Risk Factors for Venous Thrombotic Disease

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Introduction

Venous thrombosis occurs in about 1 per 1,000 individuals per year.1,2 It usually affects the deep veins of the leg, but may occur in other sites, such as the upper extremities, cerebral sinus, liver and portal veins, or retinal veins. It also may occur in the superficial veins, usually in the leg. The predilection of thrombosis occurring in the leg is the result of the upright position of man, with the resulting slow antigravitational flow of blood in the veins of the leg. Embolization occurs when parts of the clot dislodge and are transported by the blood flow, usually through the heart to the vasculature of the lungs.3

Thrombosis is a serious disorder. It may be fatal by pulmonary embolism, although this is rare (case fatality rate of venous thrombosis is estimated at 1% to 2%). A common, and often disabling, consequence of deep vein thrombosis is post-thrombotic syndrome, with symptoms ranging from discoloration to pain and ulceration.4 Because thrombosis is not very rare and often has serious consequences, prophylactic treatment is focussed on preventing first events and recurrences through adequate knowledge about risks and risk factors.5

Risks and Risk Factors

Risk factors are conditions associated with an increased incidence of disease which association is considered to be causal. Risk predictors or risk markers are factors that also are associated with an increased disease frequency, but not necessarily in a causal way. The effect of risk factors may be expressed in several ways, depending on the purpose and design of the study in which they are being investigated. Generally, absolute risk measures (i.e., difference of the two frequencies) or relative risks (i.e., ratio of the two frequencies) or derivatives of these (e.g., attributable risks, etiologic fractions) are used. Although relative risks are useful to evaluate whether a factor is associated with an increased risk (as opposed to chance outcomes), it is not the best measure to assess the importance of a particular risk factor. For a patient, the absolute risk is most relevant. On a population level, attributable risks are appropriate6 and indicate that proportion of the disease in a particular population that can be attributed to the risk factor under study, or, in other words, by which proportion the frequency of disease would decrease if the factor was eliminated. This attributable fraction is a function of both the relative risk and the prevalence of the risk factor and will be presented throughout this paper.

Risk Factors for Thrombosis

Virchow has postulated three groups of causes of thrombosis: reduced blood flow, changes in the vessel wall, and changes in blood composition.7 Most of the risk factors for thrombosis fall in the first (stasis) and third group (changes in blood coagulability), although nowadays usually a different classification is made, which includes genetic and acquired risk factors. Acquired causes are associated with decreased flow (i.e., immobilization, paralysis, surgery, plaster casts) or blood coagulation, such as the lupus anticoagulant, pregnancy, oral contraception, malignancies (Table 1).

Some of these acquired causes have been known for centuries: old writings report “milk leg”; thrombosis that occurs in puerperium was thought to be associated with breastfeeding.8 Genetic causes were described much more recently. In 1965, Egeberg described familial thrombophilia—a tendency to thrombosis—with a deficiency of antithrombin.9

Acquired Causes of Thrombosis

Age

The risk of thrombosis increases sharply with age, from roughly 1 per 10,000 people per year before age 40 to 1 in 100 per year for those over age 75 years.1,2 It is not entirely clear why the risk is dependent on age, but the most likely reason is a combination of decreased mobility, decreased muscle tone, increased morbidity, and vessel wear and tear.

The age effect is highly relevant in evaluating risks, risk factors, and subsequent prophylactic treatment. For instance, both oral contraceptives and postmenopausal hormone replacement therapy (HRT) increase the risk of thrombosis about fourfold.10,12 However, oral contraceptives are prescribed to an age group with a baseline incidence of 1 per 10,000, and HRT is prescribed to women with a baseline incidence more than 1 per
1,000 per year. The net effect will be 3 additional cases per 10,000 in oral contraceptive users, as compared to nearly 40 per 10,000 HRT users. Quite similarly, the effect of oral contraceptives in a young woman who carries factor V Leiden may be less than the effect of age (i.e., the risk may still remain lower than in a 40-year-old carrier of factor V Leiden who does not use oral contraceptives).

