARDS mortality	Uncommon	Decreased	Yes
Protection from diabetic nephropathy	Common	Increased	Yes
Fertility			
Disadvantages			
Placental abruption	Common	–	Yes
Pre-eclampsia	Common	–	Yes
Intra-uterine growth restriction	Common	–	Yes
Early pregnancy loss (<24 wk)	Common	–	Yes
Late pregnancy loss (≥24 wk)	Common	–	Yes
Advantages			
Fecundity females	–	–	Yes
In vitro fertilization success	–	–	Yes
Fecundity males	–	–	Yes
Sperm count	–	–	Yes

Table adapted from a previous review.[54]

*Common: More than 5/10 000 cases per year in general population. Uncommon: 0.1 to 5 per 10 000. Rare: <0.1 per 10 000.

†When present, does the disease or phenotype influence the chances of having fertile offspring, by affecting either the mortality at or before the fertile age, or the chances of successful mating?

women with previous abruption but not in any of the other subgroups of previous complications. It should be noted that over time, the associations of inherited thrombophilia and pregnancy complications became less strong, or were even absent, when higher-quality prospective studies were assessed.[52]

Inherited thrombophilia: is there a double edge to the sword?

As factor V Leiden causes VTE and pregnancy complications that would be detrimental to survival and reproduction, many speculations arose about potential survival and reproduction benefits of the mutation (Table 3). For example, factor V Leiden might be associated with less menstrual blood loss, decreased risk for intracranial hemorrhage, lower susceptibility to severe sepsis, and higher survival during sepsis and famine.[53,54] Furthermore, intriguingly, factor V Leiden may lead to improved fertility, which could counteract the negative effects of the mutation in pregnancy. Fecundity (ie, reproductive rate) was investigated in an epidemiological study among male and female factor V Leiden carriers older than 85 years, who were in their fertile years before contraceptive methods were in use.[55] The time between a person's

marriage and the birth of the first child was used as a proxy for fecundity. Male factor V Leiden carriers were 3.5 times more likely to have a firstborn within 1 year of marriage than were noncarriers. These findings inspired us to investigate male fertility by means of sperm counts in a pilot study among 19 male carriers identified in our previous family study.[56] Next, we identified 37 factor V Leiden carriers and 921 noncarriers in a prospective cohort study of male partners of subfertile couples in whom an established diagnosis of abnormal spermatogenic function was ruled out.[56] The total sperm count appeared higher in factor V Leiden carriers than in noncarriers, but the difference was not statistically significant. Although the results drew some attention on conference presentations, it took a long time before the manuscript was accepted in a peer-reviewed journal, which may have been because of an absence of a biological explanation. Recently, we were able to extend our cohort, and the results are in line with our previous findings.[57] Interestingly, no such effect was found for the prothrombin 20210A mutation. Hence, a coagulation-related mechanism is not directly apparent, and a plausible alternative explanation could be genetic linkage of factor V Leiden with a nearby locus that affects spermatogenesis. Work is in progress to elucidate the biological basis for this association.

In women, a negative effect on fecundity would have been expected as a result of the increased risk for pregnancy loss associated with factor V Leiden. Because no effect on fecundity was observed among female carriers in the previously mentioned study,[55] this led us to hypothesize that female carriers would become pregnant more quickly, with neutral fecundity being the result of such a counterbalance. Indeed, in the ALIFE trial, women who were not pregnant at time of randomization were included in an analysis of time to conceive.[58] The median time to pregnancy for factor V Leiden carriers was shorter, at 11 weeks vs 23 weeks for noncarriers. This difference remained statistically significant after correction for potential confounders. Interestingly, success rates of in vitro fertilization may be beneficially influenced by the presence of factor V Leiden.[59] Whether similar effects are also present in the rarer inherited thrombophilias is not known. The deficiencies of the natural anticoagulants are caused by numerous different mutations. The rarity of the deficiencies also limit the power to investigate effects such as those described for factor V Leiden.

Thrombophilia testing: where are we in clinical practice?

The currently most commonly tested inherited thrombophilias include levels of antithrombin, protein C, or protein S to identify a deficiency, as well as factor V Leiden and prothrombin G20210A.[28,60] It is noteworthy that some laboratories also include other, less well established polymorphisms in their thrombophilia panel, such as MTHFR 677TT and PAI-1 4G/5G, which have a weak association with VTE at most.[61] I have reviewed the clinical implications of testing for thrombophilia in greater detail previously,[62,63] and will summarize the main considerations in the following paragraphs.

