Aetiology and treatment of venous thromboembolism
Bank, I.

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chapter 2

Hereditary and Acquired Thrombophilia

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Abstract
During the past decade knowledge about the aetiology of venous thromboembolism (VTE) has increased tremendously. Inherited and acquired risk factors for VTE are common in patients, as well as in the general population. Whether the presence of most of these risk factors has consequences for the management of symptomatic and asymptomatic individuals is not fully clear at present. Therefore, while searching for new thrombophilic defects, it is crucial to determine the absolute risk for (recurrent) VTE as well as other clinical manifestations in carriers. However, tentative guidelines for managing patients and their families are given in this review.
Introduction

Venous thromboembolism (VTE) is a common disease with an incidence of 2 to 4 per 1000 inhabitants per year in Western societies \(^1\). This entity comprises a wide spectrum of clinical manifestations varying from a small thrombus in the deep leg veins to fatal pulmonary embolism.

The pathologist Rudolf Virchow (1821-1902) postulated a trias of pathophysiological factors, that can induce thrombosis: stasis of blood, alterations in blood composition, and changes in the vessel wall \(^2\). Now, more than a century later, it has become clear that VTE is indeed a multifactorial disorder.

Although it had been known that all patients with VTE have an increased risk for recurrent episodes and that the tendency toward this disease occurs in some families more often than in others, it is in the past decade that much progress has been made in understanding hereditary risk factors for thrombosis. At present, so-called hereditary thrombophilia can be found in approximately 70% of patients who have experienced an episode of VTE (Table 1). For some abnormalities it is yet uncertain whether they are truly hereditary.

Acquired conditions can also lead to an increased tendency toward thrombosis. The well known (mostly) reversible risk factors for VTE are surgery, immobilisation, trauma and, for females, also pregnancy and use of oral contraceptives. In addition, more permanent risk factors are for instance the presence of cancer, the antiphospholipid antibody syndrome and heparin induced thrombocytopenia.

Here we will review the established hereditary, possibly hereditary and acquired permanent thrombophilic disorders, focusing on the mechanisms, epidemiology, clinical aspects, and implications for medical practice.

Mechanisms of Thrombophilic Risk Factors

Deficiencies of proteins involved in the natural anticoagulant pathways were the first identified hereditary thrombophilic defects.

In antithrombin deficiency, the antithrombin-heparin sulphate pathway is impaired. Antithrombin inactivates thrombin, factor Xa, factor IXa, and factor

<table>
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<th>Table 1 Established thrombophilic defects.</th>
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<tbody>
<tr>
<td><strong>Hereditary</strong></td>
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<tr>
<td>Antithrombin deficiency</td>
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<tr>
<td>Protein S deficiency</td>
</tr>
<tr>
<td>Protein C deficiency</td>
</tr>
<tr>
<td>FV (^5^{*}) mutation</td>
</tr>
<tr>
<td>FV (^2^{*}) mutation</td>
</tr>
<tr>
<td>Prothrombin 20210A mutation</td>
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XIIa by forming an irreversible complex with these activated clotting factors. In case of decreased levels of antithrombin, these enzymes are not inhibited sufficiently, thereby leading to an increased tendency toward VTE.

In the anticoagulant protein C pathway, activated protein C selectively inactivates factors Va and VIIIa and by this way regulates the formation of thrombin. Free protein S acts as a cofactor in this process. Therefore, deficiency of protein S or protein C increases the risk of thrombosis. There are two subtypes of these natural anticoagulant deficiencies. In the type I deficiencies, levels of both antigen and activity are decreased. In the type II deficiencies, there are normal antigen levels, but because of functional defects in the proteins their activities are significantly impaired.

Activated protein C (APC) resistance is another impairment in the anticoagulant protein C pathway. This phenomenon is most often caused by a point mutation at the cleavage site of FVa (FV:Q506 mutation or FV Leiden mutation) resulting in resistance of factor Va for inactivation by APC. APC-resistance, both hereditary and acquired (i.e. without the mutation), is an independent risk factor for VTE.

Increased levels of some coagulation factors have also been identified as thrombophilic factors. The prothrombin (20210 A/G) mutation is associated with an increased risk of thrombosis and elevated levels of factor II, whereas this is, also in the absence of the mutation, an independent risk factor. The inheritance pattern of both the natural anticoagulant deficiencies and the above mentioned mutations is autosomal dominant.