### Malignancies

Venous thrombosis is a common complication in cancer patients. In fact, 10% to 20% of patients with venous thrombosis have cancer. In 1865, Trousseau first pointed out that thrombosis was often seen in cancer patients. Migratory thrombophlebitis (“saltans et migrans”) has been considered a specific sign for occult cancer, especially of the pancreas, and case reports also have linked deep vein thrombosis to both clinically overt and occult cancer.

Several mechanisms have been proposed for the thrombogenic effect of cancer. It seems likely that there are layers of mechanisms. First, the tumor itself, which may have not only humoral effects (i.e., production of procoagulants), but also mechanical effects (i.e., venous obstruction) and general effects (i.e., acute phase reactions). Effects of the disease (for example, reduced mobility or reduced dietary intake of vitamins) and effects of treatment, which may be surgical or radiologic scarring or chemotherapeutics may also play a role in the thrombogenic effect of cancer.

Although case reports and series are available that offer support for the occurrence of all of these mechanisms, most authors consider humoral effects the most important. Malignancies may induce changes in the coagulation system and lead to a hypercoagulable state. Cancer cells may have direct procoagulant effects by the production of tissue factor and of cancer procoagulant (CP). Estimates of the prevalence of cancer among patients with venous thrombosis vary from 3% to 18%,. In a population-based study in Sweden, 19% of patients with thrombosis had a malignancy known at the time of diagnosis. Cancer was diagnosed in the year after the thrombotic event in an additional 5%. Because most studies were performed with the aim of evaluating the need for cancer screening in thrombosis patients rather than establishing cancer as a risk factor for thrombosis, comparisons with control groups and estimates of relative risk are scarce. An approximation of the relative risk can be found in the follow-up of patients testing positive and negative for thrombosis. Overall, the risk of thrombosis was seven-fold increased in those with cancer. The prevalence of cancer in the population depends on several factors, of which age may be the most important. After middle age, the prevalence of cancer in a population may be 2% to 3%, which implies that cancer, with a relative risk of 7, accounts for 10% to 15% of all events of thrombosis.

### Surgery and Trauma

Major surgery is one of the strongest risk factors for thrombosis, especially in orthopedic surgery and neurosurgery. In orthopedic surgery of the hip and knee, the risk of thrombosis reaches 30% to 50%. High risks have been described in abdominal surgery (up to 30%), gynecologic surgery, and urologic surgery (in particular open prostatectomy). The risk of thrombosis also is high after major trauma, with risk estimates of 50% to 60% in patients with head trauma, spinal injury, and pelvic fractures. Even higher risks are reported after femoral and tibial fractures.

Although the relative risks of thrombosis in surgery and trauma are extremely high, the impact of these on the overall occurrence of thrombosis is decreased by the widespread use of prophylactic anticoagulation. The number of thrombosis cases will vary between countries, depending on regional policies on anticoagulant prophylaxis. In the Leiden Thrombophilia Study, 18% of patients with thrombosis had undergone surgery shortly before the thrombosis, as compared to 3.6% of controls in a similar time window (Table 2). With a relative risk of 6, then, surgery still accounted for 16% of all thrombotic events.

### Immobilization

Bed rest is a well-known cause of thrombosis. It explains the occurrence of thrombosis in a variety of situations, such as paralysis, plaster casts, and prolonged travel. All these situations interfere with the function of the calf musculature in pumping the blood upstream though the veins. Even traffic jams, when of gargantuan proportions, may cause venous clots.

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### Table 1. Risk Factors for Venous Thrombosis

<table>
<thead>
<tr>
<th>Acquired</th>
<th>Inherited</th>
<th>Mixed/unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Antithrombin deficiency</td>
<td>Hyperhomocysteinemia</td>
</tr>
<tr>
<td>Previous thrombosis</td>
<td>Protein C deficiency</td>
<td>High levels of factor VIII</td>
</tr>
<tr>
<td>Immobilization</td>
<td>Protein S deficiency</td>
<td>APC-resistance in the absence of FVL</td>
</tr>
<tr>
<td>Major surgery</td>
<td>Factor V Leiden (FVL)</td>
<td></td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>Prothrombin 20210A</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>Dysfibrinogenemia</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td></td>
<td></td>
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<tr>
<td>Hormone replacement therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloproliferative disorders</td>
<td></td>
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<tr>
<td>Polycythemia vera</td>
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</table>
thrombosis. The impact of immobilization on the overall occurrence of thrombosis is not readily calculated because definitions of immobilization may vary, as do policies regarding the administration of prophylactics. In the Leiden Thrombophilia Study, 15.6% of patients had been immobilized in the time before the event (both during hospital admission and at home), while for the control subjects, this figure was 1.7%. From this follows a relative risk of 11.1 and an attributable risk (i.e., the contribution of immobilization to all thrombotic events) of 15%.

