Thrombophilia ad dies vitae

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Chapter 2

Thrombophilia and venous thromboembolism: implications for testing

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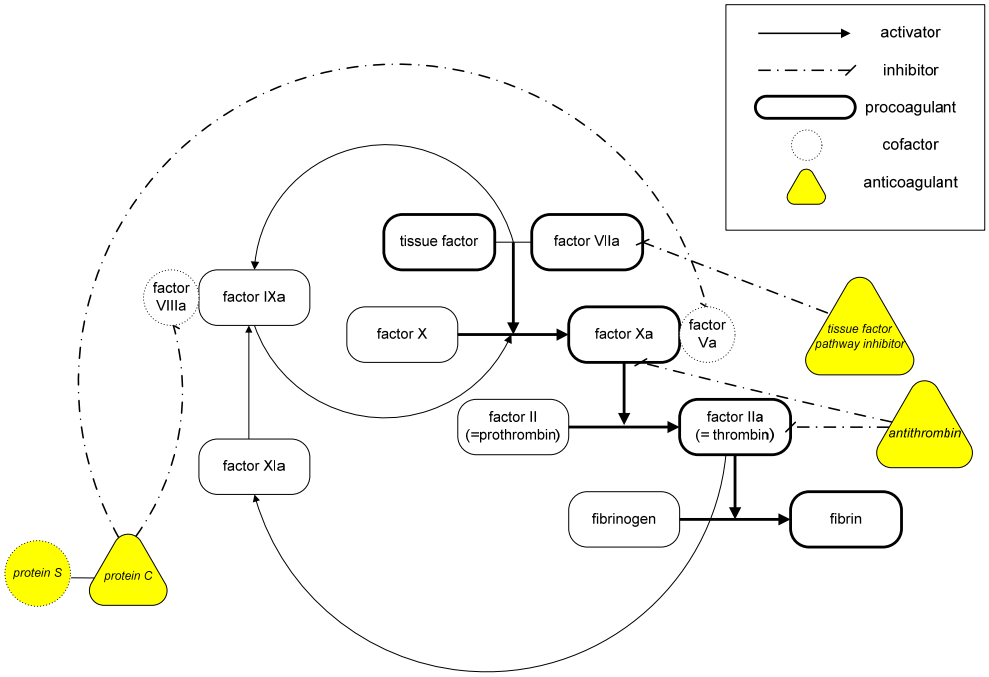
Background of thrombophilia

Venous thromboembolism (VTE) is a common disease with an annual incidence of approximately 2-3 per 1,000 inhabitants in Western societies.[1-3] Its manifestations are deep venous thrombosis, pulmonary embolism or a combination of both. VTE is a multicausal disease, in which both exogenous and endogenous risk factors have been identified.[4] Established exogenous risk factors are cancer, pregnancy, puerperium, surgery, immobilisation and oral contraceptive use. The endogenous risk factors for VTE contribute to the term "thrombophilia". The definition of thrombophilia (an inherited or acquired predisposition to VTE) has expanded over the past century. It was introduced in 1965 by a physician called Egeberg, when he described a Norwegian family with a high tendency to venous thrombosis due to a deficiency in the natural anticoagulant antithrombin.[5] Antithrombin deficiency increases the risk of VTE by a less pronounced inhibition of thrombin formation (and factor Xa) (see Figure 1 for the effects of thrombophilia on fibrin formation). Subsequently, in the 1980s, deficiencies of the other natural anticoagulants, protein C and its cofactor protein S, were found to increase the risk of VTE.[6,7] A deficiency of one of the latter proteins leads to a reduced inactivation of clotting factors Va and VIIIa. Many mutations have been described in the coding genes for antithrombin, protein C and protein S and, in fact, heterozygous mutations already cause a deficiency of the affected protein. Deficiencies of natural anticoagulants (antithrombin, protein C and protein S) are rather uncommon, with a prevalence of <1% in the general population and a prevalence of at most 5% among patients with thrombosis.[8-11]