Clotting factor VIII, which is known to increase during acute phase reactions, is probably in part determined genetically, and has been found to be an important thrombophilic factor. Finally, increased levels of factor XI, another component of the intrinsic pathway of coagulation, were recently found to be associated with an increased thrombotic risk. It is still unknown whether elevations in factor XI are hereditary.

In contrast to homocystinuria, a rare congenital syndrome usually due to homozygous cystathionine b-synthase deficiency, (mild) hyperhomocysteinaemia occurs in all ages and is a risk factor for both arterial and venous thrombotic disease. Hyperhomocysteinaemia is often found in families, although a direct link to known mutations or genetic defects has not been established so far. An important factor leading to acquired hyperhomocysteinaemia is folic acid deficiency, but pyridoxine and vitamin B12 are also important in the metabolism of methionine. Deficiencies of the latter can lead to accumulation of homocysteine. At present, how hyperhomocysteinaemia induces VTE is not well understood.
Antiphospholipid antibodies were first detected in patients with systemic lupus erythematosus and were found to be related to a thrombotic tendency. The precise pathogenic mechanisms leading to a prothrombotic state are complex and not well elucidated, but the presence of lupus anticoagulant (a clotting test phenomenon), or autoantibodies directed against phospholipids or phospholipid binding proteins, have been associated with an increased risk of venous and arterial thromboembolism. In patients without systemic lupus erythematosus, lupus anticoagulant and antiphospholipid antibodies are also found and, when persistent, they are associated with thrombophilia.

Heparin induced thrombocytopenia is caused by antibodies (IgM, IgG) directed against a complex formed by platelet factor 4 and heparin. This can occur 4 to 14 days after a patient has been given heparin for the first time, but sooner in patients previously exposed to this substance. This clinical feature is associated with arterial, venous, and microvascular thrombosis.

Finally, it is well known that the presence of cancer leads to an increased risk of VTE, and that a diagnosis of cancer is made more often in patients who present with idiopathic VTE. A plausible mechanism is that malignant cells invade vessel walls, inducing damage to the endothelium. It has also been postulated that expression of tissue factor and factor X on the surface of cancer cells lead to enhanced thrombin generation.

**Epidemiology and Thrombotic Risk**

Approximately 70% of consecutive patients presenting with a first episode of VTE have a detectable hereditary thrombophilic disorder. These defects are also found, in a lower frequency, in the normal population.

The prevalences of deficiencies of antithrombin and protein C in the normal population are about 0.3% and 0.5%, respectively. For protein S deficiency, no reliable estimates are available. More prevalent inherited risk factors for VTE are the factor V Leiden mutation and the prothrombin (20210 A/G) mutation. The overall prevalences of these mutations have been estimated to be around 5% and 1-2% in Western societies, respectively, but they are much lower in native Americans, Africans and Asians. Levels of clotting factor VIII above 150% are present in approximately 10-15% of the Dutch population. Plasma concentrations of clotting factor XI above the 90th percentile are, by definition, found in 10% of the normal population. Mild hyperhomocysteinaemia is usually defined as homocysteine levels above the 95th percentile of normals.

In consecutive patients with VTE, one of the classical anticoagulant deficiencies
can be found in approximately 8% \(^3^2\). The prevalence of the factor V Leiden mutation in unselected patients with VTE is approximately 20% \(^3^3,^3^4\), whereas the prothrombin mutation is found in 5-6% \(^1^1\). Elevated levels of factor VIII (>1.50%) and a high factor XI (>90th percentile) are present in no less than 25-30% and 19% of patients, respectively \(^3^3,^1^4\). Mild hyperhomocysteinemia (>9.5th percentile) is detected in about 10-25% of patients \(^1^8,^1^9\). In selected patients, i.e., those referred to tertiary centers because of a strong personal or family history of VTE, the probability of identifying thrombophilic disorders is even higher.