**Oral Contraceptives**

The first case of thrombosis associated to oral contraceptive use was reported in 1961 by Jordan and concerned a nurse who developed pulmonary embolism shortly after starting oral contraceptives. The thrombogenicity of “the pill” was subsequently confirmed in numerous reports. Early oral contraceptives contained 100 µg or more of estrogen (ethinylestradiol). Today, this has been reduced to 30 µg ethinylestradiol. It is unclear whether this has led to a concomitant decrease in the risk of thrombosis. Studies in the 1960s found relative risks for idiopathic deep vein thrombosis ranging from 4 to 8.6,38,39 Two large follow-up studies in the 1970s and 1980s found relative risks of 11 and 7, respectively.40,41 The most recently published large studies on the risks of thrombosis associated with oral contraceptive use do not differ significantly from the results obtained in earlier studies. In the study by the World Health Organization (WHO), oral contraceptives led to a four-fold increased risk,42 as they did in an international study43 and in the Leiden Thrombophilia Study (Table 2). In this latter study, a head-on comparison between formulations with 30 µg and 50 µg ethinylestradiol showed no differences.44 In another study, however, the lower-dose oral contraceptives appeared to carry a lower thrombotic risk.45 There are no data to suggest that the newest oral contraceptives containing 20 µg ethinylestradiol are associated with a reduced risk of thrombosis.46 It seems clear that the effects of lowering the ethinylestradiol content below 50 µg are marginal. Overall, the risk of thrombosis is still present with the currently used low-dose oral contraceptives.

It has been argued that the association of oral contraceptives with thrombosis might be partly or fully explained by so-called referral or diagnostic suspicion bias. This bias would result from physicians preferentially referring women who use oral contraceptives for diagnostic tests for thrombosis, which would lead to an excess of pill-users in the patient group when compared to a randomly selected group of control women without thrombosis. It has recently been shown that this bias does not play an important role and that the risk estimates are valid.47 Women referred for diagnostic tests for thrombosis who tested positive were compared to women referred who tested negative. Here, oral contraceptive use was associated with a four- to five-fold increased risk of thrombosis. Because both patients and controls were referred under the same suspicion of thrombosis, referral and diagnostic suspicion bias was eliminated.47

The risk conferred by oral contraceptives is not restricted to the estrogen content; it also depends on the progestogen content. Oral contraceptives containing desogestrel or gestodene (so-called third-generation progestogens) confer a two-fold higher risk than oral contraceptives containing levonorgestrel (so-called second-generation progestogens).48,49 Extensive adjustment for all possible confounding variables, such as age, family history, factor V Leiden, duration of use, previous pregnancy, and obesity, did not materially affect these results. Nevertheless, these findings have given rise to considerable controversy. Therefore, WHO convened an independent panel of experts who concluded that, in all likelihood, the risk is further increased by contraceptives containing desogestrel or gestodene. Recent laboratory work has, demonstrated that the response to activated protein C (APC) in a prothrombin-time based assay is more affected by these contraceptives than by the previous ones.51