Testing for thrombophilia to modify the risk for recurrent VTE

Thrombophilia testing is most often considered in patients with VTE, particularly if they are young, have recurrent episodes, have thrombosis at unusual sites, or have a positive family history for the disease. Although such a strategy will lead to an increased yield of testing, a positive test result does not alter management, as inherited thrombophilia only modestly increases the risk for recurrent episodes (Table 1).[64,65] Some debate is ongoing about whether this is also the case for the more severe inherited thrombophilias. In a large pooled study of thrombophilic families, we observed a cumulative incidence of VTE recurrences after 10 years of 55% in relatives with a deficiency of antithrombin, protein C, or protein S deficiency, compared with 25% in those with the factor V Leiden mutation, the prothrombin 20210A mutation, or high levels of factor VIII.[66] For homozygous or double heterozygous carriers of factor V Leiden and/or the prothrombin 20210A mutation, the estimated risks for recurrence vary between studies, with a pooled estimate of a 2.7-fold increased risk (95% CI, 1.2-6.0).[65,67] Even if one considers this risk increase high enough to modify treatment, given the rarity of homozygous or double heterozygous thrombophilias in unselected patients with VTE, a very large number of patients need to be tested to identify such a rare thrombophilic defect.[68] A randomized controlled trial in which testing for thrombophilia in patients with a first episode of VTE is the intervention, and recurrent VTE is the outcome, would provide the ultimate high-level evidence to decide whether testing is justified. Testing should lead to a predefined strategy to prevent recurrence, with, for instance, indefinite duration of anticoagulant therapy. Such a trial was my first experience with setting up a randomized trial, which unfortunately did not succeed and had to be discontinued because of slow recruitment and lack of funding.[69,70] To investigate whether testing, with real-life clinical decisions based on the outcome of testing, reduces the risk for recurrence, we analyzed the practice of thrombophilia testing in patients with a first episode of VTE who had been included in the MEGA study.[71] Thrombophilia tests had been performed at the time of first VTE in 35% of patients who had recurrent VTE during follow-up compared with 30% of patients who did not experience recurrent VTE (odds ratio, 1.2; 95% CI, 0.9-1.8). This indicates that testing at time of a first VTE did not reduce the risk for recurrent VTE.

At this time, not testing patients with VTE for thrombophilia is on the Choosing Wisely list endorsed by many specialty societies, including ASH. ASH actually further pins this down to "adult patients with VTE provoked by major transient risk factors," and further states that "when VTE occurs in the setting of pregnancy or hormonal therapy, or when there is a strong family history plus a major transient risk factor, the role of thrombophilia testing is complex and patients and clinicians are advised to seek guidance from an expert in VTE." This year, a useful guidance statement from the Anticoagulation Forum on evaluation and treatment of thrombophilia has been issued.[72] It is recommended that thrombophilia testing not be performed in most situations. When performed, it should be used in a highly selective manner, and only in circumstances in which the information obtained will influence a decision important to the patient and outweigh the potential risks of testing. As all patients with an episode of unprovoked VTE should be considered for indefinite treatment with anticoagulants, unless they have a high bleeding risk,[73] thrombophilia testing is not indicated in this situation either.[72] Patients with a transient clinical risk factor have a low risk for recurrence and should be treated for 3 months, regardless of the presence of inherited thrombophilia.[72,73]

Testing for thrombophilia to modify the risk for a first VTE

Requests for thrombophilia testing often come from asymptomatic individuals with a family history of VTE, in which the index patients may or even may not have a known specific thrombophilic defect. Having a family history of VTE is a very poor predictor of the presence of thrombophilia, but in itself is associated with a 2-fold increased risk for VTE.[7,74,75] A potential advantage of testing patients with VTE for thrombophilia may be the identification of asymptomatic family members to take preventive measures if relatives have tested positive, and to withhold such measures if relatives

Table 4. The double-edged sword of thrombophilia testing

Reasons to test for inherited thrombophilia	Reasons not to test for inherited thrombophilia
To decide on preventive measures in case of a positive test result; eg,	Decisions on preventive measures will not be modified on the basis of the test result
Not to take oral contraceptives	Patients with a negative test result are being falsely reassured
To use anticoagulant prophylaxis in high-risk situations; eg, pregnancy, after minor surgical procedures (arthroscopy)	Patients with a positive result will be harmed as a result of preventive measures taken (eg, bleeding associated with anticoagulation, unwanted pregnancies resulting from suboptimal contraceptive measures)
To have an explanation for the disease	High number to test to identify 1 individual with thrombophilia
Patient's request (eg, the patient feels thoroughly investigated, well taken care of)	Very high number to test to avoid 1 episode of VTE
The physician thinks it can show his or her expert skills	High costs
	Pitfalls in laboratory diagnosis
	Psychological and social effects; eg, issues with acquiring life insurances

have tested negative. For such clinical decisions to be rational, a test result should clearly dichotomize carriers and noncarriers in terms of their risk for a first episode of VTE. Table 2 summarizes the absolute risks for a first episode of VTE in family cohort studies. Women with antithrombin, protein C, or protein S deficiency have a high absolute risk for VTE provoked by use of oral contraceptives, but in these families, women without a deficiency also have a markedly increased risk for oral contraceptive–related VTE compared with pill users from the general population (0.7% vs 0.04% per year of use), reflecting a selection of families with a strong thrombotic tendency. The number of women with such an inherited deficiency who would need to avoid (1 year of) oral contraceptive use to avoid 1 VTE is estimated to be only 28 (hence, 56 tested), but a negative thrombophilia test in these families may lead to false reassurance.[62,63] For factor V Leiden and the prothrombin 20210A mutation, 333 carriers would need to avoid use of oral contraceptives to avoid 1 VTE, with a number needed to test of 666. Also from these families, women without the mutation have a higher incidence of pill-related VTE than women in the general population (0.2% vs 0.04% per year of use).