These prevalences in the normal population and in patients with VTE indicate that deficiencies of antithrombin, protein C, and protein S are stronger risk factors for VTE than the other thrombophilic defects. The relative risk for any natural anticoagulant deficiency was found to be 10 in a large family study that compared deficient relatives with those with normal plasma concentrations \(^3^5\). For the factor V Leiden mutation, this relative risk was found to be around 3 in similar family studies \(^3^3,^3^6\), whereas case-control studies showed odds ratios of 3 to 7 \(^8,^3^7\). Elevated factor VIII levels are associated with a dose-dependent 4- to 10-fold increased risk of VTE for concentrations exceeding 150% and 200%, respectively \(^3^3,^1^1\). The odds ratio for VTE for increased levels of factor XI is approximately 2 and somewhat higher for mild hyperhomocysteinemia \(^1^3,^1^9\).

Although relative risks and odds ratios are important in identifying risk factors for VTE, knowledge of the absolute risk for thrombosis, both spontaneously-as well as during high-risk situations, is crucial for patient management and counseling of families. A large retrospective study of asymptomatic relatives of patients with VTE and a thrombophilic disorder revealed that the incidence of a first episode in individuals with a deficiency of antithrombin, protein C, or protein S, was approximately 1% per year \(^3^5\), whereas a prospective cohort study showed incidences of 4.0, 1.6%, and 1.3%, respectively \(^3^8\) (Table 2). For the factor V

<table>
<thead>
<tr>
<th></th>
<th>Retrospective studies</th>
<th>Prospective studies</th>
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<tbody>
<tr>
<td>Antithrombin deficiency</td>
<td>1.0-2.9 (^1^4,^1^5)</td>
<td>1.0 (1.3-8.8) (^9^6)</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>1.0-3.1 (^9^3,^3^5)</td>
<td>1.3 (0.1-3.0) (^3^9,^4^0)</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>1.0-3.0 (^9^3,^3^1)</td>
<td>1.6 (0.5-3.5) (^3^8,^3^7)</td>
</tr>
<tr>
<td>Factor V Leiden mutation</td>
<td>0.3-0.5 (^3^3,^3^0)</td>
<td>0.5 (0.1-1.3) (^3^9,^4^0)</td>
</tr>
<tr>
<td>Prothrombin 20210A mutation</td>
<td>0.5 (^1^0)</td>
<td></td>
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</tbody>
</table>
Leiden mutation, this rate was found to be about 0.5% in retrospective and prospective studies and appears to be in the same range in carriers of the prothrombin mutation. The rates are probably somewhat lower in carriers derived from the general population and higher in carriers selected from families with a strong tendency for VTE. For individuals with hyperhomocysteinemia or elevated levels of factor VIII or factor XI, no studies on the absolute risk for thrombosis are available.

In all carriers of thrombophilia, the risk of VTE increases during high-risk situations, such as immobilisation, trauma, and surgery, and in women during pregnancy and the post-partum period. Furthermore, it is known that use of oral contraceptives increases the risk for thrombosis in thrombophilic women in a multiplicative fashion. For instance, the baseline risk for women without the factor V Leiden mutation who do not use oral contraceptives was found to be increased 8-fold by the mutation itself, 4-fold by use of oral contraceptives alone, but 30-fold by the combination of factor V Leiden and oral contraceptive use. Use of so-called third generation preparations (ethinylestradiol combined with desogestrel or gestodene as progestin), is associated with an even greater risk with an odds ratio of 2 when compared with so-called second generation oral contraceptives (usually containing levonorgestrel as a progestin). Again, for counseling carriers, the absolute risks for VTE are important. Table 3 summarises these risks during high-risk situations and oral contraceptive use in asymptomatic individuals with antithrombin, protein C, or protein S deficiency, or the factor V Leiden mutation. For the other inherited defects, no such data are available at present. For instance, a woman with an antithrombin, protein S, or protein C deficiency has a risk of approximately 4% of developing a first episode of VTE during each year of oral contraceptive use.

Table 3 Risk of venous thromboembolism in asymptomatic carriers of thrombophilic defects during transient high risk situations.