During the past two decades, newer and more prevalent thrombophilic defects have been discovered, such as the factor V Leiden mutation (1994) and the prothrombin mutation (1996).[12,13] Factor V Leiden -the most common genetic risk factor for VTE- is a single point mutation on coagulation factor V (G1691A) which leads to an amino acid substitution (R506Q) on the major cleavage site for activated protein C (APC), thereby causing a phenomenon called "APC resistance". The protein C anticoagulant system is twofold affected by factor V Leiden: 1) by impaired degradation of mutant factor Va by APC because of the elimination of its most important cleavage site and 2) by impaired degradation of factor VIIIa, since mutant factor V is a poor cofactor to activated protein C in the degradation of factor VIIIa.[14] A single point mutation (G20210A) in the 3`untranslated region of the prothrombin (factor II) gene is the second most common genetic risk factor for VTE. The function of the prothrombin protein is unaffected, however the plasma levels of prothrombin are slightly increased as a result of the mutation.[14]

Figure 1. Coagulation system and points of action of thrombophilic disorders



Also, persistently elevated levels of factor VIII have shown to be a risk factor for thrombosis.[15,16] It has been found that (mild) hyperhomocysteinaemia is a risk factor for VTE, but its clinical relevance seems small, especially since lowering the homocysteine level did not show a reduction in the recurrence of VTE.[17,18]

The only established acquired thrombophilic disorder is the primary antiphospholipid syndrome (APS). This syndrome is characterized by a heterogenic group of auto-antibodies directed against plasma proteins that bind to negatively charged phospholipids. The well established, clinically most relevant antibodies can be divided into three categories: lupus anticoagulant, anti-cardiolipin antibodies and anti-β2-glycoprotein-1 antibodies. APS is a clinical diagnosis, based on at least one episode of arterial or venous thrombosis or recurrent miscarriage, combined with the persistent presence of anti-phospholipid antibodies.[19]

In approximately half of patients presenting with VTE, one or more thrombophilic defect can be identified.[20,21] This has led to widespread testing for thrombophilia, also in patients

with a first episode of VTE despite the fact that -at present- it is unclear whether this strategy is beneficial.

Clinical implications of thrombophilia testing

The (dis)advantages and implications of thrombophilia testing are discussed in the following section. Reasons for testing for thrombophilia might be clarification of the cause, the opportunity to adjust therapeutic regimes of VTE in thrombophilic patients for the optimal prevention of recurrence, and the opportunity to track asymptomatic family members (and subsequently take preventive measures). Conversely, testing for thrombophilia might lead to needless expenses, anxiety, and social problems.

Reasons to test for thrombophilia

It is often argued that patients and their doctors would like to have an explanation for the episode of VTE, although this has never been explicitly studied. It should be realized however, that the existence of a thrombophilic defect does not exclude other reasons for a prothrombotic state. For example, a 60-year-old male presenting with an unprovoked deep VTE of the leg might have an occult cancer as well as a thrombophilic defect. An important argument in favour of testing for thrombophilia would be the opportunity to adjust therapeutic measures for treatment of a VTE (by means of intensity or duration of treatment). The optimal therapy for VTE depends on the risk of recurrence, the (dis)comfort of the therapy and the risk of side effects, such as (major) bleeding. The estimated risk of recurrence for VTE in general is ~5% per year [22,23] (although unprovoked episodes tend to recur more frequently: ~20% in the first 2 years compared with provoked episodes).[24] Standard therapy for patients with a first VTE includes anticoagulant treatment with vitamin K antagonists for 3 to 6 months, with international normalized ratios between 2.0 and 3.0.[25] This therapy ensues an annual bleeding risk of 0.25% for fatal bleeding and 1.0% for life-threatening bleeding.[26,27] A different approach to thrombophilic patients, compared with non-thrombophilic patients is only justified if the former have a different risk of recurrence. Even though thrombophilia has shown to increase the risk of a first VTE, it is to date still controversial whether thrombophilia also increases the risk of recurrent VTE. The estimated relative risk of recurrence in patients with thrombophilia is small, as compared with patients without thrombophilia (Table 1). The estimated odds ratios (ORs) for the natural anticoagulant deficiencies, as described mainly in retrospective analyses, were 2.5.[28-30] In one prospective study, the follow-up of the Leiden Thrombophilia Study