Considering thrombosis prophylaxis around pregnancy related to thrombophilia remains a complicated issue that is discussed extensively in the American College of Chest Physicians 2012 guideline and the recent Anticoagulation Forum guidance statement.[46,76] In short, postpartum prophylaxis should be considered in asymptomatic women with all types of inherited thrombophilia and a positive family history of VTE, based on a risk for pregnancy-related VTE of 2% to 4% (Table 2), and in all women who are homozygous for factor V Leiden or prothrombin 20210A. Although the risk for pregnancy-related VTE in women who do not have the inherited thrombophilic defect but come from families with VTE is higher than in the general population, the estimated 0.5% risk does not justify 8 months of antenatal prophylaxis. In women who are homozygous for factor V Leiden and who have a positive family history of VTE, the risk for pregnancy-related VTE of 16% is so high that antepartum prophylaxis also is recommended. For the deficiencies, most notably antithrombin deficiency, the indication for antepartum prophylaxis remains a matter of debate, and an individual decision based on the physicians' and patients' preference should be made.

Thrombophilia testing in patients with arterial cardiovascular disease

There is no evidence that the presence of inherited thrombophilia, which is at best weakly associated with arterial thrombosis (Table 1), should lead to different secondary prevention, and testing in this clinical setting is not justified.

Thrombophilia testing in women with pregnancy complications

As discussed in a previous section, therapeutic options (ie, anticoagulant treatment) to prevent pregnancy complications in women with inherited thrombophilia are currently not based on solid evidence. Hence, testing women with pregnancy complications for inherited thrombophilia can only be justified in the context of subsequent enrolment into a clinical trial, such as ALIFE2.[46,48]

Thrombophilia in clinical practice: a double-edged sword

Although the ability to diagnose inherited thrombophilia in many patients with VTE is a reflection of the increased knowledge of the etiology of VTE, the sword definitely is double-edged (Table 4). First, thrombophilia testing is costly. Some studies concluded that testing for thrombophilia in some scenarios could be cost-effective, but the results are subject to great uncertainty, as a consequence of inconsistent estimates from observational studies.[77,78] In times that necessitate efficient use of healthcare resources, diagnostic tests without clinical utility should not be performed. Second, knowing that one is a carrier of a genetic thrombophilic defect has both psychological and social effects.[79,80] Third, pitfalls in laboratory testing, the risk for both false-positive and false-negative tests, and most important, the potential false reassurance of noncarriers who have an increased VTE risk based on family history are all reasons to be restrictive in testing.

Given these limitations, why are so many thrombophilia tests still being performed? In my view, a thrombophilia work-up is often perceived as equivalent to a thorough work-up by patients. In addition, it takes more time and better communication skills to explain why not to test than to simply order the tests. For thrombosis specialists, diagnosing thrombophilia may be a raison d'être. Finally, in many healthcare systems, laboratories make money by performing the tests.

Is there a future for thrombophilia testing?

Although at present, inherited thrombophilia testing should only be performed in a highly selective manner, acquiring more insight into genetic and environmental risk factors remains important. This should ultimately lead to better prediction of risk to make evidence-based decisions for patients with all clinical indications. The progress in genetic and bioinformatics techniques may facilitate finding more inherited thrombophilic defects, both in thrombophilic families as well as in population-based case control studies.[81,82] In the future, multiple single nucleotide polymorphisms analyses of genes inside

or outside the coagulation system may improve risk prediction and become feasible in clinical practice.[83]

With the current guidelines recommending indefinite anticoagulant therapy to most patients after a first episode of unprovoked VTE,[73] being able to identify patients in whom this strategy is not justified is urgently needed. This goal has not been reached with testing for the currently known inherited thrombophilias.

Conclusions

Despite the increasing knowledge about the etiology of VTE, testing for inherited thrombophilia is most often not helpful to guide clinical decisions and should not be performed on a routine basis. Current areas of research are whether women with inherited thrombophilia and selected pregnancy complications benefit from anticoagulant therapy with regard to improving the chance of a successful pregnancy. Potential effects of inherited thrombophilia, most notably factor V Leiden, on improved embryo implantation in women and sperm counts in men are intriguing, but are currently poorly understood.

Acknowledgments

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