The impact of oral contraceptive use on the overall incidence of thrombosis depends heavily on the prevalence of use. Because thrombosis is rare among young women, the impact on overall occurrence in a population may be relatively low; however, among young women, oral contraceptive use is the predominant cause of thrombosis. When we apply data from the Netherlands, where more than one-third of women ages 15 to 49 use oral contraceptives, oral contraceptive use accounts for one-half to two-thirds of all thrombotic events in women in this age group.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Patients (n=474) n (%)</th>
<th>Controls (n=474) n (%)</th>
<th>Ratio Odds</th>
<th>CI95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>85 (18)</td>
<td>17 (3.6)</td>
<td>5.9</td>
<td>3.4-10.1</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>59 (12)</td>
<td>6 (1.3)</td>
<td>11.1</td>
<td>4.7-25.9</td>
</tr>
<tr>
<td>Immobilization</td>
<td>17 (3.6)</td>
<td>2 (0.4)</td>
<td>8.9</td>
<td>2.0-38.2</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>8 (5.0)</td>
<td>2 (1.3)</td>
<td>4.2</td>
<td>0.9-19.9</td>
</tr>
<tr>
<td>Puerperium</td>
<td>13 (8.2)</td>
<td>1 (0.6)</td>
<td>14.1</td>
<td>1.8-109</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>109 (70)</td>
<td>65 (38)</td>
<td>3.8</td>
<td>2.4-6.0</td>
</tr>
</tbody>
</table>

*Time window for surgery, hospitalization (without surgery), and immobilization (not in the hospital, > 13 days) was 1 year preceding the index date (i.e., date of thrombosis diagnosis in patients, similar date in controls. For puerperium, the time window was delivery 30 days or less prior to the index date. For pregnancy and oral contraceptive, the time window was at the index date.

*Data on pregnancy, puerperium, and oral contraceptive use refer to women of reproductive age. CI 95 = 95% confidence interval.
Hormone Replacement Therapy
Several recent studies, including a randomized trial, have demonstrated that HRT is also associated with a two- to four-fold increased risk of thrombosis.\textsuperscript{11,12,52,53} This was surprising for two reasons. First, the dose of estrogen in HRT is very low (i.e., equivalent to 5µg of estradiol), again showing that the relation between estrogen dose and thrombosis risk is not linear. Second, the relative risk estimates are remarkable because they are not very different from those found for oral contraceptive use, even though they apply to a much older group of women. The baseline incidence of thrombosis is much higher in postmenopausal women than in women of reproductive age. As a result, HRT leads to a much higher number of women developing thrombosis (absolute risk) than does oral contraceptive use. In populations with a high use of HRT, its impact on the overall frequency of thrombosis may be substantial.

Pregnancy and Puerperium
The risk of thrombosis in pregnancy is around 0.5 per 1,000 pregnancies, which translates to 0.67 per 1,000 pregnant women-years.\textsuperscript{54-56} These incidence rates are lower than the overall population incidence of thrombosis of about 1 per 1,000 per year. This is the result of pregnant women being younger than the average age of the population. When compared to the same age group,\textsuperscript{7} the risk appears about ten-fold increased. In the Leiden Thrombophilia Study, pregnancy was associated with a four-fold increased risk of thrombosis, and puerperium was associated with a 14-fold increased risk (Table 2). Most studies have found a three to five times higher risk of thrombosis in the postpartum period than during pregnancy.\textsuperscript{54,55} A recent study, however, reported twice as many events antenatally as in puerperium.\textsuperscript{56}

Antiphospholipid Antibodies
In systemic lupus erythematosus (SLE), the risk of thrombosis is increased in individuals with antiphospholipid antibodies (i.e., lupus anticoagulant or anticardiolipin antibodies).\textsuperscript{57} These abnormalities are found in about one-half of patients with SLE.\textsuperscript{58} Because SLE is a rare autoimmune disorder, antiphospholipid antibodies in SLE will only account for a very small proportion of all thrombotic events (i.e., less than 1%). The risk of thrombosis is also increased in patients who do not have SLE but who do have a lupus anticoagulant.\textsuperscript{59,60}

Among patients with venous thrombosis, a lupus anticoagulant has been reported in 5% to 15%.\textsuperscript{59,61} This abnormality has been estimated to lead to a nine-fold increased risk of thrombosis.\textsuperscript{39} The frequency of lupus anticoagulant in the general population is not well known. Among 117 healthy subjects, none were found with the lupus anticoagulant,\textsuperscript{62} whereas among 300 healthy blood donors, 6 were found (2%).\textsuperscript{62} With a population prevalence of 1% to 2% and the varying estimates of the prevalence among patients, it can be calculated that lupus anticoagulant will account for 2% to 14% of all cases of thrombosis in the population.