(LETS), the risk of recurrence appeared even more moderate, with an OR of 1.8.[11] Two meta-analyses studied the risks of recurrence in patients with the common thrombophilias: factor V Leiden and the prothrombin G20210A mutation. The risk of recurrence was found consistently to be 1.2 to 1.4-fold higher in patients with factor V Leiden and 0.7 to 1.7-fold higher in patients with the prothrombin mutation.[11,31-33] For the other thrombophilic defects, less data are available. Three studies assessed the risk of recurrence in patients with high levels of FVIII coagulant activity (FVIII:c) compared with patients with normal levels. One case-control study showed that elevated levels of FVIII:c above 150% were associated with an approximate 2-fold increased risk of recurrent VTE, compared with patients with a single episode. In two cohort studies, the estimated relative risk of recurrent VTE was 6-fold increased in those with FVIII:c levels above the 90th percentile, corresponding to 234% and 294%, respectively.[34,35] These results could not be reproduced in the LETS follow-up study, in which an OR of only 1.3 was found.[11] The data on estimated risk of recurrence for elevated levels of FIX and FXI are scarce, but their impact on recurrence seems negligible.[11] The attribution of mild hyperhomocysteinaemia in terms of risk of recurrence appears low (1.8 to 2.7), and treating hyperhomocysteinaemia did not show a decrease in the number of recurrences.[18,36-38] The risk of recurrence in antiphospholipid or anticardiolipin antibodies was investigated in four studies.[39-42] The outcomes regarding relative risk for recurrence ranged between 2- and 6-fold. These results are difficult to interpret, given that in these studies the antiphospholipid and anticardiolipin antibodies or lupus anticoagulant were not tested repetitively (as suggested by international guidelines).[19] Moreover, duration of anticoagulant treatment differed substantially. Adjustment of anticoagulant treatment in

Table 1. Estimated Relative Risk of VTE recurrence in patients with thrombophilia

type of thrombophilia	relative risk
natural anticoagulant deficiencies [11,28-30]	1.8-2.5
factor V Leiden [11,31-33]	1.2-1.4
prothrombin G20210A [11,31-33]	0.7-1.7
elevated levels of factor VIII:c [11,34,35]	1.3-6
elevated levels of factor IX [11]	1.2
elevated levels factor XI [11]	0.6
mild hyperhomocysteinaemia [18,36-38]	1.8-2.7
antiphospholipid antibodies [39-42]	2-6

thrombophilic patients after a first VTE has only been addressed for a difference in intensity. This has not shown to be beneficial in patients with VTE, regardless of thrombophilia. Reducing the intensity of VKAs below 2.0 led to an increase of recurrence risk (1.9 versus 0.6%)[43,44], whereas major bleeding complications did not differ between a low-intensity and regular-intensity treatment (0.96 versus 0.93%).[44] A higher intensity of VKA in patients with antiphospholipid antibodies showed no reduction in the risk of recurrence, but led to an increase in the bleeding risk.[45,46] Whether clinical outcome of patients with VTE and thrombophilia improves with prolongation of anticoagulant has never been investigated. Current trials focus on whether such an intervention outweighs the bleeding risk, as oral anticoagulant medication is known to prevent VTE by more than 90%, as long as it is used.[47] Finally, a potential advantage of testing patients with VTE for thrombophilia may be the identification of asymptomatic family members. These individuals have a 2- to 10-fold increased risk for VTE as compared with non-carriers.[48-51] Regardless of this increased relative risk, the overall absolute risk remains low (Table 2). It is often argued that asymptomatic family members with thrombophilia may benefit from targeted prevention in high-risk situations (e.g., pregnancy, puerperium, surgery, immobilization, and trauma), and the avoidance of acquired risk factors, most notably oral contraceptives.

Table 2. Absolute risk of VTE in asymptomatic carriers of thrombophilia

type of thrombophilia	overall (%/year)	surgery, trauma, or immobilization (%/episode)	pregnancy (%/pregnancy)	oral contraceptive use (%/year of use)
natural anticoagulant deficiencies [48,61-65]	0.4-4.0	8.1	4.1	4.3
factor V Leiden [48,50,51,61,64,66,67]	0.1-0.7	1.8-2.4	1.9-2.1	0.5-2.0
prothrombin 20210A [67-69]	0.1-0.4	2.0	2.8	0.2
elevated FVIII:c [70]	0.3	1.2	1.3	0.6
mild hyperhomocysteinaemia [71,72]	0-0.2	0.9	0.5	0.1

It is clear from Table 2 that bleeding risk associated with continuous anticoagulant treatment outweighs the risk of VTE. It is notable that the figures considering surgery, trauma and immobilization, as shown in Table 2, have been collected for the larger part in times before standard prophylaxis was routine patient care. For pregnancy, ~80% of the episodes occur in the postpartum period. Whether this should lead to administration of prophylaxis in the postpartum period is a matter of physician and patient preference, given

that the number needed to treat is 25 in case of a deficiency in the natural anticoagulants and approximately twice as high in patients with the common thrombophilias. Finally, it is clear from data in Table 2 that the use of oral contraceptives should be weighed against the disadvantages of other contraceptive methods.