<table>
<thead>
<tr>
<th></th>
<th>Factor V Leiden mutation</th>
<th>Antithrombin deficiency, protein C deficiency and protein S deficiency</th>
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<tbody>
<tr>
<td>Operation, trauma, immobilisation</td>
<td>8.0-10.0%</td>
<td>2.0-11.0%</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>0.0-1.2%</td>
<td>0.0-1.9%</td>
</tr>
<tr>
<td>Postpartum period</td>
<td>3.0-12.0%</td>
<td>0.0-1.7%</td>
</tr>
<tr>
<td>Use of oral contraceptives (% year)</td>
<td>0.0-1.3%</td>
<td>0.0-0.7%</td>
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All data are derived from both prospective and retrospective studies with different types of anticoagulant prophylaxis used.
It is unclear whether patients with hereditary thrombophilia have an increased risk for recurrent VTE after discontinuation of anticoagulant therapy. In patients with the factor V Leiden mutation, several studies that assessed this issue showed controversial results \textsuperscript{16-22}, whereas a single study in carriers of the prothrombin studies did not find a higher rate of recurrences in patients with the mutation \textsuperscript{23}. Only limited retrospective data on the absolute risk of recurrent VTE in patients with antithrombin, protein C, or protein S deficiency are available. In these studies, all recurrent episodes of VTE were included in the calculation of the annual incidence of recurrence, making it impossible to assess the incidence of a first and a second recurrence separately. In one study, the annual incidence of recurrent VTE was 4.8%, with a decrease to 1.4% per year after the diagnosis of inherited thrombophilia had been made, possibly because more aggressive anticoagulant prophylaxis was used during high-risk situations \textsuperscript{31}. In a review of available family studies in patients with antithrombin or protein S deficiency, a much higher annual incidence of recurrent VTE of 13 to 17% was found \textsuperscript{35}. In a retrospective family cohort study, an incidence of recurrence of 10% after 1 year, accumulating to 23% after 5 years of follow-up, was observed, suggesting a decline in the risk of recurrent VTE after the first year. In a study of factor V Leiden carriers, the risk of recurrence varied between 0.45% to 4.8% annually, depending on the presence of transient or concomitant thrombophilic risk factors \textsuperscript{36}. It is obvious that more properly designed studies that address this issue are needed.

As already mentioned, antiphospholipid antibodies can be found in various conditions. In case-control studies in which individuals with antiphospholipid antibodies have been compared to controls, odds ratios for developing VTE were between 5 and 10 \textsuperscript{23-27}. The risk of recurrent thrombosis (both venous and arterial) has been reported to be between 20 and 30% per year in selected populations \textsuperscript{37-38}. These estimates are difficult to extrapolate to a general population of patients with VTE, who are found to have antiphospholipid antibodies.

Cancer is known to be one of the most common acquired causes of thrombosis. Few data have been published about the thrombotic risk in patients with a malignancy. Up to 26% of patients with a malignancy have overt VTE, and some postmortem studies have found an incidence of approximately 50% \textsuperscript{29-41}. The incidence of heparin induced thrombocytopenia depends on the method of detection, but is reported to be as high as 50% \textsuperscript{42}. However, only a minority of patients with heparin induced thrombocytopenia antibodies develop the complete clinical syndrome of thrombocytopenia and arterial or venous thrombosis.
Clinical Manifestations

The most common clinical manifestation of thrombophilia is deep vein thrombosis or pulmonary embolism. Venous thrombosis at unusual sites, such as the cerebral sinus or portal vein is less common.

Inheritable thrombophilic defects are also associated with a number of obstetric complications (Table 4). Antiphospholipid antibodies were first found to be associated with recurrent fetal loss. Also, women with antithrombin, protein S, or protein C deficiency or the factor V Leiden mutation have an increased risk for miscarriages and stillbirth. Finally, preeclampsia and fetal growth retardation are found more often in women with these defects. Although the pathophysiological mechanisms are not entirely understood, uteroplacental insufficiency or fetal thrombosis is a likely explanation.

Homzygous protein S and protein C deficiency are associated with neonatal purpura fulminans, and adult patients are prone to skin necrosis after initiation of therapy with vitamin K antagonists. Generally, hereditary thrombophilia is not associated with an increased tendency toward arterial vascular diseases, although there are a few reports about a possible association with antithrombin deficiency, the factor V Leiden mutation, and the prothrombin mutation. Hyperhomocysteinemia was first found to be a risk factor for premature atherosclerotic disease before it appeared to increase the risk of VTE.

Table 4 Clinical manifestations of thrombophilia.