Genetic Causes of Thrombosis
Traditionally, genetic causes of thrombosis and thrombophilia were studied in the setting of family studies. This is still the obvious choice to study a putative hereditary risk factor because the highest frequency of such defects may be expected in families clinically exhibiting a tendency to thrombosis. Comparisons of the frequency of thrombosis in families with a particular abnormality will help researchers to better understand the thrombogenicity of the factor under study. Although this is useful for etiological research, it yields no information about the prevalence of the abnormality. The relative risk is difficult to interpret and is not directly applicable in other settings (i.e., unselected patients).

Protein C Deficiency
Since 1981, many family studies have pointed to an increased risk of thrombosis in heterozygous deficiency of protein C.\textsuperscript{63,64} No difference in risk was found between individuals with different types of deficiency (i.e., type I, type II) or underlying mutation. These family studies have suggested high risks associated with protein C deficiency, with the majority of carriers experiencing thrombosis before middle age.\textsuperscript{65} It is likely, however, that these estimates are too high because of additional defects in these families, in particular factor V Leiden.\textsuperscript{66} Therefore, these high risk estimates only apply to highly selected families with thrombophilia, and not to an unselected patient with thrombosis who is diagnosed with protein C deficiency.

Three large studies of unselected patients with venous thrombosis led to very similar findings of a prevalence of thrombosis of 3% among protein C-deficient individuals.\textsuperscript{51,67,68} In a direct comparison with controls, the relative risk conferred by protein C deficiency was 6.5.\textsuperscript{68} In a large study among healthy individuals, the population prevalence was estimated at 0.2%.\textsuperscript{69} This population prevalence, combined with a frequency of 3%, points to a relative risk of 15. Because of the rarity of the abnormality, however, the attributable risk for the overall thrombosis incidence is only 1% to 2%.

Protein S Deficiency
Families with protein S deficiency have been reported since 1984.\textsuperscript{70} In these families, the risk associated with thrombosis was impressive. In one of the largest and best characterized families with protein S deficiency, the majority of carriers had developed venous thrombosis before age 40.\textsuperscript{71} Studies among unselected patients, however have not led to a clear picture. This may be because type I (i.e., low total protein S and low free protein S) and type III (i.e., low free protein S with normal total protein S level) deficiency,\textsuperscript{72,73} which are two phenotypic variations of the same underlying defect, can coexist in families. The apparent difference is the result of marked effects of other factors, notably age, on total protein S levels.\textsuperscript{73} This led to the conclusion that the best way to determine protein S deficiency would be by measurement of free protein S.\textsuperscript{74} In a large, population-based study in the Netherlands, no difference was found in the prevalence of low levels of total protein S (1.1% in
patients vs 1.3% in controls). Low levels of free protein S were found in 3.1% of patients and 2.1% of controls. In a subsequent Italian population-based, case-control study, low levels of free protein S were found in 3.1% of patients and 1.3% of controls. Taken together, these two studies suggest that protein S deficiency, defined as low free protein S levels, has only a mild effect on the risk of thrombosis and increases the risk by only about two-fold. A higher frequency among consecutive patients was found in the Spanish EMET study, where 5.7% of patients had low levels of free protein S; however, since this study included no healthy controls and population frequencies might differ regionally, this does not necessarily suggest a higher relative risk.

The currently available evidence points to a substantial difference in risk associated with protein S deficiency in thrombophilic families and in unselected consecutive patients. It seems plausible that the effect in families is the result of interaction with other defects in those families. In that case, protein S deficiency is, at most, a mild risk factor for thrombosis. With a population prevalence of 1% and a relative risk of 2, protein S deficiency accounts for only 1% of all thrombotic events in the population.

The conclusion that protein S deficiency is only a mild risk factor may not be entirely convincing, especially since in selected families the risk seems comparable to protein C deficiency. It is possible that the population prevalence of protein S deficiency is much lower than 1%. An over-diagnosis of a deficiency when the diagnosis is based on low levels of the protein may occur more often for protein S than for the other anticoagulant deficiencies, since the levels of protein S are affected by many exogenous factors (age, oral contraceptives, hormonal status), thus rendering the interpretation of laboratory results difficult. Some evidence for this may be found in the EMET study, where only half of all type III protein S deficiencies diagnosed based on low levels of free protein S could be confirmed in family studies. When protein S deficiency is more than just a mild risk factor, it will also be more rare in the population, and therefore, still account for only a very small fraction of all thrombotic events in a population.