Reasons not to test for thrombophilia

Disadvantages of testing patients with a VTE for thrombophilia might be the cost of testing, which is approximately €500.[52] Several sophisticated studies focused on the cost-effectiveness of testing for thrombophilia.[53,54] These studies focused on selected patient groups, because universal testing was considered less cost effective. It is of note that the external validity of the results may be distorted by the fact that the findings were based on a range of various assumptions. One study, by Marchetti et al, assessed the cost effectiveness of testing for double heterozygosity of factor V Leiden and the prothrombin mutation, and subsequently prolonging anticoagulant therapy in those tested positive for both common thrombophilias.[53] This strategy was considered cost effective, as testing all patients with VTE provided one additional day of life at the cost of $13.624/quality-adjusted life-years. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening study assumed that testing for thrombophilia might be efficacious in high-risk situations. The cost effectiveness of four different testing scenarios was calculated: (1) testing all women prior to prescription of oral contraceptives and restricting prescription only to those tested negative for thrombophilia; (2) testing all women prior to prescribing hormone replacement therapy and restricting prescription only to those tested negative for thrombophilia; (3) testing women at the onset of pregnancy and prescribing prophylaxis to those tested positive for thrombophilia; and (4) testing all patients prior to major elective orthopaedic surgery and prescribing extended thromboprophylaxis to those tested positive for thrombophilia. It was concluded in this study that the second scenario would be most cost effective, compared with the other scenarios. Nevertheless, selective screening based on the presence of previous personal or family history of VTE was considered to be more cost effective than universal testing in the four different scenarios. Furthermore, the psychological impact and consequences of knowing that one is a carrier of a (genetic) thrombophilic defect could be regarded as a drawback of testing. Most studies that focused on impact of testing for thrombophilia showed that patients had experienced low psychological distress following thrombophilia testing.[55,56] Nevertheless, qualitative studies described several negative effects. Bank et al conclude from their study that parents were

worried that their children ''would be negatively influenced by factor V Leiden'' and that some carriers ''felt stigmatized.''[57] Finally, a disadvantage of testing for thrombophilia could be its potential social consequences (for instance problems with health insurance or life insurance), although little data are available on this issue.

Thrombophilia testing scrutinized

As mentioned above, thrombophilia tests are performed widely, even though their clinical benefits are yet to be established. We attempted to assess whether testing for thrombophilia after a first VTE and prolonging anticoagulant treatment in patients with thrombophilia is justified.[58] The NOSTRADAMUS (Necessity Of Screening for ThRombophilia At Diagnosis of venous thromboembolism to Assess Most Unresolved iSsues) trial, a multicentre randomised controlled trial, was designed to assess whether this strategy is beneficial in terms of clinical outcomes (the composite endpoint of recurrent VTE and bleeding risk), quality of life and costs. We aimed to include 1336 patients with a first VTE, whom we would randomly assign to one of two groups. The intervention group would be tested for thrombophilia and subsequently receive the test results. Additional anticoagulant treatment for a predefined period would be initiated in patients found to have thrombophilia, while others would receive a standard predefined duration of treatment. Patients in the control group they would receive the standard predefined duration of treatment. Primary outcomes were the risk of recurrent VTE, clinically important bleeding and the composite outcome of both. Other outcomes included overall quality of life and costs associated with outcome measures 18 months after the initial episode of VTE. However, the NOSTRADAMUS trial was prematurely terminated due to a low inclusion rate.[59] Several reasons account for this: delay of approval by medical ethics committees in participating centres, competition with industry-initiated intervention studies with a higher financial compensation in potentially eligible patients, and the lack of study staff and allowance of expenses. To date, no randomized controlled trials have been completed to assess whether testing for thrombophilia and subsequent therapeutic consequences reduces the risk of recurrent VTE. However, in a case-control study the rate of recurrence was shown not to be influenced by testing for thrombophilia.[60]

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