<table>
<thead>
<tr>
<th>Clinical Manifestation</th>
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<tbody>
<tr>
<td>VTE at a young age</td>
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<tr>
<td>Recurrent VTE</td>
</tr>
<tr>
<td>Thrombosis at an unusual site (e.g. cerebral sinuses, mesenterial, portal)</td>
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<tr>
<td>Recurrent fetal loss</td>
</tr>
<tr>
<td>Preeclampsia</td>
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<tr>
<td>HELLP syndrome</td>
</tr>
<tr>
<td>Vitamin K induced skin necrosis</td>
</tr>
<tr>
<td>Neonatal purpura fulminans</td>
</tr>
<tr>
<td>Heparin resistance</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
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</table>
Approach to Asymptomatic Carriers of Thrombophilic Defects in Medical Practice

In the management of thrombophilia one should always balance the risks and benefits of prophylaxis with anticoagulants, the (recurrent) thrombotic risk, the complications of the disease and the preferences of the individual counseled. Because crucial data are often unavailable, all guidelines presented here are tentative.

Vitamin K antagonists reduce the incidence of recurrent VTE with 87 to 96% 

serious hemorrhages during long-term anticoagulant prophylaxis occur in 2-3% of treated individuals each year and the annual rate of fatal bleeding is 0.25% . Because of the relatively low annual incidence of a first spontaneous VTE in individuals with inherited thrombophilia and the high bleeding risk associated with the use of vitamin K antagonists, a general policy of primary prophylaxis for these carriers is not justified. Standard prophylaxis with low-molecular weight heparin should be used in case of transient high-risk situations such as trauma, surgery, and immobilisation. Besides inducing hemorrhages and heparin induced thrombocytopenia, this treatment reduces the risk of VTE in these situations with 70-80% . Similar reductions have been observed in retrospective cohort studies in carriers of the protein S, the protein C and the antithrombin deficiency . Prolonging prophylaxis after hospital discharge may be an option in carriers of the antithrombin, protein S or protein C deficiency.

The risk of VTE during pregnancy does not justify prophylaxis with low-molecular weight heparins, but because of the high thrombotic risk in the relatively short postpartum period (Table 3), prophylaxis may be considered for 4 to 6 weeks after delivery. Use of oral contraceptives increases the risk of VTE in women with anticoagulant deficiencies to approximately 4% per year of use, while it is lower in women with the factor V Leiden mutation (0.5 to 2% annually) . Therefore, in asymptomatic women with the deficiencies, alternative birth controlling methods are probably indicated. Whether the same is true for F V Leiden carrying women is a matter of debate. However, levonorgestrel-containing oral contraceptives are preferred because their lower thrombotic risk as compared to newer pills containing desogestrel or gestodene . Although to a lesser extent, hormone replacement therapy is also associated with an increased risk for VTE . This treatment should be limited to women who have a strong medical indication for this therapy.
Approach to Symptomatic Carriers of Thrombophilic Defects in Medical Practice

The initial therapy of VTE in patients with thrombophilia consists of the standard anticoagulant treatment with (low-molecular weight) heparin for at least 5 days, until a therapeutic International Normalized Ratio (INR) is achieved with vitamin K antagonists. The optimal duration of vitamin K antagonists is still uncertain. At low risk for recurrence are the patients who developed an episode of VTE secondary to a (transient) risk factor. They can be treated for 3-6 months. At intermediate risk for recurrent disease are those with a first spontaneous episode, or those with a combination of thrombophilic disorders. Treatment for 6-12 months appears appropriate in that case. At highest risk are patients with persistent risk factors such as active cancer or patients who had multiple thrombotic episodes. For them, indefinite treatment may be justified. Nevertheless, in these patients the indication for continued prophylaxis should be re-evaluated, for example yearly, to weight the pros and cons.

Patients who develop skin necrosis after initiation of therapy with vitamin K antagonists should be fully heparinized before continuing the treatment.

The optimal prophylactic approach in patients with thrombophilia and one or more previous episodes of VTE, is uncertain. Certainly, routine prophylaxis is indicated in case of surgery, trauma, or immobilisation, whereas prolonged thromboprophylaxis can be considered after early hospital discharge.