**Antithrombin Deficiency**

Families with antithrombin deficiency have been reported since Egereg’s first report in 1965. These family studies suggest that antithrombin deficiency is a more severe disorder than deficiencies of protein C or protein S, with the majority of patients suffering thrombosis before age 25. This does not concern the variant in the heparin-binding site, which appears common, but in the heterozygous form without effect on risk. The data from family studies and case reports are again likely to be overestimates of the risk based on the presence of other defects and reporting bias. In a study within a well-characterized, large, single pedigree with antithrombin deficiency, a much lower 20% cumulative lifetime incidence of thrombosis was found. In a population-based, case-control study, antithrombin deficiency was associated with a five-fold increased risk of thrombosis. Here, the abnormality was found in 1.1% of patients and 0.2% of controls. In other series of unselected patients with thrombosis, antithrombin deficiency was present in 15% and 0.5%. Among 4,000 blood donors, antithrombin deficiency was present in 0.02%. These data show that antithrombin deficiency is a very rare disorder, which in itself explains why it is difficult to reliably estimate its effect on the risk of thrombosis. It is possible that antithrombin deficiency is indeed a stronger risk factor than protein C deficiency. For example, a prevalence among patients of 1% as compared to 0.02% in the population suggests a 50-fold increased risk. The contribution of antithrombin deficiency to thrombosis in the population is very small and accounts for less than 1% of all thrombotic events.

**Factor V Leiden**

Among Caucasian populations, factor V Leiden (factor V R506Q) is the most common genetic defect causing thrombosis currently known. The mutation, first described in 1994, underlies resistance to APC, which was first described in 1993. The frequency of factor V Leiden carries among Caucasians varies between 2% and 15%. Heterozygous factor V Leiden increases the risk of thrombosis three- to eight-fold, whereas homozygous individuals have an 80-fold increased risk.

Factor V Leiden has been found in 20% of unselected patients with deep vein thrombosis and more than half of probands from selected families with familial thrombophilia. It is, therefore, also the most commonly found abnormality among patients with thrombosis.

In the Netherlands, with 4% of the population being carriers of factor V Leiden and having a relative risk of 8, factor V Leiden accounts for 22% of all thrombotic events. When the population prevalence is lower, this figure becomes lower. For very high population prevalences, such as in southern Sweden, factor V Leiden may account for up to half of all thrombotic events.

**Prothrombin 20210A**

A mutation in the 3'-untranslated region of prothrombin at position 20210 (G→A, PT20210A) is associated both with prothrombin levels and the risk of thrombosis. This mutation was found in a high prevalence (18%) in individuals from selected families with thrombosis and in 6.2% of unselected patients with a first thrombosis, yielding an odds ratio of 2.8. Interestingly, the increased prothrombin levels appear to be the way the risk is mediated because in those with wild-type prothrombin, the risk of thrombosis is also associated with prothrombin levels. Many reports have confirmed the association between this mutation and venous thrombosis. The population prevalence among Caucasians is about 2%, with remarkable geographic variation and with higher frequencies in southern than in northern Europe. These different population frequencies have implications for the relevance of the mutation and the occurrence of thrombosis in various populations. In northern Europe, where the prevalence is around 2%, and the relative risk around 2, PT20210A accounts for at most 2% of all thrombotic events. In the Catalan region of Spain, where a high prevalence of 6.5% in controls, and a relative risk of 2 was reported PT20210A accounts for more than 6% of all thrombotic events. In southern European countries, PT20210A is likely to be the cause of more thrombotic events than factor V Leiden.
Blood Group
It has been known since the 1960s that ABO blood group is associated with the risk of venous thrombosis, with those with blood group O having the lowest risk.97 Estimates of the relative risk for non-O blood groups, which are present in more than 50% of the Caucasian population, range from 2 to 3.7,98,99 This implies that blood group non-O accounts for one-third to more than one-half of all thrombotic events in the populations from which these figures are derived. Blood group is related to the levels of von Willebrand factor (vWF),100 which in turn is the major determinant of plasma factor VIII levels.101 As such, individuals with non-O blood groups have the highest levels of vWF and factor VIII. It has been shown that, when all these factors are taken into account simultaneously, the effect of blood group on risk largely disappears, suggesting that the mechanism by which blood group leads to thrombosis is through the elevated factor VIII levels.99 The association of blood group with thrombotic risk is a strong indication that the observed relation of factor VIII levels with risk is not brought about by prothrombotic effects on factor VIII.

Other Plasma Abnormalities Associated with the Risk of Thrombosis

Hyperhomocysteinemia
Mildly elevated plasma levels of homocysteine are associated with an increased risk of venous thrombosis.102-105 Two studies among unselected patients may be used to calculate attributable risks. In the Netherlands, levels exceeding 18.5µmol/l were found in 5% of healthy individuals and were associated with a two-fold increased risk.103 In an Italian study, 10% of controls had levels exceeding 18.5µmol/l, also doubling the risk.104 These figures imply that hyperhomocysteinemia accounts for 5% to 10% of all thrombotic events.

Hyperhomocysteinemia may be the result of genetic and acquired conditions.106 Low vitamin intake (i.e., B6, B12, folic acid) leads to elevated levels of homocysteine.107-109 Heterozygous carriership of cystathionine β-synthase (CS) deficiency, which in homozygous form causes classic homocystinuria with extremely high levels of homocysteine,110 is only an infrequent cause of hyperhomocysteinemia. A common genetic cause is the variant of the methylene tetrahydrofolate reductase (MTHFR) gene (677 C to T) that leads to a thermolabile variant of the enzyme and mildly elevated homocysteine levels.111-113 It is controversial whether this MTHFR variant is a risk factor for cardiovascular disease.114-116 Although associated with hyperhomocysteinemia, when MTHFR 677TT is not itself a risk factor for thrombosis, the causality of the association between hyperhomocysteinemia and thrombosis becomes doubtful.

High Levels of Factor VIII
Plasma levels of factor VIII are a risk factor for thrombosis. The risk of thrombosis increases steadily with factor VIII level.99 Relative to those people with levels below 100 IU/dl, those with levels over 150 IU/dl have a six-fold increased risk.99 When a dichotomy is at 150 IU/dl, those people with higher levels have 2.7-fold increased risk. Because factor VIII levels exceeding 150 IU/dl were found in 11% of the population, such high levels account for 16% of all thrombotic events.

Factor VIII is an acute phase reactant and may cause one to question the causality of the association. Are not factor VIII levels, when studied in a case control setting, increased because of the previous thrombotic event, for instance by ongoing inflammatory processes that are part of the postthrombotic syndrome in some patients? First, the observation that non-O blood group, being associated with factor VIII levels, is a risk factor in univariate analysis, but not when adjusted for factor VIII levels, suggests that this is not the case. Second, it has been shown that adjustment for acute phase reaction, by measuring C-reactive protein, also did not alter the association.117 It is, therefore, very likely that high levels of factor VIII are causally-linked to venous thrombosis.

The origin of high levels of factor VIII is only partially known. Major determinants are blood group and vWF levels (i.e., genetic factors); however, there is additional variation in factor VIII levels and additional effects on the thrombotic risk. These variations of factor VIII levels cluster within families, and so a genetic component is likely.118

APC-Resistance Not Caused by Factor V Leiden
The response to APC varies by factor V genotype but also within each genotype. Because of the clear association of factor V Leiden carrier status (i.e., heterozygosity and homozygosity), with both the response to APC and the risk of thrombosis, it has been hypothesized that response to APC may determine risk of thrombosis, even in the absence of factor V Leiden.119,120 Indeed, a gradual dose-response relationship was observed between APC sensitivity and risk of thrombosis.121 Because APC sensitivity is a continuous measure, the relative risks depend on the cut-off values applied. When quartiles are used, the risk in the lowest quartile is a 4.4-fold increase compared to the quartile of the highest APC-sensitivity (Table 3). This effect was similar for men and women.