Although the risk of recurrent VTE during pregnancy is unknown, low-molecular weight heparin in therapeutic dosages should be started as soon as possible. Vitamin K antagonists are teratogenic during the period of embryogenesis, but can be considered during the post partum period. Prophylaxis should be continued for 4 to 6 weeks postpartum. If possible, low-molecular weight heparin treatment should be discontinued about 12 hours before delivery and restarted soon thereafter. Some clinicians prefer unfractionated heparin in the peripartum period.

Both oral contraceptives and hormone replacement therapy are contraindicated in symptomatic females with thrombophilia.

Management of Individuals with (Mild) Hyperhomocysteinemia

A recent meta-analysis revealed that the actual level of homocysteine has no predictive power for cardiovascular disease and that it is questionable whether lowering homocysteine levels decreases the risk of cardiovascular disease. However, awaiting clinical trials on efficacy and safety, folic acid with or without addition of pyridoxine is mostly recommended for patients who have experienced
VTE in the past. These individuals should receive routine prophylaxis during surgery, trauma and immobilisation, but there are no general guidelines for management during pregnancy and the postpartum period. Estrogen use should be discouraged in these women. Because of the lack of data about potential side effects of long-term treatment with vitamins, this approach appears not to be justified in asymptomatic persons.

**Management of Individuals with Acquired Thrombophilic Conditions**

Symptomatic patients with the antiphospholipid antibody syndrome should be treated for at least one year because of the high recurrence rates, but asymptomatic patients do not differ in their management from other asymptomatic carriers of thrombophilic defects.

In patients with cancer, the risk of VTE is determined by many factors including type of malignancy, stage of disease, surgery, and concurrent treatment with anti-coagulation, treatment with danaparoid, a mixture of various glycoamino-glycans, is a good alternative.

**Screening**

An important question is whether all patients with VTE should be screened for thrombophilia. Consequently, after identification of a propositus with an inherited abnormality the issue is whether his or her family members need to be offered screening. The main purpose of screening for risk factors is the potential consequence for the management of individuals with thrombophilia, such as prolonging the duration of anticoagulant therapy after an episode of VTE or intensifying prophylaxis during transient high-risk situations. Furthermore, use of oral contraceptives or hormone replacement therapy could be avoided if necessary.

In case of asymptomatic carriers of hereditary thrombophilic defects, it is questionable whether the benefits of identifying the defect outweigh the potential side effects of screening such as inducing psychological problems and stigmatisation leading to problems with, for instance, obtaining life assurance. For women, avoiding the use of oral contraceptives would leave otherwise healthy women without the most efficacious type of contraception. On the other hand, one could adjust the type of oral contraceptive (levonorgestrel-containing instead of desogestrel/gestodene-containing pills) if the female family member has proved to be a carrier of the same defect. Therefore, when a propositus is found
to be deficient for antithrombin, protein S, or protein C, identifying asymptomatic relatives would probably have consequences, such as discouraging estrogen use and active thromboprophylaxis in the postpartum period and during high-risk situations. Whether the same is true for the other inherited thrombophilias, is questionable and a matter of opinion.

In patients with VTE, the optimal duration of vitamin K antagonist treatment, regardless of the presence of thrombophilia, is still a matter of intense research, making the question of whether routine screening in all patients is justified hard to answer at present. For practical purposes, testing for inherited thrombophilia is recommended if there is some index of suspicion 93; for instance, a strong family history, VTE at a young age, thrombosis at unusual sites and recurrences.

For cancer, extensive screening does not appear to improve the prognosis of patients with a diagnosed malignancy. Only if a thorough history and physical examination and a chest x-ray suggest the presence of a malignancy, further investigations are justified 93.

Conclusions
VTE is a multifactorial disease that is relatively common in the general population. Nearly 70 percent of all patients with this disease have one of the known inherited thrombophilic defects. The identification of others occurs rapidly, but many questions still have to be answered before patients and asymptomatic carriers can be offered the best possible care. Not until the absolute incidences of (recurrent) venous thrombosis in carriers are known, the risks and benefits of anticoagulant prophylaxis can be balanced against the side effects of screening, such as ineffective use of health care resources, iatrogenic and psychological harm, unwanted pregnancies, and false reassurance when no thrombophilic defect is found.

References