The origin of reduced APC sensitivity in the absence of factor V Leiden is not well known and is likely to be of mixed genetic and acquired origin. A genetic basis can be inferred from the description of families with APC resistance without factor V Leiden119 and the recent reports on a mutation in the 306 APC cleavage site (factor V Cambridge),122 which lead to APC resistance. Pregnancy and oral contraceptive use are acquired conditions associated with APC resistance.51,123,124

When an APC-SR of 0.92 is taken as a cut-off level, the risk for levels below this value is increased by 2.9-fold compared to levels above this value. With this cut-off level, APC resistance (in the absence of factor V Leiden) accounts for 24% of all thrombotic events (in individuals without factor V Leiden). When we add the figures of those with factor V Leiden, which invariably leads to an n-APC-SR below 0.70, the relative risk associated with an n-APC-SR below 0.92 becomes 4. This implies that APC resistance, defined by an n-APC-SR below this cut-off, regardless of factor V Leiden, accounts for 36% of all thrombotic events.
Table 3. Risk of Thrombosis by APC-Sensitivity for Wild-type Factor V

<table>
<thead>
<tr>
<th>n-APC-SR</th>
<th>Patients N (%)</th>
<th>Controls N (%)</th>
<th>Odds ratio</th>
<th>CI95</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1.05</td>
<td>58 (17)</td>
<td>156 (34)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>0.99-1.05</td>
<td>68 (20)</td>
<td>116 (25)</td>
<td>1.6</td>
<td>1.0-2.4</td>
</tr>
<tr>
<td>0.92-0.98</td>
<td>89 (26)</td>
<td>108 (24)</td>
<td>2.2</td>
<td>1.5-3.4</td>
</tr>
<tr>
<td>&lt; 0.92</td>
<td>122 (36)</td>
<td>75 (16)</td>
<td>4.4</td>
<td>2.9-6.6</td>
</tr>
</tbody>
</table>

n-APC-SR = normalized APC-sensitivity ratio
CI95 = 95% confidence interval

In this study, 81 patients who were factor V Leiden carriers and 14 control subjects were excluded from this analysis. They all had n-APC-SR below 0.70; therefore, to calculate the overall contribution of APC-resistance to thrombosis, they may be added to the lowest category.

Conclusion

Venous thrombosis is a multicausal disease. Risk factors resulting from genetics, environment, and behavior may bring about thrombosis. Some risk factors are common. These may explain a substantial part of the thromboses occurring in a population. This is expressed as the attributable fraction (i.e., the proportion of all thrombotic events in a given population that would not take place when the risk factor was taken away), given that the risk factor is indeed a cause of thrombosis. Although the attributable fraction may be seen as the contribution of a particular risk factor to thrombosis, it should be borne in mind that the sum of all attributable fractions is not 100% but it is, instead, infinity. Because only combinations of risk factors lead to disease, removal of one risk factor may lead to 30% decrease, another to 40% decrease, and so on, adding to more than 100%. When thrombosis is invariably the result of interaction between genetic and environmental risk factors, removal of all genetic risk factors would lead to 100% reduction of the occurrence of thrombosis, as would the removal of all environmental risk factors. The attributable fraction is also population-specific. When two populations differ widely in thromboprophylaxis surrounding surgery, the attributable fractions for surgery will differ, as for other factors—even genetic ones.

When risk factors exert their action simultaneously, these effects may interact, and the joint effect may exceed the sum of the separate effects (e.g., oral contraceptives and factor V Leiden). This may be viewed as the presence of subpopulations (e.g., factor V Leiden carriers), where a particular other risk factor (e.g., oral contraceptives) has a much higher attributable fraction.

The importance of an attributable fraction lies at the population level and may steer policy making on this level. This is not necessarily confined to the general population. On the contrary, one may consider guidelines for subgroups based on interaction (i.e., with regard to use of oral contraceptives in factor V Leiden carriers, or with regard to thromboprophylaxis in patients with trauma or malignancies). For the individual patient, the absolute risk is most important (i.e., the probability to develop thrombosis and the possibilities to lower this probability). This can only be adequately assessed when an individualized risk profile is available, taking into account the baseline risk for a patient with a specific age and sex, the risk factors present, and the possible interaction between these risk factors.

References

8. White C. An inquiry into the nature and cause of that swelling in one of both of the lower extremities which sometimes happen to in-lying women together with the propriety of drawing the breasts of those who do and also who do not give suck. London: Warrington; 1784.


